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Review article

Different concepts of controlled ovarian stimulation for management of poor responders during IVF treatment

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Abstract

Management of poor responders in assisted reproduction still remained a big challenge for fertility specialists, despite of the high number of published papers on poor ovarian response in literature for the past two decades. Until now definition for poor responder patients is still not universally accepted in the field of the scientific community. However, these groups of patients usually have a lower controlled ovarian stimulation or IVF treatment outcomes when compared with normal responders. The limitation in identifying and solving the challenges of poor ovarian response in IVF treatment is due to the difficulty of no universally accepted definition in most of the literature. Poor responders are patients unable to develop sufficient number of mature oocytes for collection or the production of ≤ 3 follicles after a standard stimulation protocol. The number of developed follicles and number of eggs retrieved after a standard stimulation of ovary are the two major criteria used in predicting poor ovarian response. In this review, we have discussed the different concepts of controlling ovarian stimulation for the management of poor responders during *in vitro* fertilization (IVF) treatment.

Keywords: Follicle, IVF treatment, ovarian stimulation, poor responders.

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Introduction

The introduction of IVF in 1978 as one of the assisted reproductive technologies has been a great step forward made in recent years in terms of clinical knowledge and technological development. This review focused on the application of IVF treatment on the group of patients with unexplained infertility associated with poor ovarian reserve, advanced reproductive age and unexpected poor IVF cycle outcome in normal responders. A literature search based on Medline searching of "poor responders" and "diminished ovarian reserve" from 1980 to 2015 was used for this review. One of the fundamental steps to reach the success is still related to the number of eggs obtained after hormonal stimulation by gonadotropins in combination with GnRH analogues. In patients defined as poor responders, their limited numbers of obtained eggs remain the main problem in optimizing the live birth rates. The fact that poor responders usually have a lower number and poor quality oocytes retrieved, leads to fewer embryos selected to be transferred and subsequently these patients have lower pregnancy rates per transfer with decreased cumulative pregnancy rates per started cycle compared with normal responders. The Bologna ESHRE criteria on poor responders gave a unified definition based on age, biochemical parameters and morphological characteristics, and concluded that at least two of the three features must be present; (i) a previous episode of poor ovarian response with ≤ 3 oocytes in standard dose of medication, (ii) abnormal ovarian reserve with AFC < 5-7 follicles or AMH < 0.5-1.1 ng/mL; (iii) women above 40 years of age or other presenting risk factors like previous ovarian surgery, chemotherapy, radiotherapy, genetic defects or autoimmune disorders [1]. However, these ESHRE criteria were criticized in 2012 by Younis [2] through his letter to the editor on ESHRE consensus, raising an issue that although there is a step forward; work is yet to be accomplished. He stated that based on the literature, it is necessary to have a guideline for physicians to identify risk factors and integrate them with diagnosis of poor responders, especially for young women. The chances of conception with IVF in patients with severely diminished ovarian reserve are low but not negligible. Some fertility centers do not deny patients IVF treatment based on only ovarian markers. Young poor responders could do better than their older counterparts with similar ovarian reserve test outcome. Preemptive steps are taken to maximize ovarian response by predicting poor response, thereby increasing dose and/or combination of medication; pre-treatment cycle with DHEA or GH, or using the GnrRH antagonist protocol.

Doses and combination of medications

An increase in dosage of gonadotropins could also increase the sizes of follicles available and not the number of follicles available for growth during ovarian stimulation. This is because the number of follicles for each month is fixed and cannot be

changed by increasing the dose of medication. However, only few studies have demonstrated advantages to such strategy. The high starting gonadotropins is been a widely practiced protocol after a poor response following standard dosing range of 150-300IU/day of FSH. Most authors demonstrated a starting dose of at least 300IU/day, while some evaluated a daily dose of 450 IU/day of FSH for poor responders [3, 4]. Some researchers found from their retrospective studies in mid-1990s that there is no additional benefit in oocyte retrieved or pregnancy rates when FSH dosage was more than 450 IU/day [5-7]. Tariatzis et al. also reviewed some prospective trials published in 2003, and found out a limited evidence for the efficacy of dose increases even to 450 IU of FSH [8]. Hypothetically, increase in gonadotropins could potentially be detrimental to follicular development and its growth, resulting either as none or little oocyte and/or poor quality oocyte that yields poor embryo quality. These potential risk factors due to medication increase can be explained as a result of its impact in decreasing the number of follicular stimulating hormone receptors (FSHR) in granulosa cells, inducing presence of FSHR binding inhibitors in follicular fluid or causing more size increase of oocyte during the prolonged exposure to the follicular environment.

Different kinds of medication regimen have been widely applied in order to solve the problem of prolonged exposure of FSH to oocytes by using combined medication that will attract low dose and short duration of the FSH protocol with the objective of having a maximized success rate. Mild stimulation is a regimen that achieves this success as already been recognized by ISMAAR Association in 2007, that mild stimulation can be an alternative to conventional (long) stimulation. They stated this through the definition of controlled ovarian hyperstimulation (COH) when gonadotropins (Gn) are administered at a lower dose and/or for a short duration, or when oral compounds (e.g. clomiphene citrate) are used either alone or in combination with Gn aiming at collecting 2-7 oocytes [9, 10]. This mild stimulation can be used in place of failed attempted review of 29 clinical studies in 2007 by Siristatidis et al. to re-evaluate the maximal effective FSH dose in poor responders [11], which ended up with a maximal starting dose of 450 IU of FSH from the late luteal phase of the cycle and may then reduce the dose once adequate response has been established. However, in most of the mild stimulations such as short GnRH agonist protocol and GnRH antagonist plus maximal FSH stimulation in the treatment of poor responders, the high dose of FSH can still affect the oocytes. The mild regimen with a combination of clomiphene citrate with minimal FSH stimulation minimizes OHSS risk, decreases the treatment burden on patients, reduces cost, and removes patient's discomfort with a lesser dose of Gn in decreased stimulation duration.

Pretreatment adjuvants using dehydroepiandrosterone (DHEA)

Dehydroepiandrosterone (DHEA) is a hormone in both male and female that can be used as a precyle supplementation medication in assisted reproduction. Casson et al. described it in a case series, while Barad and Gleicher talked about it in a case report [12, 13]. DHEA has fertility benefits of enhancing early stage of follicular maturation as it converts to testosterone (androgen) when administered or ingested. It increases the level of testosterone in low ovarian reserve patients and can be used in both older women above 40 years and younger women with poor ovarian response. These two groups of patient usually have low androgen levels and could benefit from pretreatment with DHEA supplements for 3-4 months before IVF cycle. A few retrospective studies on the use of DHEA supplementation dose of 25mg three times daily for 4 months before IVF treatment, showed an improvement in the number of good qualities of fertilized embryos [14]. DHEA also decrease cancellation and miscarriage rates; and improves clinical pregnancy rates [15, 16]. Although DHEA supplementation for poor responders remains controversial due to the limitations in the available data, such as selection bias, one of the retrospective studies still showed there is an increase of AMH with DHEA treatment in a population undergoing IVF cycle [17]. It was also postulated that DHEA supplementation reduces follicular apoptosis, hence improving the pool of primordial follicles [18].

Drainage of simple cyst before stimulation protocol

Follicular cyst formation is one of the most known side effects of pituitary downregulation with GnRH agonists in COH protocols. The incidence ranges from 8-53%, depending on different size criteria used for the diagnosis [19]. This follicular cyst formation may be related to endogenous gonadotropin flare in response to mid-luteal GnRH agonists. Although it is still controversial, some evidence had shown a poor IVF performance in patients that form follicular cysts in response to GnRH agonist in both poor and normal responders.

Severe condition was found in cysts > 15 mm in an operative characteristics analysis, while other studies have failed to confirm the negative prognosis of cyst formation in IVF outcome [20- 22].

Markers for ovarian reserve

Some of the markers used in IVF centers for ovarian reserve assessment are antral follicle counts (AFC), anti-Mullerian hormone (AMH) level and day 3 follicle stimulating hormone (FSH) level. Antral follicles are small follicles that usually respond to gonadotropins and form large follicles that contain the oocytes. AFC are detectable in ovary by transvaginal ultrasound scanning from follicle size of 2-5mm diameter and high number of antral follicles could a more number of oocytes that will be retrieved. AMH level is presently the most commonly and reliable used marker for assessing the number of eggs remaining in the ovaries, and high level of AMH is an indication for large oocyte pool. The cut off parameter for AMH is close to 1.0 ng/ml. The FSH level is a better predictor of pregnancy, but a day 3 FSH level >10 could be expected of poor ovarian response to stimulation. AMH and AFC are currently considered as the best two markers for ovarian response prediction.

Unexpected poor IVF outcome in normal responders

Unexpected poor IVF outcome in normal responders could be a poor ovarian response due to the impact of high dose and prolonged duration of Gn exposure during follicular development. This increased dose of Gn is as a result of long luteal GnRH agonist's protocol, which attracts high dose of exogenous gonadotropin due to pituitary activity suppression. Although GnRH agonists have been the mainstay of COS because of their ability to prevent a premature LH surge, inadequate follicular development and improve pregnancy rates; it also attracts high dose of Gn during hyperstimulation in IVF that could be detrimental to follicular growth and give rise to poor quality oocytes. In summary, management or poor responders and unexpected poor IVF outcome in normal responders should be based on the protocol associated with reduced discomfort and reduced treatment burden. Therefore, since there is no evidence of superiority of one approach over another, mild stimulation protocol with Clomiphene citrate (CC) plus low dose Gn, which is associated with reduced discomfort and treatment burden, should be preferred and considered. This CC is an inexpensive and considerable medication that can be administered orally. It stimulates the secretion of endogenous gonadotropins through its competitive antagonism to estrogen [23], overcome follicular dominancy and promotes multiple follicle growth [24]; possibly stimulates ovarian aromatase activity.

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