**DEBATE—continued**

**Early ovarian ageing: are women with polycystic ovaries protected?**

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Screening asymptomatic women in the general population for ‘early ovarian ageing’ will be more effective in high-risk groups. Recent findings support the hypothesis that women with polycystic ovaries (PCO) may have actually been born with a larger pool of resting follicles. The mechanism is almost certainly genetic and occurs in fetal life. If, as is widely accepted, the rate of depletion of the ovarian reserve depends primarily on the size of the remaining pool of small follicles, women with PCO will be unlikely to undergo an accelerated depletion of their follicle pool, normally seen in the late thirties, significantly earlier. In terms of asymptomatic screening for early ovarian ageing in the general population, women with PCO constitute a low-risk group and should therefore be excluded.

**Key words:** early ovarian ageing/fetal origin/IVF/IVM/PCOS/polycystic ovaries

Ovarian reserve ‘screening’ is widely practised in assisted reproduction, mainly for predicting IVF outcome. The idea of screening asymptomatic—not infertile—young women in the general population for early decline of their ovarian reserve is more controversial (Nikolaou et al., 2002a; Nikolaou and Templeton, 2003, 2004; Lobo, 2003). On the basis of a fixed interval between menopause and accelerated decline of the ovarian reserve (Faddy et al., 1992; te Velde et al., 1998a, b; Nikolaou and Trew, 2003) it was hypothesized that up to 10% of women in the general population may undergo ‘early ovarian ageing’ (Nikolaou and Templeton, 2003, 2004). This is onset of an accelerated loss of ovarian follicles, normally seen in the late thirties, before the age of 32 years. It was suggested that some of the known ovarian reserve tests, especially the antral follicle count and anti-Müllerian hormone assay (AMH), could possibly be transferred from the field of assisted reproduction to the general population, and used as screening tools for ‘early ovarian ageing’. It was also suggested (Nikolaou and Templeton, 2003, 2004) that screening asymptomatic women for ‘early ovarian ageing’ would be more effective in high-risk groups, mainly women with a family history of early menopause, and also women with a history of ovarian surgery, heavy smoking and severe endometriosis. Women with polycystic ovaries (PCO) most likely form a low risk group for ‘early ovarian ageing’. Here we explain the reasons.

**Ovarian reserve tests and PCO**

Compared to women with ‘normal’ ovaries of the same age, women with PCO perform much better in most known basal and dynamic ‘ovarian reserve’ tests, including the IVF procedure itself. PCO are associated with a very high response to exogenous stimulation with FSH and collection of larger numbers of oocytes (Homburg et al., 1993; Buyalos and Lee, 1996) and are a risk factor for developing ovarian hyperstimulation syndrome (MacDougall et al., 1992; Agrawal et al., 1998a). The opposite situation, poor response to ovarian stimulation during IVF, has been shown to be a predictor of earlier ovarian failure (Farhi et al., 1997; Crosignani et al., 1999; De Boer et al., 2002, 2003; Nikolaou et al., 2002a; Beckers et al., 2002; Lawson et al., 2003; Nikolaou and Trew, 2003). Antral follicle counts are good predictors of IVF outcome and correlate well with chronological age (Broekmans et al., 1998; Scheffer et al., 1999, 2003; Bancsi et al., 2002). By definition, PCO have a higher number of ‘antral’ follicles than the ‘normal’ ovaries (Adams et al., 1986; Franks, 1995; Balen and Michelmore, 2002; Balen et al., 2003; Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group, 2004). PCO tend to be larger (Adams et al., 1986; Kyei-Mensah et al., 1996) and have a higher peak stromal blood-flow velocity on Doppler studies (Zaidi et al., 1995, 1996; Engman et al., 1999a). In addition, women with PCO have higher day 2 inhibin B levels (Lockwood et al., 1998), as well as higher early follicular phase VEGF (Agrawal et al., 1998b).

**Oocyte quality in ‘early ovarian ageing’ and what happens in PCO**

In ‘normal’ ovarian ageing, oocyte quantity and quality covariate, with rapid decline in the late thirties (Nikolaou and Trew, 2003). The age-related decline of oocyte quality is best explained by the ‘two hit model’ of non-disjunction
(te Velde and Pearson, 2002). The overall effect of the ‘second hit’ must be duration-dependent. As a result, in cases of ‘early ovarian ageing’, especially if it is caused by a sudden ‘step reduction’ of the small follicle pool after birth, the quantitative decline of the ovarian reserve (absolute number of oocytes) is faster than the qualitative decline (proportion of good oocytes) at a young age (Hanoch et al., 1998; Toner, 2003; Van Rooij et al., 2003; Ulug et al., 2003; de Sutter and Dhont, 2003). However, as the best follicles are selected and recruited first, even in cases of ‘step reduction’ the two processes of ‘quantitative’ and ‘qualitative’ decline become more parallel later on in life (Brook et al., 1984; Freemantle et al., 2000; Nikolaou and Templeton, 2004). IVF offers direct access to oocytes and embryos, as well as information on fertilization, cleavage, pregnancy and live-birth rates, and thus provides both a qualitative, as well as quantitative, assessment of the ovarian reserve.

Although women with PCO tend to develop many follicles in response to ovarian stimulation, initial data from IVF programmes reported that their fertilization rates tended to be relatively low (Homburg et al., 1993; Buyalos and Lee, 1996). The interpretation of these initial observations would be that, in PCO, there is compromised oocyte quality, despite the large number of follicles. Women with PCO were also thought to have a tendency to higher miscarriage rates, following both natural and assisted conception (Balen et al., 1993a, b) and had a higher incidence of recurrent miscarriage (Sagle et al., 1988). More recent data, however, have shown that all these statements are true only in cases of polycystic ovary syndrome (PCOS), i.e. menstrual irregularity and hyperandrogenism associated with polycystic ovary morphology on ultrasound (Franks, 1995; Rotterdam consensus, 2004). Current thinking is that most of the long-term reproductive disruptions and general health problems associated with PCOS are related to the degree of hyperinsulinaemia and insulin resistance (Eltig et al., 2001a). The hypersecretion of LH in PCOS is probably related to impaired negative feedback on LH secretion. Clinical studies involving women with PCO on ultrasound, but no clinical manifestations of the PCOS, have shown more oocytes, more embryos and much higher cumulative pregnancy rates in women with PCO. The miscarriage rates were similar (not higher) to women with normal ovaries, which would suggest comparable oocyte quality (Engman et al., 1999b; Nikolaou et al., 2002b). In a recent case–control study aiming to evaluate the effect on fertility of the appearance of PCO in women who had no symptoms of PCOS (Hassan and Killick, 2003), the time to pregnancy of women with PCO, but no symptoms, was not significantly longer and they were not more likely to be sub fertile than women with normal ovaries. It has also been shown that asymptomatic women with PCO (no clinical PCOS) do not have higher rates of recurrent miscarriage (Rai et al., 2000). Thus, women with PCO, but no clinical PCOS, seem to have not only a larger number, but also good quality, oocytes. In women with PCOS, the reproductive disruptions seem to be caused by abnormal final follicle maturation in vivo (Fauser, 1994). This seems to be partly improved in in vitro maturation programs, where patients with PCOS tend to have significantly more oocytes collected and higher fertilization, cleavage and pregnancy rates than women with normal ovaries (Child et al., 2001; Tan et al., 2002). In these studies the number of antral follicles at a baseline scan was more important in predicting outcome as compared to whether morphology was polycystic or normal.

**Origin of the increased antral follicle cohort in PCO**

Although the known ovarian reserve markers, including the ovarian response to gonadotrophins, reflect the size of the growing antral cohort, markers that directly reflect the size of the resting follicle pool have not been discovered. Anti-Müllerian hormone (AMH) is a member of the transforming growth factor-β family. It is involved in folliculogenesis and shows good correlation with chronological age, antral follicle counts and IVF outcome (De Vet et al., 2002; Fanchin et al., 2003). In the rat, expression of AMH starts directly after growth initiation of primordial follicles and disappears just after the small antral follicle stage has been reached (Baarends et al., 1995). It has been shown recently that, in adult women, AMH expression follows a similar pattern (Weenen et al., 2004). Because it is related to a much earlier stage of follicle development than all other common markers of the ovarian reserve, AMH measurement is the closest we can get, so far, to measuring the actual primordial follicle pool. Importantly, it has been shown that AMH concentrations are significantly increased in women with PCO (Cook et al., 2002; Laven et al., 2004).

Morphometric studies in the human (Gougeon et al., 1994; Gougeon, 1996) have shown that, generally, there is a good correlation between the cohort of growing antral follicles and the pool of resting and small pre-antral follicles. A crucial question is whether the same is true for PCO. Hughesdon (1982) had compared sampled sections from archived normal and PCO and found that there were similar numbers of primordial follicles, but the latter had twice as many growing and atretic follicles. In an important recent study, it was reported that the median density of small follicles, including those at primordial and primary stages, was 6-fold greater in anovulatory PCO than in normal ovaries (Webber et al., 2003). The primordial follicle density again did not diver between women with normal and PCO, but the difference in density of primary follicles was significant. Although the studies were done on adult ovaries, the high density of primary follicles in PCO supports the notion that these women may have actually been born with a larger ovarian reserve (Webber et al., 2003). This would be in agreement with the hypothesis that the rate of decline of the ovarian reserve depends on the size of the pool of remaining follicles (Faddy et al., 1992; Gougeon, 1996). An alternative explanation for the same density of primordial, but higher density of primary follicles in PCO, reported in both studies, could be that there is an over-recruitment of follicles into the growing stages. The result would have been accelerated ovarian ageing. This is not actually supported by data on long-term follow-up of women with PCO, which do not show any evidence of an early menopause in these women (Dahlgren et al., 1992;
Elting et al., 2000; Amer et al., 2002). A third possibility, of course, is that the larger pool of early growing follicles in PCO is only due to a slower progression through the later stages of follicle development (Mason, 2000; Webber et al., 2003; Jonard and Dewailly, 2004). There is mounting evidence that all the above are actually true. Women with PCO are probably born with a larger pool of resting follicles (Webber et al., 2003). Initially, there is accelerated entry to the early growing stages, and thereafter a relatively slow growth through the pre-antral stages (Webber et al., 2003; Jonard and Dewailly, 2004). This slow growth may be a result of the large size of the small-follicle pool. It is known that, in general, most oocytes are lost with attrition in fetal life. The main mechanism of reduction of the reserve of resting follicles in late reproductive year appears to be through accelerated entry to the late growing phase, when apoptosis is mainly located in the granulosa cells (Gougeon, 1996; Vaskivuo et al., 2001; de Bruin et al., 2004). On this basis it can be speculated that, in cases of ‘early ovarian ageing’, the ‘waves’ of follicles entering the antral stage must be more frequent. On the contrary, in women with PCO, where the initial pool of resting follicles is relatively large and the size of the cohort of growing follicles is correspondingly large, it is likely that the frequency of the waves of follicles entering the antral stage will be slower.

It is plausible that, in terms of evolution, increasing the size of the ovarian reserve at birth has been nature’s way to adjust the ovarian biological clock, in order to preserve fertility in the face of an adverse environment. In agreement with the predictions of the ‘fetal origin hypothesis’, this trait can become potentially detrimental in different conditions (Prentice, 2003), when the PCOS develops. The age of menopause has high inheritability (te Velde and Pearson, 2002) and the same is probably true for all reproductive milestones that precede the menopause and depend on the number of remaining follicles (te Velde et al., 1998a, b). Likewise, there is plenty of evidence for a genetic basis of PCOS although the genes that contribute are still uncertain (Franks, 2002). Although the literature on this point remains controversial (Cresswell et al., 1997; Ibanez et al., 1998, 1999; Sadrzadeh et al., 2003), it is possible that, in fetuses that are genetically predisposed to having a large pool of resting follicles at birth (and PCO after puberty), a certain environment at a critical ‘window’ of fetal development, such as maternal hyperandrogenaemia, hyperinsulinaemia, or stress, can cause fetal hyperandrogenaemia. This ‘programmes’ the hypothalamus–pituitary–adrenal axis towards preferential adrenal adiposity later on in life, which predisposes to insulin resistance and PCOS (Abbott et al., 2002; Eisner et al., 2002). Whether this syndrome will actually develop or not, and to what extent, will depend on the degree of hyperandrogenaemia, as well as other genetic and environmental factors acting after puberty, mainly obesity. Those women who have more follicles (hormone-producing) will be more prone to excessive ovarian androgen production in response to certain environmental stimuli. In fact, the cohort of antral follicles, like the number of small preantral follicles, is larger in women with PCOS than asymptomatic women with PCO (Elting et al., 2001b; Webber et al., 2003). The symptoms of the PCOS tend to regress or disappear when some of the follicles are lost, either in older age or following surgical intervention (Elting et al., 2000, Elting et al., 2003; Amer et al., 2002).

Conclusion

In conclusion, recent findings support the hypothesis that, in PCO, as in ‘normal’ ovaries, the large cohort of antral follicles does actually truly reflect a large pool of resting and small pre-antral follicles. The most likely explanation is that women with PCO are born with a larger pool of resting follicles, almost certainly through a genetically determined process that occurs in fetal life. The larger the initial pool of primordial follicles, the higher the likelihood of PCOS under a certain environment. As the rate of decline of the ovarian reserve depends on the number of remaining primordial and small pre-antral follicles, women with PCO are unlikely to undergo a rapid depletion of their ovarian reserve too early. In terms of screening for ‘early ovarian ageing’ in the general population, women with PCO most likely form a low-risk group and should be excluded. In the future, screening strategies for ‘early ovarian ageing’ in the general population could include, for example, antral follicle counts or AMH measurements of high-risk women every few years, from the late twenties onwards. There could be ‘ovarian reserve’ curves similar to antenatal growth charts. The better understanding of the intra-ovarian adjustments in fetal life, which, under strong genetic control, lead to a large ovarian reserve at birth and PCO after puberty, will assist our better understanding of the process of ovarian ageing.

References


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Submitted on January 5, 2004; resubmitted on April 13, 2004; accepted on June 24, 2004