FERTILITY AND STERILITY®
VOL. 80, SUPPL. 1, JULY 2003

Published by Elsevier Inc.
Printed on acid-free paper in U.S.A.

Antagonists in poor-responder patients

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Objective: To review treatment options for poor-responding patients who are undergoing infertility treatment.

Design: Review article and case studies.

Results: A comprehensive determination of potential ovarian response for the poor-responding patient is important in the individualization of treatment options for these patients. Treatment options include both the microdose flare leuprolide acetate and GnRH antagonist stimulation protocols. For GnRH antagonist stimulation protocols, individualization of treatment includes use of oral contraceptive pretreatment and alterations in duration of gonadotropin stimulation and start day of antagonist administration.

Conclusions: For poor-responding patients, the benefits of using GnRH antagonists for the suppression of premature LH surges plus the determination that stimulation protocols that include GnRH antagonists are at least as good as the microdose flare and provide better cycle outcomes than the long luteal leuprolide acetate down-regulation protocols have the potential to bring changes to the existing protocols for ovarian stimulation. (Fertil Steril® 2003;80(Suppl 1):S16–24. ©2003 by American Society for Reproductive Medicine.)

Key Words: Ganirelix, GnRH antagonist, poor ovarian response, treatment options

Individualization of stimulation regimens, prospective analysis of ovarian reserve, and setting defined goals regarding ovarian response to stimulation are all necessary to effectively perform controlled ovarian hyperstimulation (COH). Management of the "poor responder" is often quite challenging and requires even more attention to achieve a good reproductive outcome.

Although most clinicians would agree to classify patients who make few follicles in response to adequate doses of gonadotropins as poor responders, no uniform classification system exists. Moreover, few clinicians would agree on the best treatment modality for these difficult patients. A variety of protocols exist, therefore, allowing the clinician to attempt to individualize and optimize the treatment of the poor responder. These protocols have led to varying degrees of success and failure.

The objective of this review is to provide an update on the successful use of different treatment protocols, including GnRH antagonists, in poor-responder patients. Because success in these patients depends on adequate oocyte recruitment, I will discuss further the need for carefully selected individualization of COH treatment protocols. In describing the advantages and disadvantages of these different treatment modalities in COH, it is also important to have a clear understanding of inclusion criteria for the poor-responder patient.

DEFINITION OF A "POOR RESPONDER"

Characteristics that unquestionably categorize a patient as a poor responder remain to be standardized. Historically, patients who were expected to respond poorly to gonadotropin stimulation were given this classification because they exhibited various criteria. The selection of criteria used to categorize the poor-responding patient has been extensively reviewed (1–3), with the most obvious criterion being a previous poor-follicular response in an ovulation induction or IVF cycle (2).

At Reproductive Medicine Associates of New York (RMA of NY), we define a poor responder to COH as someone who exhibited a one- or two-follicle response or whose peak serum E_2 did not exceed 500 pg/mL by the time of hCG administration (4). Patients who require an excessive amount or duration of gonadotropin stimulation may also be classified as poor responders (i.e., ≥450 IU to achieve more than three follicles). In addition, poor responders may be identified by basal or

Received April 15, 2003; revised and accepted April 15, 2003.

Presented at the symposium, "Real-Life Clinical Applications of GnRH Antagonists: Individualization of Fertility Treatment," Seattle, Washington, October 16, 2002 in conjunction with the American Society for Reproductive Medicine 2002 annual meeting.

Supported by an unrestricted educational grant from Organon Inc.

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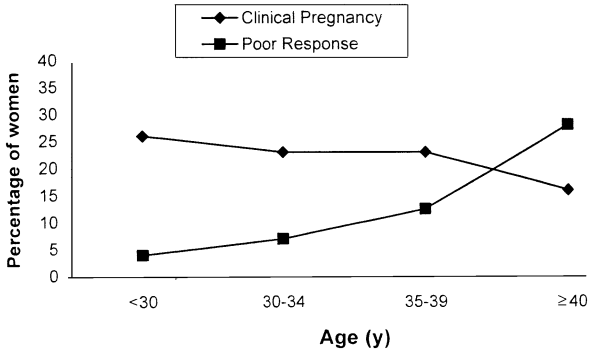
0015-0282/03/$30.00
doi:10.1016/S0015-0282(03)00765-9

FIGURE 1

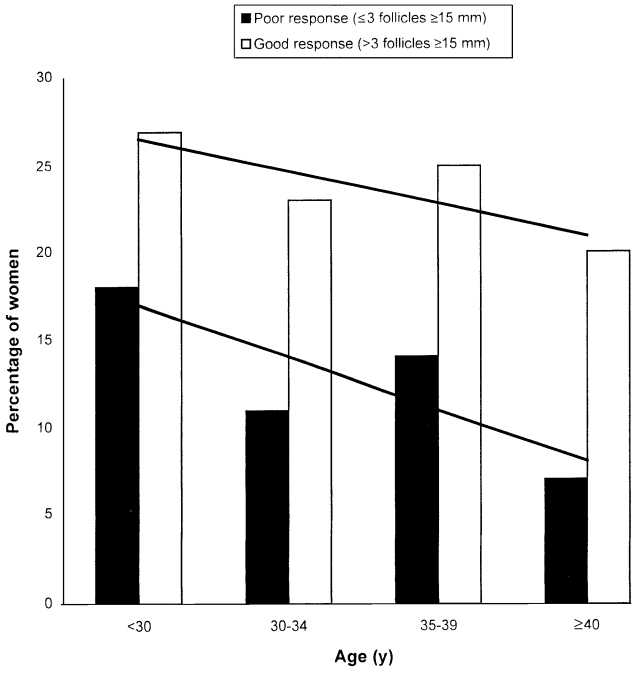
Relationship among age, declining pregnancy rates, and a rising prevalence of poor ovarian responsiveness.



Copperman. GnRH antagonist in poor-responding patients. Fertil Steril 2003.

FIGURE 2

Clinical pregnancy rates relative to ovarian response and age in IVF.



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dynamic endocrine screening of ovarian response, including basal (cycle day 3) serum FSH and E_2 levels and clomiphene citrate (CC)-stimulated serum FSH levels (5, 6). Baseline serum inhibin B levels (7) or more recently, day 5 inhibin B in down-regulated cycles (8), have also been used to predict ovarian response to gonadotropins. These and other endocrine tests are reported to be predictive of ovarian reserve and IVF outcome (9–11). Although gonadotropin stimulation tests (12) have been used to predict response, they are not widely used, as in effect, they merely demonstrate that patients with a poor ovarian response will be poor responders.

Patient age of ≥40 years may result in a designation of a patient as a low or poor responder and most probably can be attributed to a reduction in the number of ovarian follicles available for recruitment (13) and declining oocyte quality (14) (see Figs. 1 and 2). Albeit, ovarian age is not an absolute indicator of poor success in COH and setting a strict age limit is debatable. In fact, older patients with a good response to COH have a good prognosis for IVF treatment (15). Evaluating ovarian reserve by a number of predictors may be a better indicator of treatment success than age.

The sonographic appearance of the ovary may also have value in identifying the poor responder. Ovarian volume itself may very well be a simple predictor of ovarian reserve. Although total ovarian volume has been considered a good indicator of ovarian reserve, the volume of the smallest ovary may be even more predictive (16). Most clinicians do not formally calculate ovarian volume as part of the routine evaluation of every new patient, but it is part of the gestalt that one has when one does a baseline transvaginal ultrasound. Three-dimensional ultrasound has made assessment of volume significantly easier, thereby making some of the newer studies that document the importance of generating ovarian volume data even more significant.

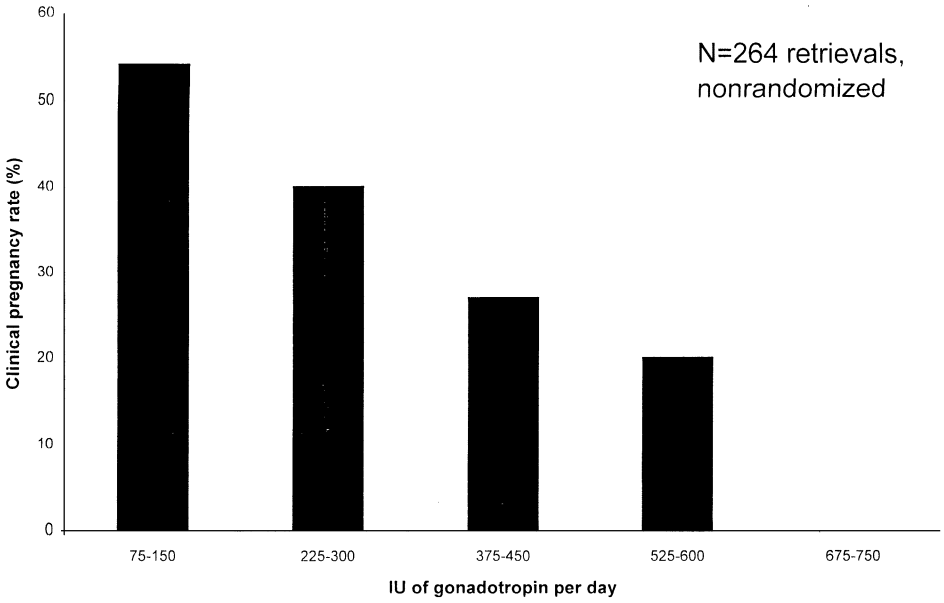
Three-dimensional imaging has also changed the way that we approach baseline transvaginal scans. This new technology provides us with the opportunity to examine ovarian basal antral follicle number, ovarian volume, stromal area, and ovarian stromal blood flow (17–19). Studies using three-dimensional imaging report that the best predictor of favorable IVF outcome is total basal antral follicle count and that this criterion provides a better prognosis of a poor response than a patient's chronologic age and current endocrine screening tests. In addition, combining the results of three-dimensional ultrasound imaging with other currently used predictors provided a more stringent forecasting of a poor ovarian response (19) and success or lack in an IVF cycle (18).

INDUCING AN OPTIMAL FOLLICULAR RESPONSE IN THE POOR RESPONDER

Inducing a multifollicular response in a patient who is a known poor responder remains a challenge. When patients do not respond appropriately to the standard dose of gonadotropins (225–300 IU), the clinician is tempted to incrementally increase the dose. Unfortunately, administering more than 450 IU per day does not appear to add significantly to the ovarian response or to improve the reproductive outcome (11, 20). In fact, patients who require more than 450 IU of

FIGURE 3

High-dose gonadotropins are associated with poor pregnancy outcomes after IVF.



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gonadotropin probably have significantly diminished ovarian reserve and will have a poor outcome, no matter what dosage is administered. Although there have been some pregnancies reported using 600 IU of gonadotropins, clinical pregnancy rates are inversely correlated with the amount of gonadotropins used to induce multifollicular development for IVF (11, 21, 22) (Fig. 3).

It is unclear whether the addition of a GnRH agonist is advantageous or detrimental in the treatment of poor responder patients. The addition of GnRH agonists has played a role in improving assisted reproductive technology (ART) outcomes (2), especially with regard to decreasing the percentage of cancelled IVF cycles. However, it is not uncommon to see a patient with normal ovulatory cycles, who, when placed on a long (luteal phase) leuprolide acetate suppression protocol and then given gonadotropins, fails to stimulate and becomes refractory. These patients have insufficient levels of serum E_2 and an absence of a follicular response, even with increased doses of gonadotropins. Effectively, these patients have been oversuppressed by the GnRH agonist. When we reviewed the cycle characteristics of such patients, the predictive factors in 40 patients who received the agonist and had a failed follicular response to gonadotropins included age >40 years, low basal antral follicle counts, small ovarian volumes, a prior history of a poor response to COH, and unexplained infertility, which is actually an independent predictor (Scott et al, personal communication). These were patients who had been cycling normally, so apparently the GnRH agonist does more than just prevent an LH surge.

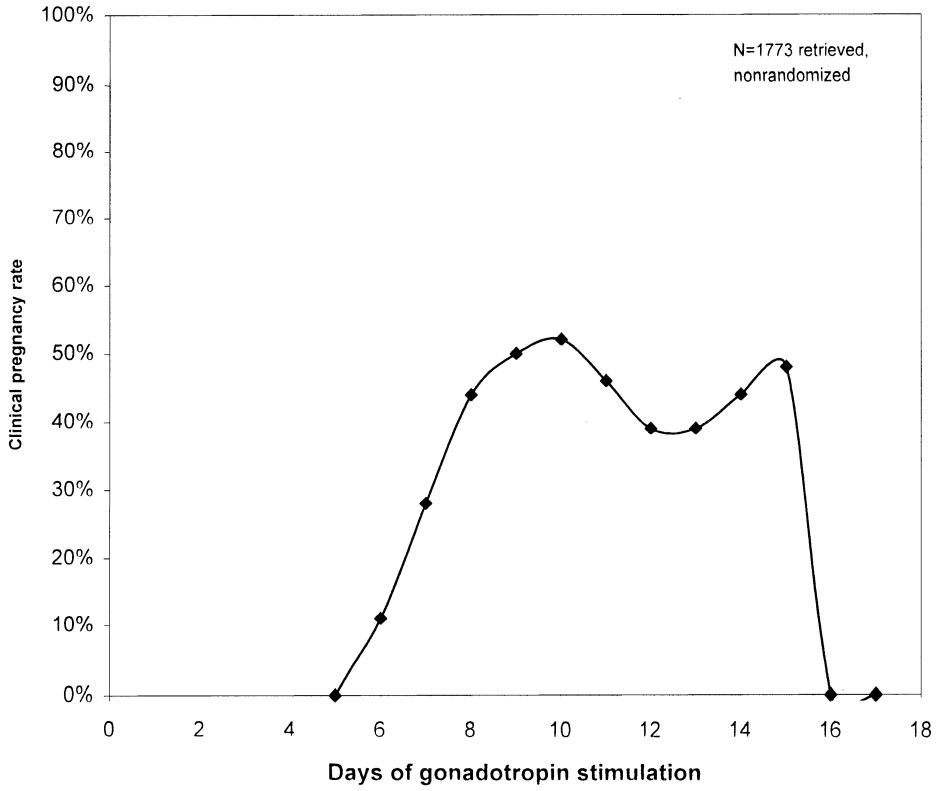
For poor-responder patients, modifying the agonist treatment may result in improved IVF outcome. For example, in comparison to the long GnRH agonist suppression protocol, the minidose GnRH agonist treatment results in higher E_2 levels, more follicles, shorter stimulations, and ultimately, improved implantation and pregnancy rates (23). Another modification is to initiate gonadotropins and a GnRH agonist together in the follicular phase (the so-called microdose flare protocol) or to initiate the microdose flare after oral contraceptive (OC) pretreatment (the co-flare) (24, 25). In a cohort of poor-responder patients using this treatment modality (25), outstanding pregnancy rates have been reported.

With the advent of the antagonists, the clinician may now address the poor-responder patient from a new perspective. The addition of the GnRH antagonist to stimulation protocols prevents premature LH surges while not causing suppression in the early follicular phase, a crucial time for poor-responder patients (26). In this group of poor-responders, cancellation, clinical pregnancy, implantation rates, and ongoing pregnancy rates were similar between the antagonist and agonist flare protocols.

The GnRH antagonist treatment regimens allow for a more natural recruitment of follicles in the follicular phase in an ovary that has not been suppressed by the absence of FSH and LH caused by a GnRH agonist. In fact, on day 3 of an

FIGURE 4

Clinical pregnancy rates relative to duration of gonadotropin stimulation.



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agonist cycle, there are extremely low serum levels of FSH and LH, with the contribution of the pituitary in the range of 1–2 IU/L of FSH and LH. Conversely, in the antagonist cycles (similar to the natural cycle), the median serum FSH and LH levels at the time of initiation of FSH therapy are in the range of 8 IU/Land 5 IU/L, respectively (27). In poor responders with low ovarian reserves, these endogenous FSH and LH levels observed without any suppression may contribute significantly to the circulating gonadotropin pools.

The follicular response in antagonist cycles is, therefore, quite different than that seen with luteal phase down-regulation. Part of the learning curve faced by the clinician learning to use the antagonist is how to approach the different characteristics of the follicular phase (primarily, the rapid early follicular growth of follicles).

In the North American Ganirelix clinical trial, at cycle day 6, more follicles were observed in the ganirelix group than in the agonist group. However, by day 10, the number of follicles were similar in the two groups and by the day of hCG treatment, one fewer follicle was observed in the antagonist group compared with the agonist group (27). The rapid emergence of follicles with gonadotropin stimulation is not an unexpected observation. In fact, as those clinicians with experience predating the introduction of the agonists will recall, this is similar to what was formerly seen in "no-lupron" cycles (28). Whenever possible, it is our practice to not trigger with hCG too early (before cycle day 11, which correlates to 9 days of stimulation) in patients receiving antagonist protocols, as their rapid follicular growth may not necessarily predict oocyte maturity.

We have recently reviewed cycle characteristics for patients in antagonist stimulation cycles in an attempt to determine optimal IVF stimulation protocols. One question that was addressed was whether the duration of gonadotropin stimulation affects clinical pregnancy rates in antagonist treated cycles. A total of 1,773 patient cycles were included in this retrospective analysis. Duration of gonadotropin stimulation ranged from 5–17 days. The GnRH antagonist was initiated when a lead follicle reached 14 mm.

The results of this retrospective review of antagonist cycles are presented in Figure 4. The clinical pregnancy rate significantly increased in a linear fashion from 5–9 days of gonadotropin stimulation as determined by linear regression

analysis ($P<.001$) at which time clinical pregnancy rates plateaued. From 9–15 days of stimulation, clinical pregnancy rates were similar and ranged from 39%–52%. No pregnancies were observed with 16 or 17 days of gonadotropin stimulation. These results suggest that clinical pregnancy rates improve with increased duration of gonadotropin stimulation, at least up to 9 days. Furthermore, the duration of gonadotropin stimulation associated with acceptable pregnancy rates is fairly broad (9–15 days).

In the antagonist stimulation cycles at our centers, we have also begun to address the optimal criteria for day of hCG administration. In a second retrospective analysis, we compared pregnancy rates with administration of hCG when the lead follicle diameter was 16–17 mm, 18–19 mm, or >20 mm. Results of this preliminary study indicated that in GnRH antagonist cycles, as the size of the follicle increased, a concomitant increase in pregnancy rates occurred. Conversely, patients in agonist down-regulation treatment regimens did not benefit from obtaining larger follicle sizes. Furthermore, it appears that increasing lead follicle size is a more accurate correlator of increasing pregnancy rates than increasing duration of gonadotropin stimulation.

It is possible that hormonal treatment in the month before an IVF cycle may have an effect on cycle characteristics. The results of a recent multicenter study reported that in normal-responding patients, OC pretreatment could be successfully used to schedule patients before COH in antagonist stimulation cycles (29). This study assessed the feasibility of OC pretreatment for scheduling women undergoing COH in GnRH antagonist cycles. The treatment regimen for these normal responders included 14–21 days of OC pretreatment beginning on days 1–3 of menses. Recombinant FSH was first administered 4 days after discontinuation of OC pretreatment with ganirelix being initiated on day 6 of FSH or when the lead follicle reached a mean diameter of 12 mm. Cycle outcomes included a mean number of 15.6 oocytes retrieved, implantation rate of 35.4%, and a per-oocyte retrieval pregnancy rate of 40.7%. These results indicate that OC pretreatment can be used successfully to schedule normal-responding patients before COH in antagonist stimulation cycles.

The use of OC pretreatment in antagonist cycles for the poor-responding patients also warrants careful consideration as their ovarian reserves may be especially sensitive to suppression of endogenous gonadotropins. To address the effect of OC pretreatment in antagonist stimulation cycles of poor responders, we compared, in this group of patients, clinical pregnancy rates when treatment regimens included OC pretreatment with a similar cohort of patients that did not receive OC pretreatment. In this retrospective study of 1,343 patients from Reproductive Medicine Associates of New York and New Jersey, poor-responding patients were those patients who had been prospectively predicted to be poor responders and were, therefore, given a starting dose of 450 IU of gonadotropin.

In the OC pretreatment group, patients were administered OC for 18–24 days, beginning on cycle day 3. Patients were first administered a combination of recombinant FSH and hMG on cycle day 3, and were administered GnRH antagonist when their lead follicle reached 14 mm. As these patients were known to have decreased ovarian reserve, standard protocol was to perform an "add-back" of an additional 75 IU of hMG beginning the first day of antagonist.

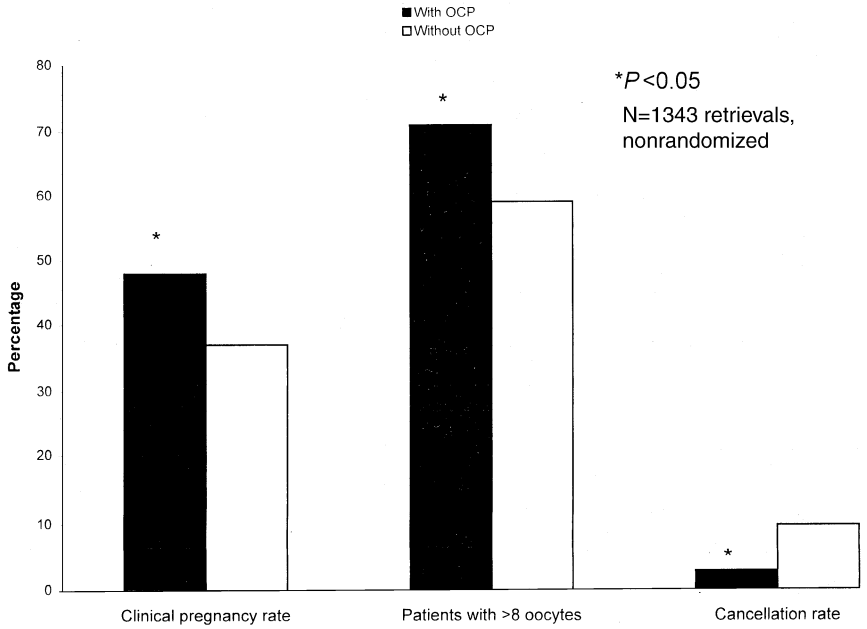
Patients whose antagonist stimulation cycle included OC pretreatment had a significantly higher pregnancy rate and a significantly lower cancellation rate ($P<.05$) (Fig. 5). In addition, a higher proportion of patients obtained more than eight oocytes when OC pretreatment was part of their treatment regimen ($P<.05$). In contrast, no differences in pregnancy rates were observed with OC pretreatment in normal responders (patients receiving <450 IU of gonadotropin; data not shown).

These results provide strong evidence that, with certain treatment regimens, inclusion of OC pretreatment can be of benefit to poor-responding patients. However, these results are in contrast to those of Shapiro et al. (30), who reported significantly increased cancellation rates in a group of poor-responding patients who received OC pretreatment (23%) compared with a similar cohort of patients not receiving OC pretreatment (9%). Such a dichotomy of outcomes in these poor-responding patients require careful examination of potential differences. Two differences in study design, one in inclusion criteria for characterizing patients as poor responders and the other in the use of add-back LH, are immediately recognizable. With regard to the first difference, Shapiro et al. (30) described poor responders as patients with a previous poor response, elevated basal gonadotropin (>12 IU/mL or E_2 >75 pg/mL), or with the previous cycle cancellation. In our data series, we included those patients with a basal antral follicle count of less than six, patients aged 40 years or older, patients with a peak serum E_2 of 500 pg/mL, and were, therefore, those who were given daily doses equaling at least 450 IU of gonadotropin. The second difference observed in the two studies when comparing Shapiro (30) with our own data was in the treatment regimens used, specifically in the addition of LH in the form of hMG or low-dose hCG, as described previously. Conversely, the treatment strategy for the poor responder in the Shapiro et al. study (30) did not include LH add-back. Whether add-back LH can compensate for any over-suppression of endogenous LH in a GnRH antagonist treatment regimen that includes OC pretreatment warrants further exploration. Furthermore, whether the LH add-back of choice, hMG, recombinant LH, or low-dose hCG provides similar outcomes should be evaluated.

Also somewhat controversial is the timing of the first dose of ganirelix acetate. Introduction too early in a cycle would be counterproductive and would lead to a shut off of poten-

FIGURE 5

Oral contraceptive pretreatment (OCP) is associated with improved cycle characteristics in IVF.



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tially helpful endogenous FSH, effectively converting the antagonist cycle into a down-regulation cycle and interfering with early follicular recruitment. Conversely, if the antagonist is added too late in the cycle, it might not effectively inhibit a premature LH surge. In our program, ganirelix acetate is administered when there is a 14-mm dominant follicle. Although the North American Ganirelix Study Group introduced the antagonist specifically on day 6 of IVF cycles (27), it would appear that individualization of treatment to patient response and patient cycle-specific characteristics will help optimize stimulation regimens.

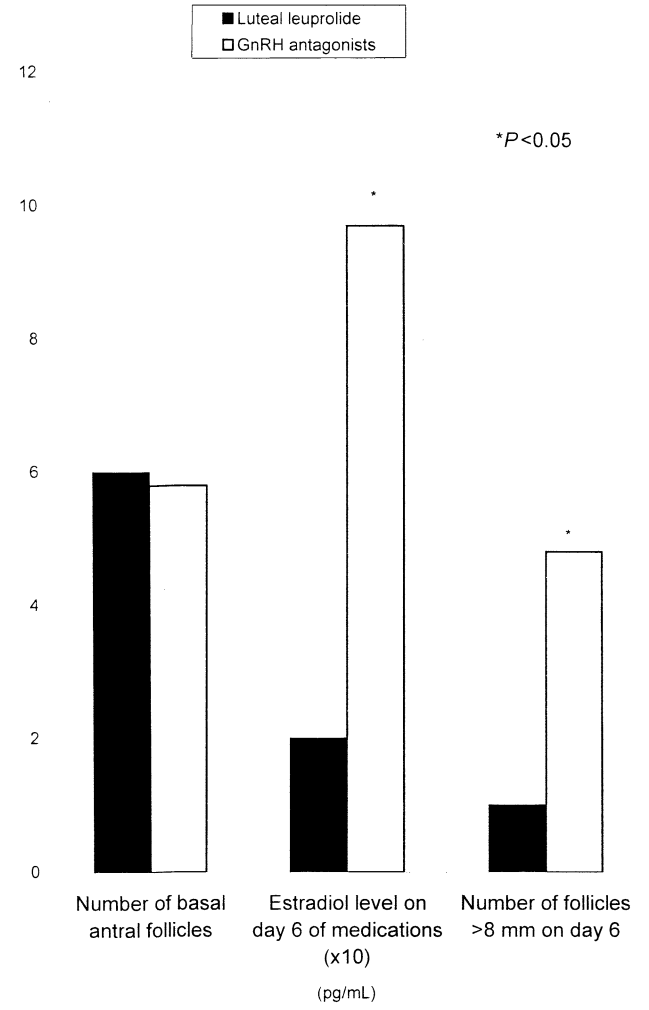
In addition to the timing of the start of administration of the antagonist, alterations in serum E_2 with the initiation of the antagonist have been examined. A small percentage of patients in the Ganirelix Dose-Finding Study Group (31) experienced a decline in serum E_2 levels 24 hours after the first injection of the GnRH antagonist (32). The significance of this finding has been debated. In a recent retrospective study, there were no differences in pregnancy outcome among patients with an increase, plateau, or decline in E_2 levels on the day after antagonist administration and these investigators concluded that no intervention, such as LH add-back, was necessary during stimulation with recombinant FSH and ganirelix acetate (30). Although this decrease in E_2 may not be a concern for the normal responder, it is possible that any decline in bioavailable gonadotropin has the potential to be problematic for the poor responder. These patients who are poor responders probably have either fewer FSH receptors or fewer normal FSH receptors and probably do require maximal stimulation. By reviewing the literature on ganirelix, including the North American Ganirelix Study Group (27) and examining our own center's data, which mirrors those of Shapiro et al. (30), our concern is sufficient that we proactively add an additional 75 IU of gonadotropin routinely to our antagonist/recombinant FSH stimulation protocols.

Clearly, the use of antagonists has advantages for the patients. For normal-responding patients, there are several recently published studies that suggest that the antagonist offers the same level of success as agonist protocols. However, one advantage of the antagonist is a lower cancellation rate (33). There is a reduction in the duration of GnRH analogue treatment, and nearly an 80% decrease in the number of injections that a patient takes over leuprolide acetate (20). Other benefits include a lower risk of ovarian hyperstimulation syndrome (OHSS) and avoidance of estrogen (E) deprivation symptoms (hot flushes, sleep disturbances, and headaches) associated with long luteal-phase leuprolide acetate suppression (34).

We retrospectively examined several hundred cycles to identify patients who were canceled for low response in a prior cycle of IVF. Using our definition, these are poor responders. We examined treatment in a stimulation cycle

FIGURE 6

Patients who were cancelled for poor response in a prior assisted reproductive technology (ART) cycle.



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that included an antagonist compared with that of long luteal leuprolide acetate down-regulation in these patients. Both groups of patients had low but acceptable basal antral follicle counts (see Fig. 6). We observed that the antagonist-treated patients had significantly higher E_2 levels on day 6 of gonadotropin treatment compared with patients treated with long luteal-phase leuprolide acetate down-regulation, almost a fivefold greater serum E_2 level ($P<.05$). In addition, these patients had significantly higher follicle counts, again almost a fivefold increase ($P<.05$).

We further examined the comparison of cycle outcomes in poor-responding patients with these two stimulation protocols by dividing the patient population into those with normal or low basal follicle counts (Fig. 7). In these poor-responding patients who were treated with a GnRH antagonist, the ongoing pregnancy rates were significantly better in patients who had normal basal antral follicle counts, and in fact, also in patients who had low basal antral follicle counts. It, therefore, appears that in poor responders, stimulation protocols that include a GnRH antagonist provide better cycle outcomes than leuprolide acetate down-regulation.

There are very few studies that actually compare the agonist flare protocol and the antagonist. A randomized trial (26) compared clinical outcomes of poor-responding patients who were treated with either microdose flare (leuprolide acetate) protocol or the antagonist (cetrorelix) protocol. Patients in the microdose flare group also received OC pretreatment. There was no difference in the median total treatment doses of FSH and hMG between the two groups. Serum E_2 levels were significantly lower on the day of hCG administration in the antagonist group. No differences were observed between the two groups for numbers of oocytes retrieved, fertilization rates, number of embryos transferred, and most especially, implantation rates and ongoing pregnancy rates per transfer. These investigators concluded that the impact of these stimulation protocols in the ovarian stimulation was the same in these poor responding patients.

At Reproductive Medicine Associates, we compared cycle outcomes in poor responders who had stimulation protocols that included an antagonist with those with the microdose flare protocol. This study was a retrospective analysis in which historic controls were used as the comparator and patients were not matched. In addition, there may have been a physician bias in placing patients into one treatment group or the other. Patients were placed in the antagonist or microdose flare treatment group usually after failing in a leuprolide down-regulation cycle, and these patients could be considered the poorest of the poor responders. As a result, a direct comparison could not be made between either the antagonist or the microdose flare protocol and the leuprolide down-regulation cycles. For this analysis,

FIGURE 7

Pregnancy rates in GnRH antagonist-treated cycles in patients with low and normal BAF counts.

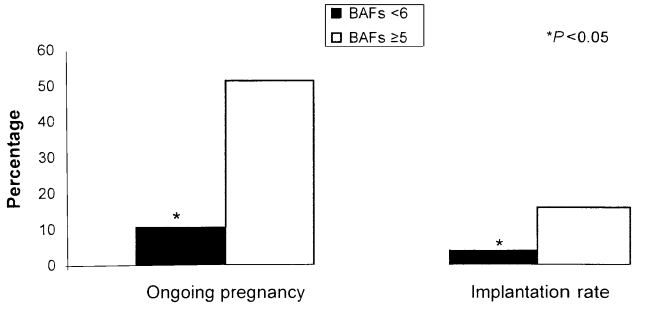

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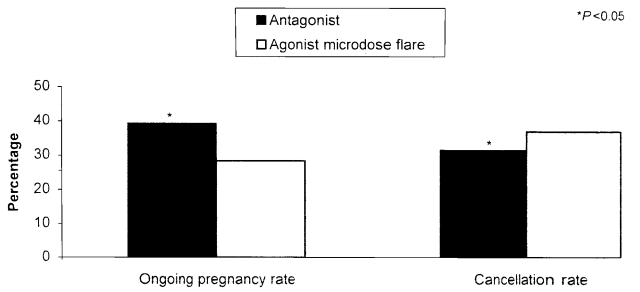
FIGURE 8

Comparison of cycle outcomes in patients with low BAF counts treated with GnRH antagonist or microdose flare agonist protocol.



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poor responders were described as those with a basal antral follicle count of less than six who received a daily dose of 450 IU of gonadotropin. The results of this retrospective analysis indicated that for these poor responders, the inclusion of a GnRH antagonist in the treatment regimen significantly increased clinical pregnancy rates and significantly lowered cancellation rates compared with patients treated with the microdose flare protocol ($P<.05$) (Fig. 8).

In conclusion, optimal stimulation of the poor responder remains a challenge. Leuprolide acetate down-regulation may over-suppress some poor responders and does not appear to be the stimulation of choice. Pretreatment with OC under specific treatment regimens that include some form of LH add-back (hMG, recombinant LH, low-dose hCG) may help time cycles and may actually improve IVF outcome and decrease cancellation rates in poor-responding patients. Increasing the dose of gonadotropin >450 IU does not appear to provide benefit. In our practice, we ensure some level of LH, with either hMG or low-dose hCG, especially after introduction of an antagonist into the stimulation protocol. Outcome in Ganirelix cycles may be improved by increasing the duration of gonadotropin stimulation to achieve a larger follicle size. Although the use of both a GnRH antagonist and a microdose flare protocol are effective at preventing an LH surge, selection of an antagonist protocol may improve cycle outcomes, including a higher pregnancy rate and lower cancellation rate. For antagonist cycles, individualization of patient treatment protocols to optimize duration of gonadotropin stimulation, start of ganirelix administration and OC pretreatment is an important consideration for all patients, but especially for the poor-responding patients. In addition, if there is no ovarian reserve, that is, no preantral follicles to stimulate, there will not be a good outcome with IVF, no matter which stimulation protocol is attempted.

Finally, antagonists can provide immediate control of LH and an absence of the flare effect. Therefore, the addition of the antagonist avoids ovarian suppression at the start of the cycle when it is, most likely, least beneficial for the poor-responding patient and prevents premature LH surge at midcycle when it is most crucial to do so. Based on accumulating data, more patients classified as poor responders who attempt IVF will get to oocyte retrieval. The patient benefits of the antagonists plus the determination that they provide better outcomes than leuprolide acetate down-regulation and at least as good, and potentially improved, outcomes compared with the microflare dose treatment have the potential to bring changes to our existing COH protocols for the poor-responding patient.

Acknowledgments: The author thanks Richard T. Scott, Jr., M.D., Paulbergn, M.D., and Brooke Bauman of RMA of MJ for their analysis of the data and preparation and assistance with this manuscript.

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