Review Article

Adjuvant therapy in poor ovarian response – Where do we stand?

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Abstract

In the current era, there is an ever increasing incidence of poor ovarian response. Many strategies have been studied and hypothesized for the management.

Androgens have been widely used and studies in the management of Poor ovarian response. The two prime androgens used in poor ovarian response are Dehydroepiandrosterone [DHEA], Androstenadione and testosterone.

Use of Growth hormone, recombinant luteinizing Hormone and vasoactive substances have been analyzed based on the current evidence.

Keywords: Adjuvants, androgens, poor ovarian responder

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The cornerstone of a successful ART (artificial reproductive technique) programme is the multi-follicular development. In the current era, with an ever-increasing incidence of dwindling ovarian reserve in patients, it is a common challenge encountered by the treating specialists.

A poor response is defined as failure to develop a sufficient number of mature follicles to proceed to oocyte retrieval or yielding only a few oocytes following ovarian stimulation.

The diagnostic criteria of the poor ovarian responders have been changing over the years in 2011 being the Bologna Criteria and the latest being the new POSEIDON (Patient-Oriented Strategies Encompassing Individualized Oocyte Number) classification. The patients were divided into four categories based on quantitative and qualitative parameters – age, the antral follicle count and/or AMH and the ovarian response – if any previous stimulation performed.[1]

Various therapeutic modalities have been proposed for the management of diminished ovarian reserve, with varying efficacies. In this writing, we provide you with a comprehensive overview of the modalities, their therapeutic response.

In the review presented by Cochrane, in the year 2010, it was very clearly stated that there was no specific therapeutic agent that offered an outright benefit in management of poor ovarian responders.[2]

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ANDROGENS

The primary androgens used in poor ovarian response are dehydroepiandrosterone (DHEA), androstenedione and testosterone.

Mechanism of action: The postulated mechanism of action is the expression of insulin like growth factor (IGF-1) in the serum, which in turn improves the response to gonadotropins. Further these hormones are believed to modulate ovarian physiology, including oocyte and follicle maturation, and could have local effects on the endometrium during ovulation and implantation.[3]

Side effects: The side effects of such low dosage are minimal and related to its androgenic effects, which include hair loss, oily skin and acne vulgaris. Other reported effects include better energy and increased libido.

DEHYDROEPIANDROSTERONE

Benefit of DHEA in patients with diminished ovarian reserve was studied as early as the year 2000 by Casson. In his study, he demonstrated a clear benefit in the overall response to ovulation induction for patients with poor ovarian reserve.[4]

A total of 48% to 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, antral follicle count (AFC), peak oestradiol, number of oocytes retrieved, number of metaphase II oocytes and high-quality embryos.[3]

Dosage: DHEA 25 mg in three divided doses or a single 75-mg dose. DHEA supplementation should be initiated before taking up the patient for *in vitro* fertilisation cycle. Barad *et al.* reported that positive DHEA effects occur within 2 months and peak after 4 to 5 months of supplementation and therefore suggested DHEA supplementation for at least 6 weeks prior to *in vitro* fertilisation.[5]

A meta-analysis performed in 2015 by a Chinese group included eight studies ($n = 647$). They concluded that the use of DHEA increased the clinical pregnancy rate (relative risk (RR) 2.13; 95% CI 1.12–4.08). However, the effects of DHEA on oocyte retrieval, implantation, and abortion were not significant. So supplementation with DHEA has a positive effect in women undergoing IVF/intracytoplasmic sperm injection (ICSI) treatment for diminished ovarian reserve (DOR).[5]

However, in a very recent retrospective analysis conducted in Australia of 626 patients, it was observed that the patients with adjuvants of either growth hormone (GH) and DHEA showed better live birth rates which was significant as compared to no adjuvant therapy.[6]

TESTOSTERONE

Most commonly used in the transdermal form, testosterone has also shown to have beneficial effects on the poor ovarian reserve patients. It can be administered by gel or spray form.

A dose of 10 mg of testosterone gel is applied on external side of thigh for 21 days starting from first day of menstruation prior to initiation of ovarian stimulation.

In a systematic review of meta-analysis performed with around 225 patients, it was observed that transdermal testosterone significantly increased live birth and reduces the doses of FSH required. Although the analysis of these findings support a synergistic role of androgens and FSH on folliculogenesis, but due to smaller numbers, it should be interpreted with caution.[7]

However, the reviewers in the Cochrane board were of a varied opinion. In women identified as poor responders undergoing ART, pre-treatment with DHEA or testosterone may be associated with improved live birth rates. The overall quality of the evidence is moderate.[8]

Their evidence still is insufficient to draw any conclusions about the safety of either androgen. Definitive conclusions regarding the clinical role of either androgen await evidence from further well-designed studies. Androgens (DHEA or testosterone) are required for women undergoing assisted reproduction.[8]

GROWTH HORMONE

GH plays an important role in the functioning of granulose cells. It promotes ovarian steroidogenesis and follicular development in the ovary.

A meta-analysis of the included 663 patients and 11 studies showed that GH supplement increased serum oestradiol (E_2) level on human chorionic Gonadotropin (HCG) day, metaphase II oocyte number, 2PN number

and obtained embryo number; however, there was no significant difference on clinical pregnancy rate.[9]

GH-releasing hormones increase the sensitivity of ovaries to gonadotropin stimulation and thereby enhances follicular development. It also enhances the 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. It is started concomitantly with gonadotrophins.

The dose varies from 4 to 8 IU daily or 10 to 24 IU on alternate days in patients with diminished ovarian reserve.

Although the use of GH in poor responders has been found to show a significant improvement in live birth rates, they were unable to identify which sub-group of poor responders would benefit the most from adjuvant GH.[10]

According to the Cochrane review, the results still need to be interpreted with caution, and the included trials were few in number and small sample size. Therefore, before recommending GH adjuvant in *in vitro* fertilisation further research is necessary to fully define its role.[11]

RECOMBINANT LH

LH helps in maintaining the concentrations of intraovarian androgens and as a result promotes steroidogenesis and follicular growth. It has been observed by various studies that the poor responders would benefit from addition of LH in their stimulation cycles.

A systematic review and meta-analysis of eight trials in 2014 found no significant improvement in clinical pregnancy rate with use of recombinant LH.[12]

A phase III, randomised, single-blind, parallel-group trial in women undergoing *in vitro* fertilisation and/or intracytoplasmic sperm injection called The Efficacy and Safety of Pergoveris in Assisted Reproductive Technology trial was designed. This involved 946 women from 18 countries in ages of 18 to 41 years. This was formulated to investigate the hypothesis that a fixed-ratio (2:1) combination of recombinant follicle stimulating hormone (r-hFSH)/r-hLH was generally safe and superior to r-hFSH alone. The primary outcome was the total number of retrieved oocytes per participant. Secondary outcomes were the ongoing pregnancy rate, live birth rate, implantation rate, biochemical pregnancy rate and clinical pregnancy rate. Safety end points include incidence and severity of ovarian hyperstimulation syndrome, and of adverse events and serious adverse events in terms of the number of oocytes retrieved, for controlled ovarian stimulation (COS) in patients with poor ovarian response (POR).

Among the women with POR investigated in this study, although the number of oocytes retrieved was similar following stimulation with either a fixed-ratio combination of r-hFSH/r-hLH or r-hFSH monotherapy. Furthermore, a *post hoc* analysis showed that there was a lower rate of total pregnancy outcome failure in patients receiving r-hFSH/r-hLH, in addition to a higher live birth rate in patients with moderate and severe POR. Although these findings are clinically relevant, further investigations and studies are required for a definitive proof.[13]

According to a systematic review of meta-analysis in 2010 for 603 patients: Currently, based on the best available evidence, addition of rLH in poor responders undergoing ovarian stimulation for IVF using recombinant follicle stimulating hormone (rFSH) and gonadotropin releasing hormone (GnRH) analogues does not seem to increase the probability of clinical pregnancy.[14]

Dose: The optimal timing to administer rLH appeared to be the mid-follicular phase, which, in a large proportion of cases, corresponds with GnRH-antagonist administration.

The optimal quantitative and qualitative ovarian response and the embryo quality were achieved by using rLH (150 IU/day) independently from the total administered dose.

Regarding the effects on the endometrium of rLH supplementation, the total dose had a greater effect than the timing of administration in improving endometrial thickness.[15]

VASOACTIVE SUBSTANCES AND STEROIDS

Increasing the ovarian vascularity has been hypothesised to improve the outcomes in patients with poor ovarian response by promoting the delivery of gonadotropic hormones or other growth factors essential for folliculogenesis, whereas an impaired ovarian blood flow would lead to a decreased ovarian response. Based on this rationale, vasoactive substances such as aspirin and argiprime have been studied.

Some papers have reported some beneficial effects of aspirin from the day of embryo transfer; others have failed to confirm these findings, also in poor responders.

In a prospective randomised trial performed at Italy, it was demonstrated that adjuvant therapy with aspirin and prednisolone did not improve uterine blood flow, implantation and pregnancy rates in patients undergoing IVF.[16]

In 2007, a meta-analysis and a systematic review including the literature of over the past 26 years was performed, they concluded that clinical pregnancy rate per embryo transfer was not found to be different between patients who received low-dose aspirin and the control group.[17]

On the basis of updated evidence, a low dose of aspirin has no substantial positive effect on the likelihood of pregnancy, and it should not be routinely recommended for women undergoing IVF.

ADDITION OF OESTRADIOL IN THE LUTEAL PHASE

The use of oestradiol as a priming agent in the luteal phase would improve synchronization of the pool of follicles available to controlled ovarian stimulation.

It has been studied that if used along with/without GnRH antagonist decreases the risk of cycle cancellation and increases the chance of clinical pregnancy in poor responder patients.[18]

Although the aforementioned trials had major pitfalls, large randomised trials need to be conducted before determining the use in poor ovarian reserve patients.

CURRENT LIMITATIONS IN EXPECTED POR MANAGEMENT

The aetio-pathogenesis of poor ovarian reserve is diverse, with multiple underlying causes. There has been major research in this field and the new POSEIDON criteria consider age as a proxy for the aneuploidy rate and ovarian response, albeit this classification still needs to be validated in clinical trials.

The clinical management of expected POR is still limited to a few adjuvant therapeutic modalities as discussed in this article. The efficacy of these treatments is still of a questionable value, considering the lack of adequate number of studies and good-quality research.

FUTURE MODALITIES IN MANAGEMENT OF POR PATIENT

Few modalities have still been used on experimental basis in patients undergoing IVF. They have shown to be of value but still need to be included in practice guidelines. Intra-ovarian androgen 'priming' is a therapy used in the normal ovarian reserve patient,[19] *in vitro* follicle activation is prescribed for the primary ovarian insufficiency patients.[20] Autologous mitochondrial transfer to improve the implantation potential and quality of the embryos also been tried in some centres.[21] Pharmacogenomics is taking the genome of the patient into consideration when designing drugs and planning a treatment, and one of the most potential modalities is the use of stem cells in patients with ovarian failure.

CONCLUSION

An individualised approach in the management of an expected POR patient needs to be taken up. This would include all steps of ART, including the choice of GnRH analogue, gonadotropin type and dose, ovulation trigger, and the possible use of adjuvant therapies. Future research in this field would provide a 'ray of hope' for this group of patients.

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Conflicts of interest
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