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Review Article

Poor Ovarian Response: Diagnosis And Management

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ABSTRACT

Management of women with poor ovarian response is a challenging task for reproductive medicine clinicians, which limits the success of any treatment modality. The approach should rather be identification of expected poor responders and plan the stimulation protocol accordingly. In addition, these women should receive appropriate counselling and adequate psychological support too. Case based approach can help in effective management.

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INTRODUCTION:

Management of patients with "Poor Ovarian Response" or "Poor responders" is one of the most controversial and complex clinical challenge to the reproductive medicine experts which limits the success of any treatment modality for infertility. It is a condition of decreased quality as well as quantity of oocytes in women of reproductive age group. Poor Ovarian Reserve or Diminished (DOR/POR) depicts a woman at risk of poor outcome with ART (Artificial Reproductive Technique). The most extreme phenotype of DOR in young age is represented by Premature Ovarian Failure (POF) which is characterized by amenorrhea, hypoestrogenism and high gonadotropin levels in young women of less than 40 years of age.

The aim of this article is to define, predict, diagnose and manage women with "poor ovarian response".

Incidence-The incidence of poor responders is 9-24% of IVF cycles.[1] The incidence of spontaneous POF is 1%in less than 40 years of age, 0.1% in less than 30 years and 0.01% in less than 20 years of age.[2,3] Moreover the incidence of POF is on the rise in young women with the increase in cancer cure in pediatric population.[4]According to American Society of Reproductive Medicine(ASRM) data,14.1% patients showed initial cycle cancellation rate due to poor ovarian reserve and 50% were poor responders.

Definition-A systematic review of 47 randomized controlled trials have shown 41 different definitions of Poor Ovarian Response.[5]In 40% of these trials, the number of oocytes retrieved has been adapted as criteria of poor ovarian response. Most of the trials considered the following parameters during ovarian stimulation as predictors of poor ovarian reserve: low peak Estradiol concentration in conventional ovarian stimulation (300-500 pgm/ml), low number of Antral Follicle Count(<4) or less number of retrieved oocytes and age more than 40 years. Hence there was a lack of standardization and universality. Thus Ferrariti in 2011 introduced **Bologna Criteria** in consensus meeting of ESHRE working group on POR definition. **Bologna Criteria** is based on;(1)advanced maternal age(>40 years) or and other POR risk factor;(2) a previous incidence of POR; and (3) a low ovarian reserve test in terms of Anti Mullerian hormone(AMH) and Antral Follicle Count(AFC).[6] Two out of these criteria are needed to make diagnosis of POR. However, in addition, two cycles with POR after maximal stimulation are sufficient enough to classify a patient as poor responder even in the absence of the above-mentioned criteria.

Though this criterion helped in prediction of outcome of IVF thereby helping in couple counselling accordingly, yet it posed a problem in clinical trials as it tends to classify women with significantly different biological characteristics (hence different line of management) in one group.[7]

Thus, in order to achieve uniformity and improvement in the treatment outcome by suggesting case based clinical management, definition of POR which was based on heterogeneous criteria was shifted to the concept of "low prognosis". The **POSEIDON group** (**P**atient-**O**riented **S**trategies **E**ncompassing **I**ndividualized **O**ocyte **N**umber) suggested a new classification of ART in patients with a reduced ovarian reserve or unexpected inappropriate ovarian response to exogenous gonadotropins.[8] This group suggested 4 subgroups based on qualitative and quantitative parameters like (1) age and the expected aneuploidy rate; (2) ovarian biomarkers (AFC and AMH) and ;(3) ovarian response-provided a previous stimulation cycle was performed. This classification system gives more apt guidance to the treating clinician about optimal management of the patients according to the group in which they are classified. It also introduced a new measure of successful ART treatment i.e. the ability to retrieve the number of oocytes needed for specific patient to obtain at least one euploid embryo for transfer. It focuses specifically on diagnosis and management of "low prognosis" patients.

POSEIDON GROUP1:

Young patients<35 years with adequate ovarian reserve parameters (AFC>=5; AMH >=1.2 ng/ml) and with an unexpected poor or suboptimal ovarian response. Subgroup 1a: <4 oocytes* Subgroup 1b:4-9 oocytes retrieved* (* after standard ovarian stimulation)

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

POSEIDON GROUP 3:
Young patients (<35 years) with poor ovarian reserve pre-stimulation parameters (AFC<5;AMH <1.2 ng/ml)

POSEIDON GROUP 4:
Older patients (>=35 years) with poor ovarian reserve pre-stimulation parameters (AFC<5; AMH,1.2ng/ml)

Evaluation for poor ovarian reserve

Risk Factors:
It is very important to know the risk factors for poor ovarian response in a woman before subjecting her to any treatment modality.

Short menstrual cycle length, single ovary, history of ovarian cystectomy, history of chemotherapy or radiotherapy or genital tuberculosis, history of uterine artery embolization for fibromyomas, smoking, unexplained infertility or history of auto immune disease like hypothyroidism (25%), Addison's disease (3%) and Diabetes Mellitus (2.5%) are the known risk factors .Ovarian ageing has been seen to be about 6 years earlier in Indian women. Among genetic factors, family history of POF should be taken into account.

Age is another important factor. The higher the age, poorer is the quality and quantity of Ovarian Reserve.

Menstrual history should be recorded diligently. Many of them have abnormal menstrual history at the time of diagnosis. Sometimes they may just present with asymptomatic cessation of periods or lack of resumption of normal periods after a pregnancy or stopping of Oral contraceptive pills. The onset can be sudden. Primary POF is characterised by primary amenorrhea or oligomenorrhea in women less than 40 years with or without flushing. Those with primary amenorrhea generally have underlying chromosomal abnormality like deletions and translocations in X chromosome, X monosomy and FMR1 gene mutation (responsible for fragile X syndrome).

Symptoms:
Where on one hand patient with Iatrogenic POF (those due to surgery or anticancer therapy), are frequently associated with symptoms like vaginal dryness, depressive episodes and flushing, those with POF developing at earlier age (<20 years of age) do not frequently show these symptoms.

Other causes to be ruled out:
In all cases of amenorrhea to establish the diagnosis of POF, its mandatory to rule out other causes like pregnancy, PCOS, thyroid and prolactin abnormalities. Once diagnosis is reached try to find out the cause. Karyotyping can be advised for this.

Ovarian Reserve Assessment
This is very important to predict and to identify poor responders in the infertile female population as this will enable us to tailor a specific stimulation protocol for these women.

There are so many studies regarding this. There is currently no perfect ovarian reserve test. Both AFC and AMH have good predictive value and are superior to day-3 FSH.[9]

Serum Anti Mullerian Hormone (AMH):
It is a glycoprotein produced by the granulosa cells within the preantral and early antral follicles. Its value is independent of menstrual phase and is actually the most consistent marker of decline in reproductive potential and poor ovarian response.[10,11]

Antral Follicle Count (AFC):
It refers to the number of follicles<10 mm which can be detected sonographically in early follicular phase. AFC (<4) and AMH(2 pmol/L or 0.28 ngm/ml are discriminatory for POR.[11].Although there are several other tests too that can help in prediction of poor ovarian response. These are high levels (>12-15 mIU/ml) of Serum FSH (day 2/3), high levels (>30-75pgm/ml) of Serum Estradiol (E2)(day 2/3), low levels(45pgm/ml) of Serum Inhibin-B (day 2/3) and low levels of Insulin Like Growth factor(IGF-1) in follicular fluid. Sonographic examination can help in detection of decreased ovarian volume and ovarian stromal blood flow; however the role of these tests in routine is not clear. Clomiphene challenge test (CCT), FSH Ovarian Reserve Test (FSHORT) and GnRH Agonist Stimulation Test (GAST) have also been abandoned now.

Management

The various protocols and options for poor responders are use of high dose gonadotropins with addition of various dosages and timing of GnRh analogs, natural cycle IVF or modified natural cycle. Use of some supplements or adjuncts like Dehydroepiandrosterone, Growth Hormone, Estradiol and androgens has also shown benefit in these. Those who are at high risk of POF but not trying for conception, oocyte cryopreservation is a potential tool for help. However in those with greatly reduced ovarian reserve, the strategy that provides the greatest chance of conception is oocyte donation.

IVF protocols

Gonadotropins

Dose of Gonadotropins:In order to increase the chances of oocyte production in patients with POR, according to many authors, initial dose of atleast 300 IU/day Gonadotropnins is added. The maximum recommended dose is 450 IU/day with GnRH agonist with long, stop or microdose flare protocol or GnRH antagonist protocols.[12]Although this high dose of Gonadotropins helps in better follicular growth and decreases cycle cancellation rates ,it also increases the side effects and overall cost of the treatment. The different ovarian response to different dose of Gonadotropins stimulation in these women is due to FSH receptor gene polymorphisms and poor ovarian response to low doses of Gonadotropin stimulation is associated with low expression of FSH- receptor in granulosa cells of these women.

Choice of gonadotropin:

It is again important in a stimulation protocol of a poor responder. In older women with poor ovarian response, it has been seen that highly purified HMG gives a better response than rFSH.[13]However in young women with poor ovarian response, according to some authors, LH supplementation confers benefits.[14,15]

Luteal initiation of FSH:

Although in normal IVF cycles the results of luteal start of exogenous LH are not encouraging as it has led to more cancellation rates, decreased number of oocytes collected, low pregnancy rates, increased FSH doses and longer stimulation periods but luteal start of exogenous FSH in poor responder women has shown a significant increase in the number of metaphase II oocytes.[16]

GnRH analogues

The most important advantage of using GnRH analogues is pituitary down regulation followed by exogenous Gonadotropin administration thereby achieving better cycle control. The long luteal protocol using Gonadotropins and GnRH agonists, used in normo-responders has detrimental effect in poor responders as it may lead to over-suppression of ovary eventually leading to a reduced or absent follicular response. A variety of approaches using GnRH agonists have shown benefits for the poor responders. These are short/ultrashort protocol, microdose GnRHa protocol, microdose flare GnRHa protocol and GnRHa 'stop' protocol.

1) **Short and ultra-short, microdose GnRH-a and microdose flare GnRH-a protocol**:
   These protocols help to reduce the duration of suppression by decreasing the duration of GnRH agonist use. The advantages of short protocol is decrease in exogenous gonadotropin requirement, higher clinical pregnancy rate and reducing miscarriage rates .However significant increase in LH and progesterone levels lead to follicular atresia. The advantages of micro-dose GnRH agonist protocol are decrease gonadotropin requirement, shorter duration of cycle, high estradiol concentration on day of stimulation, increase in number of mature oocytes, good embryo quality and reduced cycle cancellation rates.
2) **Stop protocol**:
   This protocol refers to lowering or stopping (after pituitary suppression) the dose of GnRH agonists started during the luteal phase (i.e. day 21).There is no premature LH surge.
3) **GnRH antagonist protocol:**
   This protocol uses GnRH antagonists along with gonadotropins to prevent premature LH rise during the mid-late follicular phase. The advantages of this protocol is prevention of premature LH surge, short treatment period, natural follicular recruitment and cost-effectiveness due to reduced gonadotropin requirement

In a study by Detti et al to assess the efficacy of three different GnRH-agonist protocol; stop protocol(GnRh-a 500 microgram/day from midluteal phase to the start of periods, then gonadotropins from day2 onwards),microdose flare protocol(GnRH-a 20 microgram administered twice daily with gonadotropins from day2 to the day of HCG administration)and regular dose flare(gonadotropins staring with GnRH-a on day2 at 1 mg/d for 3 days, followed by 250 microgram/d until the day of HCG administration. Out of these three, microdose flare protocol for poor responders showed higher delivery rates.[17]

However, Lambalk et al(2017) in a meta-analysis comparing GnRH antagonist and agonist protocols showed that while in general IVF population, antagonists are associated with lower pregnancy rates compared to long protocol agonists, but in poor responders, GnRH antagonists do not seem to compromise on-going pregnancy rates and are associated with less OHSS and therefore can be considered as standard treatment.[18]

In a Cochrane review to compare the effectiveness of different treatment interventions in poor responders ,after review of 10 trials with eight different comparison groups it was found that the number of oocytes retrieved were significantly less in the conventional GnRHa compared to the stop protocol and GnRH antagonist protocol. Total dose of gonadotropins used was significantly higher in the GnRHa long protocol group compared to the stop protocol and GnRH antagonist protocol. Cancellation rats were significantly higher in the GnRHa flare up group compared to the GnRHa long protocol group. However this review concluded that there is insufficient evidence to support use of any particular intervention either for pituitary down regulation, ovarian stimulation or adjuvant therapy in the management of poor reponders.[19]

Natural cycle IVF

These are relatively easy for patients as it minimizes physical and emotional stress, costs of treatment and lab tests, allows natural selection of oocytes and thus improved embryo quality, high endometrium receptivity.[20]But in view of high cancellation rates(as high as 30%),difficult programming of oocyte retrievals, failure to recover oocytes during Oocyte Pick up(16.7%-71.4%) and low pregnancy rates per Embryo transfer cycle, Natural cycle IVF should not be the first option and should only be considered after repeated ovarian response failures with classical stimulation protocols.[21]

Modified natural cycle/mild stimulation GnRH antagonist cycle IVF

This refers to administration of GnRH antagonists administration when follicle reaches 13 mm size along with daily FSH Or HMG during antagonist administration to promote follicular growth on one hand with prevention of OHSS and premature LH surge as well as cutting the total cycle cost. Yoo et al has recommended this mild stimulation protocol in poor ovarian responders over 37 years of age.[22]

Adjunctive treatment

Pre-treatment with COCP/progesterone:

Oral contraceptive pills pre-treatment helps in synchronisation of follicles, prevention of premature ovulation, decreased cyst formation and reduced length of stimulation cycles. It is started from day 3/4 of previous cycle given for at least 21 days. Progesterone (medroxy progesterone acetate) 10 mg twice daily from day15 of preceding cycle for 14- 21 days can also be given .However Cochrane review f 29 RCTs on COCP pre-treatment found fewer live pregnancy rates in women undergoing ovarian stimulation in antagonist protocols. There was insufficient evidence to determine whether rates of live birth or ongoing pregnancy were influenced by pre-treatment with progestrogens /estrogens/COCP using other stimulation protocols.[23] Thus routine pre-treatment with these agents in poor responders is not advisable.

Addition of Estradiol in luteal phase:

Luteal phase Estradiol administration prior to COH (Controlled Ovarian Hyperstimulation), helps in inhibiting FSH in early luteal phase and thus a more coordinated follicular cohort recruitment in response to stimulation.

Addition of androgens:

Use of transdermal testosterone helps in increasing follicular FSH receptor expression in granulosa cells, helps in initial development of primordial follicle,

increases the developing pre-antral and small follicles. It has been shown to have a better response compared with a high dose gonadotropin and minidose GnRH agonist protocol.[24]

DHEA (Dehydroepiandrosterone):

In ovary follicle DHEA gets converted to androstenedione and estrone, which further gives testosterone and estradiol according to two cell-two gonadotropin theory. DHEA helps in increasing ovarian reserve (75 mg of micronized DHEA per day for three to four months) in poor responders by improving follicular micro-environment. Cochrane review of 17 randomised controlled trials concluded that women identified as poor responders undergoing ART, pre-treatment with DHEA or testosterone maybe associated with improved live birth raes.[25]

Growth Hormone(GH):

Kolibianakis et al in a systematic review and meta-analysis of 6 randomised trials concluded that addition of GH during COH in poor responders has resulted in significant increase in clinical pregnancy rate, live birth rates and dramatic reduction in cycle cancellation.[26]GH and its intermediary, Insulin like Growth Factor-1(IGF-1) are 2 of the most well characterised factors which decrease apoptosis and improve proliferation of granulosa cells which is important for maturing oocytes. Also by increasing intracellular estradiol level, it improves oocyte quality. Use of GH in poor responders has shown significant improvement in live birth rate[27]

Recombinant LH:

Addition of LH in stimulation protocol of poor responders may help as it increases intra-ovarian androgens and promote steroidogenesis. Use of r-LH in poor responders significantly increases number of mature oocytes and higher clinical pregnancy rates.

However Jeve YB et al in their systematic review and meta-analysis of 8 trials did not show significant improvement in Clinical pregnancy rates.[28]

Vasoactive substances:

Vasoactive substances like Aspirin and L-Arginine have been shown to increase ovarian vascularity needed for folliculogenesis which can help poor responders theoretically. But there is no robust evidence for empirical use of these adjuncts in poor responders.

Oocyte cryopreservation

The option of oocyte cryopreservation should be utilised in **t**hose who are at high risk of POF(like young patients with ovarian malignancy undergoing Chemotherapy) but not trying for conception.

Oocyte donation

Use of donor oocytes is a successful alternative treatment for infertile women with poor ovarian reserve. But in many countries, this may not be legal or available. Thus best possible effort should be put in to use patient's own oocytes for a successful pregnancy.

Psychological /emotional support

The patients with infertility have great psychological and social pressure. They must be handled with tender loving care along with psychological and emotional support which will ease their treatment journey.

Conclusion

Management of poor responders is a challenging task go reproductive medicine experts. The approach should rather be identification of expected poor responders and plan the stimulation protocol accordingly. These women should receive appropriate counselling and adequate psychological support. There is no universally accepted Controlled Ovarian Stimulation protocol for poor responders. Thus individualized tailored approach is needed to increase the cost-effectiveness. Latest evidence shows DHEA supplementation can help in improving ovarian reserve .Those at high risk of POF should undergo Oocyte cryopreservation. However last resort is oocyte donation.

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