Review Article

OVARIAN RESERVE AND REPRODUCTIVE AGE

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SUMMARY

Ovarian reserve is an estimate of the primordial follicle pool in the ovaries and is indicative of the reproductive age of a woman. This estimate helps in assessing a woman's reproductive potential, in predicting her possible response in assisted conception, and in screening women for "early ovarian ageing" as a possible cause for subfertility.

Over the years, several methods have been used for its determination. These include biochemical parameters such as estradiol, FSH/LH levels and ratio, inhibin-B and anti-mullerian hormone levels, sonographic measurement of ovarian volume, antral follicle count and follicular volume, dynamic tests of ovarian function, and ovarian biopsy.

In this paper these methods are briefly described, and their advantages and disadvantantages are discussed with a view to finding accurate, available and easily reproducible methods for assessing ovarian reserve.

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KEY WORDS: Ovarian reserve, Reproductive age.

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INTRODUCTION

Ovarian reserve is an estimate of the primordial follicle pool in the ovaries. It is an indication of reproductive age, as opposed to chronological age, and is a parameter for calculating reproductive potential and the remaining reproductive life span of a woman.[1,2]

The human ovary contains a fixed pool of primordial follicles, maximal at five months of intrauterine life, and numbering around 701,000 at the time of birth.[3] From this number, the pool reduces to 250,000-300,000 at the time of menarche,[4] and then declines with increasing age.[5] At 37-38 years, it contains about 25,000 follicles; and at this number, the follicular depletion accelerates, and menopause is estimated be about 12-14 years away (occurring at a mean age of 50-51 years)[3], when only a few hundred or thousand follicles remain. This age may vary in different populations, and according to a study conducted in Lahore, it was found to be 49±43.6 years in Pakistani women.[6] This model of decline has, however, been modified to one which assumes a single exponential decline, which is more biologically plausible.[5,7]

Follicular depletion occurs largely due to atresia,[8] and is accompanied by a reduction in ovarian volume, which is thus also related to age. In an 'Ovarian Cancer Screening' programme[9] conducted at the University of Kentucky, involving 13,963 women who underwent transvaginal sonography annually, a statistically significant decrease in ovarian volume was shown with each decade of life from 30 to 70 years.

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Follicular depletion and reduction in ovarian volume leading to decrease in fertility apply both to spontaneous as well as assisted conceptions.[4,10] The decreased fertility with increasing female age appears to involve several factors besides attrition and utilization of follicles, such as diminution in quality of existing oocytes (partly due to increased aneuploidy because of factors such as changes in spindle integrity), and a reduction in the frequency of intercourse.[7]

A mathematical model of decline constructed by Faddy and Gosden[5] provides an estimate of the follicle pool at any age; it can be used to assess a woman's chances of spontaneous conception and possible outcome in assisted conception; it also offers the possibility of screening women for 'early ovarian ageing' which currently affects 10% of the general population,[3] and may be an important cause of infertility in these individuals. It would also assist in predicting the possibility of a pregnancy in women who have survived childhood leukaemias,[11,12] and in counseling those considering delaying childbearing for any reason.[3]

METHODS IN USE FOR THE ASSESSMENT OF OVARIAN RESERVE

Various methods have been proposed and are currently used for the assessment of ovarian reserve.[10] These include biochemical markers such as basal follicle stimulating hormone (FSH), luteinizing hormone (LH),[13] ratio of FSH/LH[14], oestradiol (E_2),[15] inhibin–B[16] and anti-Mullerian hormone (AMH);[17,18] ultrasound measurements such as ovarian volume, antral follicle count[19,20] and ovarian stroma blood flow;[21] dynamic tests of ovarian function such as clomiphene citrate challenge test (CCCT),[22,23] exogenous FSH ovarian reserve test (EFORT)[24,25] and GnRH agonist stimulation (GAST).[26] Finally, an ovarian biopsy to determine follicular density directly assesses ovarian reserve.[27]

Some of the commonly used methods are described below.

a) Biochemical Parameters: With ovarian ageing, levels of oestradiol (E_2) and inhibin B decline, while those of FSH rise.[28] These markers constituting the classical hypothalamus–pituitary-gonadal feedback loop are interdependent.[29] The levels of serum AMH, a recently added marker,[17,18,30-34] also decline with age, with the decrease occurring earlier than changes in FSH or inhibin-B levels.

b) Ultrasound: During the past three decades, ultrasound (especially transvaginal scanning) has proved a valuable imaging technique, allowing visualization of the pelvic structures, including an assessment of their size and an evaluation of morphology.[35]

The sonographic variables used for assessing ovarian function include ovarian volume,[36-38] antral follicle count (AFC)[19,20,39], follicular volume,[2] and size of uterus and thickness of endometrium.[40] Ovarian volume, and the antral follicle count in the early follicular phase give an indication of ovarian reserve, whereas the size of the uterus and thickness of endometrium provide an indirect estimate of circulating ovarian hormones.

Total ovarian volume (calculated for each ovary by applying the formula for an ellipsoid) is a sum of the volumes of the two ovaries, AFC is a sum of follicles measuring 2-10 mm in diameter in both ovaries; the total follicular volume is a sum of the volumes of all the follicles up to 10 mm in diameter in both ovaries.[2] The total ovarian volume and AFC have been negatively correlated with age and decrease linearly with advancing age;[4,35,39] the total follicular volume also decreases with age (due to follicular atresia), though the mean follicular volume increases in later years.[2]

c) Histological Assessment: An ovarian biopsy provides a direct assessment of follicular density.[27,41,42] However the distribution of follicles in ovarian tissue has been found to be extremely uneven, differing from patient to patient and from sample to sample from the same ovary.[42] Thus, while the presence of follicles is reassuring, their low density does not necessarily indicate a low reserve. In addition, the procedure carries the risk of later adhesion formation.

DISCUSSION

The determination of ovarian reserve is a relatively new concept and has important applications in assessing reproduction potential, including prediction of success in assisted conception. Numerous tests and markers have been proposed for its assessment, their very number indicating that no satisfactory method for its assessment is available yet. In fact, a comprehensive systematic review of literature by Kwee et al[43] concluded that the ovarian reserve tests known to date have "only modest-to-poor predictive properties."

Of the biochemical variables, serum FSH, LH and E_2 levels are in common use for investigating subfertility and monitoring ovarian stimulation cycles. Raised FSH levels indicate a low ovarian reserve, but are a late finding, after considerable follicular depletion has occurred. Elevated day 3 FSH/LH ratios (>3) due to low LH concentration predict a reduced ovarian response.[14] Serum AMH is valuable; expressed in granulosa cells of growing follicles, its expression is strongest in small antral follicles, and is lost in large antral follicles.[31] Its level reflects the follicle population and is not influenced by the gonadotropic status.[17,24,44] It correlates strongly with the AFC,[17,33] and in contrast with other serum markers, remains relatively constant during the menstrual cycle.[33-35] Its level declines earlier than that of FSH and inhibin B;[26] it may, therefore, be more useful than other parameters in detecting ovarian ageing early.

A difficulty with all these biochemical variables is that they test the number of developing follicles which may not reflect the number of primordial follicles.[7]

Of the ultrasound variables, the two important ones are ovarian volume and AFC; both have been found to correlate negatively with advancing age.[2,9,39] They have also been found to be reduced in subfertile women in comparison with fertile women of the same age. They may also be decreased in young females of reproductive age due to early ovarian ageing, this being a possible cause for their subfertility[3,35]

In the "Ovarian cancer screening" programme conducted at the University of Kentucky,[9] the mean ovarian volume was 6.6 ml in women <30 years of age, 6.1 ml in women 30-39 years, 4.8 ml in those aged 40-49 years, 2.6 ml in the group 50-59 years old and 2.1 ml in women aged 60-69 years. Overall, the mean ovarian volume was 4.9 ml in premenopausal women and 2.2 ml in postmenopausal women.

Scheffer et al[2] compared the mean values and ranges of several endocrine and sonographic parameters for 3 age groups: young (25 – 34 years), middle (35- 40 years) and old (41 – 46 years). They found that values of all endocrine variables (with the exception of inhibin B) in the old age group differed significantly from those in the young group. Ovarian volume also decreased with age (being 7.4, 7.0 and 5.2 ml respectively in the three age groups), that in the oldest women differing significantly from those in the two younger groups. Importantly, the number of antral follicles showed a significant difference in all three groups (being 15, 9 and 4 respectively). In addition, total follicular volume decreased with increasing age (0.71, 0.58 and 0.39 ml), though this was less steep than the fall in AFC.[2] Ruess et al[45] too, reported a significant reduction in AFC with age in a group of women 22 – 42 years of age. These differences were independent of the stage of the menstrual cycle. The AFC, therefore, may be a sensitive parameter for assessing ovarian reserve, and its use as a single test for predicting response to controlled ovarian stimulation seems rational.[37,42]

Another notable finding in Scheffer's study[2] was an increase in mean follicular volume with increasing age, being almost double in the old group as compared with the younger groups (0.05, 0.06 and 0.09 ml). Values of E_2 also correlated positively with age, being 195 and 206 pmol/l in the younger women, and 278 pmol/l in the older women. Thus, while the number of antral follicles and total follicular volume decreased in the older women, the mean follicular volume increased and E_2 production also increased. This phenomenon suggests accelerated growth of antral follicles,[44] or more advanced follicular growth[2] in older women.

The size of the uterus and the thickness of the endometrium, measured sonographically,

give an indirect estimate of oestradiol secretion, and can be used as a bio-assay of follicular oestradiol production.[46] Ovarian biopsy[47] as a test of ovarian reserve is no longer recommended as the distribution of follicles in ovarian tissue was found to be extremely uneven,[42] and quantitative counting of primary follicles did not provide information about the quality of the oocytes embedded in them,[42,48] which is an important factor in predicting reproductive potential. The value of this procedure has therefore been questioned[49] and it is now no longer carried out for these reasons, and because of its invasive nature and the risk of later adhesion formation.

CONCLUSION

Several methods are available for assessing ovarian reserve. Of the biochemical tests, inhibin–B and AMH levels are valuable, but are expensive and performed by only a few laboratories in Pakistan. The gonadotropins FSH and LH, and the ovarian hormone oestrogen indirectly determine the adequacy of hypothalamic-pituitary-gondal axis (and hence ovarian reserve) and may be used in conjunction with other techniques, such as ultrasound. Sonographic measurement of ovarian volume and antral follicle count is an accurate direct method, which is easily performed, reproducible, readily available, besides being non-invasive.

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