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Review

Testing ovarian reserve to predict age at menopause

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ABSTRACT

In modern society with women delaying pregnancy, predicting the age of the natural menopause with its preceding infertility will allow making informed choices about when to try starting to have children. Also if premature menopause could be predicted in young women, strategies could be instigated to reduce the long term health risks of early estrogen deficiency. This review examines the physiology of ovarian ageing, with the menopause being the final outcome. Long and short term predictive markers of the age of the menopause and the preceding natural infertility are evaluated.

Many subtle changes in the endocrine regulation of ovarian function with advancing age may seem interesting but currently are not clinically useful as a predictive test. Examples are changes in concentrations of estradiol, progesterone, luteinizing hormone (LH) and activin, as well as follicle dynamics. Other features hold more promise. Among these are chronological age, family history, anti-Müllerian hormone (AMH), poor response to *in vitro* fertilization (IVF), basal follicle-stimulating hormone (FSH) and the antral follicle count for long term prediction. For short term prediction, cycle shortening and occurrence of vasomotor symptoms may prove useful. To date, none of these markers has been found to have sufficient predictive accuracy in individual women. Results of new and ongoing longitudinal studies may provide better predictive models. In particular, use of genetic profiles may add to the accuracy of currently known markers.

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1. Introduction

The menopause is the final menstrual period. The natural menopause can only be ascertained in retrospect after 12 consecutive months of spontaneous amenorrhoea. The age of the natural menopause has a normal distribution with a mean at approximately 51 years, varying between 40 and 60 years [1]. Since the introduction of a definition for premature ovarian failure for women below 40 years of age with a basal FSH of >40 IU/l [2], we regard normal menopause as occurring from age 40 onwards. Women between 40 and 45 experiencing natural menopause are regarded as reaching the menopause relatively early, but are considered as a representation of the lower end of the normal distribution. Whereas for some women the menopause may be a relief and the start of yet another phase of life, many experience this event and the associated physical symptoms and psychosocial impact as a burden.

The menopause has certain implications. It is the final sign that a woman's reproductive capacity has become exhausted. Also, early age at menopause has been associated with increased cardiovascular mortality [3], osteoporotic fracture [4] and colorectal cancer [5] as well as respiratory and urogenital disease [6].

In modern society being able to predict the age of menopause and occurrence of natural infertility may help women decide about when they should start attempting to have children. Furthermore, if premature or early menopause could be predicted with tests in young women, strategies could be instigated to reduce the long term health risks of estrogen deficiency.

Remarkably, while the average age at menarche has declined very significantly over the past 100 years, the average age of the menopause has remained quite constant. Important determinants of the age of the menopause are most likely to be epiphenomena of ovarian oocyte content and genetic factors.

This review provides an overview of the physiology of ovarian ageing. Predictive markers of the age of menopause and the preceding declining fertility are evaluated.

2. Female reproductive ageing, infertility and menopause

The reproductive ageing process is dominated by a gradual decrease in both oocyte quantity and quality [7]. From the initial 6–7 million primordial follicles present at the fourth month of fetal development [8–15], only 400,000–600,000 primordial follicles remain at menarche [7,10]. At menopause, the number of remaining follicles has dropped to below 1000 [15–17] (Fig. 1 [18,19]). From the age of 31 years onwards, the declining follicle pool heralds various reproductive events: decreasing fecundity, natural sterility, menstrual cycle irregularity and finally the menopause (Fig. 2 [1,20–23]). A fixed temporal relationship, with large interindividual variation, is thought to be present among the various reproductive events [7]. Such a relationship seems highly relevant since accurate prediction of a woman's menopause may also provide valuable information regarding her fertility lifespan. While longitudinal data documenting the relationship between reproductive events in individual women are limited [24], evidence for this hypothesis primarily stems from cross-sectional observations. In the Balsac natural fertility population study, it has been demonstrated that early loss of natural fertility is preceded by reduced fecundity already before the age of 30 years [23]. Moreover, repeated poor response to *in vitro* fertilization (IVF) is associated with an early occurrence of the menopausal transition [25–27]. Finally, the duration of menstrual cycle irregularity preceding the menopause appears to be constant and independent of the age of menopause [7,21]. In-depth research into this area is extremely difficult in view of the widespread use of hormonal contraception, so that longitudinal estimates of an individual's fertility at several points over time are not available.

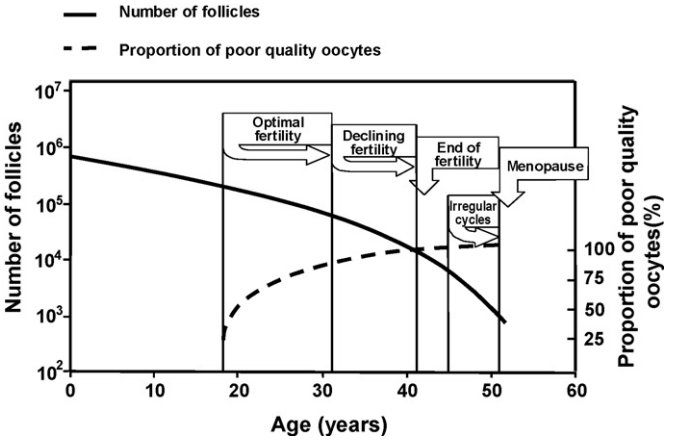

Fig. 1. The decline in follicle number and the increase in the proportion of poor quality oocytes in relation to reproductive events with increasing female age (redrawn after [18,19]).

Despite cycle regularity remaining unaffected for a period of nearly 30 years, profound changes occur at the oocyte level, causing every woman to pass through the various reproductive events mentioned in Fig. 2. Monthly fecundity dramatically decreases from a mean age of 31 years onwards [28,29]. In contemporary population studies it has been demonstrated that the chance of not

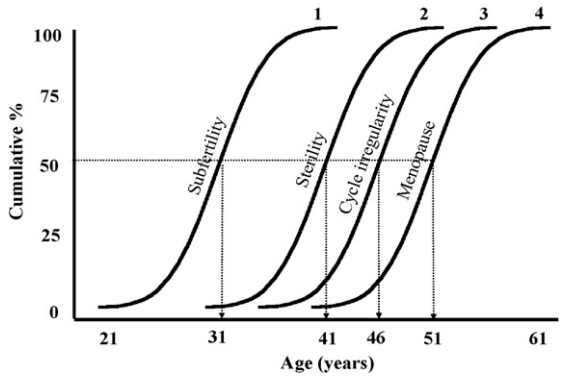

Fig. 2. The distributions of age at the onset of subfertility (cumulative curve 1), at occurrence of natural sterility (cumulative curve 2), at transition into cycle irregularity (cumulative curve 3) and at occurrence of menopause (cumulative curve 4). Mean ages for these events are depicted on the *X*-axis. Curve 4 is based on data by Treloar and Broekmans [1,20], curve 3 and its temporal relation to curve 4 is based on data from den Tonkelaar [21], curve 2 is based on data on last child birth in a 19th century natural fertility population [22] and curve 1 is a hypothetical construct based on the age distribution of related reproductive events as depicted in curves 2, 3 and 4 and partially supported by data from Eijkemans et al. [23].