Original Article

Profile of Low Responders in Assisted Reproductive Technology - A Retrospective Study

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Abstract

Aim: To analyse the various features (categorical and variables) associated with low responders in Assisted Reproductive Technology (ART). Materials & Methods: Design: Retrospective Study. Setting: Department of Reproductive medicine, Chettinad Hospital and Research Institute, Kelambakkam, Tamil Nadu, India. Patients: Out of 200 patients undergoing ART cycles (From January 2008 to March 2010) at Chettinad Hospital, 25 patients who had low ovarian response were analysed. Intervention: All of the 25 patients had been down regulated with GnRH analogue(Leuprolide acetate) 1mg in short protocol and stimulated with U. HMG/FSH with a minimum dose of 225 IU and for a period of 10days. Main Outcome Measures: This review will describe the profile of women who showed low response to ovarian stimulation. Result: Incidence of low response was 12.5% . The profile of patients with low responders in our study showeda mean age of 34.1 years, mean period of infertility of about 8.1 years, low antral follicular count, interestingly low response was also observed in women with proven fertility that is after tubectomy. Conclusion: Women with low response had low antral follicular count, higher basal FSH, Required higher dose and longer period of stimulation. Low ovarian response was observed in younger women also. Prior pelvic surgical history was observed in significant number of women.

Key Words: Low Responders in ART, Low ovarian response, GnRH analogue

Introduction

Despite the vast understanding of controlled ovarian stimulation protocols, there are still a group of women who do not respond well to ovarian stimulation and yield few oocytes at retrieval, resulting in few numbers of embryos and poor pregnancy rates[1].

This low ovarian response is one of the most controversial and frustrating issues in Assisted reproduction. Though a variety of regimens have been tested to improve ovarian response, the results are not comparable and an ideal stimulation protocol does not exist, as homogenous population was not tested in any clinical trials[2-6]. It is difficult to estimate the exact prevalence of low ovarian responders, because of its varied definition though reported to be 5-24% of patients undergoing Invito fertillization(IVF)[7]. This review will describe the profile of women who showed low response to ovarian stimulation in our study.

Definition

The pathogenesis, prediction and possible treatment options for low ovarian response have been published in numerous journals. Despite the wide spread use of the term low ovarian response to gonadotropins, no standard definition exists[8-11].

First realistic attempt to standardize a simple and reproducible definition was presented at ESHRE scientific community held in Bologna in 2010[12]. It is defined as low ovarian response when at least two of the following criteria were present:

(i) Advanced maternal age (≥40 years) or any other risk factor for low ovarian response

(ii) Previous low ovarian response resulting in less than 4 eggs to stimulation &

(iii) Abnormal ovarian reserve test (AMH 0.5-1.1 ng/ml or AFC 5-7).

In this definition the importance is given to the response to stimulation. Two episodes of low ovarian response after maximal stimulation are sufficient in the absence of advanced maternal age or abnormal ovarian reserve test to define low ovarian response.

Since it is the response to stimulation, it is essential to

have at least one stimulated cycle. However women with abnormal ovarian reserve test and advanced age can be considered as expected low responders[13].

ESHRE consensus on the definition of low ovarian response was criticized as[14] -

1. The study population was diverse
2. Detailed risk factors were not explained
3. Clear cut cut-off for the ovarian reserve test were not suggested especially, in case of Anti Mullerian Hormone
4. Bologna criteria was based on previous studies rather than scientific experiments
5. The number of oocytes were quantitative rather that qualitative and was not outcome (prognosis) based predicting the results of in vitro fertilization.

Aetiology of Low Ovarian Response

Beyond the well-established relation between advanced maternal age and low ovarian response to gonadotropins, there are number of other factors, which may be important[15,16]. Previous ovarian surgery, ovarian endometriosis, Pelvic inflammatory disease, systemic illness, radiotherapy, chemotherapy, chronic smoking, environmental factors, and specific conditions affecting the ovaries may all influence the ovarian response to gonadotropin stimulation[17-22].

Short menstrual cycle, endometriotic cystectomy and chronic smoking have been associated to affect both the quantity as well as quality of retrieved eggs, hence the pregnancy rate[23,24]. Our study analyses the various features associated with Low responders in ART. Numerous categorical and numerical variables were analyzed in the study.

Materials and Methods

This is a retrospective study of 200 ART cycles between January 2008 and March 2010 at Department of Reproductive medicine, Chettinad Hospital and Research Institute, Kelambakkam, Tamilnadu, India. All of them had down regulation with GnRH analogue (leuprolide acetate 1mg) in a short protocol and stimulation with u-HMG/FSH with a minimum dose of 225 IU and for a minimum period of 10 days.

Several numericals such as age, body mass index (BMI), number of present children, number of previous IVF cycles, serum follicle stimulating hormone (FSH), total gonadotropin dose administered, number of total and mature oocytes, and number of embryos transferred] and categorical variables (infertility diagnosis, period of infertility, previous ovarian surgery, tubec tomy, abnormal menstrual pattern) were recorded.

The eligible cohort were women with follicular response of three or less dominant follicles on the day of HCG trigger. This group of women was taken as low responders and their association with other categorical and numerical variables was analyzed.

Results

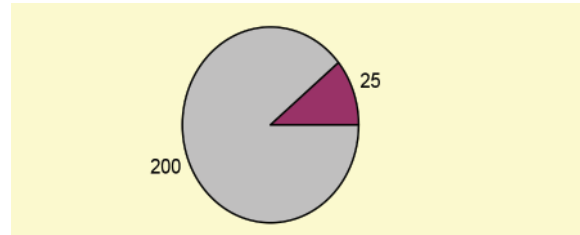The incidence of low responders was 12.5% [25/200] in our study group(Fig 1). The age distribution was 22

Fig 1 - Incidence of low responders
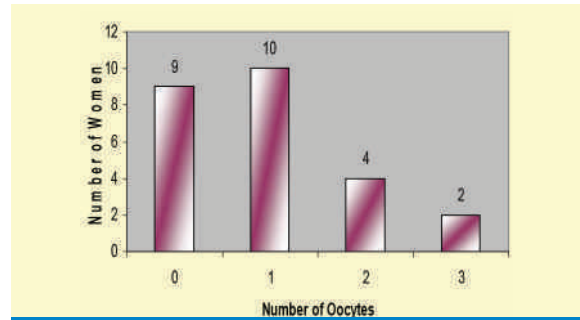

Fig 2 - Ooctye yield in women analysed

women < 40 years, 3 women > 40 years. Primary infertility was the predominant type in 80% women. Prolonged period of infertility was observed in 85% of women [> 5 years]. We had interestingly 9 women out of 25 [36%] with history of pelvic surgeries/ adhesions. Low response was seen in 3 women who had undergone tubectomy (Table 1). 2 out of 25 women[8%] had history of surgery done for endometriosis. Menstrual history was normal in 92% of women. BMI above 30 was observed in 16% of these women.

Stimulation dose of 300 IU of u- FSH/HMG per day for 10-15 days was used in the majority -76%. The total antral follicular count was less than 5 in 68% of women.

Basal FSH value was >10 in 56% and <10 in 44%. Adequate endometrial thickness was seen in 88% of women. No oocyte was obtained in 9/25 women [36%] Fig 2 . Only 9 women reached stage of embryo transfer [36%]. Some prior good responders showed a subsequent low response in repeat cycle [4 women] (Table 2).

PARAMETERS	FREQUENCY (%)
TOTAL NUMBER OF WOMEN WITH LOW OVARIAN RESPONSE	25/200 [12.5%]
CYCLE CANCELLED	5 [20%]
OPU DONE - NO OOCYTE	9 [36%]
OOCYTE OBTAINED	16 [64%]
EMBRYO TRANSFER DONE	9 [36%]

Table 1 - Parameters of the women analysed in the study

Discussion

Ovarian age is an independent variable critically affecting IVF outcome, while chronological age assumes a less important prognostic role, once the diagnosis of diminished ovarian function has been made[26-28]. This

theory is supported by previous reports that stressed that the age at which the ovarian reserve declines is highly variable and therefore age alone could have a limited predictive value with respect to reproductive potential. In fact, AFC and AMH Levels, as a measure of ovarian reserve, has been shown to be a better predictor of a woman's chance to conceive than her chrono logical age [24].

Low Responders	Feature	Percentage
Serum FSH	>10 miu/ml	56%
AFC	<5 AFC	68%
DOSE OF GONADOTROPINS	Required 300 iu and above	76%

Table 2 - Features of low responders

In assisted reproduction programs, the performance of "good responders" or "low responders" to exogenous FSH is individualized and the ovarian response to intense gonadotropin stimulation is difficult to predict. The response to stimulation can be low even in some patients, who showed no abnormal ovarian reserve tests.

Even though various predictive markers like antral follicle count, FSH, AMH, age, ovarian volume and ovarian Doppler flow pattern have been studied, serum AMH &antral follicle count takes a better predictive value. Combined application of both has been considered more reliable, whereas Serum AMH has not been assayed in our study[29-31]. Although antral follicle count is measured in all patients, objective reporting by the same observer was not available for all patients[32,33]. The Practice Committee of the American Society for Reproductive Medicine supports the use of AMH as a screening test for low ovarian response than the use of AFC [34].

It is critical that women considering IVF have proper ovarian reserve testing to be sure that they are not wasting their time, money, or emotions by pursuing IVF, when it has little or no hope of success. Poor success rate in IVF cycle in patients with low responders puts the couple in to a real state of confusion and concern to proceed to fertility treatment of ART.

The ultimate goal of every ART cycle is a live birth. The challenge is more in the low responder group. Although various protocols and drugs have been suggested to improve the outcome, the ideal drug and regime remain elusive.

Conclusion

The profile of the Low responders in our study showed a mean age of 34.1 years, with mean period of infertility of 8.1 years. Low ovarian response was observed in younger women also [52% in women <35 years][23,24].

Low antral follicular count was observed in majority. Low response was not always consistent with higher basal FSH levels[25]. Prior pelvic surgical history was observed in significant number of women. Low response was also observed in women with proven fertility, that is after tubectomy. Higher dose and

longer period of stimulation were required in these women. Higher dose of stimulation did not alter the outcome. None of the poor responders had a positive pregnancy outcome in our study.

The authors declare no conflict of interest.

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