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Review

Disordered follicle development

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ABSTRACT

Alterations of ovarian follicle morphology and function have been well documented in women with PCOS. These include increased numbers of growing preantral follicles, failure of follicle growth beyond the mid-antral stage, evidence of granulosa call degeneration, and theca cell hyperplasia. Functional abnormalities include paradoxical granulosa cell hyperresponsiveness to FSH which is clinically linked to ovarian hyperstimulation during ovulation induction. In addition, there is likely a primary theca cell defect that accounts for the majority of excess androgen production in this disorder.

The precise mechanisms responsible for altered follicle function are not completely clear. However, several factors appear to influence normal advancement of follicle development as well as impair ovarian steroidogenesis. These include intra- as well as extraovarian influences that distort normal ovarian growth and disrupt steroid production by follicle cells.

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1. Introduction

The classical description of women with polycystic ovary syndrome (PCOS) includes evidence of excess androgen production, irregular or absent menstrual bleeding as a result of chronic anovulation, and polycystic ovaries. The lack of regular ovulatory function in these women designates PCOS as the leading cause of anovulatory infertility (Franks et al., 2008). The mechanism(s) responsible for failure of ovulation is not known, although abnormalities of the follicle and its respective cellular investments – specifically, the oocyte, granulosa cell (GC), and theca cell (TC) – have been well documented. In particular, among early and mid-antral stage follicles, the degenerative appearance of GCs on histology belies their sustained functional ability to respond to FSH and LH stimulation. Nevertheless, in women with PCOS, alterations of GC function likely contribute to the poor response to gonadotropin administration during controlled ovarian hyperstimulation. Aberrant follicle growth and development does not, however, preclude successful ovarian responsiveness to careful gonadotropin stimulation during ovulation induction. Given these observations, it is likely that extra- or intraovarian factors and not inherent defects of GCs are responsible for disruption of progressive follicle development, leading to mid-antral arrest. In contrast, a primary defect of TC steroidogenesis appears to account for androgen excess in this disorder. Whether and to what degree local androgen overproduction may impact GC activity is not clearly known. However, evidence suggests that androgen excess facilitates abnormal follicle formation and, perhaps, follicle viability.

2. Morphology of the polycystic ovary

The ovaries of women with PCOS are slightly enlarged and contain numerous small (2–9 mm) antral follicles, which are commonly arranged on the periphery with increased central stroma. This distinctive appearance has been codified to establish diagnostic criteria for the polycystic ovary as more than 12 follicles per ovary or an ovarian volume over 10 ml (Rotterdam, 2004a,b). Histologically, growing preantral follicles appear similar to those of normal ovaries. In addition, early antral follicle formation may also appear normal. However, normal development beyond the mid-antral stage is not observed as the follicle begins to exhibit evidence of arrested growth and degenerative change. There is progressive accumulation of follicular fluid and expansion of the antrum. As the follicle enlarges, the GC layer undergoes apoptosis and becomes increasingly atretic. Eventually, the follicle wall may become devoid of GCs, leading to the appearance of a thin-walled cyst.

3. Increased follicle number

A distinctive feature of the polycystic ovary is a pronounced increase in follicle number as the population of growing preantral and antral follicles exceed by 2–3-fold that of normal ovaries (Hughesdon, 1982; Webber et al., 2003; Maciel et al., 2004). The process responsible for excessive follicle formation in PCOS ovaries has not been established; however, several possibilities have emerged, including increased primordial follicle activation, slowed preantral follicle development, increased follicle survival and/or decreased atresia, or a combination of these processes.

3.1. Preantral follicle population

In one of the earliest descriptions of PCOS ovaries, Hughesdon found a 2-fold increase in the number of growing follicles, but the same number of primordial follicles in PCOS ovaries and normal ovaries (Hughesdon, 1982). These findings suggested that the increased number of preantral and early antral follicles in polycystic ovaries was not likely due to either an increased initial primordial pool or an accelerated rate of primordial follicle activation. Subsequent studies have shown increases in the number of total follicles; however efforts to determine the size of the primordial pool have been inconsistent. Webber et al. calculated that the number of healthy primordial follicles as a percentage of total follicles present was lower in both anovulatory and ovulatory polycystic ovaries compared to normal ovaries (Webber et al., 2003). This was interpreted to suggest that increased primordial follicle activation might contribute to the greater number of follicles in PCOS. An alternative explanation is that the growth of preantral follicles occurs more slowly in PCOS, resulting in an accumulation of growing follicles. This possibility is consistent with a study by Maciel et al., in which there were similar numbers of primordial follicles in PCOS and normal ovaries but a higher number of growing preantral follicles in PCOS (**Fig. 1**) (Maciel et al., 2004). As a result, the proportion of resting primordial follicles to the total number of growing follicles would remain decreased. Furthermore, there is no evidence that women with PCOS exhibit early menopause (Webber et al., 2003) as might be expected with accelerated primordial follicle recruitment. Taken together, these data clearly indicate that there are higher numbers of growing follicles in PCOS compared to normal ovaries with no consistent effect on primordial follicle number. However, the mechanism for this pattern remains to be determined.

3.2. Prolonged follicle survival

The observation of an increased preantral follicle population in PCOS suggests either increased entry into or decreased exit from the growing follicle pool. To investigate the latter possibility, small

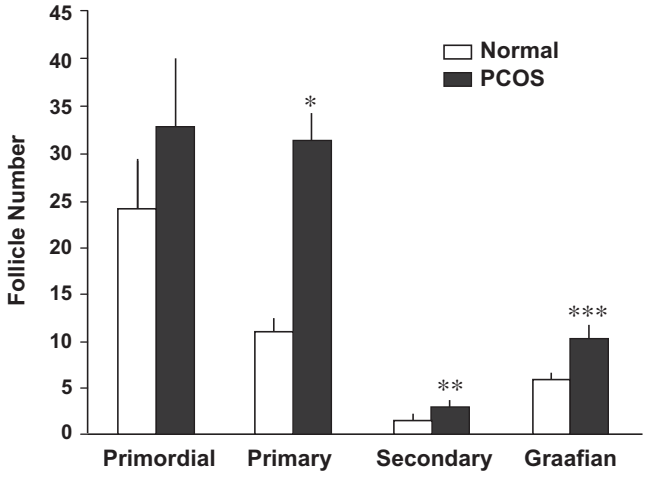

Fig. 1. The size (mean ± SE) of the follicle population (primordial, primary, secondary, and Graafian) in sections of ovaries from normal and PCOS patients. $^{*}P = 0.001$; $^{**}P = 0.02$; $^{***}P < 0.001$.