Aberrant follicle development and anovulation in polycystic ovary syndrome

Développement folliculaire aberrant et anovulation dans les syndromes des ovaires polykystiques

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Abstract

Endocrine factors appear to play an important part in arrest of antral follicle maturation in polycystic ovary syndrome (PCOS) but are unlikely to have an impact on early, preantral follicle development, which is clearly abnormal in PCOS. Disordered early folliculogenesis in PCOS is characterised by a higher proportion of follicles entering the growing phase and more prolonged survival of small follicles than in normal ovarian tissue. The factors responsible for aberrant preantral follicle development remain to be determined but IGFs, growth factors of the TGFβ family and androgens may all have a role.

Keywords: Follicle; Anovulation; Polycystic ovary syndrome

1. The endocrine environment and antral follicle development in polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) is the major cause of anovulatory infertility being the major cause of delay in conception in more than 80% of couples [1]. The classic endocrine abnormalities of PCOS are hypersecretion of luteinising hormone (LH) (with normal levels of follicle stimulating hormone (FSH)) and increased secretion of androgens (principally of ovarian origin) [2]. In recent years however, PCOS is also characterised by a typical metabolic disturbance, central to which are peripheral insulin resistance and the associated hyperinsulinaemia [3].

Granulosa cell function is abnormal, particularly in anovulatory women with PCOS. Follicles from women with PCOS are more heterogeneous than those from normal ovaries and include a significant sub-population that hypersecrete both oestradiol and progesterone [4]. These follicles are prematurely responsive to LH. Hyperinsulinaemia appears to have a significant role in the abnormal response of these follicles to LH. Paradoxi-
cally, granulosa cells of the ovary in women with PCOS remain responsive to insulin despite peripheral insulin resistance. This phenomenon may be explained by differential resistance in insulin-signalling pathways within granulosa cells of the ovary [5]. Serum FSH concentrations are within the normal range but inappropriately low to allow follicle maturation. Mathematical modelling of follicle dynamics in PCOS supports the view that the slightly, but inappropriately, high oestradiol levels (compared with the normal follicular phase) seen in anovulatory women with PCOS could modify the normal feedback regulation of FSH and result in dysfunctional and arrested maturation of large antral follicles. Indeed, increasing FSH levels by the use of anti-estrogens or exogenous FSH results in ovulation in most cases [6]. Another important aspect of improving the endocrine environment and aiding successful induction of ovulation is reducing hyperinsulinaemia by weight reduction and lifestyle modification (the preferred method in overweight women with PCOS) [7].

Surprisingly however, given the abnormalities of granulosa cell function described above, there are few indications that oocyte and embryo quality are significantly compromised in women with polycystic ovaries – at least as far as in vitro maturation (IVM) and fertilisation are concerned. Oocyte quality, as judged by rates of fertilisation and embryo cleavage, is similar to normal in eggs obtained from polycystic ovaries, for IVM with or without ovarian stimulation by gonadotrophins [8]. Women with polycystic ovaries have normal rates of fertilisation and embryo cleavage after superovulation for IVF [9,10]. Indeed, blastocyst cell numbers were found to be significantly higher, following a “titrated” gonadotrophin regimen, in women with PCO than in those with tubal infertility.

Nevertheless, certain endocrine abnormalities in PCOS may influence oocyte or embryo quality. In insulin-resistant women with PCOS, lower fertilisation and implantation rates after IVF have been noted [11], suggesting that hyperinsulinaemia and/or insulin resistance may have an adverse effect. Furthermore, Teissier et al. [12] reported a lower proportion of meiotically-competent oocytes obtained from follicles with higher testosterone and progesterone concentrations, suggesting that these eggs may have been obtained from prematurely “luteinised” follicles. These data are consistent with the observations regarding prematurely responsive to LH and hypersecretion of progesterone – a phenomenon which, as discussed above, may be related to excessive exposure to insulin [4].

2. Abnormal preantral follicle development in polycystic ovary syndrome

Aberrant growth of early preantral follicles [13] may also contribute to the mechanism of anovulation. Until recently however, little was known about the earlier, preantral follicle development in polycystic ovaries, other than the fact that a classic histological study (published more than 20 years previously) indicated that, from the primary stage onwards, follicles of all sizes were increased in density in PCOS [14]. That led us to investigate the possibility that abnormalities of folliculogenesis originate from the very earliest stages of follicle development when the influence of endocrine factors is minimal. Using small cortical biopsies obtained at routine laparoscopy, we found an overall increase in the density of preantral follicles (Fig. 1) and confirmed the increased density of primary follicles in polycystic ovaries [13]. Furthermore, we were able to demonstrate that, in tissue from both anovulatory and ovulatory women with polycystic ovaries, the proportion of primordial (resting) follicles was reduced and the proportion of growing follicles was reciprocally increased compared with normal ovaries. It might be expected, therefore, that there would be premature exhaustion of the follicle pool in PCOS but, firstly, we found no reduction in the density of primordial follicles in the adult polycystic ovary and, secondly, there is no evidence of an earlier than normal menopause in women with PCOS [15]. We then went on to demonstrate that preantral follicles from polycystic ovaries were less likely to undergo atresia in culture (ie showed evidence for prolonged survival) when compared to follicles from normal ovaries [16]. We have also shown that the initial growing stages of preantral follicles in polycystic ovaries were characterized by increased proliferation of granulosa cells in comparison with follicles from normal ovaries [17].

The cause of abnormal preantral follicle development in polycystic ovaries remains unclear. The role of endocrine or metabolic factors is likely to be less than their influence on antral follicle function. Local paracrine/autocrine factors are better candidates. Sex steroids and growth factors have been implicated in control of preantral follicle growth and survival. Candidate growth factors include insulin-like growth factors and members of the transforming growth factor-beta (TGFβ) super-family, some of which have been shown to be specifically expressed in ovarian follicles e.g. growth differentiation factor-9 (GDF-9), which stimulates follicle development and anti-Müllerian hormone (AMH), which inhibits it. Indeed, we have shown that expression of AMH is reduced in early preantral follicles in polycystic ovaries when compared with follicles from normal ovaries [18]. Androgens may have an important role in early follicle development. Studies in the adult Rhesus monkey have shown that short-term treatment with androgens stimulates initiation of follicle growth [19] and has mitogenic effects on porcine granulosa cells [20] and studies (including those in our own laboratory) using a sheep model demonstrate that prenatal exposure of sheep to excess androgen results in abnormal preantral folliculogenesis in the fetal lambs [21] or in ewes as they enter puberty [22]. In preliminary studies, we have been able to demonstrate
the presence of androgen receptor (AR) by IHC in human ovarian follicles at all stages of development. Initial comparison of early growing follicles in normal and polycystic ovaries suggests that AR protein expression is enhanced in follicles from PCOS.

3. Summary and conclusions

Endometrial factors appear to play an important part in arrest of antral follicle maturation in PCOS but are unlikely to have an impact on early, preantral follicle development, which is clearly abnormal in PCOS. Disordered early folliculogenesis in PCOS is characterised by a higher proportion of follicles entering the growing phase and more prolonged survival of small follicles than in normal ovarian tissue. The factors responsible for aberrant preantral follicle development remain to be determined but IGFs, growth factors of the TGFβ family and androgens may all have a role.

Conflict of interest

None.

References