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ORIGINAL ARTICLE

The value of different ovarian reserve tests in the prediction of ovarian response in patients with unexplained infertility

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Abstract *Background:* Ovarian reserve tests in unexplained infertility patients before management either by ovulation induction or IVF program are a worthy procedure as it saves unnecessary procedures, induction complications, canceled cycles, wasted resources and emotional stress to the couple in case of low estimate, and can as well help in adjusting the doses to obtain the most appropriate response. *Aim of work:* To determine the value of mean ovarian volume, AFC, maternal age, FSH and AMH in infertile patients undergoing ovulation induction or IVF cycles. Primary outcome is to predict the best parameter of ovarian reserve. *Design:* Prospective cross-sectional study. *Patients and methods:* One hundred infertile women received treatment in the form of induction of ovulation and timed intercourse/IUI or IVF. They had basal FSH, AMH, AFC and mean ovarian volume assessment. The response was then evaluated according to the number of follicles on the day of hCG or the number of oocytes retrieved in IVF cycles. *Results and conclusion:* The total AFC and AMH are found to correlate significantly with the ovarian response with p values < 0.001 and 0.03 respectively, indicating that they are good predictors of ovarian reserve. The basal FSH and ovarian volume do not correlate with the ovarian response indicating their poor value as predictors of ovarian reserve.

1. Introduction

Ovarian reserve refers to the residual oocyte–granulosa cell repertoire that, at any given age, is available for procreation. Both quantitative and qualitative deterioration in the oocyte complement, and therefore a waning ovarian reserve, are recognized phenomena associated with advancing age (1).

Ovarian reserve tests and prognostic markers are indirect measurement of a woman's remaining follicular pool and give an estimate of her sensitivity to ovarian stimulation and her

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prognosis for success with fertility treatments. They cannot be used to predict future fertility or the exact timing of the decline or cessation of fertility (2).

A spectrum of markers prognostic of ovarian reserve is validated to varying degrees in the infertile population. These include biochemical markers (FSH, estradiol-E2, inhibin B, AMH, FSH-LH ratio) (3) and ovarian morphometric markers (ovarian volume, antral follicle count, and mean ovarian diameter) (4) that are assessed in the early follicular phase (basal) of the menstrual cycle except for AMH. Several studies showed that AMH is a better marker and is superior to other markers. Since serum AMH levels reflect the ovarian follicular pool, any reduction in serum AMH level indicates reduction in the number of small growing follicles (5).

Recent studies have shown that AMH and the antral follicle count are equally effective in predicting poor ovarian response in an IVF program (6). In addition, it has been demonstrated that performing both together does not increase the predictive power (7). Choosing which test to implement is primarily based on convenience, acceptability and cost.

This study aimed at prediction of the best parameter from the different ovarian reserve tests for prediction of ovarian response in infertile patients receiving induction of ovulation.

2. Materials and methods

This is a prospective cross-sectional study including 100 women diagnosed with infertility and seeking management in the form of induction of ovulation and timed intercourse/IUI or IVF. The study was conducted in Alkasr Alainy hospital and the Egyptian IVF centre from February 2013 to September 2014.

Patients included were $\leqslant 40$ years old, seeking infertility management after one year of unprotected intercourse and without the use of contraception and those diagnosed as unexplained infertility having normal uterine cavity demonstrated by normal ultrasound and HSG, patent tubes proved by HSG, normal ovarian function proved by regular cycles and normal semen parameters according to WHO 2010 criteria (8).

Patients excluded were those having an ovarian cyst or follicle measuring more than 10 mm on the day of measuring the AFC, in order not to bias the basal AFC or the number of leading follicles counted to detect response. Those with history of ovarian surgery, endometrioma excision or ovarian drilling were excluded as well, to exclude the effect of the surgery on the ovarian reserve.

Ethics committee approval and written consent from the patients were obtained.

All the patients prior to the start of IVF cycle or induction of ovulation program were subjected to full history taking and systemic clinical examination to assess the general condition and local pelvic examination. General disease as a contraindication to induction or pregnancy was excluded, such as stage 3 & 4 cardiac patients, uncontrolled diabetics or hypertensive or any medical problem contraindicating pregnancy and labor. Quantitative assessment of basal serum level of Follicle stimulating hormone (FSH) (by ELIZA, Immulite 2000 analyzer, Siemens) on days 3–5 of the cycle was done as well as quantitative assessment of serum anti-mullerian hormone (AMH) (by the AMH ELIZA two site immunoassay, Beckman Coulter Kit, Beckman Coulter). Transvaginal ultrasound using 7.5 MHz intracavitary probe (SIUI, Voluson, Mindray N3 and Z5) was performed on days 3–5 of the menstrual cycle to assess the basal antral follicle count (AFC) and the ovarian volume using 2D ultrasonography.

For the ovarian volume, three rotatable perpendicular planes (frontal, median sagittal and horizontal) were displayed for each ovary to obtain the largest dimensions, then the volume was calculated by a built-in computer program. Each ovarian volume was recorded and the mean ovarian volume was recorded.

For the antral follicle count, the stromal area of each ovary was meticulously examined and the number of antral follicles (2–10 mm) was carefully obtained.

For those receiving ovulation induction protocol, they started clomiphene citrate 50 mg tablets (Clomid, Aventis) from day 5 of the cycle taking 4 tablets daily for 5 days, then started HMG injections (Menogon, Ferring Pharmaceuticals) 75 IU/day every other day from day 9 of the cycle and followed up by ultrasound scan every other day to count the number of ovarian follicles and adjust the dose accordingly. When leading follicle reaches 18–20 mm, hCG (Choriomon 5000 IU, Ibsa) was administered. The patients were advised for timed intercourse every other day (9). In case of missing period, a pregnancy test was done in urine and clinical pregnancy was confirmed by the presence of gestational sac(s) and fetal pole(s) with positive pulsations by ultrasonography at 7 weeks.

For those undergoing IVF cycles,
one of the following protocols was applied:

The long protocol: they started GnRH agonist (Decapeptyl, Ferring Pharmaceuticals) during the midluteal phase, day 20 of the cycle then subsequent gonadotropins (Menogon, Ferring Pharmaceuticals) treatment is started after confirmation of downregulation when E2 levels are low after 14 days of GnRH agonist administration. HMG (dose is set based on patients age, BMI and past history) is started initially for one week and then monitoring of ovulation, based on response the dose is adjusted according to the age, results of ovarian reserve and continued based on the response (5).
The short (flare-up) protocol: Sequential treatment with GnRH agonists started on day 1 and gonadotropins from day 3 according to the response till the day of hCG administration (5).
The ultrashort protocol: The GnRH agonist is used for 3 days starting from day 1 then stopped. Gonadotropins treatment then follows till response is obtained. This was prescribed for patients with expected poor response, low AMH, and previous poor ovarian response to induction and they usually started with a high dose of 375–450 IU (10).
The antagonist protocol: Gonadotropins were started from day 3 of the cycle then GnRH antagonist (Cetrotide, Merck Serono) is started from day 6 or when leading follicle is 16 mm and continued till response is obtained (11).

When > 3 follicles were 18 mm or more, 10,000 IU hCG injection was given, TV ultrasound guided ovum pick-up was