Early ovarian ageing: a hypothesis

What is early ovarian ageing?

Rogerio A. Lobo

Department of Obstetrics and Gynecology, Columbia University College of Physicians and Surgeons, PH-16 Room 28E, 622 West 168 Street, New York, NY 10032-3784, USA. E-mail: ral35@columbia.edu

A concept of early ovarian ageing has been advanced. This theory suggests that some women will experience problems of fecundity at an early age given that the age of menopause is earlier for some women, and there is a fixed time of accelerated atresia leading up to menopause. Various components of this theory are examined based on existing literature. While the theory has merit, and is important to consider in terms of reproductive health, it remains a hypothesis. It is also plausible to consider that a segment of the population will have later ovarian ageing in that menopause can be as late as 58 years for some women. Further, it is not known whether there really is a fixed time of accelerated atresia leading up to menopause in all women. The practical considerations dealing with this hypothetical concern also are not trivial. How will certain women with early ovarian ageing be identified, what hormonal and other factors should be measured, and what advice is reasonable for these young women?

Key words: atresia/fecundity/menopause/ovarian ageing

Introduction

Nikolaou and Templeton (2003) offer an interesting hypothesis, which, if correct, has significant implications for the reproductive health of women. The two key questions regarding this hypothesis are, (i) is it correct? and (ii) what should be (or can be) done about it clinically?

What we think we know

The greatest number of oocytes (several million) are present at ~20 weeks gestation. At birth, this number is ~1–2 × 10⁶, and then the rate of atresia/apoptosis is relatively constant until age 37.5 years when there are ~25 000 oocytes. From this point, atresia accelerates until the average age of menopause (51 years) when only 1000 oocytes remain. (Faddy et al., 1992; Gougeon et al., 1994) The accelerated rate of atresia at age 37–38 is often associated with increases in FSH, decreased fecundity (Scott et al., 1989; Wood et al., 1992) and an increased rate of aneuploidy. It is thought that elevations of FSH result in increased recruitment, which is coupled with accelerated loss of oocytes. What the proximate signal is for FSH elevation is not apparent, nor is the explanation for the enhanced recruitment process. It is important to note that at this critical time, endocrine and gametogenic functions are dis-associated. Endocrine function (secretion of estrogen, androgen, and progesterone) remains unchanged as are menstrual cycles (Sherman and Korenman, 1975; Lee and Lenton, 1988; Hughes et al., 1990) while an accelerated loss occurs in the number and quality of the gametes.

Age of menopause has remained relatively constant throughout the ages. This phenomenon is largely controlled by genetic factors (Cramer et al., 1995; Torgerson et al., 1997; Snieder et al., 1998; Treolar et al., 1998), but there are some minor environmental influences as well, such as smoking, which advances menopause by 1–2 years (Midgette and Baron, 1990; McKinlay et al., 1992). Most of the data on age of menopause have been cross-sectional and retrospective. However, a prospective study has put the median age of perimenopause at age 47.5 years (defined by cycle irregularity) and the median age of menopause at 51.3 years (McKinlay, 1992). Since age of menopause is critical to the hypothesis of Nikolaou and Templeton (2003), it is important to understand the variability in years around the median age of menopause. Because the distribution of this range is asymmetric (40–55), it is more common to use a range of 48–55 years in citing the age of menopause. Only 10% of women enter menopause before age 45, and <1% before age 40.

It is not clear what causes the increased rate of atresia at the average age of 37.5 years. Observed increases in serum FSH, sometimes subtle, have been thought to play a major role in conjunction with alterations in inhibin, and in other members of the TGFβ family. A theory has been advanced that FSH interacts with activin, resulting in an autoregulatory loop which accelerates follicle growth and development, producing a
disrupted maturation process and meiotic spindle in the oocyte. (Erickson, 2000)

### Early ovarian ageing

The premise brought forth (Nicolaou and Templeton, 2003) is that there is a 13-year window between the beginning of the accelerated phase of atresia (38 years) and the average age of menopause (51 years). During this time, fecundity is significantly reduced, although as pointed out above, endocrine function (and menstrual cyclicity) are largely unaffected. In that the notion suggests that this 13-year window is ‘fixed’, a woman who enters natural menopause at age 45 begins the process of accelerated atresia (early ovarian ageing) at age 32, requiring earlier testing and intervention to prevent reproductive failure.

There are two general concerns challenging this hypothesis. The first concern is related to the epidemiology of menopause. While it is estimated that 10% of the population enters menopause at age 45, up to 10% of the population enters menopause after age 55, and 50% after age 51.3 years. (McKinlay et al., 1992) Therefore, this ‘window’ can be shifted significantly to the right and in reproductive terms early ovarian ageing for a certain percentage of women can be ‘late’ ovarian ageing.

The second issue is the ‘fixed’ nature of this window of 13 years. Basically, we just do not know if this is the case. While it was originally assumed that oocyte loss occurred as a constant logarithmic function (Block, 1952), it is more accepted now that there is an accelerated depletion after age 38 years (Richardson et al., 1987; Gougeon et al., 1994). However, it is not at all clear what the variability is in the slope of this line. Rate of atresia may be variable in different women, and this variability may occur before age 38, as well as in the time period after age 38. At least two conditions have been theorized to alter (increase) the rate of atresia (genetic variations in the X chromosome and thymectomy) (Singh and Carr, 1966; Lintern-Moore, 1977). On the other hand, starvation may improve ovarian reserve. (Lintern-Moore, 1978). Also, in mice, morphine (Lintern-Moore et al., 1979) and epidermal growth factor (Lintern-Moore et al., 1981) decrease follicle recruitment, thereby enhancing ovarian reserve. Therefore, there may be biological variables which affect the rate of atresia in different women.

The 13-year window (which is assumed to be the average time frame for women) may not be 13 years per se and is likely to be less or more on an individual basis.

In fairness, however, we really do not have definitive information about the variability in rates of atresia. The purported classical teaching that there is an increased rate of atresia in gonadal dysgenesis and other X chromosomal disorders (Singh and Carr, 1966) may as easily be explained by the fact that with X chromosomal defects, the maximum oocyte number (in utero) may be less to begin with, and the atresia rate is, in fact, similar to that of normal women.

Obviously we need more accurate information in order to determine what is correct. There are several questions: What are the true confidence limits around the 13 years? Is this 13-year interval fixed for all women? We should be able to get clues into this by merely looking at some data. In women who entered menopause at age 45, we should be able to find out that what their fecundity rates were in the years immediately preceding this. If the number of pregnancies were similar between ages 32–45 as in other women with a later menopause, then we know that the 13-year time period is not a ‘fixed’ determinant.

### Practical clinical considerations

Let us assume we accept the ‘13-year’ hypothesis. First of all, how are we to know which 10% of the population to target (whether a woman will have early versus late menopause)? I agree that with time we may have genetic tools to uncover this, but not at present. All we can do at present (and this is viewed as being important) is to look into family history of the age of menopause (mothers, grandmothers, older sisters).

Then if we know whom to target, what should we measure? There is cycle to cycle variability with day 3 FSH levels. How intensively will we test? Some FSH levels have been found to be ‘normal’ in women with diminished reserve who were treated for childhood cancers, (Larsen et al., 2003) suggesting a lack of specificity. Should we employ the clomiphene citrate challenge (CCC) test? Recent data suggest that the CCC test is no better than FSH basal determinations (Jain et al., 2003). Clearly, there are other possible markers as well: inhibin B and Müllerian inhibitory factor (MIF) are the two which stand out the most. (Klein et al., 1996; de Vet et al., 2002; Van Rooij, 2002). Perhaps we need a battery of tests. This would be akin to the quadruple screen for fetal aneuploidy. Suffice it to say this is not a simple matter.

Finally, suppose we identify a 32-year-old to be ‘at risk’ (easier said than done), what is she to do? In our goal oriented society, suggesting to a woman that she postpone or modify her career may be a difficult pill to swallow. Currently in the USA, nearly half of college-educated women have their first birth after age 30. This percentage was only 10% 25 years ago (Heck et al., 1997). Oocyte or embryo ‘banking’ is not an easy solution either, particularly when the woman does not have a partner. This complicated predicament has very individual scenarios, and its full discussion is beyond the scope of this commentary.

### Final thoughts

Whether the theory of Nikolaou and Templeton (2003) is correct or not, I believe the authors bring up interesting and important issues for further study. From a very practical perspective, we should target ‘at risk’ younger women for this very difficult discussion. These women would include those with a strong family history of early menopause, and those having had ovarian surgery, radiation or chemotherapy.

### References
