Poor ovarian reserve

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ABSTRACT

Poor ovarian reserve (POR) is an important limiting factor for the success of any treatment modality for infertility. It indicates a reduction in quantity and quality of oocytes in women of reproductive age group. It may be age related as seen in advanced years of reproductive life or may occur in young women due to diverse etiological factors. Evaluating ovarian reserve and individualizing the therapeutic strategies are very important for optimizing the success rate. Majority or women with POR need to undergo *in vitro* fertilization to achieve pregnancy. However, pregnancy rate remains low despite a plethora of interventions and is associated with high pregnancy loss. Early detection and active management are essential to minimize the need for egg donation in these women.

KEY WORDS: Anti-Mullerian hormone, antral follicle count, *in vitro* fertilization, ovarian reserve tests, poor ovarian reserve

INTRODUCTION

Ovarian reserve defines the quantity and quality of the ovarian primordial follicular pool. Poor ovarian reserve (POR) indicates a reduction in the quantity of ovarian follicular pool in women of reproductive age group and is an important cause of infertility in many couples. Existence of POR has been unmasked due to an increasing acceptance of *in vitro* fertilization (IVF) as a modality of treatment for infertility. It is believed that approximately 10% of the women undergoing IVF will show poor response to gonadotropin stimulation.[1-3] However, the incidence may be much higher in the infertile population as many may never undergo a complete evaluation or IVF.

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.[4] 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.[5,6] However, recent evidence challenges this and POR may be associated with low pregnancy rates irrespective of age[7-9] and a high pregnancy loss.[10,11]

Lack of universally accepted diagnostic criteria for POR has limited a meaningful comparison of therapeutic interventions in these women. Majority of women with POR need to undergo IVF and accept lower oocyte yield and lower pregnancy rates than those with normal ovarian reserve. However, role of simple treatment modalities in such women and implications of POR in a general population of women in reproductive years are areas of great clinical relevance.

This review looks at the diagnosis and management of POR and its implications to fertility and long-term health of such women. Literature search was made using the keywords "ovarian reserve" and "'poor ovarian reserve," using electronic database MEDLINE (1966-2016). A total of 2722 articles were found. Further searches were

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made for individual etiological factors using their titles as keywords. Appropriate cross-references were manually searched.

DIAGNOSIS

Identifying POR, whether age-related or otherwise is important as, such women have a lower pregnancy rate and higher pregnancy loss compared to age-matched controls with normal ovarian reserve.[11] Shortening of the menstrual cycles due to early follicle development and ovulation is an indicator of POR.[12] However, this variable symptom cannot be utilized as a diagnostic criterion. Various ovarian reserve tests (ORTs) have been in use to assess ovarian reserve and predict response to ovarian stimulation.[13,14] Increasing age is associated with a declining oocyte yield in IVF and reduced pregnancy and live birth rate.[15,16] However, POR may occur in young women; hence, other markers of ovarian reserve are needed to identify such women who would otherwise be labeled as 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.[16] Antral follicle count (AFC) and anti-Mullerian hormone (AMH) are the most sensitive markers of ovarian reserve identified to date and are ideal for planning personalized 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.[17]

Majority of the attempts at definition of POR have considered certain parameters noted during ovarian stimulation for IVF: Either a low peak estradiol concentration following conventional ovarian stimulation (300–500 pg/ml)[3,4,18] or a low number of follicles (≤five follicles) and/or eggs (≤five eggs).[18,19] Some definitions consider the age of ≥40 years, an abnormal value of ORT, or previous poor response for diagnosing POR.[20-22] In essential, it is a retrospective diagnosis following at least one cycle of IVF with conventional stimulation. A review in 1999 had already documented 35 definitions of POR.[23]

To overcome the limitations imposed by lack of universality in definition for conduct of any research and implementation of meaningful interventions, Bologna criteria have been introduced following the consensus meeting of "ESHRE working group on POR definition" held in 2011.[24]

Bologna criteria recommend 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 (≤three oocytes with a conventional stimulation protocol)
iii. An abnormal ORT (i.e. AFC, 5–7 follicles or AMH, 0.5–1.1 ng/ml).

Two episodes of POR after maximal stimulation are sufficient to define a patient as poor responder in the absence of advanced maternal age or abnormal ORT. By definition, the term "POR" refers to the ovarian response and hence a retrospective diagnosis following one stimulated cycle. However, women over 40 years of age with an abnormal ORT may be classified as "expected poor responders" since both advanced age and an abnormal ORT may indicate reduced ovarian reserve and act as a surrogate of ovarian stimulation cycle.[24]

Bologna criteria have been criticized mainly because of the diversity of the risk factors included such as pelvic infection, endometrioma, ovarian surgery, and extensive periovarian adhesions as the impact of each of these factors on ovarian reserve is highly variable. However, ESHRE consensus is acknowledged as the most important step toward a uniform definition of POR and that these criteria be used in any future randomized controlled trial involving intervention strategies for POR.[25,26]

MECHANISM AND ETIOLOGY OF POOR OVARIAN RESERVE

Reproductive aging is a continuous process from before birth till menopause.[27] Women have a finite number of germ cells whose number peaks at 6–7 million by gestation week 20. From mid-gestation onward and throughout reproductive life, an irreversible attrition progressively diminishes the germ cell pool of the gonad.[28]

Fertility peaks before the age of thirty and thereafter, it is believed to decline gradually. This is due to a reducing primordial follicular pool as a result of ovulation and but predominantly because of follicular atresia. A mathematical model proposes that women experience a biphasic exponential decline in ovarian follicles - a slow decay from birth till 38 years of age with an accelerated decline thereafter.[4] Recent evidence challenges this view and suggests that the decline is due to a progressively increasing rate of atresia throughout the reproductive period.[27] This power model also highlights the difference in the size of the nongrowing follicular (NGF) pool between women. Even among those with "normal ovarian reserve" of the same age, the difference in the size of the follicular pool can be as high as 100-fold. However, it is unclear at present whether this is due a difference in the size of the initial follicular pool or due

to differences in the rate of depletion. Available data suggest that NGFs at different ages may have a differing response to changes in hormone levels associated with age.[27]

Follicular atresia has important clinical implications for ovarian stimulation as the magnitude of recruited of follicles is proportional to the size of the NGFs. In addition, women of all age groups with NGFs below the normal range would have a suboptimal response to ovarian stimulation and experience a shortened reproductive lifespan. Considering a fixed time interval between end of fertility and menopause, these women would undergo an early menopause.[29]

In addition to the "natural" age-related decline, factors that may further deplete the ovarian reserve during reproductive years are diverse. Endometrioma, certain pelvic infections, ovarian surgery, all can reduce the ovarian reserve. Such etiological factors are believed 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.[30-33]

Endometrioma and its surgical excision is known to cause POR.[34] 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.[35]

Genital tuberculosis, even in its latent form, is increasingly being recognized as a cause of POR in Indian women. Such women are known to have abnormal ORTs[36] and show signs of poor response, requiring high doses of gonadotropins for ovarian stimulation, and reduced oocyte yield during IVF.[37] The mechanisms involved in the absence of obvious structural damage is not understood at present. Chlamydial infection is known to adversely influence the ovarian response in those undergoing IVF.[3] In recent years, uterine artery embolization for treatment of fibroids is found to be yet another etiological factor for POR.[38]

Improved management modalities in various malignancies have led to an increased survival of affected children and young adults. Both chemotherapy and radiotherapy are known to affect the ovarian reserve adversely.[39-41] Obesity and chronic smoking are other factors known to be associated with POR.[42,43]

Women of certain ethnicities are known to have POR as determined by ovarian reserve markers or exhibit signs of POR while undergoing IVF. In a study of Indian women undergoing IVF, ovarian age of Indian women was found to be approximately 6 years older than their Spanish counterparts.[44] In comparison to White European women, those from India, Southeast Asia, Middle-East, and Afro-Caribbean undergoing IVF in the UK showed a lower live birth rate indicating a possible causative role of ethnicity.[45] Another study examining the ovarian reserve markers in women among different ethnicities found that Chinese, Latina, and African women had a lower ovarian reserve compared to Caucasian women of similar age.[46] However, a study evaluating the disparities in ovarian reserve between different ethnicities showed that Bangladeshi women who migrated to UK as adults or living in Bangladesh had lower ovarian reserve compared to those who migrated in childhood or European women. The role of ethnicity may not be a simple one and early developmental factors may need to be taken into consideration while evaluating inter-group variations.[47]

Altered expression of certain genes in cumulus and granulosa cells have been implicated in the etiology of POR in young women.[48,49] FSH receptor (FSHR) polymorphism is considered to be an important cause of unexpected poor response in young women undergoing IVF. Mutations, polymorphisms, and alternatively spliced variants in FSHR have varied effects on receptor function. They are believed to bring about structural change in the receptor, thereby reducing the hormone-binding ability or hormone-induced signaling ability.[50] Certain types of mutations in FMR1 gene are known to be associated with reduced ovarian functional reserve in young women.[51]

MANAGEMENT

The overriding concern that women with POR have a limited reproductive lifespan to conceive with their own eggs governs all aspects of the management. The vast majority of available evidence on efficacy of various therapeutic interventions in women with POR is in the context of IVF and shows a lowered pregnancy and live birth rate irrespective of age.[7-9,52] Avoiding profound and prolonged pituitary suppression, prevention of premature luteinizing hormone (LH) surge, and controlled ovarian stimulation (COS) to maximize oocyte yield and achieve embryos with good implantation potential form the basis of all therapeutic interventions in poor responders. A common hurdle for comparison of treatment strategies has been the different criteria used by investigators to define POR, and Bologna criteria offer an important step in the right direction to identify homogenous groups for evaluating efficacy of various therapies.[53-55]

Controlled ovarian stimulation for *in vitro* fertilization

Most widely used ovarian COS protocols in poor responders involve stimulation with high doses of FSH (300–450 IU/day) to maximize the oocyte yield.[54,55] The addition of LH in the early follicular phase may have beneficial effect on the

oocyte and hence embryo quality. However, the available evidence regarding addition of recombinant LH to FSH is inconclusive.[56] Low-dose HCG supplementation or addition of pure HMG where HCG is the source of LH activity has shown some improvements in the oocyte yield.[57,58] Luteal start of FSH has been used to influence the recruitment of follicles without any reported clinical benefit.[59]

Agonists

Agonists are widely used in poor responders undergoing IVF to prevent an endogenous LH surge. Long agonist protocol increases both duration of treatment and total dose of gonadotropins necessary to effect follicular development in poor responders. However, agonists due to their initial flare effect may help in recruitment of the follicles. Hence, short agonist protocol where agonist administration is initiated in the early follicular phase before gonadotropin administration is one of the most widely used agonist protocols in poor responders.[60] Microdose flare and ultrashort protocols are preferred by some clinicians, in an effort to minimize the pituitary suppression, but have not shown to improve the clinical outcomes.[54,55]

Antagonists

Antagonist protocol is increasingly used in the management of women with POR undergoing IVF in the last decade. Antagonists provide an effective way of preventing premature LH surge without prolonging the treatment duration. Pregnancy rates achieved are similar to short agonist protocol. Two meta-analyses have not found any difference in the pregnancy rate between antagonist and short agonist protocols.[61,62]

Natural cycle *in vitro* fertilization

Natural cycle IVF is used as an alternative to the high-dose regimens in POR to reduce the gonadotropin burden, with possible improvement in oocyte quality, and to reduce the financial burden of high-dose regimens.[63-65] Modified natural cycle IVF with the addition of antagonists and small doses of FSH[66-69] or minimal stimulation combining oral letrozole or clomiphene citrate along with small doses of gonadotropins[70] to improve the number of follicles and successful oocyte retrieval are alternatives to high-dose protocols in women with POR. Cancellation in natural cycles can be as high as 50%. The pregnancy rates have been reported as 8–18% per patient and these protocols provide an alternative for poor responders when the more widely used high-dose FSH protocols are unsuccessful.[54,55]

Pretreatment

Pretreatment with oral contraceptive pills (OCPs), progesterone, or ethinyl estradiol is meant as a strategy to improve follicular synchronization, prevent premature ovulation, and scheduling of cycles. Even though there are no differences noted in the pregnancy rates, pretreatment with OCP may increase the duration of stimulation.[71,72]

Adjuvant therapy

Androgen supplementation in the form of oral dehydroepiandrosterone or transdermal testosterone in poor responders has been explored as it is believed to improve the intrafollicular environment and follicular sensitivity to exogenous FSH. Available evidence shows a modest improvement in various parameters including number of oocytes, embryo quality, and live birth rates.[73-76]

Growth hormone (GH) supplementation is another adjuvant therapy used in combination with COS in an attempt to improve oocyte yield and pregnancy rates in poor responders. Limited evidence involving small number of women suggests that GH as an adjuvant may be beneficial in poor responders.[77]

Low-dose aspirin has been used in IVF in an attempt to improve pregnancy and live birth rates, and a recent study shows no improvement in IVF outcomes in poor responders following low-dose aspirin supplementation.[78]

A plethora of therapeutic interventions in the management of POR is summarized in Table 1.

As mentioned earlier, the existing evidence favors an early recourse to IVF in women with POR as protracted courses of simpler treatment modalities have minimal success rate and IVF offers the highest possibility of live birth in such women.

Limited data available suggest that intrauterine insemination (IUI) yields very few pregnancies with increasing age and it is suggested that in women above 40 years of age, no more than one cycle of COS and IUI should be offered as they still have a reasonable pregnancy rate with IVF.[79,80] Pregnancy rate is low with all modalities of treatment with an increased risk of pregnancy loss across all age groups.[10]

IMPLICATIONS

Ovarian follicular pool undergoes a progressive decline from before birth to menopause.[27] Even though oogonial stem cells have been identified in adult ovaries, there is no conclusive evidence toward their contribution to the size of follicular pool in the postnatal period.[81]

The impact POR is most often seen in the context of infertility where the time available to achieve pregnancy is limited. Pregnancy rates are very low with simple forms of treatment, and IVF in such women offers the highest probability of pregnancy. Irrespective of the age, women with POR have a lower pregnancy rate than those with normal ovarian reserve.[10] Diagnosis of POR imposes a high

Table 1: Therapeutic interventions in women with poor ovarian reserve undergoing *in vitro* fertilization

Gonadotropins (300-450 IU/day)
HMG
rFSH
rFSH+rLH
rFSH+HCG (100-200 IU/day)
Luteal FSH start
Agonists
Short agonist
Microdose flare
Ultra-short
Long agonist
Antagonists
Fixed multiple dose
Flexible multiple dose
Natural/minimal stimulation IVF
Natural cycle
Modified natural cycle (antagonist + small dose of FSH)
Minimal stimulation (letrozole/clomiphene + FSH + antagonist)
Pretreatment interventions
OCP
Progesterone
Ethinyl estradiol
Adjuvants
Growth hormone
DHEA
Testosterone
Aspirin

HMG=Human menopausal gonadotropin, IVF=*In vitro* fertilization, rFSH=Recombinant follicle-stimulating hormone, rLH=Recombinant luteinizing hormone, HCG=Human chorionic gonadotropin, FSH=Follicle stimulating hormone, DHEA=Dehydroepiandrosterone, OCP=Oral contraceptive pill

financial and emotional burden on such couples. When repeated attempts at treatment become unsuccessful, the only options that remain are recourse to oocyte donation or adoption.

Whether ovarian reserve testing should be offered to women who wish to delay childbearing to assist in making an informed decision remains debatable. However, AMH is increasingly being used as a tool to predict fertility potential of such women. They then have the choice of changing their priorities and decide not to delay conception or may undergo IVF to freeze eggs or embryos for future use (social freezing).[82]

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.[50]

It is known that there is a fixed time interval between onset of POR and menopause.[29] Young women with POR are hence likely to undergo menopause at an earlier age than the normal population. This has long-term health implications beyond fertility to such women, including bone and cardiovascular health.

CONCLUSIONS

POR is an indicator of reduced size of primordial follicular pool, and the resulting eggs are likely to be of suboptimal quality as well. An early recourse to IVF remains the only option with reasonable chance of achieving pregnancy in such women. None of the available therapeutic interventions have the ability to overcome the barriers of low quantity and quality of eggs in women with POR. Women with POR need to be counseled regarding a limited reproductive lifespan, high cost of treatment modalities with lower than normal pregnancy rates. At present, there is no known mechanism to reduce the follicular atresia and prolong fertility. Social egg freezing is a step toward this but does not always ensure pregnancy and childbirth. Delaying childbirth as seen in most of the societies in recent years combined with an increasing incidence of POR poses a great hurdle and challenge to the concerned individuals, the specialists offering fertility services, and the researchers working on various aspects of ovarian reserve.

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Conflicts of interest
There are no conflicts of interest.

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