Ovarian Reserve Testing

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14.1 Introduction

The general purpose of ovarian reserve testing is to assess the quantity and quality of the remaining oocytes in an attempt to predict reproductive potential. Ovarian reserve testing should be performed in women older than 35 years who have not conceived after 6 months of attempting pregnancy (or women less than 35 who have not conceived after 1 year) and women at higher risk of diminished ovarian reserve, such as those with a history of cancer or other medical condition treated with gonadotoxic therapy and/or pelvic irradiation, or women who have had ovarian surgery for endometriomas.

Available tests for ovarian reserve include biochemical markers, i.e., FSH, estradiol, AMH, and inhibin B and ovarian ultrasound imaging, i.e., antral follicle count and ovarian volume [1] (Fig. 14.1). For general obstetrician-gynecologists, the most appropriate ovarian reserve screening tests to use in practice are basal FSH plus estradiol levels or anti-Müllerian hormone (AMH) levels. An antral follicle count (AFC) may also be useful if there is an indication to perform transvaginal ultrasonography. These screening tests are better predictors of oocyte yield from ovarian stimulation during in vitro fertilization (IVF) than rate of pregnancy. Low ovarian response to stimulation, usually defined as fewer than three to five developing follicles during an IVF cycle, is an indicator of a poor reproductive outcome. It is important to recognize, however, that a poor result from ovarian reserve testing does not signify an absolute inability to conceive and should not be the sole criteria considered to limit or deny access to infertility treatment. Although these tests are used to assess oocyte quantity and quality, the best surrogate marker for oocyte quality is age. At this time, ovarian reserve testing results cannot be extrapolated to predict the likelihood of spontaneous conception.

		Poor Response to Ovarian Stimulation		Nonpregnancy*				
Test	Cutpoint	Sensitivity	Specificity	Sensitivity	Specificity	Reliability	Advantages	Limitations
FSH (international units/L)	10–20	10–80	83–100	7–58	43–100	Limited	Widespread use	Reliability Low sensitivity
AMH (ng/mL)	0.2–0.7	40–97	78–92	†	†	Good	Reliability	Limit of detectability Two commercial assays Does not predict nonpregnancy
AFC (n)	3–10	9–73	73–100	8–33	64–100	Good	Reliability Widespread use	Low sensitivity
Inhibin B (pg/mL)	40–45	40–80	64–90	†	–	Limited	–	Reliability Does not predict nonpregnancy
CCCT, day 10 FSH (international units/L)	10–22	35–98	68–98	23–61	67–100	Limited	Higher sensitivity than basal FSH	Reliability Limited additional value to basal FSH Requires drug administration

Abbreviations: AFC, antral follicle count; AMH, antimüllerian hormone; CCCT, clomiphene citrate challenge test; FSH, follicle-stimulating hormone.
Note: Laboratories ELISA.
*Failure to conceive
†Insufficient evidence
Testing and interpreting measures of ovarian reserve: a committee opinion. Practise Committee of the American Society for reproductiveMedicine. Fertile Steril 2012;98:1407-15.

Fig. 14.1 Available tests for ovarian reserve include biochemical markers, i.e., FSH, estradiol, AMH, and inhibin B and ovarian ultrasound imaging, i.e., antral follicle count and ovarian volume

As women age oocytes decrease in quality and quantity and do not regenerate. The number of human oocytes in a female peaks at six to seven million during fetal life around midgestation, followed by profound atresia. Approximately one to two million oocytes are present at birth, 300,000–500,000 at the start of puberty, and 1000 at 51 years of age, which is the average age of menopause in the USA [2]. Factors such as genetics, lifestyle, environment, and medical issues including endometriosis, ovarian surgery, chemotherapy, and radiation can influence the quantity and quality of a woman's oocytes [1] (Fig. 14.2). Cross-sectional studies suggest that fertility declines before the onset of the premenopausal transition.

The goal of ovarian reserve testing is to add more prognostic information to the counseling and planning process so as to help couples chose among treatment options. Ovarian reserve tests should not be the sole criteria used to deny patients access to assisted reproductive technology or other treatments. Evidence of decreased ovarian reserve does not necessarily equate with inability to conceive.

In women from the general population, with no known history of infertility, who are attempting to conceive naturally, cumulative probability of pregnancy has been shown to decrease with age [3]. Cross-sectional studies have shown that chronological age is correlated with ovarian reserve, as measured by the size of the follicle pool in histologic studies of ovaries. Chronological age is strongly associated with other biomarkers of ovarian reserve including antral follicle count, anti-Müllerian hormone (AMH) levels, and early follicular phase follicle stimulating hormone (FSH) levels. Chronological age is an excellent predictor of fertility among infertile women undergoing assisted reproduction [4].

Existing research on ovarian reserve testing is often confusing because of heterogeneity among

- Advanced reproductive age (older than 35 years)
- Family history of early menopause
- Genetic conditions (eg, 45, X mosaicism)
- *FMR1* (Fragile X) premutation carrier
- Conditions that can cause ovarian injury (eg, endometriosis, pelvic infection)
- Previous ovarian surgery (eg, for endometriomas)
- Oophorectomy
- History of cancer treated with gonadotoxic therapy or pelvic irradiation
- History of medical conditions treated with gonadotoxic therapies
- Smoking

Data from Testing and interpreting measures of ovarian reserve:a committee opinion. Practice Committee of the American Society for Reproductive Medicine. Fertile Steril 2012;98:1407–15; Gurtcheff SE, Klein NA_Diminished ovarian reserve and infertility. Clin Obstet Gynecol 2011;54:666–74; te Velde ER, Pearson PL Thevariability of female reproductive ageing. Hum Reprod Update 200;8:141–54; *and* Ferraretti AP, La Marca A, Fauser BC, Tarlatzis B, Nargund G, Gianaroli L. ESHRE consensus on the definition of 'poor response' to ovarian stimulation for in vitro fertilization: the Bologna criteria. ESHRE working group on poor Ovarian Response Definition. HUM Repord 2011;26:1616–24.

Fig. 14.2 Risk factors for diminished ovarian reserve

tested populations (the general population, infertility patients of all ages, infertility patients more than 35 years old, etc.). No single result is definitive, since findings must be interpreted in context and should be repeated or supplemented as appropriate. This chapter will discuss the application of ovarian reserve tests in evaluating fertility.

Clinical Case

A 38-year-old nulligravid female and her male partner present with a 3 year history of infertility. She has regular cycles. A hysterosalpingogram shows a normal uterine cavity and bilateral patent tubes. Her AMH level is 0.7 ng/mL. Day 3 FSH and estradiol levels are 11 IU/L and 20 pg/dL, respectively. Her partner had a semen analysis which showed normal semen parameters. The couple has failed three cycles of controlled ovarian stimulation using clomiphene citrate in combination with intrauterine insemination (IUI). How would you counsel this patient regarding her treatment options and chance of pregnancy success?

14.2 Basic Principles of Screening Tests

The purpose of using ovarian reserve testing as a screening test is to identify infertility patients at risk for decreased ovarian reserve, who are likely to exhibit a poor response to gonadotropin stimulation and to have a lesser chance of achieving pregnancy with IVF. Good screening tests have validity as measured by sensitivity and specificity. A valid test correctly categorizes persons who have disease as test positive (highly sensitive) and those without disease as test negative (highly specific).

For clinical purposes, specificity is the test characteristic that should be optimized to decrease false positives, or wrongly categorizing patients with normal ovarian reserve as having decreased ovarian reserve (DOR). Graphically, the sensitivity and specificity of different cut-points of a diagnostic test can be plotted as receiver operating characteristic (ROC) curves.

Positive predictive value (PPV) and negative predictive value (NPV) are screening test characteristics that change with the prevalence of disease (DOR) in the study population. The PPV is the probability that a woman who tests positive truly has DOR. The NPV is the probability that a woman who tests negative has normal ovarian reserve. Ovarian reserve testing is most useful in identifying DOR in women at high risk for DOR. Ovarian reserve testing in women at low risk for DOR will yield a larger number of false-positive results (lower PPV).

14.3 A Shortened Menstrual Cycle

As the ovary ages, the size of the follicle pool declines. Fewer follicles result in less production of AMH and inhibin. Because of lower inhibin levels, FSH rises prematurely or more rapidly leading to elevated early follicular phase serum FSH levels. Premature and rapid follicular growth results in elevated early follicular phase estradiol levels and a shortened follicular phase and overall shortened menstrual cycle. A short menstrual cycle length is associated with a lower probability of conceiving naturally or following IVF [5]. The cutoff value to define "short" cycle length varies by study ranging from 25 to 26 days.

14.4 Biochemical Markers of Ovarian Response

14.4.1 Basal Follicle Stimulating Hormone

Follicle stimulating hormone is released by the pituitary gland in response to gonadotropin-releasing hormone from the hypothalamus and is subject to negative feedback from estradiol and inhibin B. In the setting of a smaller follicular cohort and decreased estradiol and inhibin B levels, an increase in pituitary FSH secretion occurs, which can be identified as an elevated early follicular phase FSH level. This higher FSH level stimulates rapid ovarian follicular growth, which results in higher estradiol levels as well as a shorter follicular phase and menstrual cycle.

FSH is typically measured by immunoassay on cycle day 3. The basal FSH level can vary, so a single FSH value has limited reliability. Moreover, there is variability among different FSH assays. Although basal FSH is commonly used to assess ovarian reserve, and high values (>10–20 IU/L)

are associated with diminished ovarian reserve and poor response to ovarian stimulation, the test is not predictive of failure to conceive [6]. If FSH values are consistently elevated, a poor reproductive prognosis is likely; in contrast, a single elevated FSH value in women younger than 40 years predicts a lower oocyte yield during IVF but does not predict the rate of pregnancy [7].

Early follicular phase FSH levels have not been a sensitive test for nonpregnancy, suggesting that an elevated FSH is an excellent predictor of nonpregnancy following ART, but a normal level is not predictive of pregnancy. The value of serum or urinary FSH levels as predictors of reproductive potential in the general population has not been determined. Testing is cycle day specific (cycle days 2–4), limiting flexibility.

Women having an abnormally elevated FSH value will have DOR. The PPV of FSH for poor response to ovarian stimulation or failure to conceive is higher in older women. Limited evidence suggests that women with fluctuating FSH levels should not wait for the ideal cycle, wherein the FSH concentration is normal, to undergo IVF stimulation [8].

FSH is a late marker of dwindling ovarian function. With AMH and AFC demonstrating better predictive value for ovarian response than FSH, these are more likely to be the tests of choice. It remains unknown whether high FSH levels in women of reproductive age predict an earlier onset of menopause.

14.5 Basal Estradiol

Estradiol levels vary over the course of a menstrual cycle, peaking in both the late follicular and midluteal phases. As ovarian reserve declines, the follicular phase shortens because of decreasing feedback inhibition by follicles recruited during the previous cycle. As a result, an elevated day 3 estradiol level could reflect diminishing ovarian reserve.

Estradiol is released from the ovary during follicular development. The estradiol level is usually low (<50 pg/mL) on days 2–4 of the menstrual cycle. An elevated value (>60–80 pg/mL) in the early follicular phase can indicate reproductive aging and hastened oocyte development. Through central negative feedback, a high estradiol level can suppress an elevated FSH concentration into the normal range. The value of obtaining an estradiol level is that it allows the correct interpretation of a normal basal FSH level. Basal estradiol has low predictive accuracy for poor ovarian response and failure to conceive and, therefore, this test should not be used in isolation to assess ovarian reserve [9].

14.6 Anti-Müllerian Hormone

AMH is a homodimeric glycopeptide that is produced predominantly by granulosa cells. AMH is believed to downregulate FSH-mediated folliculogenesis. AMH expression is highest in secondary, preantral, and small antral follicles. AMH seems to have a role in selecting the dominant follicle in addition to generally mediating preantral follicular recruitment. AMH levels start undergoing a log-linear decline approximately 15 years prior to menopause and drop to very low levels approximately 5 years before menopause [10].

The anti-Müllerian hormone concentration is fairly stable within and between menstrual cycles [11]. As the number of ovarian follicles decreases with age, a concomitant decrease in AMH levels occurs, which reflects this age-related oocyte depletion [12]. Although an undetectable AMH level suggests diminished ovarian reserve and can identify individuals at risk of poor ovarian response to stimulation, undetectable and low AMH levels (0.2–0.7 ng/mL DSL ELISA) are not predictive of failure to conceive [13]. AMH levels may allow treatment to be tailored to each individual. Lower AMH levels are associated with reduced ovarian response to stimulation and high levels are associated with a brisk ovarian response to stimulation [13]. Although the AMH level is a good predictor of oocyte quantity, it may not provide information about egg quality. Young women with low AMH levels may have a reduced number of oocytes, but normal age-appropriate oocyte quality [14].

One limitation of AMH level testing is the variability of results between the available assays. In clinical practice, individual AMH level test results must be interpreted based on the normal range of the assay used [15]. AMH level testing is a useful screening test in women at high risk of diminished ovarian reserve and in women undergoing IVF [16, 17].

The nonpregnancy predictive value of a low AMH value appears to increase if older women

at risk for ovarian aging are tested. The use of AMH as a routine screening tool for DOR in a low-risk population is not recommended.

AMH level testing may be valuable in assessing ovarian reserve in young women with cancer before and after chemotherapy [18]. AMH may enable assessment of ovarian reserve before and after ovarian surgery and for women at high risk of primary ovarian insufficiency. AMH level testing may in future provide an accurate method of predicting the reproductive lifespan and the timing of menopause [19].

AMH has the advantage over FSH in that AMH levels remain relatively stable over the menstrual cycle, thus measurement does not need to be cycle day specific. A recent meta-analysis of earlier studies showed no significant association between AMH, modeled as a continuous variable, and pregnancy following ART [20]. However, more recent studies of larger sizes, modeling AMH using cutoff values, have shown lower odds of pregnancy and live birth following ART among women with low AMH levels [21–24].

High AMH values are associated with polycystic ovary syndrome (PCOS) and may identify women at risk for OHSS. It is believed that AMH remains a valid assay even when ovarian suppression occurs through oral contraceptives, although age-specific AMH percentiles decrease by 11% with oral contraceptives. [25].

14.7 Inhibin B

Inhibin B is a glycoprotein hormone that is secreted primarily by preantral and antral follicles. The serum concentration of inhibin B decreases with the age-related decrease in the number of oocytes. Inhibin B has central negative feedback that controls FSH secretion. Therefore, a decrease in inhibin B levels leads to increased pituitary FSH secretion and higher early follicular FSH levels.

Inhibin B levels exhibit high intra-cycle variability [16]. Inhibin B levels also vary significantly between menstrual cycles [16]. Inhibin B levels are a late finding for diminished ovarian reserve and typically start falling around 4 years prior to menopause [10] and are thus suboptimal. Inhibin levels are measured by immunoassay. Inhibin B is typically measured on the third day of the menstrual cycle. Inhibin B has limited sensitivity and specificity. This marker does not reliably predict a poor response to ovarian stimulation and thus, is not a recommended test.

14.8 Clomiphene Citrate Challenge Test

Clomiphene is a selective estrogen receptor modulator (SERM) that inhibits negative feedback inhibition by estradiol on the hypothalamus thereby increasing FSH secretion, which enhances follicular recruitment. Clomiphene can be used for ovulation induction and superovulation.

The clomiphene citrate challenge test is performed by measuring serum FSH on cycle day 3, administering 100 mg clomiphene citrate daily on cycle days 5–9, and again measuring serum FSH on cycle day 10. An elevated FSH level on day 10 of the CCCT is suggestive of diminished ovarian reserve. However, cycle-to-cycle variability in ovarian biomarkers limits the reliability of this provocative test [26]. The stimulated FSH level on cycle day 10 of the CCCT is predictive of poor ovarian response but is not predictive of failure to conceive [27]. Compared with the basal FSH level and the antral follicle count, the cycle-day-10 FSH level does not improve the prediction for poor ovarian response [27]. In studies comparing the test performance of basal (cycle day 3) and stimulated (cycle day 10) FSH values, stimulated FSH levels have higher sensitivity but lower specificity than basal FSH concentrations [27].

In summary, basal measure of FSH may be preferable to the CCCT, unless one is using the test to purposely increase sensitivity. It is unclear if the CCCT confers any benefit over basal FSH alone, and it is less cost-effective. The CCCT may have a role in helping to discriminate normal ovarian reserve from poor ovarian reserve in patients with potentially borderline function.

14.9 Home Fertility Tests

Available home fertility tests use a urine sample to assess the FSH level on cycle day 3. The tests are marketed directly to consumers. The limitations of these tests include misinterpretation of

instructions and results and the unavailability of a medical professional to interpret and explain the results [1]. Although these tests are used commonly by women at low risk of diminished ovarian reserve, the results may provide false reassurance or raise unnecessary concern.

14.10 Ultrasound Evaluation of Ovarian Reserve

14.10.1 Antral Follicle Count

The antral follicle count records the number of visible ovarian follicles (2–10 mm mean diameter) that are observed during transvaginal ultrasonography in the early follicular phase (cycle days 2–5). The number of antral follicles correlates with the quantity of remaining follicles and with the ovarian response during controlled ovarian stimulation. Good intercycle and interobserver reliability has been demonstrated [16]. A low antral follicle count is considered three to six total antral follicles and is associated with poor response to ovarian situation during IVF, but it does not reliably predict failure to conceive; in a meta-analysis, a low antral follicle count was a mean of 5.2 (2.11 SD) total antral follicles [28]. When AFC was compared to age, basal FSH, basal estradiol, AMH, inhibin B, and ovarian volume, antral follicle count, and AMH were the most significant predictors of poor response to ovarian stimulation but were not predictive of failure to conceive [29].

Low AFC cutpoints are highly specific for predicting poor ovarian response, but have lower sensitivity [28]. The high specificity of a low AFC makes the test useful for predicting poor ovarian response and treatment failure, but its clinical utility is limited by its low sensitivity. Inter- and intra-observer variability also may be limiting. There is debate regarding the effect of oral contraceptives on the measurement of antral follicle count.

14.11 Ovarian Volume

The calculation of ovarian volume requires ovarian measurements in three planes and the use of the formula for the volume of an ellipsoid: $D1 \times D2 \times D3 \times 0.52$. Mean ovarian volume, the average volume calculated for both ovaries from the same individual, is the value used to assess ovarian reserve. With age, changes in ovarian volume are concordant with the age-related decrease in ovarian follicles.

Several studies have demonstrated that low ovarian volume, typically <3 mL, predicts poor response to ovarian stimulation with high specificity and a wide range of sensitivity [16]. In general, ovarian volume has been a poor predictor of pregnancy.

The generalizability to patients with ovarian pathology is limited. Ovarian volume may vary in response to normal physiologic changes and coexisting medical conditions (such as endometriomas). Exogenous hormones can decrease ovarian volume. For these reasons, AFC is believed to be a better marker for ovarian reserve.

14.12 Combined Ovarian Reserve Tests

AMH and AFC are the most accurate predictors, but combinations of a few tests are only slightly better than a single test. Models of combined ovarian reserve tests do not significantly improve the ability to predict poor reproductive outcomes over a single ovarian reserve test [29]. Furthermore, the use of multiple ovarian reserve tests may increase the expense of screening. Further research is needed to determine an optimal combination of tests.

14.13 Repetitive Testing

Repetitive testing of biomarkers of ovarian reserve to assess reproductive potential appears to be of little benefit. In general, hormonal biomarkers do not appear to fluctuate greatly between cycles [30]. However, intercycle variability does appear to increase with age, suggesting that repetitive testing may be valuable among older women to rule out DOR. Fluctuations in biomarker values reflect diminished ovarian reserve. However, within a given individual, the probability of conceiving in a given ART treatment cycle does not appear to correlate with the cycle-specific biomarker level [8, 31].

14.14 Conclusions

The primary goal of ovarian reserve testing is to identify women at risk of decreased ovarian reserve, with a secondary goal of individualizing treatment strategies for each woman. Although these may predict ovarian response to infertility treatment, they do not reliably predict failure to conceive.

Generally, women of the same age with higher FSH levels seem to have lower fecundability. Younger women with elevated FSH levels often have much better fecundability than older women with comparably elevated FSH and age can be a better predictor of outcome than FSH. The assay in general has suboptimal sensitivity for both ovarian response and pregnancy rates, as reflected by receiver-operator curves. AMH and AFC have a better balance of sensitivity and specificity than FSH. AMH and AFC seem to be emerging as the best approaches to procreative testing [1] (Fig. 14.3). These measures can also be used to predict hyperstimulation.

No ovarian reserve test should be used as a sole criterion for the use of ART. Combined tests do not consistently improve the ability to predict ovarian response. Combined testing is unlikely to be cost-effective. Though some ovarian reserve tests appear better than others in predicting ovarian response to stimulation, most are limited at best in predicting pregnancy, and this predictive value is highly dependent on patient demographics within a study. The number of false-positive test results will increase when screening tests for DOR are used in low-risk populations.

In summary, biomarkers of ovarian reserve are associated with natural and treatment-related fertility. However, controversy remains as to their ability to predict reproductive potential. Cutoff values vary tremendously in the literature. For infertile women undergoing ART treatment,

Fig. 14.3 AMH and AFC seem to be emerging as the best approaches to procreative testing

Test	Details
FSH plus estradiol	• Serum level on cycle day 2–3 • Variation between cycles possible • High FSH value is associated with poor response to ovarian stimulation • Does not predict failure to conceive
AMH	• No specific timing for the test • Stable value within and between menstrual cycles • Low AMH value is associated with poor response to ovarian stimulation • Does not predict failure to conceive
AFC	• Number of visible follicles (2–1 0 mm) during transvaginal ultrasound • Performed on cycle days 2–5 • Number of antral follicles correlates with ovarian response to stimulation • Does not predict failure to conceive

Abbreviations: AFC, antral follicle count; AMH, antimOllerian hormone; FSH, follicle-stimulatin hormone.

these biomarkers tend to be highly specific but not sensitive for cycle failure (nonpregnancy). Biomarkers of ovarian reserve are being used as fertility tests in the general population. The value of these biomarkers as predictors will likely depend on the study population, with the highest predictive value likely to be observed in women at risk for ovarian aging (older reproductive age women). Among the laboratory biomarkers, AMH appears to have the most promise as a measure of reproductive potential; however, studies are especially limited in the general population. Further studies are needed to determine test characteristics in the prediction of natural fertility or infertility in the general population.

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