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EDITORIAL

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Assessing ovarian preserve

Introduction

Controlled ovarian stimulation is individualized according to the purpose of stimulation (intrauterine insemination, in vitro fertilization or oocyte donation) and an assessment of ovarian reserve. Both the quantity and quality of eggs are strong influences on treatment outcome. Ovarian physiology and ageing forms the basis of assessing ovarian reserve. Numerous tests have been used to predict ovarian reserve. These are broadly grouped into clinical data (age, previous history), passive *tests* (hormonal assays, ultrasound), dynamic tests (clomiphene citrate challenge test, gonadotrophin analogue stimulating test, exogenous FSH ovarian reserve test) and histology (ovarian biopsy).

Clinical Data: Age

Increasing age is associated with decline in natural fecundity and pregnancy rates. The effect of maternal age on fertility has been the subject of considerable research. In one such study, pregnancy success rates as a result of intrauterine insemination (IUI) were evaluated in terms of maternal age. The poorest outcomes were consistently seen among women 36 years of age or older [1]. This observation was confirmed by data 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 years [2]. IVF treatments involving women aged 40 or older have been associated with fewer oocytes obtained per cycle, low estradiol (E2) on the day of hCG administration, and considerably lower embryo implantation rates when compared to women 32 years of age or younger. Even if pregnancy does occur in women who are 40 or older, there is a high risk for unfavorable outcomes. As maternal age increases, miscarriage occurs more frequently, as does the chance of fetal chromosomal abnormalities [3]. Age seems to be a better predictor of egg quality, implantation and miscarriage rate than merely the number of eggs retrieved in an IVF cycle [4].

Clinical data: Previous cycles

Recent studies have shown that a history of cancelled cycles due to poor follicular response in a standard stimulation protocol is a better predictor of cancellation in subsequent treatment cycles than age or FSH [5]. A multicentric retrospective study conducted in the USA reported pregnancy rates per cycle for cycles 1, 2, 3, 4 and over 4 to be 33.7%, 33.9%, 28.9%, 25.9% and 21.0%, respectively, the corresponding delivery rates were 27.0%,27.4%, 23.4%, 16.1% and 15.4%, respectively [6]. Couples should be informed that the chance of a live birth following in vitro fertilization treatment is consistent for the first three cycles of treatment, but that the effectiveness after three cycles is less certain.

Passive Tests: Basal FSH

As a woman ages, more FSH is produced in an attempt to force the aging ovary to respond. A rise in early follicular-phase FSH is also accompanied by a decline in oocyte quality. Subtle but measurable increases in FSH precede menopause by approximately five years in some women [7]. 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. Women undergoing IVF with a day 3 FSH of less than 15 mlU/ml were twice as likely to conceive as women with FSH values between 15 and 24.9 mIU/ml [8]. Other investigators confirmed these results, and FSH values emerged as superior to age as a method for determining ovarian reserve and IVF outcome [9]. Indeed, one series reported that when day 3 FSH levels exceed 20 IU/L, conception rates fell sharply [10]. Limitations of measurement of basal FSH include the lack of a clear cutoff point, monthly variations and disparities between different laboratory assays [11].

Passive Tests: Other hormonal assays

It has been suggested that measurement of basal estradiol in addition to FSH might improve prediction of ovarian response compared with basal FSH and chronological age alone. Evidence suggests that elevated early follicular E2 levels are associated with poorer prognosis [12].

Early follicular inhibin B correlates inversely with early follicular FSH levels in perimenopausal women and has been nominated as an early indicator of decreasing ovarian reserve. One center observed that when day 3 inhibin B was less than 45 pg/mL, the response to fertility treatment was lower, the cancellation rate was higher, the number of retrieved oocytes was less, and the pregnancy rate was significantly reduced

when compared to subjects with day 3 inhibin B values greater than or equal to 45pg/mL [13]. Serum AMH levels may be used as a marker of ovarian reserve, representing the quantity and quality of the ovarian follicle pool [14]. In women, Anti Mullerian Hormone (AMH) is solely produced by the granulosa cells of growing preantral and small antral ovarian follicles. Its use in ovarian response assessment is experimental.

Ultrasound

The number of antral follicles in the early follicular phase correlates with ovarian reserve. Low numbers of antral follicles are a sign of ovarian ageing, and are observable earlier than a rise in FSH serum level. It has been proposed that Antral Follicle Count (AFC) is possibly a better prognostic indicator than age or endocrine markers [15]. AFC is a better predictor of cancellation rates due to reduced egg production than pregnancy rates. This suggests that it predicts oocyte quantity but not quality.

Ovarian size decreases with age. Sonographic measurements of ovarian volume have been shown to be important predictors of success of ovulation induction and pregnancy rates. Small ovaries are associated with poor response to superovulation and a high cycle cancellation rate in IVF [16].

Ovarian stromal blood flow has also been studied as a predictor of ovarian reserve. Measurement of ovarian stromal peak systolic velocity (PSV) by transvaginal pulsed Doppler ultrasound after pituitary suppression correlates well with ovarian response [17].

Dynamic Tests

The purpose of dynamic tests is to study various hormone markers in response to ovarian stimulation. In theory, these tests were designed to detect low ovarian reserve that would not be discovered by a single FSH and/or E2 measurements. The Clomiphene Citrate Challenge Test (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. Serum FSH level is measured on day 3 of the menstrual cycle, and then 100 mg of clomiphene citrate is given daily from day 5 to day 9. An elevated day 10 FSH indicates an abnormal test. Several investigators have confirmed the good predictive value of CCCT before treatment. One study found CCCT to be a better predictor of ovarian reserve than day 3 FSH measurement alone [18]. Similar tests have been devised with administration of GnRH agonist and FSH. However, since these involve multiple hormone assays, the use of expensive agents and usually do not add much extra information to basal hormone testing, their use in clinical practice is limited.

Ovarian Biopsy

This measure of ovarian reserve is strictly theoretical. The number of follicles per unit volume of cortical ovarian tissue can be calculated and defined as follicular density. However, ovarian biopsy is somewhat restricted in that, apart from the invasiveness of the procedure, a shallow biopsy specimen may inaccurately represent follicular density of the whole ovary. There is also the risk of inducing adhesions and distorting the tuboovarian relationship.

Conclusions

Various means of predicting ovarian reserve have been identified. Of these, age, basal FSH and ultrasound estimates of antral follicle count are the most useful. The predictive power of these markers for delivery is low but they are important tools for picking the right stimulation protocol. As a rule of thumb, basal FSH and AFC are better predictors of ovarian reserve in terms of oocyte number. Age is a better predictor of implantation and potential of resulting embryos. The apparent strength of one marker over the other in any particular study has more to do with range of FSH levels and age and stimulation protocols than any underlying physiological principles. They should be used in conjunction to predict ovarian response and pregnancy rates. The place of dynamic ovarian reserve testing is limited.

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