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Methods of evaluation of the ovarian reserve

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Abstract

The chances of pregnancy decrease with the natural aging process of the infertile couple. During treatment of an infertile couple, the clinicians are usually asked questions about the chance of conception. Ovarian reserve describes the reproductive ability of the woman. An ideal ovarian reserve test should be affordable, convenient and sensitive. Ovarian reserve tests help to predict a poor response or hyper-response to ovarian stimulation and help to formulate the treatment plan in an infertile couple. Decreased ovarian reserve refers to women whose ovarian response to exogenous gonadotropin stimulation is reduced compared to similar women of the same age.

Key words: ovarian, reserve, evaluation.

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Introduction

Ovarian reserve describes the reproductive ability of the woman, through identification of the number and the quality of the oocytes available in her ovaries [1].

It also guides the clinician to decide about the treatment and individualize the treatment protocols. Ovarian reserve is a complex clinical phenomenon that is greatly influenced by age, genetics and environmental variables. The decline in a woman's ovarian reserve is an irreversible phenomenon. The rate at which a woman loses her primordial follicle varies from person to person [2].

Ovarian reserve refers to the residual oocyte granulosa cell that is available for fertilization at any given age. The quantitative and qualitative decline of these cells is seen with advancing age. Ovarian reserve provides information regarding the follicles that can be stimulated and the oocyte that can be retrieved from the ovary.

Infertility specialists are often faced with the challenge to predict the fertility potential of women. The ovarian reserve test adds more prognostic information to counsel the infertile couple. It helps to identify patients who are likely to have a poor response or hyper-response to gonadotrophin stimulation, but it cannot predict the clinical outcome such as pregnancy [1, 2]. It helps to differentiate patients with normal ovarian reserve from those with decreased ovarian reserve (DOR) and helps in deciding treatment protocols in women with DOR. It also helps in avoiding aggressive treatment in women with normal reserve. However, it should not be used to exclude an infertile couple from seeking assisted reproductive technology (ART) [1].

Various clinical and biochemical markers have been studied to test the ovarian reserve. An ideal ovarian reserve test should be affordable, minimally invasive, convenient, inexpensive and sensitive with good predictive value [2].

Clinical biomarkers of the ovarian reserve

Age

Studies have shown that the fecundability declines after the early 30s [3]. The prevalence of infertility increases significantly after the age of 35 years, and by the age of 45 around 99% of patients are expected to be infertile [4]. Genetic factors, smoking, infections and adnexal surgery are the other determinants of DOR in older women [5]. Tehraninezhad *et al.* found that age is a good predictor of clinical pregnancy [6].

Menstrual cycle

The pattern of the menstrual cycle in a woman remains consistent until the late 40s, after which a gradual shortening in cycle length is seen. In addition, in the late 30s, a higher serum level of follicular stimulating hormone (FSH) and lower serum levels of inhibin are frequently seen.

Brodin *et al.* found a significant correlation between the menstrual cycle length and both the pregnancy and the delivery rate [7]. Brodin *et al.* observed that in women with cycles > 34 days, the delivery rate was twice as high as in those having cycles < 26 days. In addition, they found a significant association between the menstrual cycle length and the ovarian response to gonadotropin and the quality of the embryos obtained during *in vitro* fertilization (IVF) cycles [7].

Biochemical markers of the ovarian reserve

Ovarian reserve can be evaluated biochemically by the follicle stimulating hormone (FSH), estradiol (E2), inhibin, and anti-Mullerian hormone (AMH).

Follicle stimulating hormone

Early follicular phase serum FSH (day 3) is commonly used to evaluate the ovarian reserve. It is an indirect marker of the ovarian reserve, based on the feedback inhibition of FSH secretion by the ovarian hormones. At the beginning of the menstrual cycle, the E2 and inhibin B levels inhibit FSH secretion from the pituitary. In women with DOR, the production of ovarian hormones is insufficient with subsequent elevated pituitary FSH secretion.

Van der Steeg *et al.* found that the chance of pregnancy reduced when the FSH levels exceeded 8 IU/ml [8]. Ashrafi *et al.* found that in women with serum FSH levels ≥ 15 IU/ml, fewer oocytes were retrieved, and they found a higher rate of cycle cancellation in women with FSH levels ≥ 15 IU/ml than women with lower FSH levels, with no significant difference in gonadotropin doses administered [9]. Van Montfrans *et al.* found that the basal FSH should not be the decisive factor for the initial management of infertile women with regular menstrual cycles [10]. Barbakadze *et al.* stated that FSH is less reliable than other markers such as AMH and antral follicle count (AFC) for assessing the ovarian reserve [11]. Hence, high FSH levels should not be used alone to exclude women from ART [11].

Estradiol

It has been observed that women with E2 levels < 20 pg/ml or ≥ 80 pg/ml have a higher ART cycle cancellation rate [12]. E2 with FSH assay on cycle day 3 reduced the incidence of false-negative tests obtained when FSH was used alone. The elevation of both indicates poor ovarian response.

E2 has low predictive accuracy and lacks high sensitivity and specificity [13]. It may be used as a guide for starting stimulation with gonadotropins; however, it should not be used alone for assessment of the ovarian reserve and its measurement should be combined with measurement of serum FSH [14].

Inhibin B

Inhibins are glycoproteins secreted by the granulosa and theca cells. They play a major role in the selection of the dominant follicle and have a regulatory effect on the secretion of FSH [15]. Although Seifer *et al.* found that women with inhibin B concentration levels ≥ 45 pg/ml have an increased oocyte retrieval rate and lower cycle cancellation rate [16], other authors found that inhibin B alone is not a very useful marker for assessment of the ovarian reserve [17].

Anti-Müllerian hormone

Anti-Müllerian hormone is a glycoprotein hormone expressed by the granulosa cells of the secondary, pre-antral and antral follicles < 4 mm in size and its expression decreases as the follicles grow. Anti-Müllerian hormone thus acts as a modulator of follicle recruitment and plays an important role in folliculogenesis [18]. Serum AMH is a reliable marker for ovarian ageing and reproductive status [19].

Women with polycystic ovary syndrome (PCOS) have an increased number of antral follicles compared with normal women [20]. Serum AMH levels were found to be two to three times higher in women with PCOS [21]. Women with low AMH levels prior to IVF may have either an increased risk of cycle cancellation or poor response to stimulation. Van Rooij *et al.* observed that the serum AMH levels correlated well with pre-induction AFC and the number of oocytes retrieved in ART cycles [22].

A meta-analysis found that AMH levels have similar predictive value as AFC in identifying poor responders [23]. Authors have proposed a cut-off value range of 0.7–0.75 ng/ml for AMH for the identification of poor responders [24, 25]. Others have considered serum AMH levels < 0.1–0.35 ng/ml as the cut-off to minimize false positives [26, 27]. High AMH before IVF is useful in identifying women at risk for hyper-response and ovarian hyper-stimulation syndrome (OHSS).

Vembu *et al.* suggested a cut-off value of serum AMH to predict the hyper-response in the PCOS group as 6.85 ng/ml and in the non-PCOS group as 4.85 ng/ml [28]. In these patients starting a low dose of FSH followed by the use of GnRH antagonists or using a GnRH antagonist for the triggering of ovulation instead of hCG can be done to prevent the development of OHSS [29].

Serum AMH is useful to detect poor responders, cycle cancellation and OHSS during ART cycles. It is also used for individualization of treatment strategies in patients undergoing IVF treatment.

Ultrasound markers of the ovarian reserve

Antral follicle count (AFC)

Antral follicle count is the total number of follicles observed in both ovaries in the early follicular phase using transvaginal ultrasonography (TVS). It is a very reliable marker of the ovarian reserve [30]. A count of 8–10 considered as a predictor of a normal response. The diameter of the follicle used to define antral follicles ranges from 2 to 10 mm.

Haadsma *et al.* observed that the number of small antral follicles 2–6 mm in size declines with age but the number of those 7–10 mm in size remains constant. They said that the small antral follicle correlates well with the ovarian reserve tests and appears to represent functional ovarian reserve better [31].

Compared to other tests, AFC has the best discriminating potential for a poor ovarian response. It lacks the sensitivity and specificity to predict the occurrence of pregnancy [32]. The presence of > 14 antral follicles is considered a good predictor for ovarian hyper-response [33].

Maseelall *et al.* observed that women with AFC ≥ 11 (follicles measuring 2–10 mm present on both ovaries) were more likely to have a live birth [34]. A meta-analysis found that women with AFC ≤ 4 were 8.7 times more likely not to be pregnant and 37 times more likely to have their cycle cancelled than women with AFC ≥ 4 [35].

The sensitivity and the specificity of AFC to predict cycle cancellation was 67 and 95%; respectively. However, due to low sensitivity the AFC should not be used alone for ART evaluation of ovarian reserve. It is a useful tool for counseling on the low probability of pregnancy and individualizing the treatment protocols in IVF cycles [35].

Ovarian volume

The routine use of ovarian volume as a predictor of ovarian reserve is controversial. Gibreel *et al.* observed 93% and 92% specificities for the prediction of non-pregnancy and cycle cancellation, respectively with a 3.0 ml cut-off ovarian volume [35]. A meta-analysis of Hendriks *et al.* found that the predictive value of ovarian volume for poor responders was low [32].

Ovarian blood flow

Ovarian blood flow has been studied in natural and stimulated reproductive cycles [36]. Shrestha *et al.* found that high-grade ovarian perifollicular blood flow in the early follicular phase during ovarian stimulation was associated with a higher clinical pregnancy rate [37]. However, the value of the ovarian blood flow is still indeterminate [35].

Dynamic tests for evaluation of the ovarian reserve

Clomiphene citrate challenge (CCC) test

The CCC test involves assessment of the FSH on day 3 and day 10 of the menstrual cycle after 100 mg clomiphene citrate (CC) daily from day 5 to day 9 of the menstrual cycle. High serum FSH after clomiphene stimulation suggests DOR [38].

However, a meta-analysis has shown that the CCC test is no better than basal FSH in predicting clinical pregnancy [39].

Exogenous FSH ovarian reserve test

The exogenous FSH ovarian reserve test (EFORT) measures the increase in E2 and inhibin B 24 h after the administration of 300 IU of recombinant FSH on cycle day 3 [40]. It tests the functional response of the ovary. Increased levels of E2 and inhibin B after EFORT have a good predictive value for the number of ovarian dominant follicles that can be obtained and/or retrieved after stimulation [40].

Gonadotrophin releasing hormone agonist (GnRH agonist) stimulation test

In this test, serum estradiol is measured on day 2 of the cycle followed by the subcutaneous administration of a gonadotropin analogue (triptorelin 100 µg). E2 levels are measured on day 3 (24 h later) and values are compared. A rise in E2 level is considered indicative of good ovarian reserve. The

GnRH agonist stimulation test is a good predictor of poor ovarian reserve, but is not superior to inhibin B or AFC in detection of ovarian reserve [41].

Summary

The ideal ovarian reserve test should be affordable, minimally invasive, convenient, and inexpensive with good predictive value. It should also have the ability to identify women at risk of developing OHSS. Evidence demonstrates a greater clinical value of AMH and AFC compared to FSH [42]. The AMH has better reliability than other markers to predict the ovarian reserve and the ovarian response to exogenous stimulation [43–45]. Ovarian reserve tests provide prognostic information about women at increased risk of DOR, such as women who: 1) are over 35 years old; 2) have a family history of premature ovarian failure; 3) have a past history of ovarian surgery or radiation; 4) have unexplained infertility [1].

According to the NICE guidelines, sufficient ovarian reserve is diagnosed by either AFC of > 4 or serum AMH level > 5.4 pmol/l or serum FSH level < 8.9 IU/I [46].

Conflict of interest

The authors declare no conflict of interest.

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