A randomized prospective trial comparing gonadotropin-releasing hormone (GnRH) antagonist/recombinant follicle-stimulating hormone (rFSH) versus GnRH-agonist/rFSH in women pretreated with oral contraceptives before in vitro fertilization

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Objective: To compare the effects of oral contraceptive (OC) pill pretreatment in recombinant FSH/GnRH-antagonist versus recombinant FSH/GnRH-agonist stimulation in in vitro fertilization (IVF) patients, and to evaluate optimization of retrieval day.

Design: Prospective, randomized, multicenter study.

Setting: Private practice and university centers.

Patient(s): Eighty patients undergoing IVF who met the appropriate inclusion criteria.

Intervention(s): Four study centers recruited 80 patients. The OC regimen began on cycle days 2 to 4 and was discontinued on a Sunday after 14 to 28 days. The recombinant FSH regimen was begun on the following Friday. The GnRH-agonist group was treated with a long protocol; the GnRH-antagonist was initiated when the lead follicle reached 12 to 14 mm. When two follicles had reached 16 to 18 mm, hCG was administered.

Main Outcome Measure(s): The primary outcome measures were the number of cumulus–oocyte complexes, day of the week for oocyte retrieval, and total dose and days of stimulation of recombinant FSH. Secondary efficacy variables included pregnancy and implantation rate; serum E_2 levels on stimulation day 1; serum E_2, P, and LH levels on the day of hCG administration; follicle size on day 6 and day of hCG administration; the total days of GnRH-analogue treatment; total days on OC; total days from end of OC to oocyte retrieval; and the cycle cancellation rate.

Result(s): Patient outcomes were similar for the days of stimulation, total dose of gonadotropin used, two-pronuclei embryos, pregnancy (44.4% GnRH-antagonist vs. 45.0% GnRH-agonist, $P=.86$) and implantation rates (22.2% GnRH-antagonist vs. 26.4% GnRH-agonist, $P=.71$). Oral contraceptive cycle scheduling resulted in 78% and 90% of retrievals performed Monday through Friday for GnRH-antagonist and GnRH-agonist. A one day delay in OC discontinuation and recombinant FSH start would result in over 90% of oocyte retrievals occurring Monday through Friday in both groups.

Conclusion(s): The OC pretreatment in recombinant FSH/GnRH-antagonist protocols provides a patient-friendly regimen and can be optimized for weekday retrievals. No difference was seen in number of 2PN embryos, cryopreserved embryos, embryos transferred, implantation and pregnancy rates between the two stimulation protocols. (Fertil Steril® 2005;83:321–30. ©2005 by American Society for Reproductive Medicine.)

Key Words: GnRH-antagonist, oral contraceptive scheduling, IVF, GnRH-agonist

Gonadotropin-releasing hormone (GnRH) antagonists, recently made available for clinical use in the United States, have many advantages for patients and physicians with regard to convenience and flexibility of administration. The endocrine milieu during controlled ovarian hyperstimulation (COH) is different than with the GnRH-agonist protocols, mainly because of their inherently different mechanism of action (1). The lack of suppression during the early to middle follicular phase in antagonist cycles results in a more precipitous rise in E_2 during this time period. Although not significantly different, initial multicenter clinical trials displayed slight differences in pregnancy and implantation rates, which were thought to be due, in part, to lack of physician experience with the endocrine differences between these GnRH-analogue protocols (2, 3).

As physicians gained greater experience and comfort with GnRH-antagonist regimens, comparable outcomes in pregnancy and implantation rates were achieved (4). Once phy-

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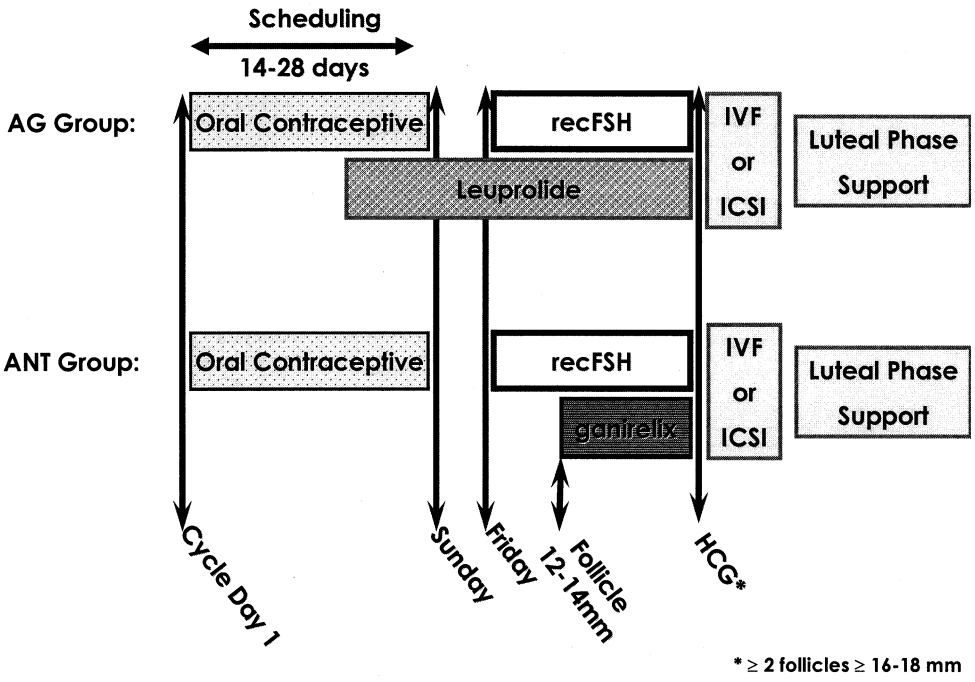
FIGURE 1

Schematic representation of the two stimulation protocols: GnRH-agonist (AG) and GnRH-antagonist (ANT). Oral contraceptives were begun on cycle days 2 to 4 and continued for 14 to 28 days and discontinued on a Sunday. The GnRH-agonist (AG) group patients had a 5-day overlap of leuprolide with the OC. Recombinant FSH was begun five days after OC had begun, on the subsequent Friday. Ganirelix was started with a leading follicle of 12 to 14 mm.



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sicians began integrating GnRH-antagonists into regular clinical use, the flexibility of administration led to interest in how best to use antagonists in certain patient populations (5–10). Initial clinical research used a fixed start day for antagonist administration, but more recent research has supported tailored antagonist protocols based on follicular size criteria for administration (5, 7, 9, 11–14).

Because the mechanism of action of agonists and antagonists differ, a great deal of research has focused on endocrinologic differences between agonist and antagonist protocols as well as differences within antagonist protocols and their potential effects on the ovarian, endocrine, and endometrial response of the patient.

Both a fixed-day and a flexible-day start with a GnRH-antagonist generally require fewer days of gonadotropin stimulation than a long agonist protocol (2–4) but require an adjustment in patient scheduling for in vitro fertilization (IVF) because they are not down-regulated at the start of stimulation. Because of the altered patient monitoring requirements and flexibility required of the medical staff, interest has been expressed regarding the use of oral contraceptives (OCs) to aid in patient scheduling with GnRH-antagonists (10). Pretreatment with an OC has been used to allow greater control over patient response rate (15), to reduce the incidence of luteinizing hormone (LH) surges in patients not treated with a GnRH-analogue (16, 17), and potentially to increase the oocyte yield (17).

A retrospective nonrandomized evaluation of 1,343 patients on a GnRH-antagonist protocol showed that OC pretreatment increases clinical pregnancy rates while reducing cancellation rates in poor responders but not normal responders (18). The use of GnRH-agonists in combination with an OC has become common practice in many assisted reproductive technology clinics. One study compared an OC pretreatment versus a flexible-start regimen on GnRH-antagonists and found a decrease in pregnancy rate in the flexible-start protocol. These researchers noted an increase in the LH serum area under the curve (AUC) and speculated that the use of OC pretreatment may blunt the elevated serum LH and normalize the pregnancy rate (7).

The purpose of our prospective, randomized, controlled trial was to compare the endocrine and clinical effects of GnRH-antagonist with GnRH-agonist cycles after OC pre-

treatment and to evaluate the ability to schedule patient treatment during the 5-day workweek.

MATERIALS AND METHODS

Patient Population

This study was approved by each center's institutional review board, and written informed consent was obtained from each participant. A total of four study centers equally recruited a total of 80 patients who were eligible to undergo IVF or IVF/intracytoplasmic sperm injection (ICSI). Patients who met the study criteria were randomized in a 1:1 fashion via sealed randomization envelopes. Randomization envelopes were blocked into groups of 10 (five patients/group/block) to reduce the chance that more patients in one group would be randomized to one time period during the study.

Diagnosis and Inclusion/Exclusion Criteria

The study population included couples undergoing IVF with or without ICSI. All hormonal screening values had to be measured within 3 months of patient enrollment. For inclusion into the study, patients had to be younger than 39 years of age, have a day-3 FSH level of ≤10 and E_2 level of <60 pg/mL, a basal antral follicle >5 with a menstrual cycle range of 26 to 34 days, and no more than one previous failed IVF or IVF/ICSI cycle. Patients had to have a body mass index of between 19 and 32 kg/m^2 and have no hydrosalpinx present by hysterosalpingogram, laparoscopy, or ultrasound within the past year.

Male factor infertility cases could be included (ICSI and/or frozen sperm) with the exception of nonobstructive azoospermia. Only one study cycle was allowed. Patients were excluded from the study if they had a history of previous poor response (<4 follicles and/or an E_2 level of <500 pg/mL on the day of hCG), had taken infertility medications (clomiphene and/or gonadotropins) within the past month, or had failed to consent to taking OCs, GnRH-analogues, or gonadotropins.

Design

This was a multicenter, randomized, open-label, prospective study to evaluate [1] the effect of OCs on scheduling IVF/ICSI cycles for Monday through Friday oocyte retrievals and [2] the endocrine effects of OCs combined with a long leuprolide acetate (Lupron; TAP Pharmaceuticals, Chicago, IL) suppression with recombinant FSH (follitropin-beta, Follistim; Organon USA, Roseland, NJ) versus OCs combined with a GnRH-antagonist (ganirelix acetate, Antagon; Organon USA) suppression with recombinant FSH (Fig. 1).

All of the women began OC (Desogen; Organon USA) on cycle days 2 to 4 and were immediately randomized to the GnRH-antagonist or GnRH-agonist group. Patients discontinued OC treatment on a Sunday after 14 to 28 days of administration. On the following Friday (5th day after OC), an evening dosing of recombinant FSH was started at 300 IU/day, given SC in the abdominal wall. Individualized dose adjustments of 75–150 IU of recombinant FSH were allowed after determining the patient's response by ultrasonographic and hormonal assays.

In the patients randomized to receive leuprolide (GnRH-agonist group), the GnRH-agonist was initiated at a dose of 0.5 mg per day during the midluteal phase with approximately a 5-day overlap with the OCs. The OC pretreatment was discontinued on a Sunday. Pituitary down-regulation was monitored on the following Friday; patients with adequate pituitary desensitization started their recombinant FSH regimen on Friday, and the dose of GnRH-agonist was reduced to 0.25 mg per day.

Patients who had a serum E_2 level of >60 pg/mL or a cyst >20 mm were continued on the same leuprolide dose for another week. Patients who continued to have elevated E_2 levels (>60 pg/mL) and a cyst were removed from the study. If the E_2 level was <60 pg/mL and the cyst was still present, it could be aspirated and the patient would remain enrolled in the study and begin their recombinant FSH administration on Friday, along with a reduction of the GnRH-agonist dose to 0.25 mg per day.

In patients randomized to the GnRH-antagonist group who had an E_2 level of <60 pg/mL, they could begin recombinant FSH on that Friday (5th day after OC). If they had a cyst >20 mm, they were canceled from the study. A daily evening dose of 250 μg ganirelix was initiated when a lead follicle obtained a mean diameter of 12 to 14 mm. This dose of ganirelix was given immediately before the recombinant FSH. Ganirelix acetate was continued up until the day of hCG administration and was not given on the day of hCG administration.

When two follicles reached ≥16 to 18 mm, 5,000 to 10,000 IU of hCG (Pregnyl; Organon USA) was administered and oocyte retrieval occurred 35 to 36 hours later. In cases at risk of ovarian hyperstimulation syndrome, the physician could give a dose of 5,000 IU of hCG. Embryo transfer occurred on day 3 or 5 per each study site's usual practice. The ET number was determined by following the American Society for Reproductive Medicine (ASRM) guidelines. Progesterone luteal phase support was provided based on the investigator's routine practice and standard of care.

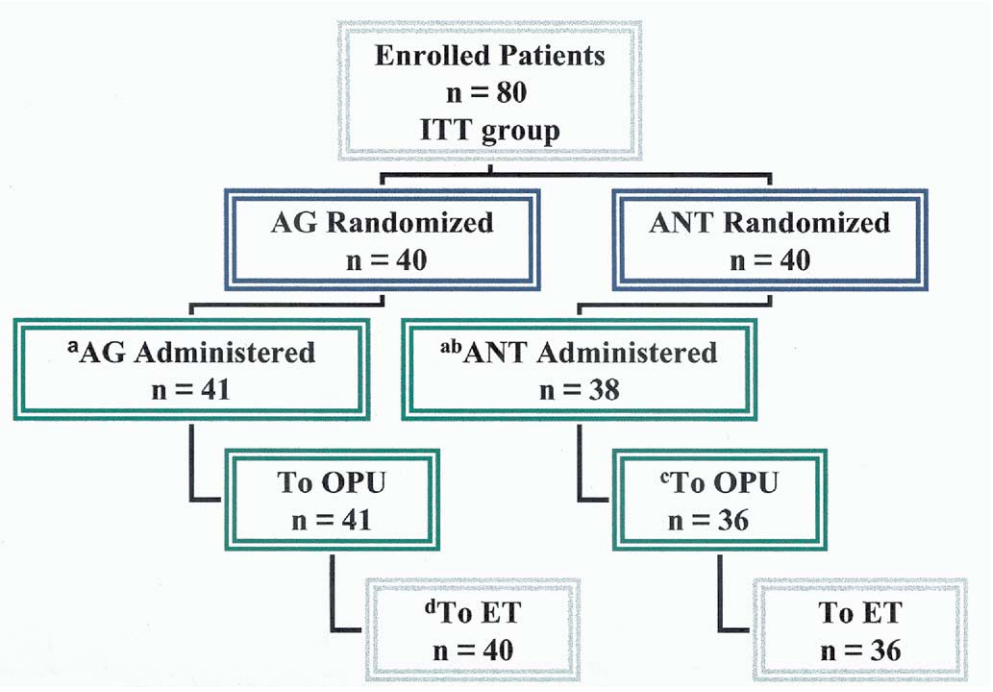
One center treated patients with P, 25 mg IM, on the day of retrieval, followed by P, 50 mg IM daily, with some patients being supplemented with hCG 2,500 IU on days 3 and 6 after retrieval. The other centers prescribed luteal support with a daily dose of P (50 mg IM).

Assessment of Response

Primary efficacy measures were the number of cumulus–oocyte complexes, day of the week for oocyte retrieval, and total dose and days of stimulation of recombinant

FIGURE 2

Flowchart of patient disposition throughout the study. [a]Patient randomized to GnRH-antagonist (ANT) but received GnRH-agonist (AG). [b]Patient withdrew during oral contraceptive treatment after being randomized. [c]Two patients canceled for poor response. [d]One patient with fertilization failure. ITT = intent to treat; OPU = oocyte pickup; ET = embryo transfer.



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FSH. Secondary efficacy variables included pregnancy and implantation rate; serum E_2 levels on stimulation day 1; serum E_2, P, and LH levels on the day of hCG; follicle size on day 6 and day of hCG; the total days of GnRH-analogue treatment; total days on OC; total days from end of OC to oocyte retrieval; and cycle cancellation rate.

A cycle was considered for cancellation if the patient did not down-regulate, had a premature LH surge, was at a significant risk of ovarian hyperstimulation syndrome, had a poor response with <2 mature follicles, or experienced an adverse reaction while on study medication. Serum E_2, LH, and FSH levels were determined by each investigator at their study site. Oocyte maturity was determined on the day of retrieval for ICSI patients. For IVF patients, an indirect evaluation of oocyte maturity was made during fertilization evaluations on the day following the oocyte retrieval and was based on polar body extrusion.

Pregnancy Determination

Serum β-hCG levels were measured approximately 14 days after retrieval to determine biochemical pregnancies. An ultrasound at 6 weeks confirmed clinical pregnancy, defined as sacs with fetal heart motion.

Statistical Analysis

This study was designed as a noninferiority trial when compared with the current standard of care (i.e., midluteal GnRH-agonist protocol) in efficacy, safety, and patient and clinician convenience of use. No formal sample size analysis was performed. However, the researchers decided that 80 patients could very reasonably be recruited in a short time period (to prevent any bias due to a time effect) and provide clinically relevant data. Data from the intent-to-treat group were used for evaluation of the screening and demographic values. Patients who received at least one dose of recombinant FSH were evaluated for the pregnancy rate per stimulated cycle. Stimulation data measures included all patients who reached oocyte retrieval (including one patient with retrieved oocytes who failed to fertilize).

Data were summarized using descriptive statistics and are unadjusted for center (listed as median, 95% confidence interval [CI], and mean ± standard error of mean [SEM] for continuous variables). Data for numerical values were evaluated with Student's *t*-test or Mann-Whitney rank sum test, as appropriate. Chi-square or Fisher's exact test was used for data listed as percentages or proportions. $P<.05$ was considered statistically significant.

TABLE 1

Patient demographic data for the GnRH-antagonist and GnRH-agonist groups.

Included patients (n = 80)	GnRH-agonist long protocol (n = 41)	GnRH-antagonist (n = 39)	P[a]
Age (y)	32 (28–38) 32.2 ± 0.4	33 (28–36) 32.4 ± 0.4	.758
Body mass index (kg/m^2)	23.6 (19.9–29.3) 23.8 ± 0.5	24.4 (19.2–31.2) 24.7 ± 0.6	.228
Weight (lbs)	139 (117–188) 143.7 ± 3.2	143 (115–197) 149.8 ± 4.3	.381
$FSH_{day\ 2/3}$ (IU/L)	6.4 (3.5–9.4) 6.3 ± 0.3	6.5 (3.8–9.9) 6.6 ± 0.3	.539
$E_{2day\ 2/3}$ (pg/mL)	37 (14.2–59) 37.1 ± 2.4	34 (10–59.6) 34.9 ± 2.4	.509

Note: Data listed as median and 95% CI and mean ± SEM.
[a]Student's *t*-test or Mann-Whitney rank sum test.

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RESULTS

The intent-to-treat population consisted of 80 recruited patients (Fig. 2). Forty patients were randomized to the antagonist group, of which 38 received at least one dose of ganirelix. One patient withdrew from the study for personal reasons after being randomized to the antagonist group and received OC pretreatment only. One patient was randomized to ganirelix but received leuprolide. Two patients were canceled for a poor response to gonadotropin treatment. In the leuprolide acetate group, 40 patients were randomized once the OC pretreatment was initiated, and 41 received at least one dose of leuprolide. One patient did not undergo ET because of failed fertilization. There were no differences in patient age, body mass index, day-3 FSH level, or days on OC between the antagonist and agonist treatment groups (Table 1).

Effect of OC on Scheduling

The OC cycle scheduling resulted in 78% and 90% of retrievals performed on five days of the week for the GnRH-antagonist and GnRH-agonist groups, respectively (Fig. 3) (18). The majority of the patients had oocyte retrieval on a Monday, Tuesday, or Wednesday in both groups (64% and 73% for GnRH-antagonist and GnRH-agonist, respectively). There was a trend toward more patients having oocyte retrieval on a Sunday in the GnRH-antagonist group (16.7%, n = 6 vs. 7.5%, n = 3), but it was not statistically significant (P=.294).

Less than 6% of oocyte retrievals per day occurred on Friday or Saturday in both groups. The overall distribution of oocyte-retrieval day was a narrower bell curve in the agonist group than in the antagonist group. By moving the stop day of OC from a Sunday to a Monday, and recombinant FSH start from Friday to Saturday, 89% and 95% of the oocyte retrievals would occur between Monday and Friday in the antagonist and agonist groups, respectively.

Stimulation and Endocrine Outcomes

A median of 9 days of gonadotropin treatment were required in both groups (Table 2) with a median dose of 2,475 IU and

FIGURE 3

Percentage of patients who had their oocyte retrieval during Sunday through Saturday. The number above the bar indicates the number of patients who had the retrieval on that day (18). AG = GnRH-agonist (AG) group; ANT = GnRH-antagonist group.

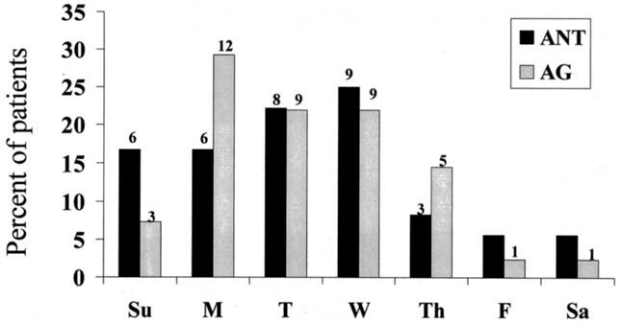

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TABLE 2

Patient clinical IVF outcomes after oral contraceptive pretreatment with a GnRH-agonist long protocol or GnRH-antagonist protocol until the day of hCG.

	GnRH-agonist long protocol	GnRH-antagonist	P[a]
Patients to oocyte retrieval[b] (n = 77)	41 (100%)	36 (95%)	.228
Days from OCP to oocyte retrieval	16 (13.6–22.9) 16.6 ± 0.4	16 (13–19) 15.8 ± 0.3	.244
Days on OC	21 (17–28) 22.5 ± 0.6	20.5 (14.8–28.6) 21.5 ± 0.8	.226
Stimulation day-1 E_2 (pg/mL)	21.5 (10–52) 26.8 ± 2.6	24.5 (13.0–54.4) 32.2 ± 5.1	.342
Recombinant FSH (IU)	2,625 (1,575–4,500) 2,724 ± 130	2,475 (1,747–4,710) 2,706 ± 146	.736
Days of recombinant FSH	9 (7–11) 9.0 ± 0.2	9 (6.3–12.0) 9.1 ± 0.3	.763
Stimulation day of ganirelix start		6 (5–9) 6.5 ± 0.2	
Days of leuprolide or ganirelix	19 (16.6–27.5) 20.1 ± 0.5	4 (2–5) 3.7 ± 0.2	<.001
$LH_{day\ hCG}$ (IU/L)	2.9 (0.8–6.2) 3.2 ± 0.5	0.7 (0–2.7) 1.0 ± 0.2	<.001
$E_{2day\ hCG}$ (pg/mL)	2,027 (955–3,258) 2,103 ± 116	1,123 (468–2,980) 1,430 ± 131	<.001
$P_{4day\ hCG}$ (pg/mL)	1.2 (0.3–2.3) 1.2 ± 0.1	1.0 (0.4–2.4) 1.2 ± 0.1	.634

Note: Data listed as median with 95% CI, mean ± SEM, or number and percentage.
[a]Student's *t*-test, Mann-Whitney rank sum test, chi-square, or Fisher's exact test.
[b]Includes only patients who received medication. One patient in antagonist group dropped out before receiving medication.

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2,625 IU (P=.736) in the antagonist and agonist groups, respectively. The number of days on OCs and the number of days between the end of the OCs and the oocyte retrieval was similar between the two groups. Similar numbers of patients were treated with IVF (24 ganirelix acetate and 18 leuprolide) or ICSI (12 ganirelix acetate and 23 leuprolide).

The duration of GnRH-analogue treatment was significantly reduced in the antagonist versus the agonist groups (4 days vs. 19 days, P<.001). Significantly lower LH values on the day of hCG were reported in the antagonist group (0.7 IU/L vs. 2.9 IU/L, P<.001 for the GnRH-antagonist vs. GnRH-agonist, respectively). There were no differences in the follicle sizes during midcycle between the agonist and antagonist groups; however, on the day of hCG, there were more 11–12 mm and 15–16 mm follicles in the agonist group compared with the antagonist-treated patients (Table 3: P=.027 and P=.042, respectively).

The slight differences in follicle numbers favoring the agonist group resulted in more cumulus–oocyte complexes and mature oocytes being retrieved in the agonist group (Table 4). However, no differences were seen in the number of two pronuclear (2PN) embryos between the two groups, with a median of eight embryos per group (P=.255). In addition, there was no difference in the number of embryos cryopreserved in the two groups. The distribution of day-3 versus day-5 transfers was similar between the GnRH-agonist and GnRH-antagonist groups (data not shown). The number of pregnancies per ET and implantation rates were comparable in the GnRH-antagonist and GnRH-agonist groups (44.4% vs. 45.0%, P=.86; 22.2% vs. 26.4%, P=.61, respectively).

There was one ectopic pregnancy and two spontaneous abortions in the GnRH-antagonist group, and the GnRH-agonist group had one spontaneous abortion. No differences

TABLE 3

Follicle size characteristics on day 6 of stimulation or on the day of hCG for the GnRH agonist or antagonist protocol.

	Day 6 agonist (n = 41)	Day 6 antagonist (n = 38)	*P*[a]	Day of hCG agonist (n = 41)	Day of hCG antagonist (n = 36)	*P*[a]
Total follicles	13 (7.6–37.3)	13 (4–33)		18 (7.0–34.4)	15 (2–31.8)	.065
9–10 mm	7 (0–27.9)	5 (0–18)	.265	3 (0–10.5)	2 (0–12.6)	.887
11–12 mm	1 (0–6.5)	1 (0–7)	.659	2 (0–13.7)	1 (0–6.6)	.027
13–14 mm	0 (0–3.5)	0 (0–3.6)	.130	3 (0–8)	2 (0–7.2)	.382
15–16 mm	0	0 (0–1)	.538	3 (0–8)	2 (0–7.2)	.042
17–18 mm	0	0 (0–0.6)	.832	2 (0–4.9)	2 (0–7.2)	.610
19–20 mm	0	0		1 (0–4.5)	1 (0–4)	.761
21–22 mm	0	0		0 (0–3.5)	0 (0–1.6)	.825

Note: Data listed as median and 95% CI.
[a]Mann-Whitney rank sum test.

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were seen in the percentage of ongoing twin gestations between the groups. A total of 17 live births out of 41 patients occurred in the GnRH-agonist group; the GnRH-antagonist group had 12 deliveries out of 38 patients with one additional patient in the 37th week of pregnancy.

DISCUSSION

Oral contraceptive pretreatment was exceptionally effective in allowing the oocyte retrieval to be scheduled during the working week, Monday through Friday. Despite slight differences in the percentage of patients who had an oocyte

TABLE 4

Patient clinical IVF outcomes after oral contraceptive pretreatment with a GnRH-agonist long protocol or GnRH-antagonist protocol from the time of oocyte retrieval.

	GnRH-agonist long protocol	GnRH-antagonist	*P*[a]
No. of oocytes retrieved	15 (6–33)	12.5 (2.3–22.0)	.031
No. of mature oocytes	13 (5–30)	10.5 (2.3–20.0)	.044
No. of 2PN embryos	8 (2–25)	8 (2–17)	.255
No. of embryos transferred	3 (1.6–4.0)	2 (1.3–4.0)	.671
Percentage of patients with cryopreservation	25%	22%	.989
Embryos cryopreserved/patient with cryopreservation	3 (1–7)	2.5 (1–5)	.274
No. of pregnancies/embryos transferred (%)	18 (45.0%)	16 (44.4%)[b]	.855
No. of pregnancies/cycle started (%)	18 (43.9%)	16 (42.1%)[b]	.947
No. of ongoing pregnancies/embryos transferred (%)[c]	18 (45.0%)	14 (38.9%)	.760
No. of ongoing pregnancies/cycle started (%)[c]	18 (43.9%)	14 (36.8%)	.682
No. of implanted embryos (%)	28 (26.4%)	20 (22.2%)	.608
No. of ongoing twin gestations (%)	8 (44.4%)	4 (25.0%)	.410
Delivered pregnancies	17/41	12/38[d]	

Note: Data listed as median with 95% CI or number and percentage.
[a]Mann-Whitney rank sum test, chi-square, or Fisher's exact test.
[b]Includes one ectopic pregnancy and one gestational sac with no fetal heartbeat.
[c]Defined as positive fetal heartbeat on ultrasound at 6 weeks.
[d]Not including one pregnancy at 37 weeks.

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retrieval on each day of the week, the vast majority of patients in both the agonist and antagonist groups scheduled for an oocyte retrieval on Monday through Wednesday. By altering the day of discontinuation of the OC by one day (Monday vs. Sunday) and concomitantly starting the gonadotropin one day later (Saturday vs. Friday), an even higher percentage of patients would have their oocyte retrieval during the working week. This slight alteration would most likely affect the antagonist group even more significantly, as they had twice as many patients scheduled for oocyte retrieval on Sunday (16.7% vs. 7.3%).

The antagonist group had a wider distribution curve than the agonist group for the day of retrieval, thus resulting in a more even workload from day to day for the IVF personnel. The agonist group had the majority of cases from Monday through Wednesday. Previous research has evaluated the impact of OC use on stimulation outcome, including the ability to schedule patient retrievals; however, none of the studies has closely evaluated the actual day of retrieval after OC pretreatment (16, 17).

Oral contraceptive pretreatment has been shown to reduce the cancellation rate in high responders (15) and increase the number of oocytes retrieved when compared with gonadotropin-only treatment (17). Other studies have failed to show a difference in the number of oocytes retrieved (16). Copperman (18), in a nonrandomized, retrospective review of 1,343 retrievals, noted that OC-pretreated patients who were poor responders had an improved clinical pregnancy rate and reduced cancellation rate after OC pretreatment when compared with patients without OC pretreatment. This researcher did not show a difference in outcomes with or without OC treatment in normal responders.

In our present study, approximately two to three fewer mature oocytes were retrieved in the antagonist group versus the agonist group. The lower number of cumulus–oocyte complexes retrieved is consistent with what other randomized clinical trials have found when comparing a long agonist protocol with a GnRH-antagonist protocol without OC pretreatment (2–4, 19). Other researchers have shown no difference in the number of oocytes retrieved between agonist and antagonist treatments (13, 20, 21).

Some of the differences between the studies that have shown no difference in the number of oocytes retrieved and our study were in the type of GnRH-analogues used and the dose of gonadotropin given. Our study used a higher gonadotropin dose than any of the previous studies. The number of fertilized 2PN and cryopreserved embryos was identical between the two treatment groups in our study, lending credence to the suggestion that only the most competent oocytes were fertilized and continued to develop normally. An earlier study demonstrated a higher number of cumulus–oocyte complexes and 2PN embryos in the agonist-treated group but also demonstrated that the agonist and antagonist groups had the same number of embryos available for transfer and cryopreservation in both groups (19).

When assessing the oocyte, embryo, and cryopreserved embryo numbers, it is helpful to look further at the follicle sizes on the day of hCG administration between the two treatment groups. The only differences seen in follicle sizes on the day of hCG were in the 11–12 mm and 15–16 mm groups. This difference in the two follicle-size categories resulted in approximately three more follicles visualized by ultrasound in the leuprolide group on the day of hCG. However, it seems that these follicles were more apparent on the day of hCG than during midstimulation because the follicle numbers visualized were identical between the two treatment groups.

Our data on the distribution of follicle sizes on the day of hCG are consistent with an initial clinical trial where ganirelix was compared with triptorelin without oral contraceptive pretreatment (4). Other researchers have also reported that the number of small follicles (11–14 mm) was lower in cetrorelix-treated patients than those treated with a long buserelin protocol (19).

When patients treated with a long GnRH-agonist protocol were compared with patients treated with an antagonist protocol where they started recombinant FSH on either cycle day 2 or cycle day 5, both antagonist groups had an identical number of small follicles on the day of hCG administration, which were significantly fewer than the number of small follicles in the patients on the agonist protocol (5). Despite having two additional days of recombinant FSH, the cycle-day-2 patients were not able to recruit more follicles than the cycle-day-5 start or to recruit as many as the long-protocol patients who also had started recombinant FSH on cycle day 2.

Estradiol and LH levels were significantly lower in the antagonist group and are probably interrelated because LH is responsible for stimulating the production of androgens, the substrate for E_2 production. This significantly lower level of serum E_2 is consistent with earlier reports in which patients were treated with recombinant FSH or hMG (2–4, 19). The pattern of E_2 response in GnRH-antagonist cycles appears consistent among different studies, with an earlier rise during midstimulation and a lower E_2 on the day of hCG when compared with multiple agonists.

It is interesting to note that the LH levels reported in this study for patients who are treated with an antagonist are markedly lower than those reported in the initial clinical trials. In fact, in all three clinical trials, the LH values were always consistently higher in the antagonist group than the agonist group (3, 4, 22), unlike what was reported in our study. This difference is most likely because the antagonist was given in the evening in this study, whereas the initial clinical trials administered the antagonist in the morning and the LH values reported were approximately 24 hours after the last antagonist injection (vs. approximately 12 to 16 hours in the current study).

The LH values reported in this study probably present a more realistic idea of what the actual suppression is under maximal ganirelix concentrations, as the half-life of ganirelix is 16.2 hours following multiple 250-μg injections (23, 24). However, it cannot be ruled out that the OC pretreatment may also have blunted the LH levels in the antagonist group more than when compared with studies with GnRH-antagonists without OC pretreatment. Studies done using hMG also show a lower E_2 level on the day of hCG in the antagonist patients when compared with those treated with an agonist (19).

Little research has been done to evaluate the effect of adding LH activity in the form of low doses of hCG during the time of antagonist administration. One report from 1995 with the second-generation antagonist Nal-Glu showed significantly higher levels of serum bioactive LH in patients treated with 50–75 IU hCG than in those patients treated with 150–225 IU of hMG (26). Other more recent papers have evaluated using recombinant FSH with different amounts of hCG, from 50 to 200 IU, after a midluteal down-regulation with triptorelin (26). Both of these researchers commented that the longer half-life of hCG lends a greater LH bioactivity than the LH derived from hMG alone (25, 26).

Although E_2 and LH levels on the day of hCG were lower in the antagonist group, no differences were observed in the number of 2PN embryos or implantation and pregnancy rates. Due to the relatively small sample size of 80 patients, we could rule out that the nonsignificant differences seen in pregnancy and implantation rates could be attributed to a type II error. However, the number of patients needed to determine differences in pregnancy outcomes between the two groups (>1,000 patients) would have introduced a very strong "time of recruitment" bias based on the number of patients who these physicians could recruit who fulfilled the inclusion criteria during a given time period.

Both regimens reported no cases of ovarian hyperstimulation syndrome, despite a relatively high starting dose of recombinant FSH. The blunting effects of the OC on endogenous gonadotropins were evident in that no patients hyperresponded on 300 IU of recombinant FSH. The GnRH-antagonists provide comparable outcomes and reduce patient injections, thereby providing a more patient-friendly regimen. With OC pretreatment, scheduling a patient during the Monday through Friday working week is readily achievable using either GnRH-analogue. This regimen, which includes OC pretreatment, recombinant FSH, and ganirelix allows a method to schedule a more consistent and reliable workload for the IVF staff.

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