Markers of ovarian reserve: is it possible to estimate an ovarian age?

Since a woman's ovary contains her life-time supply of oocyte-nurturing follicles, her reproductive life-span is dependent upon her ovarian reserve, the number of follicles remaining in her ovaries. Eventually, menopause results when follicles are depleted. A woman's fertility, however, declines years before menopause and is generally attributed to the decline in oocyte quality, resulting from the meiotic errors in the oocyte, that accompanies aging. Consequently, increased rates of aneuploidy and miscarriage are seen with advancing maternal age.

Since the success of in vitro fertilization (IVF) is dependent upon both quantity and quality of oocytes, IVF is less successful for older women. Lower birth rates are attributed to the limited quantity of oocytes, resulting in poor response to gonadotropin therapy and fewer oocytes obtained at retrieval, as well as poor oocyte quality, resulting in aneuploidy, failed implantation, and miscarriage. Over the last approximately 30 years, several tests of ovarian reserve have been proposed to predict ovarian response to gonadotropin therapy and used to counsel women about their IVF prognosis (1). At present, the commonly used measures of ovarian reserve include basal serum follicle-stimulating hormone (FSH) (measured on day 2-4 of the menstrual cycle), serum antimüllerian hormone (AMH), and antral follicle count (AFC), the number of antral follicles seen by transvaginal ultrasound in the early follicular phase (1).

It is well-established that measures of ovarian reserve reflect the remaining pool of ovarian follicles, but controversy remains as to whether ovarian reserve markers also provide insights into oocyte quality. Despite numerous studies, it is unclear if the age-related decline in oocyte quality is solely related to chronologic age or whether the hormonal environment of the aging ovary plays a role. The limited pool hypothesis (2) posits that loss of follicles from the ovary results in hormonal changes, such as elevated FSH, at the end of reproductive life that are detrimental to oocyte development, producing poor quality oocytes with increased risk of aneuploidy. According to the limited pool hypothesis, age-related decline in oocyte quality is the result of reduced oocyte quantity.

Generally, markers of ovarian reserve become abnormal as oocyte quantity and quality decline with advancing age, but chronological age does not always reflect reproductive potential. Some women develop diminished ovarian reserve (DOR) at a relatively young age. A common clinical scenario is the relatively young woman with abnormal ovarian reserve testing, suggestive of DOR, who requires IVF. Should she be counseled to invest financial resources and emotional energy to having an IVF cycle? Even with young chronologic age, women with DOR have hormonal environment similar to older women. For younger women with DOR, it is not clear whether poor tests of ovarian reserve, such as elevated basal FSH or low AFC, will also predict poor oocyte quality.

In this issue, Bishop et al. (3) address this perennial question of whether measures of ovarian reserve reflect oocyte quality, specifically whether DOR is associated with a reduction in the potential for early IVF pregnancies to survive to live birth. The article includes data from 9,489 IVF cycles, performed from 2009-2013 in 8,214 unique patients, at a single center. The study included all fresh autologous cycles performed during the study period in women, aged 21-44 years that resulted in positive human chorionic gonadotropin who had baseline FSH level recorded within 1 year of cycle start. Outcomes included pregnancy loss and live birth. Of the 1,542 patients with clinical pregnancy loss, 460 had analysis of aneuploidy in products of conception. Age-stratified comparisons were made among patients, looking at two measures of ovarian reserve, basal FSH and AFC.

With age-stratified data from more than 9,000 early IVF pregnancies, this study is able to provide insights into the prognostic value of ovarian reserve testing. As expected, compared to cycles with live birth, cycles with pregnancy loss were associated with higher age, higher baseline FSH, lower AFC, diagnosis of DOR, and diagnosis of uterine factor. When age-stratified comparisons were made, DOR (as measured by FSH $\geq$ 10 mIU/mL or lowest quartile AFC) was not associated with an increase in miscarriage among younger women (<35 years) who achieved pregnancy through IVF. No associations were found with AFC and pregnancy loss at any age. Although no associations were found between ovarian reserve measures and aneuploidy, no conclusions were drawn due to small numbers.

Overall, this data is reassuring for younger women with DOR and argues against the concept of ovarian age. For younger women in this study, DOR did not correlate with miscarriage. These findings are consistent with other reports that chronologic age is the best measure of pregnancy potential and that young age has a protective effect for women with DOR. It is interesting that among the patients, older than 35 years, elevated baseline FSH was associated with higher risk of pregnancy loss, which increased with increasing age. It is possible the ovaries from older women are more susceptible to effects of FSH (3).

This study (3), however, may present an overly optimistic picture of the likelihood of IVF success since only women who achieved pregnancy were included. Two smaller studies (4,5) also found that pregnancy outcomes did not differ between women with normal and diminished ovarian reserve – if euploid embryos were transferred. In both studies, however, women with DOR were less likely to have embryos for transfer due to higher rates of aneuploidy. Shahine et al. (5) found that within similar age groups, the rate of aneuploidy was higher in women with DOR (5). Similarly, although not controlled for age, Katz-Jaffe et al found that 35.1% of subjects with DOR had all aneuploid embryos compared to 14.3% of subjects with normal ovarian reserve (4). Results from these two studies suggest ovarian age, rather than chronologic age, is related to risk of aneuploidy.

The choice of ovarian reserve markers used in this study may also contribute to the reassuring findings. The authors acknowledge that one limitation is that AMH was not assessed. Others have found that women with DOR (defined by FSH > 10 mIU/mL along with AMH < 1 ng/mL) had greater proportion of aneuploid blastocysts (77.2%) compared to women with DOR defined solely by FSH > 10 mIU/mL (58.5%) (4). Had Bishop et al. included AMH, along with FSH, they may have been able to identify women with the oldest ovarian age who would be more at risk for pregnancy loss. Although Bishop et al. (3) assessed AFC, the use of age-stratified AFC quartiles, rather than discrete cut-offs, makes the data less generalizable. For example for age < 35 years, lower quartile was AFC of 11 or less, but for age 43-44 years, lower quartile was AFC of 6 or less. It is possible that different results would have been obtained if a standard definition of low AFC, such as fewer than 6 antral follicles (1), were used.

With their article, Bishop et al. (3) contribute to the growing body of literature regarding the prognostic value of ovarian reserve testing and definitively demonstrates that DOR (defined by FSH or AFC) is not associated with increased risk of pregnancy loss after IVF in women less than 35 years. The current concept of ovarian reserve views reproductive potential as a function of both the quantity and quality of oocytes (1). Historically, ovarian reserve tests were thought to reflect oocyte quantity and were developed to provide prognostic information for IVF cycles (1). Despite decades of research, including this excellent contribution by Bishop et al. (3), controversy remains as to whether ovarian reserve tests can also provide insight into oocyte quality and estimate an ovarian age.

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