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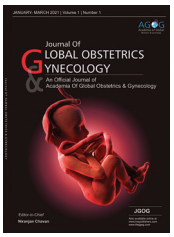
Review Article



Poor Ovarian Response - A Nightmare for Infertility Specialists

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ABSTRACT

Any treatment method for infertility must take into account poor ovarian reserve (POR) to be effective. It reveals a reduction in oocyte quantity and quality in women of reproductive age and is a significant contributor to infertility in many couples. It is a state of poor fertility defined by poor residual oocytes in the ovaries or possibly impaired preantral oocyted development or recruitment. The cause could be age-related issues as seen in women who are past the prime of their reproductive lives or it could happen to young women for a variety of etiological reasons. It is crucial to assess ovarian reserve and individualize treatment plans to significantly increase the rate of success of any ART surgery. The majority of POR patients require fast-track care to become pregnant. If provided individualized care based on their profile, may women with inadequate ovarian reserve may conceive with their own eggs. The necessity for egg donation in these women can be decreased with early discovery and precise care.

Key words: Anti-Mullerian hormone, Antral follicle count, Assisted reproductive technologies, *In vitro* fertilization, Ovarian reserve tests, Poor ovarian reserve

INTRODUCTION

The amount and quality of the ovarian follicular pool that is accessible as well as the ovaries' ability to respond to exogenous gonadotropin stimulation are key factors in ovarian reserve. Ovarian reserve testing is done on couples opting ART procedure with the goal of predicting fecundity and gaining prognostic information about the chance that the pair will respond successfully to ovarian stimulation. Poor ovarian reserve (POR) in women of reproductive age shows a smaller ovarian follicular pool.[1] The possibilities may be higher among the infertile population, though, as many would forego a full examination or IVF.

Women in their mid- to late-30s are more likely to experience diminished ovarian reserve (DOR), but younger women can also be affected. When the follicular pool falls below a key level of 25,000 at the age of 37–38, an accelerated decline is anticipated. There is therefore extremely little time for conception with one's own eggs.

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Due to the growing acceptance of *in vitro* fertilization (IVF) as a means of treating infertility, the presence of POR has been discovered. About 10% of women having ART treatments, on average, will not respond significantly to gonadotropin stimulation.[2-4]

Young women with POR may have a marginally higher likelihood of pregnancy since ageing oocytes tend to be of lower quality.[5,6] The most recent research questions this, suggesting that POR may be linked to poor conception rates regardless of age[7,8] and significant pregnancy losses.[9]

Before treatment for an infertile patient, it might be challenging to identify the "poor responder." Screening for ovarian reserve and determining the likelihood of a poor response to controlled ovarian hyperstimulation are crucial steps in the evaluation of an infertile couple. The goal of this review was to identify and treat POR and its effects on infertility and the long-term health of such women. The terms "ovarian reserve," "POR," and "DOR" were used to search the literature.[10] A review of 500 publications led to the withdrawal of significant conclusions. The proper cross-references were carefully looked up.

DIAGNOSIS

The term "poor response" refers to an insufficient response to standard protocols and inadequate recruitment of follicles.[11] This results in decreased oocyte production and the termination of the

cycle. Perceiving POR, whether connected with age or in any case becomes critical as these ladies have a lower pregnancy rate and higher pregnancy misfortune contrasted with age-coordinated controls with typical ovarian reserve.[12] Decrease of the monthly cycles because of early follicle improvement and ovulation means that POR.[13] However, this precarious variable side effect cannot be utilized as a demonstrative standards of POR. A few ovarian hold tests (ORTs) have been utilized to evaluate ovarian save and foresee reaction to ovarian stimulation,[14] like basal follicle-stimulating hormone (FSH), basal estradiol, antimullerian hormone (AMH), inhibin B, antral follicle count (AFC), ovarian volume, ovarian vascular stream as surveyed by Doppler stream, and ovarian biopsy.

Oocyte yield in IVF decreases with age, as does the rate of pregnancy and live birth.[32,33] However, because POR can occur in young women, it is necessary to use additional indicators of ovarian reserve to identify these women, who would otherwise be considered to have unexplained infertility. Ovarian hold tests (ORTs) give a circuitous proportion of a lady's remaining follicular pool. Elevated basal FSH was one of the first ORTs found to be associated with poor response. However, poor response and elevation may occur relatively late in the course of declining ovarian reserve, so a normal FSH cannot be ignored. As a result, basal FSH is not always a good way to find people who do not respond well.[33] Instead, anti-Mullerian hormone (AMH) and AFC are the most sensitive markers of ovarian reserve that have been found thus far and are ideal for planning individualized protocols for ovarian stimulation. Because these sensitive makers can be used interchangeably, clinicians can use either of these two markers to accurately predict the entire spectrum of ovarian response.[15]

Most efforts to define POR have taken into account specific aspects of ovarian stimulation for IVF, such as a low peak estradiol concentration after traditional ovarian stimulation (300–500 pg/ml)[3,4,35] or a low number of follicles and/or eggs (5 follicles and/or 5 eggs).[35,36] For the purpose of diagnosing POR, some definitions take into account age of 40 years, an aberrant ORT value, or prior subpar response. After at least one round of IVF with regular stimulation,[37-39] it may be said that the diagnosis is reflective. Thirty-five definitions of POR were listed in a review from 1999.[40]

Lack of uniformity in the description of poor responders makes it difficult to evaluate the efficacy of proposed interventions, hence, reduce the heterogeneity in the description of poor responders. Bologna criteria have been introduced following the consensus meeting of "ESHRE working group on POR definition" held in 2011.[41]

Bologna criteria suggest the presence of at least two of the following three features for diagnosis of POR:

i. Advanced maternal age (≥40 years) or any other risk factor for POR
ii. A previous POR (cancelled cycles or ≤3 oocytes with a conventional stimulation protocol)
iii. An abnormal ORT (i.e. AFC <5–7 follicles or AMH <0.5–1.1 ng/ml).[16]

In the absence of an abnormal ORT or advanced maternal age, two episodes of POR following maximal stimulation are sufficient to classify a patient as a poor responder. Ladies over 40 years old with unsteady ORT could be characterized as "expected poor responders" since both old age and an unusual ORT could show diminished ovarian save and go about as a proxy of ovarian excitement cycle.[17]

Bologna standard has been denounced for the most part due to the diversity of risk factors included such as pelvic infection, endometrioma, ovarian surgery, and extensive periovarian adhesions as the effect of every one of these elements on ovarian reserve is highly variable. However, the Eshre consensus is regarded as the most significant step toward a uniform definition of POR, and these standards should be utilized in any subsequent randomized controlled trial involving POR intervention strategies.[42,43]

The patient-oriented strategy encompassing individualized oocyte number (POSEIDON) classification has been introduced to classify women with a low chance of success IVF into four groups based on age, egg count, and response in the previous IVF treatment cycle. Treatment options, such as an increase in dose of injectable fertility drugs (the gonadotrophins luteinizing hormone [LH] and FSH), additional injections of drugs such as recombinant LH (an injectable fertility drug) and egg pooling, have been advocated. Most of these proposed treatment options need further research to prove or disapprove their apparent beneficial effect. Some of these suggested strategies are not patient-friendly and, in addition, raise the treatment cost.

- Group 1 – Age <35 years, AFC ≥5, AMH ≥1.2 ng/ml
- Group 2 – Age ≥35 years, AFC ≥5, AMH ≥1.2 ng/ml
- Group 3 – Age <35 years, AFC <5, AMH <1.2 ng/ml
- Group 4 – Age ≥35 years, AFC <5, AMH <1.2 ng/ml

The proposed treatment options in Groups 1 and 2 include increasing the starting dose of gonadotrophin and/or the addition of recombinant LH as well as the use of dual stimulation (duostim) to increase the oocyte yield (Sunkara *et al.*, 2020). For POSEIDON Groups 3 and 4, additional options of adding adjuvants and the use of dual triggers have been suggested (Haahr *et al.*, 2019; Polyzos and Drakopoulos, 2019).

MECHANISM AND ETIOLOGY OF POR

Reproductive aging is a continuous process from before birth till menopause. The number of oocytes in females reaches its highest point around the 20th week of gestation, when the ovarian cortex contains approximately 6–7 million oocytes that were arrested at the first meiotic prophase. Afterward, regulated apoptosis starts an irreversible decline in the population of germ cells. At the time of birth, number of oocytes are 1–2 millions and at puberty around 3–4 lakhs.[18] Over the next 35–40 years of reproductive life, only about 400 oocytes ovulate and the rest undergo atresia.

Precise demonstrating of pattern of follicle depletion in human ovary is significant on the grounds that the capacity to measure reproductive aging or to predict the number of remaining follicles to tell time on the biological clock would help clinician to take decision regarding individualized ART procedure.

According to a mathematical model, ovarian follicles in women suffer a biphasic exponential drop from birth to age 38, followed by

a quickening of the decline.[4] Recent evidence refutes this theory and suggests that the reduction is caused by an atresia rate that rises throughout the course of the reproductive cycle.[44] This power model also takes into account how different women's non-growing follicular (NGF) pools are sized. The amount of the follicular pool can vary up to 100 times even among individuals with "normal ovarian reserve" who are the same age. However, it is still unclear at this time whether it results from a difference in the initial follicular pool's size or from variations in the rate of depletion.

Follicular atresia has important therapeutic implications for ovarian simulation due to the fact that the extent of recruited follicles is proportional to the size of the NGFs. In addition, women of all ages who have NGF levels below the normal range would respond to ovarian stimulation sub optimally and have a shorter reproductive lifetime. These women would experience an early menopause if there was a definite period of time between the end of fertility and menopause.

Other than aging several other factors may further deplete the ovarian reserve during reproductive years such as Endometrioma, certain pelvic inflammatory diseases, genital tuberculosis, ovarian surgery, and uterine artery embolization for the treatment of fibroids. Chlamydial infection adversely affects the ovarian response in those undergoing IVF.[3] These etiological variables are predicted to induce impairment of intrafollicular endocrine and other regulatory mechanisms, reduced aromatase activity, reduced biological activity of gonadotropin surge-attenuating factor, and altered blood flow.

Endometrioma and its surgical excision can cause POR.[51] Mechanical pressure on ovarian cortex, impaired vascular networks, and alteration of cortical stroma are some of the mechanisms attributed to the damage caused to ovarian follicles.

These women show signs of poor response, requiring high doses of gonadotropins for ovarian stimulation, and reduced oocyte yield during IVF.[19]

Chemotherapy and radiotherapy in various malignancies can significantly impact the ovarian reserve. Obesity and chronic smoking are the factors which are known to be associated with POR.

Ethnicity also is known to affect OR as determined by ovarian reserve markers. The ovarian age of Indian women having IVF was shown to be about 6 years older than that of their Spanish counterparts.[20] IVF patients from India, South-east Asia, the Middle East, and the Afro-Caribbean region had a lower live birth rate than patients from White European women, suggesting that ethnicity may have a causal role in this phenomenon. Chinese, Latina, and African women have lesser ovarian reserves compared to Caucasian women of same age, according to a research that looked at the ovarian reserve makers in women of various races.[21] A research examining the discrepancies in ovarian reserve between various ethnic groups, however, revealed that Bangladeshi women who immigrated to the UK as adults or who were still residing in Bangladesh had lower ovarian reserves than those who immigrated as children or European Women. The role played by ethnicity may not be a simple one and early developmental factors may need to be analyzed while evaluating inter-group variations.[22]

Certain genes' altered expression in granulosa and cumulus cells has been linked to the etiology of POR in young women. FSH receptor (FSHR) polymorphism is thought to be a significant factor in young women's unexpectedly poor response to IVF. Mutations, polymorphisms, and alternatively spliced variants in FSHR have varied effects on receptor function. They are expected to alter the receptor's structural makeup and lessen the receptor's capacity for hormone binding or hormone-induced signaling.[23] Young women's ovarian functional reserve is thought to be diminished as a result of specific types of FMR1 gene mutations.[24]

MANAGEMENT

Women with POR have a limited reproductive lifespan and the main concern is to conceive with their own eggs. A significant portion of the information that is currently available on the effectiveness of different treatment approaches in women with POR is in the context of IVF and represents a decreased pregnancy and live birth rate regardless of age.[25] To maximize oocyte yield and get high-quality embryos, patients are treated with controlled ovarian stimulation (COS), avoidance of early LH surge, and prevention of deep and extended pituitary suppression. The varying definition of POR employed by researchers has been a common barrier to comparison of treatment regimens, though the Bologna criteria offer the right direction to recognize homogenous groups for evaluating efficacy of various therapies.[26]

COS for *In Vitro* Fertilization

To increase oocyte output, the most popular ovarian COS procedures for patients who do not react well entail stimulation with high dosages of FSH (300–450 IU/day). LH supplementation during the early follicular phase may improve the quality of the oocyte and, ultimately, the embryo. However, there is conflicting information about the addition of recombinant LH to FSH. The oocyte yield has showed some improvement with low-dose HCG supplementation or addition of pure HMG where HCG is the cause of LH activity. Without any known therapeutic benefits, luteal initiation of FSH has been utilized to affect the recruitment of follicles.[27]

Agonists

To stop an endogenous LH surge in poor responders during IVF, antagonists are frequently utilized. The long agonist regimen lengthens the course of therapy and raises the overall dosage of gonadotropins required to affect follicular growth in non-responders. However, because of its main flare impact, agonists may aid in follicle recruitment. As a result, one of the most popular agonist protocols in poor responders is the short agonist protocol, in which agonist administration is started in the early follicular phase before gonadotropin injection. Some doctors investigate microdose flare and ultrashort protocols in an effort to reduce pituitary suppression, but they have not been found to enhance clinical results.

Antagonists

In the past 10 years, the antagonist regimen has played a crucial role in the treatment of POR-positive women undergoing IVF. Antagonists offer a practical way to stop early LH surge without lengthening the course of therapy. The rates of conception are comparable to those of the short agonist regimen. There is no difference in the pregnancy rate between antagonist and brief agonist treatments, according to two meta-analyses.

Natural cycle IVF is used as an alternative to high-dose POR regimens to lessen the gonadotropin load, which may also increase the quality of the oocytes, and to lessen the significant financial burden associated with high-dose regimens. Alternatives to high-dose protocols in women with POR include altered natural cycle IVF with the addition of antagonists and small doses of FSH or minimal stimulation incorporating oral letrozole or clomiphene citrate along with small doses of gonadotropins. These techniques improve the number of follicles and successful oocyte retrieval. In natural cycles, cancellation rates might reach 50%. These procedures provide poor responders a different option if the more popular high-dose FSH regimens do not work because the reported pregnancy rate ranges from 8% to 18% per patient.[28]

Progesterone, ethinyl, or oral contraceptive pills (OCPs) pre-treatment may improve follicular synchronization, stop early ovulation, and schedule cycles. Despite no changes in conception rates were reported, pre-treatment with OCP may lengthen the stimulation period.[29]

Adjuvant Therapy

To increase the intrafollicular milieu and follicular sensitivity to exogenous FSH in poor responders, androgen supplementation in the form of oral dehydroepiandrosterone or transdermal testosterone has been investigated. Available evidence shows a modest improvement in various parameters including number of oocytes, embryo quality, and live birth rates.

Supplemental growth hormone (GH) is another adjuvant medication used in conjunction with COS in an effort to increase oocyte yield and pregnancy rates in patients who do not respond well to COS. The use of GH as an adjuvant may be helpful in patients who do not react well, according to scant data involving a limited number of women. However, treatment with GH is costly and many authors have questioned about its use in non-GH deficient patients. Initial studies were encouraging but later on there has been so many arguments about use of GH.

In an effort to increase the likelihood of pregnancy and live births, low-dose aspirin has been used in IVF. However, a recent research found no change in IVF outcomes in patients who were poor responders after taking low-dose aspirin supplements.

As previously stated, the current data support an early use of IVF in POR-affected women as prolonged courses of less effective treatment modalities have a low success rate and IVF provides these women the largest chance of having a live delivery.

All forms of therapy have a low pregnancy rate, but there is a higher chance of miscarriage for all age groups.

IMPLICATIONS

When there is a short window of opportunity to become pregnant due to infertility, the impact of reduced ovarian reserve is most frequently observed. Simple kinds of therapy have very low pregnancy rates, and IVF in these women has the best chance of success. Women with DOR have a lower pregnancy rate than normoresponders regardless of age. Such couples bear a heavy financial and emotional burden after receiving a DOR diagnosis. Sometimes these patients' sole options are oocyte donation or adoption.

It is still up for debate whether ovarian reserve testing should be made available to women who want to put off having children to help them make an educated choice. AMH is, however, increasingly being employed as a method to forecast these women's reproductive potential. Then, they have the option to decide that having children now is more important than waiting, or they may choose to do IVF and store eggs or embryos for later use (social freezing).

Due attention to conserving ovarian cortex during any pelvic surgery including endometrioma excision and avoiding overenthusiastic ovarian puncture in women with polycystic ovary syndrome are important steps in minimizing the iatrogenic risk of POR. A better understanding of genetic causes may lead to development of molecular markers to assist in choosing the most appropriate COS regimes in such women.

It is understood that the time between the beginning of POR and menopause is predetermined. Therefore, young women with POR are prone to experience menopause earlier than the general population. Beyond affecting a woman's ability to conceive, this can have long-term effects on a woman's bone and cardiovascular health.

Artificial intelligence's function: The reserve role of the ovary is quantitatively reflected in the ovarian response to COS. A poor ovarian response increases the likelihood that treatment cycles will be discontinued or that there would not be enough high-quality embryos for transfer80. Studies have shown that certain factors, including a woman's clinical data (age, body mass index, infertility cause, and duration), basal endocrine level (AMH), basal follicle stimulating hormone (bFSH), and ultrasound-related index (AFC), are significantly associated with the degree of ovarian response to COS. Age, AMH, bFSH, and AFC are among the characteristics that are presently acknowledged as having a strong influence on ovarian reserve function. It is vital to develop a thorough and precise link between the impact aspects and the COS result since they each have unique characteristics and interact with one another, which presents additional difficulties for clinical practice. Building machine learning-based clinical decision models for IVF has been increasingly popular in recent years, taking into account the pertinent prognostic aspects. Artificial neural networks, supporting vector machines, decision trees, and random forests, among others, have been used to choose the embryo, categorize the ovarian response and the embryo, and forecast the embryo, and prediction of the embryo implantation outcome.

Natural conception should always be encouraged in patients with DOR.

CONCLUSIONS

DOR represents a major challenge in reproductive medicine, as it is often associated with poor ovarian stimulation response, high cycle cancellation rate, and low pregnancy rate. POR is an important limiting factor for the success of any treatment modality for infertility. The majority of POR patients require IVF to become pregnant. Nevertheless, despite several interventions, the pregnancy rate is still low and is linked to significant pregnancy loss. To reduce the need for egg donation in these women, early identification and proactive care are crucial. Lack of universally accepted diagnostic criteria for POR has limited a meaningful comparison of therapeutic interventions in these women.

The only course of action with a decent likelihood of success for these ladies is an early IVF treatment. The limitations of the limited amount and poor quality of eggs in POR-affected women cannot be resolved by any of the treatment approaches that are now available. Women with POR need to be advised about their short reproductive lives, expensive treatment options, and lower than average pregnancy rates. There is currently no recognized method to shorten follicular atresia and increase fertility. Although it is a step in that direction, social egg freezing does not always guarantee pregnancy and delivery. Delaying childbearing, as observed in the majority of cultures recently, along with an increase in POR incidence presents a significant obstacle and challenge to those who are worried, reproductive professionals who provide services, and researchers who are interested in many facets of ovarian reserve.

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Conflicts of interest

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