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SPECIAL ARTICLE

Ovarian Reserve Assessment

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ABSTRACTS

One of the most challenges in reproductive endocrinology is the evaluation and treatment of reproductively older women who desire fertility. The pregnancy rates in natural and assisted reproduction cycles in these women are dramatically reduced, whereas the rate of spontaneous miscarriages are markedly increased. Ovarian reserve assessment can identify those women with markedly reduced ovarian reserve before starting expensive and invasive treatments. They should be counseled regarding the poor outcome of ovarian stimulation and the options of oocyte donation or adoption. Although these alternatives are frequently disappointing, they represent realistic options for many couples. This article reviews the different methods used for ovarian reserve assessment.

Key words : ovarian reserve, follicle stimulating hormone (FSH), ovary, ovulation induction, in vitro fertilization

The term “ovarian reserve” refers to a current supply of eggs from the ovaries, and is closely associated with reproductive potential. In general, the greater the number of remaining eggs means the better chance for conception. Conversely, low ovarian reserve greatly diminishes a patient’s chance for conception. Many researchers have demonstrated a direct correlation between normal ovarian reserve and fertility.[1,2]

Apart from poor IVF outcome, patients with diminished ovarian reserve appear to be at greater risk for fetal aneuploidy compared to patients with normal ovarian reserve.[3] Poor prognosis patients undergoing IVF have higher rates of chromosomally abnormal embryos as determined by preimplantation genetic diagnosis (PGD),[4,5] and exceedingly high rates of pregnancy loss, regardless of age.[6] It may also play an important role in unexplained recurrent pregnancy loss.[7,8]

There are several parameters to assess the ovarian reserve of a patient and her ability to respond to the standard ovarian stimulation protocols. Before starting an IVF cycle it is essential to study the patient’s previous medical and surgical history in depth. The development of diminished ovarian reserve generally reflects the processes of follicular depletion and decline in oocyte quality.[9-11] Women with markedly diminished ovarian reserve should be counseled on their low chances of conception with their own gametes, even with assisted reproductive technologies. This article reviews the different methods used for ovarian reserve assessment.

The effects of aging on ovarian reserve

Aging of an ovary is characterized by the reduction of the number of primordial follicles from

about a million at birth, to about 250,000 at menarche and to a very few at the end of reproductive life.[12] This loss accelerates around the age of 37 years and precedes the menopause by 10-12 years.[13,14] There is wide variation between women in the number and rate of depletion of follicles. In this aging process, the ovaries become progressively less responsive to exogenous gonadotrophins, until they are totally refractory at the time of the menopause.

Menstrual cycles in the older women are associated with poorer egg quality.[15] In general, ovarian age parallels chronological age. Therefore, it is important for clinicians to assess an infertilile patient's ovarian reserve, particularly women over the age of 35. Conception and childbirth in women of advanced age has always been uncommon. There is an evidence of reduced fertility associated with older women.[16,17] The father's age, however, appears to have only a marginal influence on fertility.[18]

The association between aging and decreased fecundity has been extensively reviewed.[19] Results from donor insemination programs reveal that cumulative pregnancy rates decrease from 94% in women under 25 years of age to 57% in women between 36 and 40, and 56% in women between 40 and 45 after 12 months of well-timed inseminations.[20] This observation was confirmed by research in an in vitro fertilization (IVF) setting, where women 37 years of age or older had a 9% ongoing pregnancy rate compared to a 26% ongoing pregnancy rate in patients younger than 30.[21] The age of the patient is crucial for the prognosis of an IVF cycle. Several studies showed that the patients over 35 have a poor IVF outcome due to their high cancellation rates and low number of oocytes and embryos, despite they have normal fertilization rates.[22,23] However, if patients over 35 have a good ovarian reserve they will probably respond well and if they receive 2 or 3 good quality embryos, their chances of getting pregnant are similar to those of patients under 35.[24] On the other hand, among poor responders with fewer than 4 oocytes, the pregnancy rates are higher in the younger group of patients.[25] There is clear evidence that age impairs not only the number of oocytes but also their quality, and the rate of oocyte chromosome degeneration and meiotic non-disjunction increases with age.[15, 26] Live birth rates are strongly influenced by the age of oocytes. Younger oocytes from donors under the age of 35 used in donor-egg cycles greatly improves the reproductive outcome.[27,28] While the recipient's age does have some negative impact on implantation rates, the effects appear limited. In fact, even if the recipient is over 40, clinical pregnancy rates approaching 59% have been achieved when oocytes from young donors are used.[29] Additional results from oocyte donation studies show that pregnancy and miscarriage rates are similar to those of women of the same age as the donor rather than those of the recipient.[29]

Methods of ovarian reserve assessment

Since a woman's age is the single most important factor in predicting a couple's reproductive potential, it has often guided infertility treatment choices. However, age alone is not a good predictor of ovarian reserve. Consequently, several methods have been developed for predicting a couple's response to infertility treatment. (Table 1)

Table 1. Methods for ovarian reserve assessment

Endocrine tests :
Basal serum FSH
Basal serum estradiol
Basal serum inhibin-B
Basal ratio of FSH/LH
Dynamic tests :
Clomiphene citrate challenge test (CCCT)
Exogenous FSH ovarian reserve test (EFORT)
GnRH agonist stimulation test (GAST)
Ultrasound assessment :
Measurement of ovarian volume
Antral follicles counts
Stromal blood flow
Ovarian biopsy

Endocrine tests

Basal serum FSH level

As a woman ages, FSH becomes elevated in an attempt to force the aging ovary to respond. However, the exact mechanism responsible for this adaptive response remains unknown. A rise in early follicular-phase FSH is also accompanied by a decline in oocyte quality, and some investigators have linked such FSH elevations to fetal abnormalities.[30] Generally, increases in FSH precede menopause by approximately five years in some women.[31]

It is difficult to establish absolute values that define how high an FSH level can be and still achieve pregnancy due to variations in laboratory assessments and treatment methods. A single measurement of day 3 FSH may not represent actual ovarian reserve. When testing reveals elevated FSH, this result should be confirmed in a later cycle. However, interpretation of fluctuations across multiple cycles is controversial. Among patients with a series of day 3 FSH values that include at least one unfavorable (elevated) FSH test, a low response to ovulation induction has been observed.[32] Another analysis revealed that patients with both high and low FSH values across multiple cycles performed as low responders during IVF.[33]

Women undergoing IVF with a day 3 FSH of less than 15 mIU/ml were twice as likely to conceive than women with FSH values between 15 and 24.9 mIU/ml.[10] When day 3 FSH levels exceed 20 IU/L, conception rates fell sharply[32] FSH values emerged as superior to maternal age as a method for determining reproductive outcome in IVF.[11] Currently, the FSH concentration is the best marker for ovarian reserve assessment and predicting response to superovulation with a good correlation with pregnancy rates.[10,11] However, lack of a clear cut-off point, extreme variations between different laboratories and monthly variations in FSH secretion limit the value of FSH measurement in assessing the prognosis of IVF treatment.[2,34]

LH measurement may also have predictive value for ovarian reserve, but FSH is considered a better marker. Since menopause approaches, FSH rises sooner and more dramatically than LH.[35,36] There may be a place for combined FSH and LH testing to estimate ovarian reserve, as some investigators have suggested an increased FSH:LH ratio may predict an elevation in FSH alone.[37]

Basal serum estradiol concentration

Evaluation of cycle day 3 E2 in IVF patients revealed no clear association between E2 and treatment outcome.[10] Low day 3 E2 levels (<80 pg/ml), combined with normal FSH, have been associated with improved stimulation response, higher pregnancy rates,[38,39] and lower cycle cancellation rates.[40] In recent study, basal E2 levels neither predicted pregnancy outcome nor correlated with ovarian response in those patients not canceled.[42]

High levels of E2 early in the menstrual cycle suggest an inappropriately advanced stage of follicular development. This may occur as the ovary ages, or when ovarian follicular cysts remain from a prior menstrual cycle. The follicular cysts can interfere with egg “recruitment” in the treatment cycle, naturally leading lead to a poor response to fertility treatment.

Basal serum inhibin-B concentration

Inhibin-B is a heterodimeric glycoprotein released by the granulosa cells of the follicle that inhibits FSH release.[42] In recent study, women with low day 3 inhibin B concentration (<45 pg/ml) had poorer response to superovulation for IVF and less likely to conceive.[43] It also showed that a decrease in inhibin-B probably precedes the increase in FSH concentrations.[44] However, other investigators failed to show any added predictive value for inhibin-B as a measure of ovarian reserve.[45,46] More data are needed before meaningful normal ranges for inhibin-B can be routinely applied in clinical practice.[44,47]

Dynamic tests

Clomiphene citrate challenge test (CCCT)

In contrast to the static hormonal measurements of ovarian reserve mentioned previously, the

clomiphene citrate challenge test (CCCT) is a dynamic approach first described in 1987.[48] Its purpose is to stimulate the ovary to initiate egg production in response to clomiphene citrate. In theory, the CCCT was designed to detect low ovarian reserve that would not be discovered by a single FSH and/or E2 measurements.

The CCCT is based on the assumption that adequate ovarian reserve is associated with a healthy group of developing follicles. This healthy group of follicles should be capable of producing enough inhibin and E2 to suppress FSH production and resist the effects of clomiphene.

Clomiphene works by shutting down the estrogen receptors on the hypothalamus and tricking the hypothalamus into thinking the patient doesn't have enough estrogen. In response, the hypothalamus works harder to induce the pituitary gland to produce more FSH and LH. This, in turn, initiates follicular growth.

When undergoing CCCT, the first step is to measure day 3 FSH and E2. Then 100mg of clomiphene is administered on cycle days 5 through 9, and FSH and E2 measurements are repeated on cycle day 10.[48] In general, a high day 10 FSH suggests poor ovarian reserve. The provocative test unmasks patients who might not be detected by basal FSH screening alone. In the original report describing the CCCT, 18 patients out of 51 had abnormal responses which resulted only one pregnancy (1 of 18, or 6%). The pregnancy rate among those with normal CCCT response was substantially higher (14 of 33, or 42%).[48] Several other investigators have confirmed the good predictive value of CCCT before treatment.[49,50] It is superior to early follicular FSH screening, but has poor predictive value in women >40 years in terms of response to superovulation and pregnancy rate in ART cycles.[50] Evaluation of a large number of infertility patients found a 10% prevalence of abnormal CCCT responders.[51] Another report found CCCT to be a better predictor of ovarian reserve than day 3 FSH measurement alone.[52]

Exogenous FSH ovarian reserve test (EFORT)

This test was introduced as a predictive test for good and poor responders in IVF cycles [53] and IVF outcome [54] using exogenous FSH (300 IU FSH/day). Increment of serum estradiol level and/or basal serum FSH were evaluated.[53, 54] It has not yet been studied in the general subfertile population, nor has it been evaluated by others.[53]

Gonadotropin-releasing hormone agonist stimulation test (GAST)

A gonadotropin-releasing hormone agonist initially elevates E2 (flare-effect), then profoundly suppresses both FSH and LH.[55] More than a decade ago, it was theorized that low ovarian reserve might be detected by evaluating differences in LH, FSH, and E2 levels following the administration of GnRH-a during IVF.[56] This approach was later formalized as a diagnostic tool known as the GnRH-a stimulation test, or GAST.[57] The test is dependent on the pituitary production of gonadotrophins and the response of the ovary to stimulation.

The purpose of GAST is to evaluate changes in E2 on cycle day 2 and 3 following subcutaneous administration of leuprolide acetate[57] or FSH increase 2 hours after buserelin injection.[58] Patients with greater elevations of E2 have correspondingly higher pregnancy rates. Four GAST E2 patterns have emerged :

1. prompt E2 elevation, then decrease by cycle day 4
2. delayed E2 rise with fall by cycle day 6
3. persistent E2 elevation
4. no E2 response after GnRH-a

Clinical pregnancy rates for these groups were strikingly different: 46%, 38%, 16%, and 6% were observed in patterns 1 through 4, respectively.[59]

In summary, GAST has been a better predictor of the functional abilities of the ovary than either FSH or age.[57] Because the GnRH-a is costly and involves an injection and repeated blood tests, the GAST is not widely used in clinical practice. However, in recent study, simultaneous evaluation of basal FSH and estradiol response to GnRH-a can be useful in

identifying subcategories of women with reduced ovarian reserve who may benefit from reduced GnRH-a administration and a higher starting dose of gonadotrophin.[60]

Ultrasound assessment

Ovarian volume and number of antral follicles

During a woman's life, ovarian volume changes from 0.7 cm^3 at the age of 10 years to 5.8 cm^3 at the age of 18 years. However, at the age of 40 years the ovaries tend to decrease in size, and they decrease even further after menopause.[61] The ovary reduces in size with increasing age, regardless of whether the woman has given birth.[61] Lass et al. also found that the lower the ovarian volume, the greater the dose of fertility drugs required to stimulate the ovaries.[62] Ultrasound ovarian volume has also been used to predict the risk for ovarian hyperstimulation syndrome.[63] However, it has been theorized that ultrasound ovarian volume done at the beginning of the treatment cycle is more closely related to the number of follicles found during the pre-treatment period rather than the number of follicles developed during treatment.[64]

By allowing physicians to view the ovaries and assess the number of follicles, transvaginal ultrasound assessment of ovarian volume is quick, accurate and cost-effective. It is uncertain that ovarian size or follicular number is a better indicator of ovarian reserve. Studies to clarify the relative predictive value of follicular number and ovarian size have yet to be done. Among patients taking GnRH-a before a treatment cycle, abnormally high E2 levels are often associated with large ovarian cysts. Such E2 elevations may be improved by short-term continuation of GnRH-a. Using this approach, the cyst frequently resolves and the treatment cycle can continue. It is important to note that the additional GnRH-a exposure during this brief interval has not been associated with significantly reduced response to fertility drugs, nor has it adversely affected pregnancy rates.[65] In conclusion, decreased ovarian volume and low number of ovarian follicles are signs of ovarian ageing that may be observed earlier than a rise in FSH concentrations. Small ovaries are associated with poor response to superovulation and a high cancellation rate in IVF.[62,66-69]

Measurement of ovarian stromal blood flow

Measurement of ovarian stromal blood flow has been introduced to predict ovarian responsiveness and outcome of in vitro fertilization treatment.[70]

Ovarian biopsy

In spite of the abundance of studies and recent comprehensive reviews on indirect tests for predicting ovarian reserve,[71,72] there are still doubts about their accuracy and interpretation.[73] Recently, novel method of quantifying the number of small follicles in ovarian biopsies from infertile patients was introduced.[74] Because follicles are found no deeper than 2 mm from the ovarian cortex, only a shallow biopsy is required. It was demonstrated that follicular density decreases significantly with increasing age. Women >35 years of age have only one third of the concentration of follicles of younger women. When the results of ovarian biopsy was compared with the results of other tests for ovarian reserve i.e. basal FSH, CCCT and GAST, none of the tests accurately reflected the ovarian reserve.[75] In conclusion, several methods have been developed to estimate the functional or biological age of the ovary. Since ovarian reserve can vary over time, any results suggesting limited ovarian reserve should be confirmed by further testing in subsequent months. It may be that inflammatory, infectious or autoimmune conditions are contributing to the abnormal results. Such potentially reversible causes of low ovarian reserve should be corrected, particularly in younger woman. The interpretation and applicability of these tests to a particular patient are very important. Some tests have been validated as useful indicators of success rates in women undergoing assisted reproduction and have never been studied outside this context. Therefore, they may not be useful measures of reproductive potential in attempting spontaneous conception. Measurement of basal FSH and a provocative test of FSH suppression, the clomiphene citrate challenge

test, are very useful and have been applied clinically as prognostic indicators of ovarian reserve. However, further researches are needed to focus on the validity of ovarian reserve tests and the extent to which such tests predict subfertility. When ovarian reserve testing confirms compromised ovarian reserve, it is important to point out that the likelihood of success with infertility treatment is low. Such patients may want to consider other options, such as donor-egg treatment.

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