Ultrashort gonadotropin-releasing hormone agonist combined with flexible multidose gonadotropin-releasing hormone antagonist for poor responders in in vitro fertilization/embryo transfer programs

To evaluate the appropriate controlled ovarian hyperstimulation (COH) protocol in poor responders, we compared the stimulation characteristics of 21 cycles, which included the ultrashort gonadotropin-releasing hormone (GnRH) agonist combined with the flexible multidose GnRH antagonist, to the patients' previous failed in vitro fertilization attempts. The use of an ultrashort GnRH-agonist/GnRH-antagonist COH protocol resulted in a statistically significantly greater number of follicles larger than 14 mm on the day of hCG administration, a higher number of oocytes retrieved and embryos transferred, and a reasonable clinical pregnancy rate (14.3%). (Fertil Steril® 2008;90:228–30. ©2008 by American Society for Reproductive Medicine.)

Controlled ovarian hyperstimulation (COH) is considered a key factor in the success of in vitro fertilization/embryo transfer (IVF-ET) because it enables the recruitment of multiple healthy fertilizable oocytes and, thereby, enabling multiple ET instead of single ET (1). However, owing to the extreme variability in ovarian response to COH, this method may yield a very small number of follicles, if any, in a subgroup of patients (2) who are collectively referred to as "poor responders" or "low responders." There is no universal definition of a poor responder, but the final test is ovarian response to stimulation; fewer than two to five oocytes retrieved in an IVF cycles has been suggested a definition.

Many strategies are available for the treatment of poor responders, including increasing the dose of administered gonadotropins, using gonadotropin-releasing hormone antagonists (GnRH-antagonists), reducing or stopping the dose of GnRH-agonist (GnRH-agonist), initiating GnRH-agonist and gonadotropins together in the follicular phase (the ultrashort and the short "flare" protocols), using a microdose GnRH-agonist flare protocol, or co-administering letrozole (2–5). Nevertheless, no compelling advantage has been hitherto established for one stimulation protocol over another.

Several years ago, Berger et al. (6) demonstrated that combining the microdose flare GnRH-agonist and GnRH-antagonist protocols in poor responders who previously had failed several IVF treatment cycles resulted in a 13% clinical pregnancy rate. This protocol, which combined the benefit of the stimulatory effect of microdose flare on endogenous follicle-stimulating hormone (FSH) with the benefit of immediate luteinizing hormone (LH) suppression of the GnRH antagonist, was thus suggested as a valuable new tool for treating poor responders. Prompted by the aforementioned observations, we further evaluated the role of the ultrashort GnRH-agonist flare protocol combined with the flexible multidose GnRH-antagonist protocol in patients who had responded poorly to a previous IVF attempt.

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PATIENTS AND METHODS

The study included poor responders who were admitted to our IVF unit during a 2-year period and were treated by an ultrashort GnRH-agonist flare combined with a flexible multidose GnRH-antagonist protocol (ultrashort GnRH-agonist/GnRH-antagonist) after having responded poorly to a previous IVF cycle. Poor response was defined as the production of fewer than five oocytes in the previous IVF cycle.

The ultrashort GnRH-agonist/GnRH-antagonist protocol entailed the administration of triptorelin (Lapidot, Netanya, Israel) at 0.1 mg/day, started on the first day of menses and continued for 3 consecutive days, followed by gonadotropins, which were initiated 2 days later with maximal doses. Once the leading follicle had reached a size of 14 mm or/and estradiol (E_2) levels exceeded 400 pg/mL, cotreatment was initiated with the GnRH-antagonist cetrorelix (Serono Laboratories, Aubonne, Switzerland) at 0.25 mg/day, which was continued up to and including the day of human chorionic gonadotropin (hCG) administration. Patients were monitored by ultrasonography and by measuring serum E_2 and progesterone levels. Routine IVF or intracytoplasmic sperm injection (ICSI) was then performed, as appropriate. Transvaginal ET was performed 48 to 72 hours after ovum pick-up. All patients received luteal support with progesterone.

The ovarian stimulation characteristics, number of oocytes retrieved, and number of embryos transferred were assessed and compared between the ultrashort GnRH-agonist/

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GnRH-antagonist cycle (study cycle) and the previous cycle (control cycle).

Statistical analysis was performed with Student's paired *t*-test and chi-square, as appropriate. Results are presented as means ± standard deviations; $P<.05$ was considered statistically significant.

RESULTS

Twenty one consecutive ultrashort GnRH-agonist/GnRH-antagonist cycles in 21 poor responders were evaluated. The patients' mean age during the study cycle was 38.4 ± 4.0 years (range: 29 to 43 years). The clinical characteristics of the IVF cycles in the two study groups are shown in Table 1.

There were no differences between the groups in the length of stimulation, the number of gonadotropin ampules administered, peak E_2 and progesterone levels, or fertilization rates, but the number of follicles >14 mm on the day of hCG administration ($P<.01$), number of oocytes retrieved ($P<.01$), and number of embryos transferred ($P<.01$) were statistically significantly higher in the ultrashort GnRH-agonist/GnRH-antagonist as compared with the control cycles.

No pregnancies were recorded in the control group versus five in the study group: two chemical pregnancies, two ongoing pregnancies, and one live birth.

DISCUSSION

The use of a GnRH-agonist during COH for IVF-ET has become widely accepted. It is associated with a reduction in cycle cancellation due to premature LH surge, thereby yielding an improved pregnancy rate per ET. However, its role in treating poor responders is unclear (2, 5, 7). The disadvantages to poor responders are the associated large increase in gonadotropin consumption, poor ovarian response due to intense endogenous FSH suppression (8), and the possible local inhibitory effect of GnRH-agonist on the ovaries (9). Attempts to overcome the adverse effects were made by the introduction of the ultrashort GnRH-agonist protocol or the microdose GnRH-agonist flare protocol (10). These protocols aimed to enhance ovarian response by enhancing the release of early follicular phase FSH with no profound inhibition of ovarian response through the ovarian GnRH receptors while sufficiently inhibiting premature LH surges (11).

The introduction of GnRH-antagonists to the COH armamentarium has raised the interest in their potential application for poor responders. Their use in poor responders has been associated with shorter length of stimulation, lower gonadotropin requirements, reduced patient costs, and shorter downtimes between consecutive cycles (3), but their superiority in terms of pregnancy rate has yielded conflicting results (3, 12, 13).

In our study, poor responders undergoing the ultrashort GnRH-agonist/GnRH-antagonist protocol demonstrated a statistically significantly higher number of oocytes retrieved and embryos transferred as compared with the patients' previous IVF attempts. Three clinical pregnancies (pregnancy rate, 14.3%) were recorded. However, it should be emphasized that the increased pregnancy rate in the ultrashort GnRH-agonist/GnRH-antagonist protocol is *biased* due to the study design, which offered this protocol to poor responders who had failed a previous IVF attempt. These observations are in line with those of Berger et al. (6), who demonstrated the benefit of combining the microdose flare GnRH-agonist and GnRH-antagonist protocols in poor responders who previously had failed several IVF treatment cycles. Unfortunately, the report by Berger et al.

TABLE 1

Clinical characteristics of the IVF cycles in the two study groups.

	Control cycles	Study cycles	*P* values
Number of cycles	21	21	
Number of gonadotropin ampules used	70 ± 25	79 ± 35	NS
Length of stimulation (days)	11.0 ± 2.7	11.3 ± 3.7	NS
Peak E_2 levels on day of hCG administration (pg/mL)	1058 ± 1230	1034 ± 459	NS
Progesterone levels on day of hCG administration (ng/mL)	0.8 ± 1.1	0.7 ± 0.3	NS
Number of follicles >14 mm on day of hCG administration (range)	3.6 ± 1.4 (1–6)	5.7 ± 2.7 (1–12)	<.01
Number of oocytes retrieved (range)	1.9 ± 1.2 (0–4)	2.3 ± 1.7 (0–8)	<.01
Fertilization rate	43 ± 43	57 ± 35	NS
Number of embryos transferred	0.7 ± 0.9	1.9 ± 1.2	<.01

Note: NS, not statistically significant.

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(6), which is the only report dealing with the combined GnRH-agonist/GnRH-antagonist protocol, was presented only as meeting abstract, so no data are available regarding the stimulation characteristics of the control cycles.

As mentioned, no other data are available regarding the combined ultrashort GnRH-agonist/GnRH-antagonist protocols, but several studies have compared the GnRH-agonist flare to the GnRH-antagonist protocols. Posada et al. (14) compared the clinical outcome of COH in unselected patients undergoing IVF with a multidose GnRH-antagonist versus ultrashort GnRH-agonist. The GnRH-antagonist protocol was shown to reduce treatment duration and amount of gonadotropin used, but no difference was observed in pregnancy rate in patients >38 years old.

Demirol et al. (15) demonstrated that a microdose flare-up protocol seems to have a better outcome in poor responders, who had a significantly higher implantation rate when compared with patients undergoing a GnRH-antagonist multiple-dose protocol. Accordingly, Hollett-Caines et al. (16) observed a trend toward improved pregnancy rates in women ≥40 years of age using the microdose flare protocol, while those younger than 35 years benefited from the GnRH-antagonist protocol. Detti et al. (17) also demonstrated a trend toward a higher completed pregnancy rate and a higher implantation rate with the microdose flare protocol compared with the stop and short GnRH-agonist protocols. Malmusi et al. (13) compared the efficacy of the short flare-up GnRH-agonist protocol to the flexible GnRH-antagonist in poor responders and observed that the flare-up protocol appeared to be more effective than the GnRH-antagonist protocol in terms of mature oocytes retrieved, fertilization rate, and top-quality embryos transferred. On the other hand, Morgia et al. (18) determined the efficacy of natural-cycle IVF compared with COH with a microdose GnRH-agonist flare in poor responders and demonstrated that natural-cycle IVF is at least as effective as COH, especially in younger patients, and has a better implantation rate.

Poor responders produce higher oocyte yields and have better implantation and pregnancy rates with the use of the ultrashort GnRH-agonist/GnRH-antagonist protocol. Further large prospective studies are needed to elucidate the role of ultrashort GnRH-agonist/GnRH-antagonist protocols in poor responders and to identify before initiating ovarian stimulation the specific characteristics of women who would benefit from this COH protocol, which should aid in fertility counseling.

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