Management of the poor responder: the role of GnRH agonists and antagonists

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Abstract

Purpose Evaluate the relative benefit of various doses and regimens of GnRH agonists (GnRHa) and antagonists (GnRHant) in the management of the poor responder.

Methods Review of English language publications with an emphasis on prospective randomized trials where available.

Results The lack of a uniformly applied definition of the poor responder and dearth of prospective randomized trials make data analysis difficult. Traditional GnRHa flare and long luteal phase protocols do not appear to be beneficial. Reduction of GnRHa doses, “stop” protocols, and micro-dose GnRHa flare regimes all appear to enhance outcomes, although the relative benefit of one approach over another has not been conclusively demonstrated. GnRHant does improve outcomes in this patient population, although, in general, pregnancy rates appear to be lower in comparison to microdose GnRHa flare regimes.

Conclusions There is no one controlled ovarian hyperstimulation (COH) protocol which is best suited for all poor responders. Low dose GnRHa regimes appear to be most advantageous. Prediction of compromised response prior to cycle initiation by a thorough assessment of ovarian reserve as well as a careful review of past response should allow for selection of an appropriate COH protocol for each individual patient.

Keywords GnRH agonist · GnRH antagonist · in vitro fertilization · poor responder

Capsule GnRH antagonists and low dose GnRH agonists have been employed with varying degrees of success in the management of the poor responder.

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Introduction

The introduction of both agonists and antagonists of gonadotropin releasing hormone (GnRH) has revolutionized the process of controlled ovarian hyperstimulation (COH) in preparation for oocyte aspiration and in vitro fertilization. Enhanced synchronization of follicular development, minimization of premature ovulation and improved control over cycle scheduling have all been beneficial. Manipulation of these agents has also been explored in the management of the poor responder.

One of the great difficulties in evaluating research trials assessing various COH regimes is the lack of any generally accepted definition of the poor responder. When previously writing on this subject, we noted that at least 13 criteria had been employed in the literature [1]. Thus, comparing outcomes from various approaches is extremely challenging given the heterogeneous patient populations evaluated. A singular dearth of well-designed prospective randomized trials further enhances this difficulty. Nevertheless, a variety of approaches employing these agents in this patient population will be reviewed in this manuscript and are summarized in Table 1.

GnRH agonists (GnRHa): standard luteal phase downregulation

The benefit of the down-regulation of the pituitary gonadotrope induced by GnRHa was evaluated in several early trials of patients who had failed to adequately respond to gonadotropin therapy alone. Five non-randomized series evaluating over 100 women defined as poor responders employing a variety of criteria were treated by administering a GnRHa in the luteal phase and awaiting down-regulation prior to initiation of gonadotropins. The patients

Table 1 GnRH agonist (GnRHa) and antagonist (GnRHant) protocols for poor responders

Protocols
Luteal phase GnRHa
GnRHa “stop”
GnRHa flare
Minidose GnRHa
Microdose GnRHa flare ± growth hormone
GnRHant ± aromatase inhibitor ± adjuvant estradiol

generally demonstrated improved responses as reflected by enhanced maximal estradiol levels, numbers of oocytes retrieved as well as increased fertilization and pregnancy rates [2–6]. Nevertheless, the gains achieved with this approach were somewhat modest. Given the fact that luteal phase initiation of GnRHa has been shown to increase gonadotropin dosing requirements, the benefit of this approach in a patient with pre-existing diminution in ovarian reserve can be questioned [7].

Mini-dose GnRHa

An alternative approach, which would theoretically decrease the extent of endogenous gonadotropin suppression while preventing premature ovulation, would be to decrease the dose of the GnRHa initiated during the luteal phase prior to ovarian stimulation.

Feldberg and colleagues evaluated 106 patients who had previously responded poorly during two prior IVF cycles with failure to develop more than two follicles and with day 3 FSH levels >15 mIU/ml [8]. Three approaches were employed in this retrospective analysis prior to gonadotropin stimulation: (1) a single injection of the GnRHa D-Trp⁶ 3.75 mg, (2) D-Trp⁶ 0.5 mg daily until menses followed by a dose reduction to 0.1 mg daily, 3) D-Trp⁶ 0.1 mg daily until menses followed by a dose reduction to 0.05 mg daily. GnRHa was initiated in the midluteal phase for all patients. Increased E_2 levels, numbers of oocytes retrieved and embryos available for transfer were noted with the reduction in GnRHa dose. Cancellation rates were also decreased. Trends towards increases in implantation and pregnancy rates were noted. The retrospective nature of this trial with associated potential for selection bias represents a significant drawback, however.

These findings were confirmed in a prospective analysis of 98 patients who had inadequately responded to a standard long GnRHa protocol [9]. Leuprolide acetate was initiated in the mid-luteal phase at a 0.5 mg daily subcutaneous dose which was then decreased to 0.25 mg daily after menses when gonadotropin stimulation was begun. The authors reported an improvement in COH response as reflected by

increased E_2 levels, number of oocytes and good quality embryos obtained. In addition, the duration of gonadotropin stimulation and doses required were reduced.

GnRHa: “Stop” protocols

It has been hypothesized that the continuation of GnRHa even at these low doses during COH could have a deleterious effect in a patient with diminished ovarian reserve. Therefore, it is possible that complete cessation of GnRHa prior to initiation of COH, but after down-regulation has been achieved, could overcome this problem. Several investigators have assessed the benefit of short term ovarian suppression induced by mid-luteal phase GnRHa administration which was then discontinued prior to initiation of gonadotropin stimulation. However, one of the concerns with implementation of this approach is the potential for an increased incidence of spontaneous LH surges and premature ovulation.

Faber et al. prospectively analyzed 192 low responders defined as women with day 3 FSH levels ≥9 mIU/ml or a prior IVF cycle with ≤4 oocytes retrieved or peak estradiol level during stimulation ≤600 pg/ml [10]. At least 7 days of leuprolide acetate 0.5 mg was administered in the mid-luteal phase and discontinued with menses. An ongoing pregnancy rate per transfer of 24% and cancellation rate of 12.5% was reported. Only one patient exhibited a premature LH surge.

This approach was subsequently evaluated in two prospective randomized trials in which controls remained on GnRHa throughout stimulation. Garcia-Velasco et al. reported that although a significantly higher number of mature oocytes were obtained and gonadotropin doses reduced with the “stop” protocol, cancellation, pregnancy and implantation rates were similar to controls [11]. Interestingly, Dirnfeld and colleagues using a similar design noted a higher cancellation rate in the study group of which only one was due to a premature LH rise [12]. Clinical pregnancy rates were similar among the groups. It was only in a subgroup of 13 patients whose cycles had previously been cancelled with a long mid-luteal GnRHa regime that an enhanced number of oocytes were obtained.

GnRHa: flare regime

Investigators have administered standard GnRHa doses concomitantly with gonadotropins in the early follicular phase in an effort to take advantage of the initial stimulatory effect on endogenous gonadotropin release induced by the agonist while allowing subsequent suppression of endogenous LH surges [12]. Although this approach

is logical, its benefit in the management of the poor responder has not been consistently demonstrated. Three early trials did report higher pregnancy rates with a variable effect on cancellation when the flare regime was employed [13–15]. However, others have demonstrated that a flare protocol failed to improve either COH response or cycle outcome [16–19].

In a more recent prospective randomized trial, Weissman et al. compared two protocols in a group of 60 poor responders based on prior cycles [20]. One group received a “modified” flare protocol in which an oral contraceptive was administered for 14 days followed by high dose triptorelin 500 mcg daily for 4 days initiated with onset of the second withdrawal bleed. Gonadotropin stimulation was initiated on the third day of bleeding. The GnRHa dose was then decreased to 100 mcg/daily. A second group received a step-down GnRHa protocol initiated on cycle day 21. Significantly more oocytes were obtained and pregnancy rates were dramatically higher (22.5 vs 3.4%) with the GnRHa step-down protocol.

Brzyski and colleagues suggested that these poorer outcomes may have been the result of an increase in the number of atretic follicles and associated increases in circulating LH and progesterone levels during COH with a flare protocol [21]. San Roman et al. reported similar hormonal changes with this approach along with an increase in circulating testosterone levels in comparison to controls receiving GnRHa initiated in the luteal phase [22]. In evaluating acute endocrine responses to GnRHa in the absence of COH, Gelety and coworkers described significantly greater rises in androgen and progesterone levels with early follicular as opposed to mid-luteal initiation of a standard dose of leuprolide acetate employing patients as their own controls [23]. This may be the result of a deleterious effect of gonadotropin stimulation on rescuing the residual corpus luteum.

GnRHa: microdose flare regimes

Perhaps one of the most successful approaches to the management of the poor responder has been that of the microdose flare GnRHa regime. The basic hypothesis of this approach is to administer the minimal dose of GnRHa necessary to induce gonadotropin release while minimizing premature ovulation. Leuprolide acetate doses as low as 25 mcg in humans and 0.017 mcg/kg in baboons administered in the early follicular phase were sufficient to induce increases in circulating gonadotropin levels [24, 25]. However, the minimum dose necessary to induce this effect has not been established. It would also be important to minimize the incidence of corpus luteum rescue and undesired follicular phase progesterone and androgen rises.

Pretreatment with an oral contraceptive or progestin may help to accomplish this task [26, 27].

Initial reports with this approach employed patients' prior cycles as a control. Scott and Navot first described the use of microdose flare in a prospective series of 34 low responders defined by a peak E_2 level <50 pg/ml in a prior cycle during which a long GnRHa protocol had been employed [28]. These investigators administered leuprolide acetate 20 mcg every 12 h beginning on cycle day 3 with initiation of gonadotropins on day 5. They described an enhanced ovarian response marked by higher peak E_2 levels, decreased gonadotropin requirements, and enhanced numbers of oocytes obtained. No premature LH surges were noted. Although pregnancies were achieved, the rates still remained relatively low (4/34).

Schoolcraft et al. altered this protocol somewhat by administering patients the same agonist in a 40 mcg twice daily dose in conjunction with growth hormone initiated 3 days after completion of one cycle of oral contraceptives [29]. Gonadotropins were added two days later. Inclusion criteria for the 32 patients treated in this trial included prior cancellation of a cycle in which a standard luteal phase GnRHa protocol had been employed due to serum E_2 < 100 pg/ml or visualization of less than four follicles after 5 days of stimulation. The cancellation rate was dramatically decreased to 12.5%. Significantly greater serum E_2 levels and numbers of visible follicles were noted on day 5. Of the 28 patients who reached oocyte retrieval, 50% achieved an ongoing pregnancy after a mean of 10.9 oocytes were obtained. The relative benefits of adjunctive growth hormone are beyond the scope of this review and are discussed elsewhere.

Subsequently, Surrey and coworkers presented results from an investigation employing a similar regime but without growth hormone [30]. Inclusion criteria for this trial of 34 prior poor responders were slightly different and results were stratified by patient age. As a result of the microdose flare regime, cycle cancellation rates were reduced in younger patients (≤ 39 years) from 53.3 to 6.7% and in older patients (≥ 40 years) from 73.7 to 31.6%. Although peak E_2 levels were increased, the numbers of oocytes retrieved in those whose cycles were not cancelled were no different between the two cycles. Ongoing pregnancy rates in the two groups were 33 and 18.2%, respectively (Table 2). In comparison to a group of normal responders administered a traditional luteal phase GnRHa protocol, circulating FSH levels were markedly higher but there were no significant differences in circulating E_2 , LH, progesterone or testosterone levels. This is in contrast to the perturbations previously described with a traditional flare protocol [23].

Taking a different approach, Sharara and McClamrock attempted to prospectively predict which patients would be

Table 2 Clinical outcomes from the use of a microdose flare protocol (cycle 2) in comparison to prior poor response from a standard luteal phase GnRH α protocol (cycle 1) (results expressed as mean $\pm$ SEM unless otherwise indicated)

	Number (N)	Maximal E_2 (pg/ml)	Cancellations (%)	Oocytes retrieved	Ongoing pregnancy/embryo transfer
Age $\leq$ 39					
Cycle 1	15	670 $\pm$ 141	53.3	64 $\pm$ 1.4	0
Cycle 2	15	1153 $\pm$ 121*	6.7*	7.2 $\pm$ 0.9	33.3
Age $\geq$ 40					
Cycle 1	19	419 $\pm$ 67	73.7	4.0 $\pm$ 1.3	0
Cycle 2	19	692 $\pm$ 14*	31.6*	3.8 $\pm$ 0.5	18.2

Modified from Table 2, Surrey et al. [30]

* $P<0.05$ vs cycle 1

better served by receiving a microdose flare protocol based on the objective criteria of precycle ovarian volume calculated to be $<3\text{ cm}^3$ during a baseline ultrasound evaluation [31]. As opposed to comparing outcomes to prior failed cycles, only first cycles were evaluated in 30 such patients and results compared to 79 women with ovarian volume $>3\text{ cm}^3$ undergoing a standard luteal phase GnRH α regime. Although there are clearly some weaknesses inherent in this study design, results of COH, implantation and pregnancy rates were similar between the groups.

A limited number of trials have compared the microdose flare regime to other approaches in poor responders. In a prospective trial of 129 prior poor responders, women were randomized to either natural cycle IVF or a microdose flare regime [32]. Although extremely low, pregnancy rates per transfer were similar in the two groups (14.9 vs 10.1%, respectively). Interestingly, implantation rates were higher with natural cycles (14.9 vs 5.5%).

Deti and colleagues more recently reported upon the results of a retrospective cohort study of 51 IVF cycles in 48 consecutive patients over 5 years of women diagnosed as poor responders [33]. Patients received either a “stop”, traditional flare, or microdose flare protocol. There were no significant differences among the groups regarding any of the outcome parameters. However, a trend towards higher delivery rates was noted with the microdose flare regime. In a similar retrospective cohort design, Kaufman et al. compared outcomes in poor responders administered either very low dose luteal GnRH α or a microdose GnRH α flare regime noting similar results between the groups [34]. The retrospective design of the trials does not eliminate the variable of selection bias, which would be overcome by a prospective randomized trial.

GnRH antagonists

The incorporation of GnRH antagonists (GnRHant) represents an appealing alternative to agonists in the management of the poor responder. These agents act to rapidly

block pituitary gonadotrope receptors without any associated stimulatory effect. As a result, gonadotropin stimulation can be initiated prior to administration of GnRHant which would then act to inhibit the occurrence of undesirable rises in LH or progesterone [35].

A series of studies of varying design have evaluated this approach by initiating GnRHant on either a fixed cycle day or after a specific degree of follicular growth has been achieved. In an initial report, Craft et al. reported upon 18 poor responders in 23 prior IVF or GIFT cycles [36]. The treatment protocol consisted of a combination of clomiphene and gonadotropins with the GnRHant cetrorelix initiated after a leading follicle reached 14 mm in mean diameter. The cancellation rate decreased from 57 to 29% with an improvement in number of oocytes retrieved. Nevertheless, a rather compromised live birth rate of 11.8% was reported.

Takahashi and coworkers evaluated 40 women after multiple IVF failures employing a GnRH α long protocol [37]. These women were treated in a similar fashion with a combination of clomiphene, gonadotropins, and GnRHant. Although there were no differences in ovarian response, blastocyst quality was enhanced and a 42.1% ongoing pregnancy rate was achieved.

Akman et al. completed a prospective randomized trial of 40 poor responders employing cetrorelix when follicle size reached 14 mm in conjunction with gonadotropin COH [38]. Controls received neither GnRHant nor GnRH α . Trends towards lower clinical pregnancy and implantation rates, which did not reach statistical significance, were noted among those receiving the antagonist.

In a slight variation, Dragasic and coworkers evaluated 68 prior poor responders in 80 IVF cycles [39]. Patients were administered estradiol in the form of a 0.1 mg transdermal patch started in the luteal phase in an effort to provide induction or “priming” of endogenous FSH receptors. GnRHant was initiated two days later and continued for three days. Gonadotropin stimulation was begun and the antagonist was discontinued with menses. GnRHant was then reinitiated when adequate ovarian

stimulation had been achieved. A significant reduction in cycle cancellations in comparison to the prior cycle (13.6 vs 33.3%) was noted along with an increase in number of mature and fertilized oocytes obtained. An ongoing pregnancy rate of 26.2% was reported. The retrospective nature of the trial does create limitations, however.

Several prospective trials have evaluated GnRHant in comparison to alternative regimes designed for poor responders. Cheung et al. compared a fixed start (day 6) of multidose GnRHant to a long GnRHa protocol in a prospective randomized trial of 66 poor responders [40]. There were no significant differences in response, although a trend towards higher pregnancy rates/transfer in those receiving GnRHant (26.38 vs 17.6%) did not achieve statistical significance. However, extremely high cancellation rates of over 30% were noted in both groups.

The combination of high dose recombinant FSH combined with clomiphene and GnRHant was compared to a long GnRHa protocol in 145 women with a prior poor response [41]. Significantly lower cancellation rates with higher E_2 levels, numbers of oocytes retrieved as well as pregnancy and implantation rates were achieved with the antagonist.

Others have compared GnRHant to a microdose flare regime in prospective randomized trials. In a trial of 48 poor responder patients of whom only 24 completed therapy, Schmidt and coworkers noted no significant differences between the protocols when administered to poor responders with regards to any outcome parameters [42]. Extremely high cancellation rates of over 41%, all of which were due to an adequate response, were noted in both groups. Employing a similar design, Akman et al. reported higher numbers of oocytes and the expected higher E_2 levels when the microdose flare regime was used [43]. Lower but similar cancellation rates of 20.8 and 25% were noted. There were no differences in ongoing pregnancy or cancellation rates between the groups.

In contrast, a recent trial of 55 poor responders reported improved outcomes with a traditional GnRHa flare regime in comparison to GnRHant with regards to reduction in gonadotropin dose requirements, number of oocytes and high quality embryos obtained and fertilization rates [44]. Nevertheless, implantation and pregnancy rates were similar.

Using a different approach, Schoolcraft et al. compared outcomes protocol in a large series of 531 infertile women classified as poor or potentially poor responders based on ovarian reserve testing randomly assigned to either a GnRHant protocol to which the aromatase inhibitor letrozole was added or a microdose flare protocol [45]. It was hypothesized that letrozole might play a role in stimulating endogenous gonadotropin release without a deleterious effect on endometrial receptivity. Ongoing pregnancy and implantation rates were higher with the

microdose flare regime despite similarities in numbers of oocytes retrieved, embryo quality, fertilization rates and numbers of embryos transferred. The role of aromatase inhibitors in the management of the poor responder is beyond the scope of this article and will be addressed elsewhere in this series.

In an elegant review of the role of GnRH antagonists in poor responders, Mahutte and Arici concluded that although GnRHant does provide the advantages of a shorter duration of stimulation with reduced gonadotropin requirements, a trend towards lower pregnancy rates remains concerning [46].

Summary

The lack of a large number of adequately designed prospective randomized trials and inconsistency in inclusion criteria makes it extremely difficult to conclusively demonstrate an advantage of a single protocol for all poor responders. Evidence would suggest that minimizing GnRHa doses would be advantageous. The use of GnRHant in this patient population has not been demonstrated to be consistently beneficial although the use of adjuvant estrogen priming may be of help.

It is clear, however, that in order to minimize expense and frustration, the clinician should adequately evaluate the ovarian reserve of each patient, along with age, body habitus and prior history, prior to initiating a cycle. In this way, an appropriate stimulation regime can be planned for the first cycle, and not after an initial poor response.

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