# Ovarian Reserve Tests and Their Application to Infertility Management

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## Opinion

Over the years, the family dynamics have changed. Couples are either delaying the start of their family or individuals are seeking treatment alone. This is increasing the number of people seeking assistance through reproductive clinics. To counsel patients' effectively, a greater understanding of fertility potential is needed. There is still yet to be a single definitive test that is able to evaluate ovarian reserve and predict the outcome. Multiple investigations are currently used to assign treatment protocols. In the United Kingdom, the National Health Service (NHS), is unable to fund all investigations discussed within this article, due to limited evidence supporting their role and efficacy.

Follicle Stimulating Hormone (FSH) is an essential hormone in the menstrual cycle. It is synthesized and secreted by the anterior pituitary. The main role of this hormone is the development of graafian follicles from an immature to a mature follicle during the follicular phase of the cycle. Day 2-5 FSH is currently a routine test performed to evaluate ovarian response in patients seeking fertility treatment and is often used as a predictor for the success of Assisted Reproductive Treatments (ART) [1]. Age and Day 3 serum FSH levels used in combination are superior predictive markers of ART outcomes [2]. A meta-analysis of 21 studies has demonstrated basal FSH levels to be a moderate predictor of diminishing ovarian response. The recommendation from this meta-analysis was that basal FSH in women undergoing ART, should not be used as a single indicator of ovarian reserve [3].

A good body of evidence suggests that age when compared to basal FSH levels is a better predictor of ovarian reserve. A study including 1045 women who were undergoing their first IVF cycle, revealed that basal FSH levels alone could not accurately predict pregnancy outcomes, however, age was seen to be a better predictor [4]. It was also noted that high FSH levels are more prevalent in women above 35 years of age. In another study including more than 300 women looking at basal FSH levels and ongoing pregnancy rates, the study concluded that there was a general decline in pregnancy rate with an increase in FSH levels. The group of patients with a FSH level of less than 10IU/L had a 65% ongoing pregnancy rate compared to the group with a FSH level of more than 15IU/l who had a 28% ongoing pregnancy rate [5].

Antral follicles are commonly referred to as resting follicles. They are noted to be small in diameter, mostly between 2 to 8mm and are normally measured via transvaginal ultrasonography. It has been seen that the reproductive age can be predicted based on the total antral follicle count [6]. A study comparing women (n =83) with different types of ovaries focused on women with a history of ovarian cystectomy performed for an endometrioma, known existing endometrioma and women with unaffected ovaries. The results demonstrated no difference in the antral follicile count between either groups. However, a statistically significant result was seen for the area under the curve for the prediction of low response, 0.83 (95% CI 0.68-0.99), and over response, 0.84 (95% CI 0.70-0.97) [7].

A meta-analysis including 10 studies looking at ovarian volume and 17 studies looking at antral follicle count showed that due to significant heterogeneity the sensitivity and specificity of these studies were inaccurate. However, the authors concluded that the antral follicle count was a better predictor of ovarian reserve compared to the measurement of ovarian volume via ultrasound [8]. One of the major challenges with ultrasonography is reproducibility. A study looking at 29 women revealed that three-dimensional ultrasonography and power Doppler angiography created excellent intra and inter observer reproducibility. In this study, the authors mainly evaluated the

assessment of ovarian response and oocyte quality. The results revealed that the coefficients for both groups were close to unity in the ovarian volume category, and 0.964 for intra observer and 0.978 for inter observer in reference to the antral follicle count measurements [9].

Anti-Mullerian hormone (AMH) is a glycoprotein that is secreted from the granulosa cells of the pre-antral and small antral follicles of the ovary from 36 weeks gestation [10]. The main function of AMH is to inhibit the primordial follicles from being recruited into the antral follicle pool [11]. AMH also has a significant advantage over basal FSH wherein it is not altered by intra cycle or inter cycle variability [12]. This allows AMH to be reliably measured at any point during the menstrual cycle. One of the challenges in interpreting AMH results in the general population is the variation in the assay. Evidence has been published highlighting differing outcomes with the use of different assays in the same population. This therefore limits the role of AMH and the context in which it is used. However, it is well established that the extremes of AMH results have a reliable prediction of fertility potential [13].

When compared to antral follicle count, AMH has been seen to be on par in the assessment of ovarian reserve [14], however, it is seen to be superior when compared to FSH and Inhibin B levels [15].

Serum Inhibin B is a polypeptide mainly found in the follicular phase of the menstrual cycle. It is secreted by the granulosa cells of the antral follicles [16]. The levels of Inhibin B are normally seen to peak during the early follicular phase [17]. A study that looked at the value of Inhibin B, demonstrated that women with an Inhibin B value above 45pg/ml had a better estrogenic response to stimulation, reduced cancellation rates, higher pregnancy rates and increased oocyte retrieval [18]. When comparing ART success, a study looking at 120 women found that basal FSH was a better predictor of outcome compared to Inhibin B. These women had blood drawn at a 3-month interval following their IVF attempt to assess the levels of FSH and Inhibin B [19]. However, it has been shown that serum and follicular Inhibin B levels have a strong correlation with the number of oocytes retrieved, but sadly the same cannot be said for the prediction of pregnancy rates [20].

When looking at dynamic testing the serum estradiol response to exogenous FSH administration has been seen to be a reliable predictor of implantation and pregnancy rates. Women who have had an estradiol level above 30pg/ml 24 hours following the administration of exogenous FSH have had higher implantation and pregnancy rates compared to patients with values below 30pg/ml [21]. This test is called exogenous FSH ovarian reserve test (EFFORT).

In some local centers, clinicians also use the clomiphene citrate challenge test. This involves performing a basal FSH level on Day 3 followed by the routine administration of clomiphene citrate for 5 days of the cycle starting on Day 5 up to Day 9. This is then completed with a repeat serum FSH level on Day 10. Patients who fall into the category of FSH level above 12.5 units are thought to be comparable to patients who have a normal basal FSH level in terms of predictability of pregnancy outcomes [16].

It is clearly evident from the literature available and the significant variation in practice that there is still yet to be a single test to be hailed as a gold standard investigation for ovarian reserve testing. The test available to clinicians today when used with caution and generous counseling is able to produce a result that is in keeping with scientific needs. The difficulty therein lies in what a patients understanding of these needs would be and the clinicians ability to counsel the patients appropriately. There are also other limiting factors in this cohort of patients to consider such as age and body mass index, with the clinician needing to make a sound judgment with the available evidence. This is surely an art that is honed with experience, which is a trade built with time and effort.

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