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Polycystic Ovary Syndrome and Oocyte Developmental Competence

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Abstract

Folliculogenesis is a complex process, in which multiple endocrine and intraovarian paracrine interactions create a changing intrafollicular microenvironment for appropriate oocyte development. Within this microenvironment, bidirectional cumulus cell-oocyte signaling governs the gradual acquisition of developmental competence by the oocyte, defined as the ability of the oocyte to complete meiosis and undergo fertilization, embryogenesis and term development. These regulatory mechanisms of follicle growth, controlled in part by the oocyte itself, are susceptible to derangement in polycystic ovary syndrome (PCOS), a heterogeneous syndrome characterized by ovarian hyperandrogenism, insulin resistance and paracrine dysregulation of follicle development. Consequently only a subset of PCOS patients experience reduced pregnancy outcome following ovarian stimulation for *in vitro* fertilization (IVF). Recent data implicate functional associations between endocrine/paracrine abnormalities, metabolic dysfunction and altered oocyte gene expression with impaired oocyte developmental competence in women with PCOS. Therefore, an understanding of how developmentally relevant endocrine/paracrine factors interact to promote optimal oocyte development is crucial to identify those PCOS patients who might benefit from long-term correction of follicle growth to improve fertility, optimize follicular responsiveness to gonadotropin therapy and enhance pregnancy outcome by IVF.

Polycystic ovary syndrome (PCOS) is a heterogeneous syndrome characterized by luteinizing hormone (LH) hypersecretion, ovarian hyperandrogenism, polycystic ovaries, hyperinsulinemia from insulin resistance and reduced fecundity (1). The variable phenotypic expression of reproductive and metabolic abnormalities in PCOS patients leads to differences in oocyte developmental competence (2-6), defined as the ability of the oocyte to complete meiosis and undergo fertilization, embryogenesis and term development (7). Some women with PCOS undergoing ovarian stimulation for *in vitro* fertilization (IVF) have appropriate embryo development (2) and normal pregnancy outcome (3,4), while others have disrupted oocyte development (5,6). Women with PCOS who also are overweight are particularly vulnerable and experience low oocyte fertilization and failure of embryos to implant in their own uterus or those of other women (8).

Impaired oocyte competence in PCOS is inextricably linked with abnormal follicle development. Ovarian hyperandrogenism (9,10), hyperinsulinemia from insulin resistance (11,12) and paracrine dysregulation of growth factors, including transforming growth factor- β (TGF β)-related proteins (13,14) disrupt the intrafollicular environment, alter granulosa cell-oocyte interactions and impair cytoplasmic and/or nuclear maturation of the oocyte. This review examines how PCOS-related endocrine/paracrine abnormalities alter the intrafollicular environment and, in doing so, affect granulosa cell-oocyte interactions crucial for achievement of developmental competence of the oocyte.

DEFINITION OF PCOS

One reason for the variable effect of PCOS on oocyte development undoubtedly is the definition of PCOS itself. The 1990 National Institutes of Health (NIH)-National Institute of Child Health and Human Development-Conference of PCOS in 1990 recommended that the diagnostic criteria should be hyperandrogenism and/or hyperandrogenemia with oligoanovulation, excluding other endocrinopathies, including congenital adrenal hyperplasia (CAH), Cushing's syndrome, thyroid dysfunction, hyperprolactinemia, and androgen-producing tumors and drug-induced androgen excess (15,16) (Table 1). In 2003, the Rotterdam consensus changed the diagnostic criteria to include at least two of the following three features: 1) clinical or biochemical hyperandrogenism, 2) oligo-anovulation, and 3) polycystic ovaries (PCO), excluding the previously described endocrinopathies (15). These newer Rotterdam criteria for PCOS include all patients defined by 1990 NIH criteria (i.e., classic PCOS) and also include women with either 1) clinical/biochemical hyperandrogenism and PCO (i.e., ovulatory PCOS) or 2) PCO with ovulatory dysfunction (but without signs of androgen excess) (15,16).

Categorizing PCOS by different phenotypes is important because classic PCOS patients are at increased risk of developing reproductive and metabolic abnormalities, including menstrual dysfunction and type 2 diabetes mellitus, respectively. Ovulatory PCOS patients have a lower body mass index (17) and lesser degrees of hyperinsulinemia and hyperandrogenism than classic PCOS patients (17,18,19), which may contribute to lowered risks of developing similar reproductive and metabolic abnormalities. Women with combined PCO and oligo-anovulation (without androgen excess), who do not fulfill the diagnosis of PCOS by the Androgen Excess Society (15), appear least affected, despite greater follicle number and serum LH/FSH ratios than normal women (18). Considering androgen and insulin excess as detriments to follicular development, classic PCOS patients who manifest the greatest degrees of hyperandrogenism and hyperinsulinemia are most likely to have an abnormal intrafollicular environment and impaired developmental competence of the oocyte.

PCOS AND OOCYTE DEVELOPMENT

The relationship between PCOS and oocyte developmental competence remains obscure for several reasons. First and foremost, studies of oocyte developmental competence are limited by ethical and experimental constraints on the use of human oocytes and embryos for biomedical research. In addition, the microenvironment of each follicle is unique and has its own effect on the developing oocyte (20). Therefore, during IVF when multiple embryos are transferred simultaneously into the uterus, it is difficult to monitor relationships between follicle fluid steroid levels and successful embryo implantation.

Another problem is the gradual acquisition of necessary molecular components to complete meiosis, undergo mitosis, create an embryonic genome, modify its chromatin structure, and transcribe the correct genes to begin the developmental program (21). Such a gradual acquisition of maternal mRNAs, proteins, and other molecular components in the oocyte (22, 23) make human studies difficult, particularly during early follicle growth. Our understanding of oocyte development in PCOS, therefore, is limited to indirect markers of human oocyte

development, including studies of oocyte gene expression, correlations between follicle fluid steroid levels and oocyte development *in vivo* when it can be monitored, and actions of sex steroids on oocyte development *in vitro* (24,25,26,27).

To circumvent these difficulties, experimentally-induced fetal androgen excess has been used to induce PCOS-like traits in adult animals, in which endocrine/paracrine disruption of follicular growth and oocyte development can be examined (1,20,28,29). The prenatal testosterone-treated rhesus monkey and sheep models provide critical insights into mechanisms of oocyte development. While beyond the scope of this review, relevant findings from these two animal models are discussed, along with other appropriate mammalian models, to emphasize how endocrine/paracrine disruption of the intrafollicular environment affects oocyte development.

PREANTRAL FOLLICLE DEVELOPMENT

Human follicle development is an ordered process, in which primordial follicles are recruited into a cohort of growing follicles, from which one antral follicle normally is selected to ovulate. The time interval from recruitment of the primordial follicle to development of the mature Graafian follicle averages about 3-6 months (30,31). At the beginning, the primordial follicle contains an oocyte arrested in meiotic prophase I (i.e., a germinal vesicle [GV] stage oocyte) and surrounded by squamous granulosa cells. It contains an abundance of mitochondrial, translational and transcriptional genes, with numerous transcription repressors suggesting transcriptional suppression as the major mechanism of oocyte quiescence (32). With primordial follicle growth, the GV oocyte undergoes intensive messenger ribonucleic acid (mRNA) synthesis (33) and other structural as well as functional changes (22,23,34). Transcripts synthesized at this time can be used during oocyte growth or stored for later use during oocyte maturation and early preimplantation embryogenesis (21,33). With continued follicle growth, squamous granulosa cells enlarge into a single layer of cuboidal cells (i.e., primary follicle) (35,36) and continue to proliferate into several layers, forming the secondary follicle. Theca cells recruited from surrounding stromal cells organize into distinct layers around the follicle and establish mesenchymal-epithelial cell interactions that affect follicle growth.

Primordial follicle growth is largely gonadotropin-independent and is influenced primarily by paracrine/endocrine factors (37), including several diverse proteins of the TGF β superfamily (i.e., TGF β , anti-mullerian hormone [AMH], inhibins, activins, bone morphogenetic protein 15 [BMP15] and growth differentiation factor 9 [GDF9]) (37). Many of these factors are produced by the oocyte (i.e., GDF9 and BMP15) and its surrounding granulosa cells (i.e., activins, inhibins, AMH) and coordinate bidirectional granulosa cell-oocyte communications (36,37,38,39,40). Preantral follicle development occurs over several months, during which time follicles acquire FSH, estrogen and androgen receptors, and become physiologically coupled by gap junctions (30,31,36,41).

During normal folliculogenesis, expression of GDF9, an early follicle growth promoter (42) begins in human oocytes at the primordial-primary follicle transition and increases with preantral follicle growth (13,43). Expression of AMH, an early follicle growth inhibitor, is normally low in primordial and primary follicles, increases to maximal levels in large preantral and small antral stages, and then declines during final follicular maturation (44,45,46,47, 48,49). Moreover, activins promote preantral follicular development, while inhibins produced by the developing antral follicle stimulate theca cell androgen production for E2 synthesis (50,51).

Several of these TGF- β -related proteins are dysregulated in PCOS follicles. PCOS oocytes are characterized by reduced *GDF9* mRNA levels, from primordial follicle growth through small antral follicle development, and are accompanied by impaired follicle growth (13,52). Similarly primordial and preantral follicles of PCOS patients have reduced AMH expression

(14). Some PCOS patients also have low serum activin A levels with high serum concentrations of follistatin (a glycoprotein that binds to activin to inhibit its action [50]) (53,54), while others have an abnormal intrafollicular shift from an activin-dominant to an inhibin-dominant microenvironment during follicle growth (55,56,57). The clinical implications of these TGF β -related proteins abnormalities on the PCOS oocyte are not entirely understood.

Serum androstenedione levels in women predict the numbers of antral follicles under basal conditions (58,59) and of oocytes retrieved following gonadotropin stimulation for IVF (58). Moreover, elevated serum androgen levels in PCOS patients positively correlate with an increased cohort size of 2-5 mm follicles (59), while anti-androgen therapy reverses PCO morphology (60). Because human preantral follicles express androgen receptor mRNA (41) and differentiate in response to androgen exposure, these findings are consistent with androgen-enhanced primordial follicle recruitment in PCO, as evidenced by an increased proportion of primary follicles and a reciprocally decreased proportion of primordial follicles in ovaries of some, but not all, PCOS patients (61,62,63).

Studies using animal models provide support for this premise. Testosterone administration to adult female rhesus monkeys increases the number of primary, growing preantral and small antral follicles and the proliferation of granulosa cells within them (64,65). Androgen treatment in such monkeys upregulates mRNA expression of FSH receptor, insulin-like growth factor (IGF)1 receptor and IGF1 in granulosa cells (66,67), and enhances IGF1 and IGF1 receptor mRNA expression in primordial follicle oocytes (68). In addition, prenatal exposure of sheep to excess testosterone enhances recruitment of primordial follicles and increases the size of oocytes within them (29), suggestive of altered preantral granulosa cell-oocyte signaling.

ANTRAL FOLLICLE DEVELOPMENT

Antral follicle formation is accompanied by diminished oocyte growth and differentiation of granulosa cell layers into mural and cumulus cell subpopulations (35,36). The oocyte plays a direct role in controlling cumulus cell development (69) and, in combination with gonadotropins, androgens, IGF1 and epidermal growth factor (EGF)-like peptides, facilitates preantral to antral follicle transition (70,71,72). Human antral follicles reaching 2-5 mm in size depend upon FSH for continued growth (31). Those antral follicles reaching 6-8 mm in size acquire aromatase activity (73), allowing androgens produced by LH-stimulated theca cells to undergo aromatization to estrogens by FSH-stimulated granulosa cells. Estrogen production is further facilitated by granulosa cell-derived paracrine factors that regulate theca cell P450_{c17} activity (74), with inhibins and IGF1 stimulating aromatizable androgen production, and follistatin binding activin to inhibit its androgen-suppressing effect (75). With FSH-induced upregulation of LH receptors in granulosa cells, the maturing follicle continues growth and steroidogenesis in response to both gonadotropins, despite declining serum FSH levels before the midcycle LH surge (31).

Simultaneously, transition from the GV-stage to the mature (metaphase II) stage of mammalian oocyte development occurs. This is associated with transcriptional repression and selective destruction of transcripts (76), although gene and protein modifications continue (77,78,79). Induction of oocyte transcriptional repression is mediated by FSH via cumulus cell-oocyte interactions and is crucial for acquisition of oocyte developmental competence (80,81). Lipid accumulation, nucleolar vacuolization and protein synthesis essential for embryogenesis also are modified by steroids and growth factors (78,82,22,83,84). Consequently, oocytes from healthy large antral follicles are more apt to develop into blastocysts than similarly-matured oocytes from developmentally-delayed small antral follicles (85,86), with FSH enhancing oocyte development (87,88). A similar relationship between follicle size and oocyte development exists for *in vivo* matured oocytes in humans (89,90,91), presumably because

oocytes from large antral follicles are exposed to an appropriately timed progression of changes in the intrafollicular microenvironment.

The intrafollicular steroidogenic milieu induced by gonadotropins has a profound influence on oocyte development. Appropriate estrogen exposure appears to be critical for proper oocyte maturation (25). Estradiol (E2) exposure increases fertilization and cleavage rates of *in vitro* matured oocytes, without affecting nuclear maturation (26). This E2 action is accompanied by rapid oscillations of intracellular free calcium that occur before GV breakdown and are antagonized by androgen (27). Therefore immature human oocytes have E2-dependent, calcium-mediated mechanisms of cytoplasmic maturation that are susceptible to androgen inhibition. In support of this, low E2 production in patients with 17 α -hydroxylase deficiency is associated with *in vitro* embryonic developmental arrest (25), while a decreased E2/androgen ratio from aromatase inhibition also impairs mouse oocyte maturation *in vitro* (92).

The finding that testosterone inhibition of meiotic maturation and embryonic development is greater in cumulus-denuded than cumulus-enclosed mouse oocytes matured *in vitro* further suggests that cumulus cells protect the enclosed oocyte against hyperandrogenism through local aromatase activity (93,94). Such cumulus cell-mediated oocyte protection is important because small PCOS follicles are hyperandrogenic (95) from intrinsically increased theca cell androgen biosynthesis (96). Small PCOS follicles also have elevated 5 α -reductase activity, which increases 5 α -reduced androgens to levels capable of inhibiting granulosa cell aromatase activity *in vitro* and harming oocytes through limited E2 production (9,10). Moreover, immature oocytes recovered from such small PCOS follicles show decreased rates of *in vitro* maturation, fertilization and embryo development compared to immature oocytes from normal women (97). Similar inhibitory contributions of androgen to oocyte development have been suggested from ovarian hyperstimulation studies of a nonhuman primate model of PCOS, specifically adult female rhesus monkeys exposed to prenatal testosterone excess in early gestation. When subjected to FSH therapy alone, such adult prenatal testosterone-treated monkeys show increased 5 α -reductase and decreased aromatase activities in E2-deficient follicles accompanied by cleavage arrest after fertilization of *in vitro* matured oocytes (20). Thus, by limiting estrogen production or action during antral follicular development, hyperandrogenic PCOS follicles may impair oocyte developmental competence. In human oocytes, such oocyte impairment may actually be related more to the estrogen to androgen ratio than to the absolute amount of E2 in the follicle (27,98).

Insulin is another likely mediator of oocyte development competence. Insulin binds to its own receptors located on theca and granulosa cells, as well as oocytes (99,100), to promote follicle recruitment (101) and to stimulate steroidogenesis (102,103). Insulin increases theca cell androgen production by stimulating 17 α -hydroxylase activity, amplifying LH- and IGF1-stimulated androgen production, elevating serum free testosterone levels through decreased hepatic sex hormone-binding globulin production, and enhancing serum IGF1 bioactivity through suppressed IGF-binding protein production (102). Insulin also enhances FSH-induced upregulation of LH receptors in granulosa cells and increases their ability to produce P4 in response to LH (104,105).

Insulin sensitivity in PCOS patients is intrinsically impaired from abnormal post-receptor signal transduction, reducing insulin-mediated glucose uptake, but not ovarian steroidogenesis (102). Consequently, hyperinsulinemia from insulin resistance in PCOS is independent and additive with that of obesity, with the combination of PCOS and obesity profoundly impairing glucose-insulin homeostasis, while promoting ovarian steroidogenesis. As a result, hyperinsulinemia from insulin resistance in PCOS contributes to hyperandrogenism (102). It also promotes premature granulosa cell luteinization in small antral PCOS follicles (103, 104), as evidenced by LH receptor overexpression and P4 hypersecretion (12,104,106), causing

arrest of cell proliferation and follicle growth. The additional finding that insulin together with FSH upregulates LH receptor expression in cultured mouse cumulus-oocyte complexes and reduces blastocyst development (105) implies that hyperinsulinism during FSH-dependent antral follicle growth perturbs cumulus-oocyte signaling and oocyte development.

TERMINAL FOLLICLE DEVELOPMENT

With the onset of the midcycle LH surge, the preovulatory follicle shifts steroidogenesis from androgen and estrogen to progesterone production during meiotic resumption and final maturation of the oocyte (31). The cumulus-oocyte complex expands through production of an extensive extracellular matrix of proteoglycans, providing optimal conditions for oocyte fertilization (107). Meiotic resumption and cumulus cell differentiation are coordinated through complex interactions among several factors, including gonadotropins, androgen, IGF1, EGF/EGF-like peptides and oocyte-derived factors (69,70,71,72,107). Bidirectional cumulus cell-oocyte signaling via gap junctions (108,109) induces the oocyte to undergo GV breakdown and produce a haploid metaphase II oocyte (i.e., nuclear maturation) capable of fertilization and initial embryonic development. Nuclear maturation of the metaphase II oocyte occurs together with cytoplasmic maturation, which involves recruitment and modifications of mRNA as well as protein essential for fertilization and embryogenesis (77,110).

Terminally differentiated follicles of PCOS patients undergoing ovarian stimulation for IVF are hyperandrogenic (111,112) and contain metaphase II oocytes with distinctly abnormal gene expression profiles (24). Many of these differentially expressed genes in PCOS involve signal transduction, transcription, deoxyribonucleic acid/RNA processing and cell cycle regulation. They also share promoter sequences with putative binding sites for androgen receptor, peroxisome proliferating receptor gamma and/or peroxisome proliferating receptor gamma-retinoid X receptor binding sites.

Complementing these gene expression profiles of mature human oocytes, cumulus and mural granulosa cells express androgen receptor (Hickey T, Ph.D. Thesis, Adelaide, Australia: University of Adelaide; 2006) and insulin receptor mRNAs (99), providing rationale physiological mechanisms by which androgens and insulin as well as their excesses may affect cumulus-oocyte signaling. As examples, clinical hyperandrogenism, as determined by elevated basal serum free androgen levels, reduces the rate of ongoing pregnancy in clomiphene citrate-resistant PCOS patients undergoing rhFSH therapy for ovulation induction (113). Hyperinsulinemia from insulin resistance also lowers the chance of conception in similarly-treated PCOS patients (114). Most pertinent to oocyte development, however, is that the combination of PCOS and increased adiposity increases the miscarriage rate following transfer of normal-appearing embryos into a surrogate uterus (8). With androgen and insulin levels in the human follicle determined by PCOS and BMI, respectively (99,111), PCOS-related hyperandrogenism and adiposity-dependent insulin resistance might interact to profoundly alter cumulus-oocyte signaling and impair oocyte developmental competence.

If so, then why is impaired oocyte developmental competence not a universal finding in PCOS patients undergoing ovarian stimulation for IVF. The increased number of retrieved oocytes and embryos in women with PCOS, in spite of a higher percentage of them being compromised, may result in normal IVF pregnancy rate (3,4). Alternatively, this may be a function of variable PCOS phenotypes, which affect oocyte physiology differently: classic PCOS has the greatest degrees of hyperandrogenism and hyperinsulinemia (17,18,19). Nevertheless, lean PCOS patients also can have impaired oocyte developmental competence (6), with impaired fertilization of PCOS oocytes that show no association with gross chromosomal abnormalities or nuclear immaturity (5,115). Furthermore, South Asian PCOS patients have greater degrees of androgen and insulin excess than Caucasian PCOS patients (116) and also have reduced

oocyte fertilization and ongoing pregnancy rates versus their Caucasian counterparts (117). Therefore, genetic factors may interact with environmental influences during pre- and postnatal development to determine the degree to which the intrafollicular microenvironment affects the oocyte (20,28,29,109,117).

FUTURE DIRECTIONS

Understanding how PCOS and obesity interact to disrupt folliculogenesis is crucial to the development of new clinical strategies to enhance fecundity in PCOS patients. In this regard, the use of the insulin sensitizer, metformin, in PCOS to improve both ovarian hyperandrogenism and hyperinsulinemia has been proposed to optimize follicular growth and oocyte development. One of two prospective, randomized, double blind IVF studies shows that metformin therapy to PCOS women lowers serum fasting insulin, total and free testosterone as well as E2 levels at oocyte retrieval and enhances clinical pregnancy as well as livebirth rates; its affect on the intrafollicular microenvironment was not studied (118). The other shows that pretreatment of PCOS patients with metformin before IVF treatment does not affect ovarian responsiveness to FSH therapy nor pregnancy outcome (119). Furthermore, a recent double-blind, randomized study shows that metformin lacks superiority over clomiphene citrate in achieving live-birth in infertile PCOS patients, making the current use of metformin to improve oocyte developmental competence in PCOS controversial (120).

Also important is recognizing how metabolic signals control the intrafollicular environment. With obesity as the fastest-growing medical problem in America and with two-thirds of American adults overweight, impaired glucose-insulin homeostasis from insulin-resistance diseases, such as obesity, PCOS and diabetes mellitus, all have implications for oocyte development. As an example, insulin resistance increases the risk for miscarriage after IVF, controlling for BMI and PCOS (121). This implies that maternal and environmental factors may exaggerate the adverse effects of genetically-determined hyperandrogenism in the PCOS follicle. Additional studies of obese PCOS women must determine whether nutritional regimens, behavioral modifications and pharmacological strategies, alone or together, optimize follicle growth and oocyte development

Equally important are the regulatory mechanisms governing bidirectional cumulus cell-oocyte signaling. From an “oocentric” point of view, the ability of oocyte-derived factors, such as BMP15 and GDF9, to regulate cumulus cell proliferation, differentiation and steroidogenesis emphasizes the role of the oocyte in determining its own developmental fate and protecting itself against its own microenvironment (38,39,40,108,109). Whether oocyte-mediated, paracrine control of follicle growth accounts for the heterogeneity in follicular development among the cohort of follicles undergoing gonadotropin stimulation remains to be determined.

Finally, since experimental constraints exist on studying human oocytes, animal models will continue to pioneer the earliest aspects of oocyte physiology (1,29,108,109). Such models need to explore how developmentally relevant endocrine/paracrine factors and genes interact to promote optimal gene expression in the oocyte for later fertilization and successful preimplantation embryogenesis. They also need to examine critical times during fetal development when the endocrine status of the mother might permanently alter ovarian physiology of the fetus and modify oocyte susceptibility to disease after birth. With such information, new clinical strategies targeting long-term correction of follicle development could improve fertility, optimize follicular responsiveness to gonadotropin therapy and enhance pregnancy outcome by IVF, thereby promoting the transfer of fewer embryos into the uterus and decreasing the risk of multiple gestation and its adverse consequences on maternal-fetal health.

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Table 1

Definitions of PCOS, based upon presence or absence of clinical/biochemical hyperandrogenism, oligoanovulation and polycystic ovaries*.

Combination of signs and symptoms	Fulfills 1990 NIH, 2003 Rotterdam and 2006 AES criteria for PCOS (Classic PCOS)	Fulfills 2003 Rotterdam and 2006 AES criteria for PCOS (Ovulatory PCOS)	Fulfills 2003 Rotterdam criteria for PCOS only
Clinical/biochemical hyperandrogenism with	yes	yes	no
Oligoanovulation and	yes	no	yes
Polycystic ovaries	yes or no	yes	yes

* excluding other endocrinopathies, including CAH, Cushing's syndrome, thyroid dysfunction, hyperprolactinemia, androgen-producing tumors and drug-induced androgen excess.