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Review Article

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Poor Ovarian Responder: A Challenge

Gita Khanna[1]*, Trishya Reddy[2], Farhat Kazim[3] and Arti Gupta[4]

[1]*Scientific Director – ART Unit, Ajanta Hospital & IVF Centre, Lucknow, India*

[2]*Resident (OBGYN), Ajanta Hospital & IVF Centre, Lucknow, India*

[3]*Consultant, Ajanta Hospital & IVF Centre, Lucknow, India*

[4]*Clinical Embryologist, Ajanta Hospital & IVF Centre, Lucknow, India*

***Corresponding author**

Gita Khanna, Scientific Director – ART Unit, Ajanta Hospital & IVF Centre, Lucknow, India, E-mail: ivf@ajantahospital.com

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Introduction

Assisted reproductive technology (ART) is rapidly progressing field with many new advances in the last decade in terms of clinical knowledge and technological development. The number of oocytes obtained after controlled ovarian stimulation is of central importance to reach the success in IVF. Poor ovarian responder poses a great challenge to present era of reproductive medicine. It is an important limiting factor in success of any treatment modality for Infertility. It indicates a reduction in quantity and quality of oocytes in women of reproductive age group. Evaluating Ovarian Reserve and individualizing the therapeutic strategies are very important for optimizing success rate. Early detection and active management are essential to minimize the need for egg donation.

Incidence

10% of the women undergoing IVF will show poor response to gonadotrophin stimulation [1-3]. The incidence of poor ovarian responders among infertile women has been estimated at 9-24% but according to recent reviews, it seems to have slightly increased [4]. Data from ASRM/SART registry showed that of 14.1% of initial cycles cancelled at least 50% of these were poor responders [5]. Diminished ovarian reserve is a phenomenon often noted in women in their mid to late thirties, but it may affect younger women as well. It is believed that there is an accelerated decline in follicular pool at the age of 37–38 when it reaches below a critical of 25,000 [6]. Subsequently, there remains a very limited time for conception with one's own eggs. It is believed that this phenomenon is accompanied by a declining quality due to aging oocytes, and hence, young women with POR may have better chance at conception [7, 8]. However, recent evidence challenges this and POR may be associated with low pregnancy rates irrespective of age and a high pregnancy loss. [9-13].

How to define POR?

Majority of attempts at definition of POR have considered certain parameters noted during ovarian stimulation for IVF: [14- 20]. In fact a review in 1999 had already documented 35 definitions of POR.

- Low peak estradiol concentration following conventional ovarian stimulation [300 to 500 pgm/ml]
- Low number of follicles [<5]
- Less number of retrieved oocytes [<5]
- Some define age of >40 years, previous poor response for diagnosing POR.

The dilemma

Due to lack of universally accepted diagnostic criteria for POR, Bologna criteria have been introduced following consensus meeting of ESHRE Working Group on POR definition held in 2011 [21].

Bologna Criteria recommends the presence of at least two of the following three features for diagnosis of POR-

• Advanced maternal age [> 40 years] or any other risk factor for POR

• A previous Poor Ovarian Response [<3 oocytes with conventional stimulation protocols]

• An abnormal Ovarian Reserve Test [i.e. AFC 5-7 follicles or AMH between 0.5 – 1.1 ngm/ml]

The main points of debate and concern regarding Bologna Criteria [22, 23, 24].

- Homogeneity of population.
- Cut off values for age, number of retrieved oocytes, AFC and AMH
- Risk factors other than age
- Oocyte quantity versus quality?
- Over Diagnosis
- Large-scale validation

The POSEIDON GROUP [Patient Oriented Strategies encompassing Individualized Oocyte Number] was recently established to focus specifically on the diagnosis and management of low prognosis patients [25].

Etiopathogenesis

Reproductive ageing is a continuous process from before birth till menopause. Women have a finite number of germ cells whose number is maximum at 6-7 million by 20 weeks of gestation. After this throughout reproductive life; an irreversible attrition progressively decreases the germ cell pool of Gonads. Women beyond 30 years of age have shown fertility decline gradually due to reducing primordial

follicular pool as a result of ovulation but predominantly because of follicular atresia. Non Growing follicular pool at different ages may have a differing response to changes in hormone levels associated with age. Women of all age groups with Non Growing follicles below the normal range would have a suboptimal response to ovarian stimulation and lead to a reduced reproductive life span. These women would undergo an early menopause considering a fixed time interval between end of fertility and menopause.

Association of poor ovarian response

- Short menstrual cycle length
- Solitary Ovary
- Previous Ovarian Cystectomy
- Chronic Smokers
- Unexplained Infertility
- Previous Chemotherapy and Radiotherapy
- Genital Tuberculosis
- Uterine Artery Embolization for Fibroids
- Ethnicity: Indian Women undergoing IVF, Ovarian ageing was found to be approximately 6 years older [26].

Genetic risk factors

- Family history of Premature Menopause
- Fragile X mental retardation 1[FMR1]
- FSH Receptor [FSH R] Polymorphism is considered to be important cause of unexplained Poor Ovarian Response in young women

Predictors of POR

It is of extreme importance to predict who will be a poor responder, because stimulation protocols should be ideally individualized accordingly. There are several tests proposed to predict ovarian reserve, which can give an idea about the ovarian response [27-30].

a) Static tests

These are biochemical testing of ovarian reserve based on a single measurement of early follicular phase [cycle day 2-4].

- Serum FSH High levels [>12 or >15 mIU/ml] on cycle day 2 or 3.It is only screening test
- Serum estradiol [E2] Elevated levels [>30 – 75 pgm/ml] on cycle day 2 or 3.Limited by its very low predictive accuracy for poor response
- Serum INHIBIN-B Decreased levels [45pgm/ml] on cycle day 2 or 3.Accurate only at a very low threshold level
- Insulin like growth factor 1 (IGF 1)- Low levels of IGF-1 in follicular fluid are poor predictor in follicular fluid
- AMH: Glycoprotein produced by the granulose cells within preantral and early antral follicles. Serum AMH has become an increasingly popular and established method for assessment of ovarian reserve

Sonographic tests

- Ovarian Volume- Decreased ovarian volume is hardly suitable as a routine test for ovarian reserve assessment
- Antral follicle count (AFC)- AFC's less than 4 are more likely to have cancelled cycles

b) Dynamic tests

Clomiphene challenge test [CCT], Exogenous FSH ovarian reserve test [FSHORT] and GnRH agonist stimulation test [GSAT] are Dynamic tests but evidence suggests that dynamic tests should be abandoned.

Diagnosis of POR

Poor ovarian responder have a lower pregnancy rate and higher pregnancy loss as compared to age-matched controls with normal ovarian reserve, so it is important to identify age related POR or otherwise [31]. To assess ovarian reserve several ovarian reserve tests (ORTs) should be been done so as to predict response to ovarian stimulation [32, 33]. Advance age is directly related to declining oocyte leading to reduced pregnancy and live birth rate in IVF [34, 35]. POR may occur in young women also, so other markers of ovarian reserve should be tested to exclude such women from others having unexplained infertility. Elevated basal follicle-stimulating hormone (FSH) is one of the earliest ORTs found to be associated with poor response. However, a normal FSH does not exclude poor response and elevation happens relatively late in the course of declining ovarian reserve. Hence, basal FSH is not an ideal test to identify poor responders [36]. The most sensitive markers of ovarian reserve identified till date are Antral follicle count (AFC) and Anti-Mullerian hormone (AMH) ideal for planning personalized controlled ovarian stimulation protocols. These sensitive markers permit prediction of the whole spectrum of ovarian response with reliable accuracy and clinicians may use either of the two markers as they can be considered interchangeable [37]. AFC is defined as the number of follicles smaller than 10 mm in diameter detected by Transvaginal Sonography in early follicular phase. AFC less than 4 is discriminatory for POR. Serum AMH seems to be a better predictor of overall ovarian response and poor response compared to FSH and age, thought it cannot be the absolute predictor, levels of 2 pmol/L or 0.28 Ngm/ml is also discriminatory for POR [38].

The POSEIDON Criteria was recently established in 2016 by a group composed of Reproductive Endocrinologists and Reproductive Medicine Specialists from 7 countries. They proposed a new stratification to classify patients with reduced ovarian reserve or unexpected inappropriate ovarian response to exogenous gonadotrophins [25].

These 4 subgroups are based on quantitative and qualitative parameters:

- Age and expected Aneuploidy rate
- Ovarian Biomarkers i.e. AFC and AMH
- Ovarian Response, in the previous stimulation cycle

GROUP 1: Young patient <35 years with adequate ovarian reserve parameters (AFC >5; AMH >= 1.2ng/ml) and with an unexpected poor or suboptimal ovarian response.
Subgroup 1a: <4 oocytes (after standard ovarian stimulation)
Subgroup 1b: 4-9 oocytes retrieved (after standard ovarian stimulation)
GROUP 2: Older patients ≥ 35 years with adequate ovarian reserve parameters (AFC>5; AMH>1.2 ngm/ ml) and with an unexpected poor or suboptimal ovarian response
Subgroup 2a: <4 oocytes (after standard ovarian stimulation)
Subgroup 2b: 4-9 oocytes retrieved (after standard ovarian stimulation)
GROUP 3: Young patients (<35 years) with poor ovarian reserve pre stimulation parameters (AFC < 5, AMH <1.2 ng/ml)
GROUP 4: Older patients (≥ 35 years) with poor Ovarian reserve Pre-stimulation parameters (AFC < 5, AMH <1.2 ng/ml)

Management

Despite the fact that in last two decades large number of papers have been published in the literature, so far it has been impossible

to identify any efficient treatment to improve the ovarian response and the clinical outcome. However, the approach to management can be divided into Pretreatment, Protocols for Controlled Ovarian Stimulation and Adjuvant Treatment.

a) Pretreatment

Pretreatment with oral contraceptive pills [OCP], Progesterone and Ethinyl Estradiol is used with the aim to improve follicular synchronization, prevent premature ovulation, reduces cyst formation, and shortens the length of stimulation and schedule cycles. OCP is started from day 3/4 of previous cycle given for a minimum of 21 days and maximum of 42 days. Progesterone [Medroxy progesterone acetate 10 mg] twice daily from day 15 of cycle preceding IVF treatment for a period of 2-3 weeks. Cochrane review on OCP Pretreatment found fewer clinical pregnancies and a higher amount of gonadotrophin therapy required. Therefore routine use of OCP in Poor Responders may not be advisable [39, 40].

b) Protocols

Although many protocols with different doses types of gonadotrophins have been proposed but the mystery of ideal protocol still remains to unfold! To date there is no really efficient treatment that could solve the problem of poor ovarian response and the current question is still which is the ideal protocol for patients defined as "poor responders"? The various protocols are:

- Gonadotrophins
- GnRH Analogues
- GnRH Antagonist
- Natural cycle / Modified Natural cycle
- Oocyte Cryopreservation.

c) Adjuvant therapy

- **Addition of estradiol in luteal phase:** The addition of estradiol in luteal phase with or without the simultaneous use of GnRH antagonist decreases the risk of cycle cancellation and increase the chance of clinical pregnancy improving synchronization of pool of follicles available for controlled ovarian stimulation [41-44].

- **Addition of androgens:** Evidence for role of androgens arises from pharmacological observations that testosterone, androstenodione and dihydrotestosterone can promote early follicular growth and enhance FSH mediated action.

- **Testosterone:** The effect of testosterone on follicular response is mediated by increasing FSH receptor activity and by stimulating IGF-1.This improves number of follicles recruited, oocytes retrieved, implantation rate, clinical pregnancy rates and decrease in cycle cancellation rates.

- **Dehydroepiandrosterone [DHEA]:** 48- 50 % of follicular fluid testosterone during ovarian stimulation comes from circulating DHEAS, and DHEA could therefore act as a precursor for testosterone in the follicular fluid. 75 mg/ day of DHEA causes improvement in AMH concentration, AFC, peak estradiol, number of oocytes retrieved, number of metaphase 2 oocytes and high quality embryos.

- **Growth hormone:** GH-releasing hormones increase the sensitivity of ovaries to gonadotropin stimulation and enhance follicular development. It enhances oocyte quality by accelerating and coordinating cytoplasmic and nuclear maturation. There are some propositions that GH-releasing factor supplementation may improve pregnancy rates in poor responders.

- **Recombinant LH:** LH maintains adequate concentrations of intraovarian androgens and promotes steroidogenesis and follicular growth. It has been proposed that addition of LH to ovarian stimulation protocol may benefit poor responders.

- **Vasoactive substances:** Vasoactive substances like aspirin and L-arginine enhance ovarian vascularity required for folliculogenesis, which could contribute to improved response in poor ovarian responders.

Is there an ideal stimulation protocol for poor responders?

Ovulation stimulation protocols for poor responders are constantly under review in an attempt to improve follicular recruitment and pregnancy rates. Retrospective studies comparing the efficacy of four different protocols including GnRH agonist [long, short and Miniflare] and GnRH antagonist on pregnancy outcomes in poor responders showed no significant differences in implantation, pregnancy and overall cancellation rates between four groups. Presently the commonly used protocol is gonadotrophin / GnRH antagonist. Addition of r-LH to ovarian stimulation protocol may benefit poor responders. Empirical use of adjuvants should be avoided. Pharmaceutical advances in recombinant technology resulted in introduction of corifollitropin alfa [A hybrid molecule with sustained FSH activity and reduced injection frequency] along with HP-HMG in a GnRH antagonist regimen may be a promising protocol in poor responders [45, 46].

Implications

Ovarian follicular pool undergoes progressive decline from before birth to menopause. Even though oogonial stem cells have been identified in adult ovaries, there is no conclusive evidence towards their contribution to size of follicular pool in postnatal period. The impact of poor ovarian responders is often seen in context of infertility, when time available to achieve pregnancy is limited. IVF in such patients offers highest probability for pregnancy. Irrespective of age women with poor ovarian response have lower pregnancy rates than those with normal ovarian reserve. With repeated attempts of failure, the only option is oocyte donation/adoption which imposes financial and emotional burden. Ovarian reserve testing should be offered to women who wish to delay childbearing in order to make an informed decision remains debatable. However AMH is being used to predict fertility potential of such women. These women can make a choice not to delay childbearing or may undergo IVF for vitrification of eggs/embryos. Over enthusiastic pelvic surgery for endometriomas and laparoscopic ovarian drilling in PCO may induce iatrogenic poor ovarian reserve. Besides fertility, poor ovarian responder women will have early menopause so long term health implications involving bone and cardiovascular status are to be considered.

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