Ovarian reserve testing: systematic review of the literature

Sajal Gupta, Dipika Sharma, Nilopher Surti, Shubhangi Kesavan, Pallavi Khanna, Ashok Agarwal

OB-GYN and Women's Health Institute and Glickman Urological and Kidney Institute, The Cleveland Clinic, Cleveland, Ohio, USA

Submitted: 11 October 2008
Accepted: 24 November 2008

Arch Med Sci 2009; 5, 1A: S143–S150

Corresponding author:
Sajal Gupta, MD
Center for Reproductive Medicine
The Cleveland Clinic
9500 Euclid Avenue, Desk A19.1
Cleveland, OH 44195
Phone: 216-444-9485
Fax: 216-445-6049
E-mail: guptas2@ccf.org

Abstract

To determine which ovarian reserve tests and imaging criterion have an optimal predictive value for ovarian response to controlled hyperstimulation and fertility outcomes with assisted reproduction cycles. This systematic review was initiated by an extensive search of Medline-Ovid, EMBASE, Cochrane Collaboration database, BIOSIS and Meeting Abstracts from 1986 to 2008, as well as manual searching of review articles and cross references. Two hundred and twenty relevant articles about ovarian reserve tests, including basal follicle stimulating hormone, serum anti-Mullerian hormone, serum inhibin B, ovarian volume and total antral follicle count were studied and analyzed. The review included 90 indexed articles from PubMed that were published within the last decade. Two ultrasound markers; the ovarian volume and total antral follicle count have proven to be more promising than basal blood tests such as basal follicle stimulating hormone, serum anti-Mullerian hormone and serum inhibin B. Among the ultrasound markers, the total antral follicle count had a higher sensitivity and specificity than ovarian volume. Currently, no single ovarian reserve test is sufficiently sensitive and specific to accurately predict ovarian reserve. And there is no test which can precisely predict the fertility outcomes for counseling patients and also accurately exclude patients from treatment and consider options such as oocyte donation. However, basal blood markers and ultrasound markers can compliment each other to best predict the outcome.

Key words: ovarian reserve test, infertility, *in vitro* fertilization, pregnancy rates, FSH, anti-Mullerian hormone, antral follicle count, ovarian volume, inhibin B.

Introduction

The term "ovarian reserve" is used to define the quality and quantity of primordial ovarian follicles inside a woman at a given chronological age, which is an indirect measure of her reproductive age. Determining ovarian function in patients considering and being counseled for assisted reproductive technology (ART) is important for number of reasons. For example, if a patient who is considering *in vitro* fertilization (IVF) is found to have a low ovarian reserve, the fertility outcomes may not be optimal. In addition, ovarian reserve can be used to estimate fertility outcomes with donor oocytes, to tailor stimulation protocols, predict cycle cancellation rates for a low or hyper response to ovarian stimulation and predict pregnancy rates. It is also useful to those undergoing chemotherapy for cancer or any ovarian surgery or planning a family. Finally, it can help diagnose fertility decline in women with age and help plan fertility preservation in selected cases. As such, its use in both screening and

diagnosis requires clear demarcation of the threshold values.

There are various markers and imaging criterion for determining ovarian reserve. The most clinically relevant ones involve measuring serum basal follicle stimulating hormone (FSH) levels, serum anti-Mullerian hormone (AMH) levels, serum inhibin-B levels and ovarian volume as well as estimating the total antral follicle count (AFC). This paper will discuss these tests in an effort to determine which one, if any, has an optimal predictive value for ovarian response to controlled hyperstimulation and fertility outcomes with ART cycles.

Serum basal FSH level

Follicle stimulating hormone is a hormone that is synthesized and secreted by gonadotropes in the anterior pituitary gland. In the ovary, FSH stimulates the growth of immature Graafian follicles to maturation, is controlled by gonadotropin releasing hormone (GnRH), inhibited by inhibin, and enhanced by activin. Measuring day-3 basal FSH levels in women with normal menstrual cycles is one of the most commonly used tests for determining and predicting success in IVF treatment [1].

One prospective study [2] included 110 patients who had undergone their first IVF cycle. Levels of FSH were measured on day 3 to day 6 of the menstrual cycle that preceded the IVF cycle in order to determine the plasma estradiol level. *In vitro* fertilization outcomes and ovarian responses were analyzed. The results showed that FSH levels can be used to individualize clinical management plans and to optimize stimulation protocols in IVF.

A meta-analysis [3] assessed 21 studies to determine the predictive and clinical performance of basal FSH in IVF patients. Each study was scored on the basis of strict homogenous characteristics. The findings indicate that basal FSH levels are, at best, a moderate predictor of poor ovarian response and are a poor predictor of non pregnancy. Based on their meta-analysis, the authors recommended that basal FSH should not be used to determine ovarian reserve.

In a retrospective study [4], patients were stratified into 3 groups based on their FSH levels: <10 IU/l (n=122), 10 to 15 IU/l (n=126) and >15 IU/l (n=53). All patients had regular cycles but were subfertile. The Kruskal-Wallis test and the χ^2 test were used to compare the three FSH groups. The overall ongoing pregnancy rate decreased significantly from 65% in the <10 IU/l group, to 47% in the 10 to 15 IU/l group and 28% in >15 IU/l group. The patients with extreme FSH values above 20.0 IU/l had the lowest ongoing pregnancy rate and showed a clear decrease in ongoing pregnancy rates (16%), which was independent of age. This decrease in pregnancy rates became inconsistent when the study was adjusted for differences in age, which was done both for the treatment-independent and treatment-dependent ongoing pregnancy rates. Due to these inconsistencies in the outcomes, FSH can be used to help counsel patients considering ART but should not be used to exclude them. The decision to include or exclude a patient from treatment should be individualized and must be based on the dialogue between the infertile woman and her physician.

When attempting to predict the outcome of assisted reproduction in older women (>35 years of age), using a cutoff value for basal FSH can be helpful. A study of 83 infertile women ages 35 to 45 years stratified them into three groups according to their day 3 FSH levels (A <10 IU/l, B >10 and <15 IU/l, C >15 IU/l). Embryo quality was poorer in group B and C than in group A whereas the number of oocytes and embryos were comparable amongst all three groups. The results showed that a basal FSH cut-off of 10 IU/ml was predictive of ovarian reserve and that a value of 15 IU/ml not only predicted pregnancy potential but also oocyte quality [5].

Another study [6] looked at 2057 patients who had undergone consecutive IVF/intracytoplasmic sperm injection (ICSI) cycles. Their day 2±4 FSH levels were measured at an earlier cycle. The patients were divided into four groups based on these FSH levels: A <10 IU/l; B 10.1 to 15 IU/l; C 15.1 to 20 IU/l; and D >20 IU/l. They were further stratified into subgroups according to their age: <38 years and >38 years and the authors found that pregnancy rates fell as FSH levels increased (A 32.3%; B 19.8%; C 17.5%; D 3%) and that the live birth rates in the younger patients (A 32.2%; B 21.8%; C 20%; and D 16.7%) were significantly higher than those of the older patients (A 12.1%; B 8.3%; C 10.5%; D 0%). The results implied that IVF treatment should not be refused in cycling patients with high basal FSH levels because fairly good results can be obtained from young women in terms of both pregnancy and live birth rates.

Basal FSH levels were measured in 59 infertile women undergoing IVF (mean age: 35.8±4.5 years) in an attempt to predict ovarian reserve. The significant cut-off point for day 3 FSH was 5.25 IU/l. The results suggested that that day 3 FSH in patients undergoing IVF-embryo transfer (ET) was a good predictor [7]. In another study, cut-off values for FSH were established for 413 infertile women 23 to 40 years old to determine which one, if any, was useful in predicting IVF success. The cut-off values for day 3 and 10 FSH levels were 14.1 and 16.9 mIU/l, respectively. When the FSH levels were higher than these cutoff values, the live birth rate (LBR) was 0% and the implantation rate (IR) was 5%. No changes in the LBR or IR were observed when FSH levels fell bellow these cut-off values in patients under going ART cycles [8].

Age proved to be a better predictor of pregnancy than basal FSH in women undergoing IVF, although both were useful in predicting the quantitative ovarian reserve [9]. This study, which consisted of 1045 women undergoing their first IVF cycle, also revealed that basal FSH levels were not an independent predictor of pregnancy outcomes [9]. The high FSH levels that are commonly seen in older women (>35 years) are due to a decreased follicular pool. However, age should be considered strongly before counseling because it is an independent predictor for success [10]. Delaying treatment in older women with higher FSH levels is of no value since that will not change the outcome and once menopause occurs, the chances of pregnancy are slim to none [11].

A prospective study was performed to assess pregnancy outcomes in 129 healthy pregnant women by measuring their basal FSH values on day 3, but the study failed to find any correlation between low ovarian reserves and early pregnancy loss [12]. Due to a lack of substantial association between elevated basal FSH levels and pregnancy outcomes, basal FSH levels can not be independently used to analyze and predict ovarian reserve and pregnancy outcomes. It is important to remember that interassay and interlaboratory variability exist and that FSH levels can vary from cycle to cycle. A continued debate is warranted on the role of FSH in assessing ovarian reserve.

Ovarian volume

The ovaries contain primordial follicles that decline in number with age [13]. Various methods have been used to determine ovarian volume. In one study, it was measured by manually outlining serial parallel sections of the ovary and using a trapezoid formula to calculate the volume [13]. A more recent method involves the use of three-dimensional power Doppler ultrasound in combination with power Doppler angiography. Power Doppler imaging has multiple advantages such as angle independence and it has a higher sensitivity than color Doppler ultrasonography. The addition of three-dimensional imaging to power Doppler improves its accuracy in assessing the volume and vascularity of the ovary [14].

The ovarian volume was assessed in a group of healthy women ages 40 to 55 years using transvaginal ultrasound. The highest cutoff points were found in the women who were 48 years and older, and these women also had an ovarian volume of less than 4 cm^3. The authors concluded that a small ovarian volume is associated with ovarian aging [13, 15].

A prospective study with strict inclusion criteria was performed on 56 women undergoing IVF treatment in which ovarian volume was determined by three-dimensional power Doppler ultrasound. A mean age of 39 years was associated with a total ovarian volume (TOV) of less than 7 cm^3 and a mean age of 29 years was associated with a TOV of more than 10 cm^3. This study found a statistically significant difference in total TOV between various age groups but the overall pregnancy rates did not differ significantly [16].

In women older than 39 years who were in a pre- and perimenopausal state, the ovarian volume was smaller than that of younger women. In the perimenopausal women, the influence of obesity was ruled out, and no association was reported between ovarian volume and body mass index. A 0.2 cm^3 decline in ovarian volume was calculated with each year of increase age [17].

Intercycle variations of basal antral follicle counts and ovarian volume in subfertile females were evaluated in another study. Fifty-two subfertile but ovulatory women were observed for two consecutive spontaneous cycles. The intercycle variability of the antral follicle count and ovarian volume was assessed by calculating their limits of agreement, which were –6.9 and 6.5 and –8.3 and 8.6, respectively. Two studies found less variation in ovarian volume than in the antral follicle count in the young infertile patients when transvaginal ultrasonography was performed by the same physician [18, 19].

Three-dimensional ultrasonography and power Doppler angiography was used to determine the intraobserver and interobserver reproducibility between two observers who calculated ovarian volume to assess ovarian response and oocyte quality in 29 women in an IVF program. The first observer obtained two volumes from each ovary and the second observer performed a second analysis of the volumes obtained by the first observer. The intraobserver and interobserver reproducibility of ovarian volume was found to be excellent [14, 18, 20-24].

A retrospective analysis was performed of two prospective studies consisting of 465 anovulatory patients undergoing ovulation induction. Baseline ovarian volume was assessed on day 2 to 5, and data on ovarian response to stimulation, ovulation, cancellation rate, pregnancy rates, and hyperstimulation syndrome were collected. The authors concluded that medium-to-large sized ovaries were at a higher risk of ovarian hyperstimulation than smaller ovaries during ovulation induction by gonadotropins. Women with small ovaries (OV <7.25 cm^3) had a probability of conceiving that was equal to that of the women with large ovaries (mean ovarian volume x=11.55±6.0 cm^3) [25-28].

The MOV was found to be of limited value in a prospective cohort study with strict inclusion

criteria consisting of 267 women undergoing IVF. The overall MOV was 4.78±2.6 cm^3. Both prestimulation and poststimulation IVF parameters were mainly correlated with MOV. Linear regression analysis was used to determine whether MOV correlated with ovarian reserve and ART stimulation performance. No MOV cutoff value was predictive of either pregnancy outcome or cycle cancellation [29]. Ovarian volume was found to have a similar sensitivity and specificity to basal FSH and age in predicting menopausal status. A cross-sectional study was performed with premenopausal and postmenopausal women between the ages of 40 and 54 years. Transvaginal ultrasound was used to determine ovarian volume, and blood samples were used to measure FSH levels [30].

Ovarian volume can be easily and accurately measured with transvaginal ultrasound, and its intercycle and interobserver variability is low. However, ovarian volume offers little information when used to assess the prognostic success of IVF in terms of pregnancy outcome and cycle cancellation.

Total antral follicle count

Antral follicles are small in diameter (2 to 8 mm) and can be measured and counted with ultrasound. They are also referred to as resting follicles. In healthy women with normal fertility and regular menstrual cycles, the total antral follicle count estimated by transvaginal ultrasonography best predicts the chronological age [31].

A meta-analysis comparing 10 studies on ovarian volume and 17 studies on AFC was performed. The studies were heterogenous and therefore the calculation of sensitivity and specificity were not accurate. Ovarian reserve testing using ultrasound was inaccurate in women with a poor chance of pregnancy. The authors of this meta-analysis suggested that the predictive value of ovarian volume towards poor ovarian response was definitely low compared with AFC. Therefore, for predicting quantitative ovarian reserve, AFC can be considered before IVF [32].

In another meta-analysis, 11 studies on AFC were compared with 32 studies on basal FSH. Because P values for both the AFC and the basal FSH were less than 0.001, their homogeneity was rejected. For this reason, the evaluation of the summary point estimate for both sensitivity and specificity was found to be meaningless. Logistic regression analysis found no study to be statistically significant. However, current evidence suggests that the ability of AFC to predict poor ovarian response is high and its ability to predict nonpregnancy is low. Antral follicle count might be considered the test of choice in predicting ovarian reserve before IVF as it is easy to perform, is noninvasive and has a better predictive value than basal FSH [33].

The combination of cycle day 7 follicle counts and basal antral follicle count has high positive and negative predictive values and can lower the overall burden of cycle cancellation. This conclusion was reported in a retrospective analysis of 82 patients who had undergone 91 consecutive IVF cycles [34]. Another retrospective study was performed to predict cycle cancellation and ovarian responsiveness; the antral follicle count was measured in the patients before they underwent ovarian stimulation in an ART cycle. The study found a direct linear correlation between MOV and basal antral follicle count. Although the study included 278 patients, the authors believed that a larger sample size was needed to produce a significant threshold value that could demonstrate an inverse relationship between pregnancy outcome and basal antral follicle count [21].

According to a study using three-dimensional ultrasonography and power Doppler angiography, AFC showed excellent intraobserver and interobserver reproducibility when used to assess ovarian response and oocyte quality. In addition to AFC, ovarian volume was assessed in 29 patients with an average age of 33.9 years who had been infertile for an average of 3 years. The intra- and inter-class coefficients for AFC were 0.964 and 0.978, respectively, whereas the values for ovarian volume were close to unity [22]. Similarly, the intercycle variability of AFC was found to be higher than that of ovarian volume. Intercycle variability was measured by evaluating the limits of agreement (LOA) between two day-3 measurements (LOA – 6.9 and 6.5). The younger women (age <24.5 years) showed higher variability than the older women. For this reason, a high AFC in a given cycle for a given individual is not a marker of better response than a low AFC [18, 19, 35].

Seventy-one women with median age of 36 years were included in a retrospective study with strict exclusion criteria. The author in the study summarized that AFC can efficiently predict a woman's response to ovarian stimulation by determining the total number of oocytes retrieved and the number of mature oocytes. For this reason, AFC proved to be good marker of ovarian reserve before IVF, particularly in older patients [36].

In a prospective study that included 110 patients between the ages of 18 and 39 years with regular menstrual cycles, the number of antral follicles was compared with other techniques for estimating ovarian reserve to assess ovarian hyperstimulation during IVF treatment. The AFC was the best predictor [37].

A group of women younger than 35 years of age who were undergoing ART were retrospectively assessed in another study and compared with a group of healthy women. All of the women in the

former group had decreased ovarian reserve (DOR) as determined by AFC. The study concluded that pregnancy rates in the DOR group were markedly lower than those in the healthy group and that pregnancy rates are still fair in women with a low number of oocytes [38].

In a study of 56 patients who were undergoing IVF/ET (mean age, 33.5 years), the total AFC was found to be the best predictor of IVF amongst a number of tests including ovarian stromal blood flow, peak E_2 on HCG administration day, TOV, total ovarian stromal area and age [39]. In spite of certain drawbacks, the AFC appears to be a very promising test.

Serum anti-Mullerian hormone level

Anti-Mullerian hormone (AMH) is a member of the transforming growth factor α. It is secreted by the granulosa cells of primary and preantral follicles 4 to 6 mm in diameter [40] and has been shown to control folliculogenesis at various stages (e.g., recruitment of a primordial cohort to the primary follicles). It also plays a role in follicular dominance selection. Its secretion decreases the sensitivity of the follicles to FSH in dominance selection. Anti-Mullerian hormone is secreted by the primary follicle pool up until FSH dependence and hence can indirectly be used to assess the primordial pool of follicles [41]. Anti-Mullerian hormone has been shown to have a rather steady expression during the menstrual cycle as its secretion is under intrinsic gene expression and not an external stimulus [42]. It has also been shown to correlate strongly with the AFC (r=0.66/0.71; N=41).

The role of AMH in determining ovarian reserve has been assessed. Researchers have measured basal levels (day 3) after stimulation following pituitary suppression in ART cycles [43] as well as a part of GnRH agonist stimulation test (GAST) and so on. Recent studies have looked into the possibility that AMH plays a distinct role in ART by indicating the number of oocytes at the time of retrieval, the number of embryos and their characteristics as well as the likelihood of pregnancy outcome [44]. This study could not relate AMH levels to embryo quality and hence it concluded that that was the reason for AMH's inability to predict fertility outcomes. However, the ovarian response or the number of oocytes retrieved following ovarian stimulation could be predicted with basal AMH levels.

A recent study [45] concluded that AMH levels at the time of HCG administration could predict a better embryo score for morphology. MIS levels >2.7 ng/ml correlated with increased oocyte quality and a higher implantation rate (P=0.001), and a trend towards better clinical pregnancy rate (P=0.084). Another study by Talia et al. concluded that a cutoff basal AMH value (follicular/luteal phase) of 18 pmol/l had a positive predictive value of 67% and a negative predictive value of 61% for achieving ongoing pregnancy (P<0.01) with a receiver operating characteristic (ROC) of 0.75.

Anti-Mullerian hormone's advantage over the much relied upon AFC is its relatively lower interassay and intraassay variability, which means that it can assess follicles that are too small to be detected by by ultrasonography [46]. The interassay variability for AMH is approximately 8% and its intraassay variability is 5% [47]. The results of serum AFC are consistent and can predict age related decline in fertility very well. The day-3 AMH has been found to be a good predictor of ovarian response but did not predict the pregnacy rate [48] and it is to be considered complimentary to the AFC.

Although AMH may seem promising, it has certain drawbacks. The number of granulosa cells secreting AMH depends on the number of 2 to 5-mm diameter follicles, and even smaller ones may also secrete the hormone and raise serum levels. Hence, it may be difficult to determine the exact cohort in the reserve of the ovary [49]. Its intercycle and intracycle variability requires further studies. One study concluded that even though AMH levels could reflect ovarian reserve, its predictive capacity is too limited to be of clinical value [44]. In addition, the cost factor of the AMH assay has yet to be determined.

Serum inhibin B level

Inhibins are polypeptides secreted by granulosa cells of the ovarian follicles. They function as inhibitors of FSH synthesis and assist in regulating the menstrual cycle. Inhibins include inhibin-A and inhibin-B. Structurally, inhibin-A comprises α and βA subunits, whereas inhibin-β comprises α and βA subunits [50]. Inhibin A levels are low in the follicular phase and peak in the midluteal phase. Inhibin B levels usually peak in the early follicular phase and then decrease [51]. In a study done by Seifer et al., the threshold value of inhibin B was more than 45 pg/ml. Women with levels below this threshold had a poor estrogenic response to stimulation, decreased oocyte retrieval, increased cancellations rates and low pregnancy rates [52].

A study of 120 women whose day 3 inhibin B was assessed along with FSH as a predictor of ART success concluded that patient age and FSH are better predictors than inhibin B levels. All of the patients with homogenous inclusion criteria had a blood sample drawn on day 3 of their cycle within 3 months of the IVF attempt to determine their basal inhibin B and FSH levels [53]. In another study, 78 women who achieved pregnancy were compared with 78 women who failed to achieve pregnancy

within three cycles of ART. Inhibin B was found to be no better than patient age and number of oocytes in predicting pregnancy outcome. At baseline, no correlation was observed between age, FSH or inhibin B but a positive correlation between inhibin B and number of oocytes retrieved after gonadotropin stimulation was reported [54].

In a retrospective study, 62 women were divided into 3 groups depending on the number of oocytes that were retrieved. Serum and follicular inhibin B levels had a strong correlation with the number of oocytes retrieved and hence the ovarian response whereas inhibin B was found to be of no use in predicting pregnancy [55].

In a prospective analysis, inhibin B levels were measured at the follicular phase, mid-luteal phase and after GnRH down-regulation in 58 spontaneously ovulating women who were scheduled to undergo IVF. After controlled ovarian hyperstimulation, inhibin B was observed to have a strong correlation with the number of retrieved oocytes [56].

Females with a low ovarian reserve have diminished granulosa cell secretion of inhibin B. This was the conclusion of a study that compared serum inhibin B levels of 19 women with a normal ovarian reserve with those of 15 women with a low ovarian reserve [50]. Another study attempted to find an ovarian reserve test for sub-fertile women failed to find that inhibin B was of any clinical significance. Day 3 and 10 inhibin B levels of 106 women showed no correlation with serum estradiol or FSH levels or pregnancy rates [57]. It would not be prudent for physicians to use inhibin B to assess ovarian reserve until inhibin B values are more standardized and show better correlation with oocyte quantity and quality and pregnancy rates.

Stimulatory tests for dynamic ovarian reserve evaluation (EFFORT test)

The exogenous FSH ovarian reserve test (EFFORT) can be used to predict a woman's response to IVF treatment. Women whose E_2 levels increased by more than 30 pg/ml 24 h after exogenous FSH administration had better results i.e. higher implantation rates and pregnancy rates than patients with lower values [58]. When serum inhibin B was measured after EFFORT, it was suggested that serum inhibin B can be used to predict ovarian response prior to IVF. In another study, thirty two cycles from 32 women, 25 to 42 years of age were retrospectively selected from 100 patients. These women had a better ovarian response to hyperstimulation than other patients. Logistic regression models were used to evaluate the possible use of inhibin B as a marker of ovarian response [59, 60]. EFFORT has been reported to be a better predictor of the quality of ovarian response than the clomiphene citrate challange test (CCCT).

Clomiphene citrate challange test

Clomiphene citrate challange test is another stimulatory test that can be used to evaluate dynamic ovarian reserve. The test is performed by measuring basal FSH levels on day 2 or day 3 and then administering 100 mg of clomiphene citrate from days 5 to 9. FSH is evaluated again on Day 10. FSH levels that are more than 2 standard deviations above the basal levels are considered abnormal, and this value is reported as >12.5 units on day 10. Basal FSH and CCCT both have a comparable sensitivity and specificity in terms of prediction of clinical pregnancy as an end outcome.

Conclusions

Routine use of ovarian reserve testing has not been implemented in evaluating patients undergoing ART. Individual tests designed to measure ovarian reserve fails to demonstrate an optimal predictive value. However, based on the literature reviewed, a combination of basal blood markers and the ultrasound markers can compliment each other to best predict the outcome. There are numerous confounding factors that can influence the outcome of ovarian reserve tests such as age, parity, lifestyle factors, previous ovarian surgery and the therapeutic drugs that are administered during an ART cycle. Serial evaluations of these tests in a healthy fertile population may help identify the normal cutoff values for these tests and highlight trends in ovarian reserve in different age groups. Further studies are needed to assess the clinical impact of these tests and whether clinical management needs to be changed.

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