Cost-effectiveness comparison between pituitary down-regulation with a gonadotropin-releasing hormone agonist short regimen on alternate days and an antagonist protocol for assisted fertilization treatments

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Objective: To compare cost-effectiveness between pituitary down-regulation with a GnRH agonist (GnRHa) short regimen on alternate days and GnRH antagonist (GnRHant) multidose protocol on in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) outcome.
Design: Prospective, randomized.
Setting: A private center.
Patient(s): Patients were randomized into GnRHa (n = 48) and GnRHant (n = 48) groups.
Intervention(s): GnRHa stimulation protocol: administration of triptorelin on alternate days starting on the first day of the cycle, recombinant FSH (rFSH), and recombinant hCG (rhCG) microdose. GnRHant protocol: administration of a daily dose of rFSH, cetrorelix, and rhCG microdose.
Main Outcome Measure(s): ICSI outcomes and treatment costs.
Result(s): A significantly lower number of patients underwent embryo transfer in the GnRHa group. Clinical pregnancy rate was significantly lower and miscarriage rate was significantly higher in the GnRHa group. It was observed a significant lower cost per cycle in the GnRHa group compared with the GnRHant group ($5,327.80 ± 387.30 vs. $5,900.40 ± 472.50). However, mean cost per pregnancy in the GnRHa was higher than in the GnRHant group ($19,671.80 ± 1,430.00 vs. $11,328.70 ± 907.20).
Conclusion(s): Although the short controlled ovarian stimulation protocol with GnRHa on alternate days, rFSH, and rhCG microdose may lower the cost of an individual IVF cycle, it requires more cycles to achieve pregnancy.
Clinical Trial Registration Number: NCT01468441. (Fertil Steril® 2013;99:1615–22. ©2013 by American Society for Reproductive Medicine.)
Key Words: Controlled ovarian stimulation, GnRHa, GnRHant ICSI, pituitary down-regulation

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Pituitary suppression is a well established strategy in the protocols of controlled ovarian stimulation (COS) for in vitro fertilization (IVF). For the past 20 years GnRH agonists (GnRHa's) were used for this purpose (1). By inducing hypophyseal desensitization, GnRHa protocols

prevent premature ovulation and luteinization, and significantly reduce the cycle cancellation rate compared with cycles where gonadotropins are administered alone (2). However, the mechanism of action of GnRHa requires a long period of treatment and has a long-lasting, potentially detrimental, effect in the luteal phase (2, 3). In contrast to GnRHa, GnRH antagonists (GnRHant's) competitively block pituitary GnRH receptors, inducing a fast and reversible suppression of gonadotropin secretion (4). The use of antagonist protocols is more convenient for the patient because treatment time is shortened and fewer injections and lower amounts of gonadotropins are required (5). However, it has been suggested that GnRHant is an inhibitor of the cell cycle by decreasing the synthesis of growth factors and therefore compromises the mitotic program of follicles, embryo blastomere, and endometrium (6).

GnRHant-treated patients showed lower clinical pregnancy rates compared with GnRHa-treated patients (7). Hernandez et al. (6) reported that the embryo, as well as granulosa and endometrial cells, harbors GnRH receptors, and therefore, a direct effect from the GnRHant on these cells may be a possible cause for implantation failure. Nevertheless, this difference disappeared in frozen-thawed embryo transfers. Possibly, an endometrial impact could be attributed to this result (8). On the other hand, Bodri et al. (5), in a systematic review and meta-analysis, demonstrated that there are no statistically significant differences in ovarian response or recipient ongoing pregnancy rates with the use of either GnRHa or GnRHant protocols. Similarly, Al-Inany and Aboulghar (7) and Kolibianakis et al. (9) showed that no clear benefit regarding live birth rate was attributed to one type of GnRH analogue.

The achievement of a simple, safe, and cost-effective treatment protocol in COS is of pivotal importance to improve the quality of care in assisted reproduction. An alternative would be the use of a short GnRHa, as suggested by Orvieto et al. (10). Furthermore, the unwanted effects of the agonists are thought to be eliminated by stopping or decreasing doses of the analogues (11). A previous study of daily or alternate day administration of long-acting GnRH analogue found similar pituitary suppression with each dose (2).

Although some authors have aimed to improve IVF cycle outcome through modifications of the COS protocol (12, 13), others have focused on lowering the cost of the cycles through a reduction of the total dose of FSH administered. Some studies have demonstrated that the administration of recombinant hCG (rhCG) microdoses in the late stages of COS resulted in adequate response to stimulation and successful pregnancies (14, 15). Moreover, the addition of rhCG shortened the interval of stimulation, significantly reduced FSH requirement, and thus minimized patient cost (16). An interesting approach would be to unite the reduced costs of both pituitary suppression with GnRHa on alternate days and the administration of rhCG microdoses in the late stages of COS. Therefore, the present prospective randomized study was undertaken to compare the effects of administering a daily dose of GnRHant versus an alternate-day dosage of short GnRHa on ovarian response and intracytoplasmic sperm injection (ICSI) outcome in patients stimulated with recombinant FSH (rFSH) and rhCG microdoses.

MATERIALS AND METHODS

A randomized clinical trial, approved by the local Institutional Review Board, was performed in a private fertility center. Inclusion criteria were as follows: women of good physical and mental health, $\leq$37 years old, with regular menstrual cycles of 25–35 days, normal basal FSH and LH levels, body mass index (BMI) $<$30 kg/m^2, presence of both ovaries and intact uterus, absence of polycystic ovaries, endometriosis, or gynecologic/medical disorders, and a negative result in a screening for sexually transmitted diseases. All patients signed a written informed consent form.

No patient had received any hormone therapy for $\geq$60 days preceding the study. Eligible patients who agreed to participate were randomized into two treatment groups: GnRHa group (n = 48), and GnRHant group (n = 48; Fig. 1). Patients were allocated by a single nurse to a GnRH analogue treatment group according to a computer-generated randomization table.

Controlled Ovarian Stimulation Protocols

All patients received oral contraceptive pills (OCPs; 20 μg etinilestradiol and 75 μg gestodeno; Ginesse; Farmoquímica) to synchronize cycles.

GnRH Agonist Short Regimen (Fig. 2A)

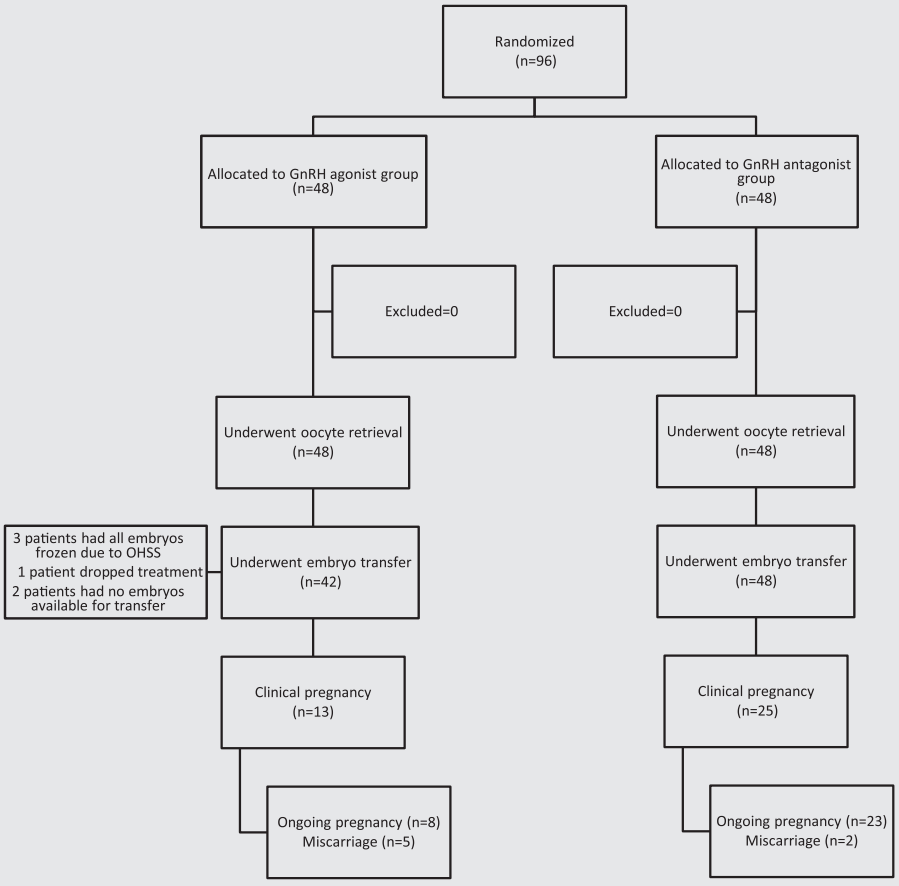
In the GnRHa group, a dose of tryptorelin (0.1 mg Gonapeptyl; Ferring) was administered on alternate days from day 1 of the menstrual cycle. After 3 days, ovarian stimulation was commenced with 225 IU rFSH (Gonal F; Serono) daily (day 1 of ovarian stimulation = S1), for 3 days. On S4, the recombinant FSH dose was reduced to 150 IU, until the visualization of at least one follicle $\geq$ 14 mm. The day after the recombinant FSH dose was reduced to 75 IU and concomitantly administered with the rhCG microdose (7.7 μg, equivalent to 200 IU hCG), which was obtained by the dilution of one ampule of 250 μg rhCG (Ovidrel; Serono), subcutaneously (SC) for 2 days. After that, the rhCG microdose was administered alone until the day of ovulation trigger (see next section).

GnRH Antagonist Regimen (Fig. 2B)

In the GnRHant group, ovarian stimulation was performed as follows. On day 3 of the cycle, ovarian stimulation was commenced with 225 IU rFSH on a daily basis (day 1 of ovarian stimulation = S1). On S4, the recombinant FSH dose was reduced to 150 IU until the visualization of at least one follicle $\geq$14 mm, at which time we began the administration of 0.25 mg cetrorelix acetate (Cetrotide; Serono) SC. The day after beginning the antagonist therapy, the rFSH dose was reduced to 75 IU and the concomitant SC administration of the rhCG microdose was initiated and continued for 2 days. After that, the rhCG microdose and GnRHant were administered until the day of ovulation trigger.

The following steps of the treatment were the same for both treatment regimens.

FIGURE 1



Study flow chart and patient outcome. OHSS = ovarian hyperstimulation syndrome.

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Criteria for hCG Administration

When at least three follicles attained a mean diameter of ≥17 mm, 250 μg hCG (Ovidrel; EMD Serono) was administered SC. Oocyte retrieval was performed 36 hours later, guided by transvaginal ultrasonography.

Preparation of Oocytes

Retrieved oocytes were maintained in culture media (Global for Fertilization; Lifeglobal) supplemented with 10% protein supplement (Lifeglobal) and covered with paraffin oil (Lifeglobal) for 2–3 hours before cumulus cell removal. Surrounding cumulus cells were removed after exposure to a HEPES-buffered medium containing hyaluronidase (80 IU/mL; Lifeglobal). The remaining cumulus cells were then mechanically removed by gently pipetting with a hand-drawn Pasteur pipette (Humagen Fertility Diagnostics).

Oocyte morphology was assessed with the use of an inverted Nikon Diaphot microscope (Eclipse TE 300) with a Hoffmann modulation contrast system under ×400 magnification, just before sperm injection (3–4 hours after retrieval). Oocytes that were observed to have released the first polar body were considered to be mature and were used for ICSI.

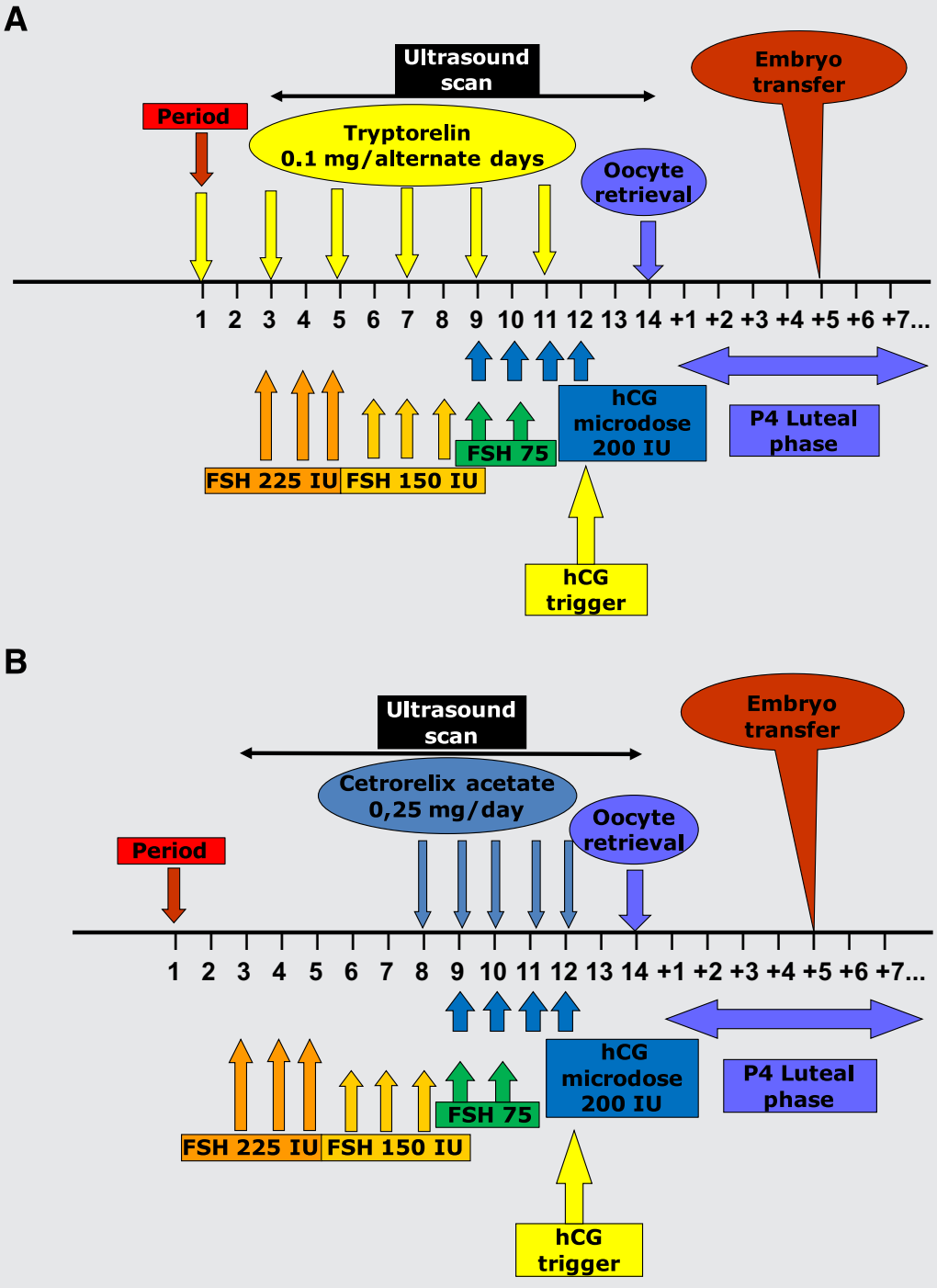
Intracytoplasmic Sperm Injection

ICSI was performed in a microinjection dish prepared with 4-μL droplets of buffered medium (Global w/HEPES; Lifeglobal) and covered with paraffin oil on a heated stage at 37.0 ± 0.5°C of an inverted microscope. Approximately 16 hours after ICSI, fertilization was confirmed by the presence of two pronuclei and the extrusion of the second polar body. Embryos were kept in a 50-μL drop of culture medium (Global; Lifeglobal) supplemented with 10% protein supplement covered with paraffin oil in a humidified atmosphere under 6% CO_2 at 37°C for 3 days.

Embryo Transfer

High-quality embryos were defined as those having all of the following characteristics on day 3 of development: 8–10 cells, <15% fragmentation, symmetric blastomeres, absence of multinucleation, colorless cytoplasm with moderate granulation and no inclusions, absence of perivitelline space granularity, and absence of zona pellucida dysmorphism. High-quality blastocysts were defined as full blastocyst onward presenting high-quality inner cell mass and trophectoderm.

FIGURE 2



(A) GnRH agonist short regimen. (B) GnRH antagonist regimen.

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All of the embryo transfers were performed by the same gynecologist on day 5 of embryo development with the use of a soft catheter with transabdominal ultrasound guidance. Two to three embryos were transferred per patient.

The luteal phase support was supplemented with vaginal administration of 600 mg micronized progesterone (Utrogestan; Farmoquímica) starting 1 day after oocyte retrieval and continued until 12 weeks of gestation in the presence of a positive hCG test.

Clinical Follow-Up

A pregnancy test was performed 12 days after embryo transfer. All women with a positive test had a transvaginal

ultrasound scan 2 weeks after the positive test. A clinical pregnancy was diagnosed when the fetal heartbeat was detected. Pregnancy rates were calculated per transfer. Miscarriage was defined as pregnancy loss before 20 weeks.

End Points

The primary end points of this study were the cost of pituitary suppression and the total cost per cycle and per pregnancy. The secondary end points were the pregnancy, implantation, and miscarriage rates.

Statistical Analysis

The sample size calculation was based on mean differences. We observed a mean cost of 600 ± 100 dollars for pituitary suppression in cycles using GnRHant with rFSH and rhCG microdose (evaluation before the study). Thus, the sample size of 40 in each group has 80% power to detect a 10% difference between means with a significance level (alpha) of .05 (two-tailed).

The two groups were compared regarding: 1) age; 2) BMI; 3) OCP administration length; 4) total dose of FSH administered (IU); 5) number of administered GnRH analogue injections; 6) duration of treatment; 7) number of retrieved oocytes; 8) oocyte yield (number of retrieved oocytes per number of follicles); 9) metaphase II (MII) oocyte rate; 10) normal fertilization rate; 11) percentage of high-quality embryos on day 3 of development; 12) number of transferred embryos; 13) pregnancy rate; 14) implantation rate; and 15) miscarriage rate. In addition, the costs of pituitary suppression, gonadotropin stimulus, hCG trigger, luteal-phase supplementation, laboratory, and medical procedures, as well as the total treatment cost and cost per clinical pregnancy, were compared between the groups.

Data were expressed as mean ± SD for continuous variables or percentages for categoric variables. Mean values were compared by Student *t* parametric test or Mann-Whitney nonparametric test. Percentages were compared by the chi-squared or Fisher exact test, when expected frequency was five or fewer. Results were considered to be significant at the 5% critical level ($P<.05$). Data analysis was conducted with the use of Minitab 16 software.

RESULTS

Patient Characteristics

Figure 1 shows the study flow chart and patient outcomes. A total of 96 patients were recruited to the study, with 48 randomized to each treatment arm. The patient demographic variables are compared in Table 1. The two treatment groups were

TABLE 1

Patient demographics, gonadotropin treatment, ovarian response, ovum retrieval, and intracytoplasmic sperm injection (ICSI) outcome in agonist and antagonist groups.

Variable	GnRHa (n = 48)	GnRHant (n = 48)	*P* value
Age (y)	31.0 ± 2.9	30.8 ± 3.2	.787
BMI (kg/m^2)	25.3 ± 4.1	23.9 ± 3.0	.095
Primary infertility [n (%)]	38 (79.2)	38 (79.2)	1.000
Infertility factor [n (%)]			
Male factor (n, %)	23 (47.9)	31 (64.6)	.099
Unexplained infertility (n, %)	7 (14.6)	5 (10.4)	.758
Tubal factor (n, %)	18 (37.5)	12 (25.0)	.186
Duration of infertility (y)	2.1 ± 0.3	2.3 ± 0.4	.612
No. of previous ICSI cycles	1.1 ± 0.2	1.0 ± 0.2	.901
Basal FSH on the 3rd day of menstrual cycle (IU/L)	6.2 ± 1.1	5.8 ± 1.3	.542
Basal LH (IU/L)	5.9 ± 0.7	5.8 ± 1.0	.581
Basal E_2 (pg/mL)	40.9 ± 6.1	43.1 ± 5.4	.716
OCP treatment length (d)	26.3 ± 9.4	26.5 ± 8.8	.914
No. of GnRH analogue injections	6.6 ± 0.6	4.6 ± 0.8	< .001
Total dose of FSH administered (IU)	1,348 ± 234	1,402 ± 272	.302
Total dose of hCG administered (IU)	693 ± 220	651 ± 153	.290
E_2 on hCG trigger day (pg/mL)	3,618 ± 2,964	3,094 ± 1,891	.313
No. of follicles	22.3 ± 16.7	21.7 ± 12.3	.856
No. of oocytes retrieved	15.1 ± 10.6	13.3 ± 7.5	.335
Oocyte yield (%)	70.8	63.7	.079
No. of MII oocytes	11.8 ± 9.1	10.5 ± 6.5	.441
MII oocyte rate (%)	77.5	79.8	.532
Fertilization rate (%)	75.4	79.8	.265
High-quality embryos rate (%)	53.4	54.7	.822
Endometrial thickness (mm)	11.6 ± 2.1	11.1 ± 1.9	.282
No. of embryos transferred	2.4 ± 0.6	2.4 ± 0.6	.593
Patients with fresh embryo transfer [n (%)]	42 (87.5)	48 (100)	.026
Implantation rate (%)	15.9	28.1	.061
Clinical pregnancy/fresh transferred cycle [n (%)]	13 (31.0)	25 (52.1)	.042
Miscarriages/fresh implanted embryos [n (%)]	5 (38.4)	2 (8.0)	.031
Patients with thawed embryo transfer [n (%)]	3 (6.2)	0 (0.0)	.242
Clinical pregnancy/transferred fresh and thawed cycle [n (%)]	15 (34.1)	25 (52.1)	.082
Miscarriages/implanted fresh and thawed embryos [n (%)]	5 (33.3)	2 (8.0)	.081

Note: Values are mean ± SD or n (%). BMI = body mass index; MII = metaphase II; OCP = oral contraceptive pill.

Maldonado. GnRH agonist short regimen and ICSI outcomes. Fertil Steril 2013.

similar regarding female age and BMI. The overall mean age was 32.9 ± 3.0 years and BMI 24.6 ± 3.6 kg/m^2. Mean female age and BMI in the agonist group were 33.0 ± 2.9 years and 25.3 ± 4.1 kg/m^2, and in the antagonist group 32.8 ± 3.2 years and 23.9 ± 3.0 kg/m^2, respectively (Table 1).

A similar percentage of couples with primary infertility was observed in both treatment groups (79.2%). The mean duration of infertility for the couples treated with GnRHa was 2.1 ± 0.3 years and with GnRHant 2.3 ± 0.4 years. No relevant differences were found between the treatment groups for the causes of infertility, which were male factor (47.9 and 64.6%, respectively), tubal factor (37.5 and 25.0%, respectively), and unexplained infertility (14.6 and 10.4%, respectively). Basal hormonal levels also did not differ between the groups (Table 1).

Stimulation and ICSI Outcomes

There were no significant differences between the two groups in the OCP treatment length (GnRHa 26.3 ± 9.4 days, GnRHant 26.5 ± 8.8 days), total doses of rFSH and rhCG microdoses administered (Table 1). The E_2 levels on the day of hCG trigger, number of follicles, oocytes obtained, oocyte yield, MII oocytes obtained, and MII oocyte rate were similar between the groups. Fertilization rate, high-quality embryos rate, number of embryos transferred, and endometrial thickness also were not different. However, we observed a significant lower number of patients with embryo transfer in the GnRHa group compared with the GnRHant group (87.5 vs. 100%; P=.026; Table 1). In the GnRHa group, one couple decided not to have embryo transfer because of personal issues, two couples did not have any embryo available for transfer, and three patients with ovarian hyperstimulation syndrome (OHSS) had their embryos frozen. All of the patients with OHSS had embryo transfer in a subsequent embryo thawing cycle. One couple did not become pregnant after the transfer of two thawed embryos. Two of them became pregnant, presenting one and two gestational sacs out of two and three embryos transferred, respectively.

Though it was not statistically significant, we observed a reduced implantation rate in the GnRHa group (15.9 vs. 28.1%; P=.061). Clinical pregnancy per transferred cycle was significantly lower (31.0% vs. 52.1%; P=.042) and miscarriage rates were significantly higher (38.4% vs. 8.0%; P=.031) in the GnRHa group compared with the GnRHant group (Table 1).

We observed a significantly lower cost for pituitary suppression in the GnRHa group compared with the GnRHant group ($132.6 ± 12.7 vs. $619.4 ± 101.2; P<.0001; Table 2). There were no significant differences between the groups regarding the costs of gonadotropin stimulus, hCG trigger, luteal-phase supplementation, and laboratory and medical procedures (Table 2). Although mean total treatment cost was significantly lower in the GnRHa group compared with the GnRHant group ($5,327.80 ± 387.30 vs. $5,900.40 ± 472.50; P<.0001), mean cost per clinical pregnancy was significantly higher in the GnRHa group ($19,671.80 ± 1,430.00 vs. $11,328.70 ± 907.20; P<.0001; Table 2).

Considering the outcomes obtained with fresh and thawed cycles (n = 93), despite the lower pregnancy (34.1% vs. 52.1%; P=.082) and miscarriage (8.0% vs. 33.3%; P=.081) rates observed in the experimental group, the significances disappeared (Table 1). Nevertheless, the cost per clinical pregnancy remained higher in the experimental group ($17,570.20 ± 1,533.40 vs. $11,328.70 ± 907.20; P<.001; Table 2).

DISCUSSION

Any simplification in pharmacologic treatment is a welcome development for infertile couples undergoing IVF procedures (17). Previously, one group showed that halving the standard daily dose of triptorelin at the start of ovarian stimulation in down-regulated women stimulated with rFSH is adequate for pituitary suppression (11). Another group demonstrated that alternate-day dosage of triptorelin is effective in achieving pituitary suppression (2).

Moreover, our previous study showed that the rhCG microdose is an efficient source of LH activity, and this strategy can be used to reduce the FSH amounts required in COS protocols, independently from the type of GnRH analogue used (1). In the present study, in an attempt to improve the cost-effectiveness of stimulation protocols, we evaluated the use of an alternate-day dosage of GnRHa in young presumably normal-responding patients stimulated with rFSH and rhCG microdoses.

TABLE 2

Detailed treatment costs (USD).

	Agonist (n = 48)	Antagonist (n = 48)	*P* value
Pituitary suppression	132.6 ± 12.7	619.4 ± 101.2	<.001
Gonadotropin stimulus	2,154.7 ± 373.5	2,240.5 ± 434.1	.302
hCG trigger	139.4	139.4	NA
Luteal-phase supplementation	77.6	77.6	NA
Laboratory cost	2,823.5	2,823.5	NA
Medical cost	0.0	0.0	NA
Total treatment cost	5,327.8 ± 387.3	5,900.4 ± 472.5	<.001
Clinical pregnancy cost	19,671.8 ± 1,430.0	11,328.7 ± 907.2	<.001
Clinical pregnancy cost/fresh and thawed embryo transfer	17,570.2 ± 1,533.4	11,328.7 ± 907.2	<.001

Note: Values are mean ± SD or n (%).

Maldonado. GnRH agonist short regimen and ICSI outcomes. Fertil Steril 2013.

Our results showed that pituitary suppression with a GnRHa on alternate days is significantly less costly than the GnRHant treatment. Though we did not observe any significant effect on ovarian response, treatment with GnRHa was associated with a decreased number of cycles with embryo transfer, a lower clinical pregnancy rate, and an increased miscarriage rate compared with the group using GnRHant for pituitary suppression.

In our experimental protocol, no cycle was cancelled before oocyte retrieval because of premature LH surge, so all patients had oocyte retrieval. However, three patients developed OHSS and had all of the embryos frozen. Two of these patients became pregnant in a subsequent embryo thawing cycle. In the GnRHant group, we did not observe any patient developing OHSS, emphasizing the protective role of the antagonist protocol against hyperstimulation. The GnRHant's have been successfully used to prevent the LH surge in IVF cycles by inducing immediate and rapid suppression of gonadotropin secretion (18–20). The use of GnRHa induces down-regulation of GnRH receptors and consequent hypogonadism (21). In the long regimen, there is an initial flare of gonadotropin release before receptors are down-regulated, and the stimulation with gonadotropins is started after the pituitary suppression (19, 22, 23). The short, or flare, protocol combines the agonist treatment with gonadotropin stimulation, with the use of the agonist flare-up of endogenous FSH to stimulate the ovaries in addition to exogenous FSH administration (22, 23).

When compared with the long GnRHa treatment, the antagonist protocol was shown to shorten the agonist schedule and diminish the amount of gonadotropin administered, among other benefits. Therefore, it was characterized as a more patient-friendly protocol (20, 24). This difference is clinically relevant, because patients are likely to prefer shorter cycles with reduced number of injections (20).

It has been previously documented that the use of SC drugs leads to a negative perception of IVF treatment (19). To increase patients' comfort, in this study we administered the short agonist protocol on alternate days and thus reduced the mean number of injections from 20 to 6.6 compared with the long agonist schedule. Nonetheless, the number of injections in the GnRHant group was still lower than in the GnRHa group. In addition, assisted reproduction is associated with elevated anxiety, psychologic and marital stress, and economic burdens, which are the main reasons for dropout from treatment (22, 25–27). Indeed, it is likely that many couples do not seek or discontinue treatment because of limited economic resources (28).

Because the cost of ovulation induction drugs is one of the main limiting factors in assisted reproduction, one possible variation in IVF costs could be attributed to different COS protocols. Several authors have expressed support for patient-friendly IVF, meaning a policy that is cost-effective, is available to the widest possible range of people, and minimizes risks and burden for the patient (19). Owing to the extremely high costs of IVF treatment, only a small proportion of infertile couples in developing countries benefit from it (29). Simplified COS protocols are needed that can be adapted for conditions in the developing world, because gonadotropins and GnRH analogues are too expensive to be used in developing countries (28). Although IVF cycles can be performed in natural cycles, there is an increased risk of cycle cancellation, poor oocyte development, and significantly lower pregnancy rate compared with cycles with ovarian stimulation (30).

Recent studies have demonstrated that the supplementation or substitution of FSH by low-dose hCG in the final days of COS leads to a >20% reduction of FSH consumption, yielding a significant reduction of the total cost of the treatment, whereas ICSI outcome was similar to traditional COS regimens (1, 31, 32). Adaptations in the dose of the GnRHa seem to be an alternative to reduce the cost of IVF treatment. Fabregues et al. (11) found that a reduced dose of triptorelin had no significant effect on ovarian response and the outcome of ICSI cycles. Karatekeli et al. (2), using an alternate-day regimen, observed pregnancy rates similar to conventional regimen. In addition, the alternate-day schedule is interesting because of the reduced number of injections, resulting in a friendlier protocol.

Reducing the dose of GnRH once ovarian suppression is attained may avoid too much suppression of LH during follicular development. Fabregues et al. (11) observed higher levels of serum LH during the follicular phase after GnRH reduction. Accordingly, Filicori et al. (32) observed that the administration of low-dose hCG alone in the late COS stages resulted in a more estrogenic intrafollicular environment. Because high LH levels lead to decreased egg quality, lower implantation (33, 34) and pregnancy rates (35), and increased miscarriage rates (33, 34), we could hypothesize that an induced estrogenic action was responsible for the lower implantation and pregnancy rates and higher miscarriage rate obtained with our protocol.

In the present study, we aimed to develop a protocol in which fewer GnRH injections and gonadropin amounts are required, thus reducing the total cost of IVF treatment. We reached our primary end point, which was demonstrated by a significant reduction in the pituitary suppression cost per cycle. However, our secondary end point was not achieved, because the GnRHa group had significantly lower pregnancy and higher miscarriage rates compared with the GnRHant group, resulting in a higher cost per pregnancy achievement. When subsequent embryo thawing cycles were included, the significant differences in pregnancy and miscarriage rates disappeared, but the cost per pregnancy was still significantly higher in the agonist group.

Our recommendation is that although it is more practical than a long agonist schedule (reduction from ~20 to ~7 injections), less costly, and as effective as the antagonist protocol for pituitary suppression (no premature ovulation), the short agonist protocol administered on alternate days increases the risk for OHSS; therefore, it is not a safe protocol for COS. However, we think that it is important to identify which patients, if any, would benefit the most from this protocol to obtain a less costly and friendlier COS without compromising the treatment outcomes.

REFERENCES

1. Cavagna M, Maldonado LG, de Souza Bonetti TC, de Almeida Ferreira Braga DP, Iaconelli A Jr, Borges E Jr. Supplementation with a recombinant

human chorionic gonadotropin microdose leads to similar outcomes in ovarian stimulation with recombinant follicle-stimulating hormone using either a gonadotropin-releasing hormone agonist or antagonist for pituitary suppression. Fertil Steril 2010;94:167–72.
2. Karatekeli E, Ozornek H, Jamal H, Ergin E, Ongun B. Administration of alternate day triptorelin for controlled ovarian hyperstimulation is cost effective. Fertil Steril 2006;85:518–9.
3. Cheung LP, Lam PM, Lok IH, Chiu TT, Yeung SY, Tjer CC, et al. GnRH antagonist versus long GnRH agonist protocol in poor responders undergoing IVF: a randomized controlled trial. Hum Reprod 2005;20:616–21.
4. Diedrich K, Diedrich C, Santos E, Zoll C, al-Hasani S, Reissmann T, et al. Suppression of the endogenous luteinizing hormone surge by the gonadotrophin-releasing hormone antagonist Cetrorelix during ovarian stimulation. Hum Reprod 1994;9:788–91.
5. Bodri D, Sunkara SK, Coomarasamy A. Gonadotropin-releasing hormone agonists versus antagonists for controlled ovarian hyperstimulation in oocyte donors: a systematic review and meta-analysis. Fertil Steril 2011; 95:164–9.
6. Hernandez ER. Embryo implantation and GnRH antagonists: embryo implantation: the Rubicon for GnRH antagonists. Hum Reprod 2000;15: 1211–6.
7. Al-Inany H, Aboulghar M. GnRH antagonist in assisted reproduction: a Cochrane review. Hum Reprod 2002;17:874–85.
8. Akman MA, Erden HF, Tosun SB, Bayazit N, Aksoy E, Bahceci M. Addition of GnRH antagonist in cycles of poor responders undergoing IVF. Hum Reprod 2000;15:2145–7.
9. Kolibianakis EM, Collins J, Tarlatzis BC, Devroey P, Diedrich K, Griesinger G. Among patients treated for IVF with gonadotrophins and GnRH analogues, is the probability of live birth dependent on the type of analogue used? A systematic review and meta-analysis. Hum Reprod Update 2006;12: 651–71.
10. Orvieto R, Nahum R, Rabinson J, Gemer O, Anteby EY, Meltcer S. Ultrashort flare GnRH agonist combined with flexible multidose GnRH antagonist for patients with repeated IVF failures and poor embryo quality. Fertil Steril 2009;91:1398–400.
11. Out HJ, Braat DD, Lintsen BM, Gurgan T, Bukulmez O, Gokmen O, et al. Increasing the daily dose of recombinant follicle stimulating hormone (Puregon) does not compensate for the age-related decline in retrievable oocytes after ovarian stimulation. Hum Reprod 2000;15:29–35.
12. Escudero E, Bosch E, Crespo J, Simon C, Remohi J, Pellicer A. Comparison of two different starting multiple dose gonadotropin-releasing hormone antagonist protocols in a selected group of in vitro fertilization-embryo transfer patients. Fertil Steril 2004;81:562–6.
13. Kolibianakis EM, Tarlatzis B, Devroey P. GnRH antagonists in IVF. Reprod Biomed Online 2005;10:705–12.
14. Koichi K, Yukiko N, Shima K, Sachiko S. Efficacy of low-dose human chorionic gonadotropin (hCG) in a GnRH antagonist protocol. J Assist Reprod Genet 2006;23:223–8.
15. Serafini P, Yadid I, Motta EL, Alegretti JR, Fioravanti J, Coslovsky M. Ovarian stimulation with daily late follicular phase administration of low-dose human chorionic gonadotropin for in vitro fertilization: a prospective, randomized trial. Fertil Steril 2006;86:830–8.
16. Filicori M, Cognigni GE, Samara A, Melappioni S, Perri T, Cantelli B, et al. The use of LH activity to drive folliculogenesis: exploring uncharted territories in ovulation induction. Hum Reprod Update 2002;8:543–57.
17. Dal Prato L, Borini A, Coticchio G, Cattoli M, Flamigni C. Half-dose depot triptorelin in pituitary suppression for multiple ovarian stimulation in assisted reproduction technology: a randomized study. Hum Reprod 2004;19:2200–5.
18. Sbracia M, Colabianchi J, Giallonardo A, Giannini P, Piscitelli C, Morgia F, et al. Cetrorelix protocol versus gonadotropin-releasing hormone analog suppression long protocol for superovulation in intracytoplasmic sperm injection patients older than 40. Fertil Steril 2009;91:1842–7.
19. Devroey P, Aboulghar M, Garcia-Velasco J, Griesinger G, Humaidan P, Kolibianakis E, et al. Improving the patient's experience of IVF/ICSI: a proposal for an ovarian stimulation protocol with GnRH antagonist co-treatment. Hum Reprod 2009;24:764–74.
20. Younis JS, Soltsman S, Izhaki I, Radin O, Bar-Ami S, Ben-Ami M. Early and short follicular gonadotropin-releasing hormone antagonist supplementation improves the meiotic status and competence of retrieved oocytes in in vitro fertilization–embryo transfer cycles. Fertil Steril 2010;94:1350–5.
21. Bloch M, Azem F, Aharonov I, Ben Avi I, Yagil Y, Schreiber S, et al. GnRH-agonist induced depressive and anxiety symptoms during in vitro fertilization-embryo transfer cycles. Fertil Steril 2011;95:307–9.
22. Hayden C. GnRH analogues: applications in assisted reproductive techniques. Eur J Endocrinol 2008;(159 Suppl 1):S17–25.
23. van Loenen AC, Huirne JA, Schats R, Hompes PG, Lambalk CB. GnRH agonists, antagonists, and assisted conception. Semin Reprod Med 2002;20: 349–64.
24. Al-Inany HG, Abou-Setta AM, Aboulghar M. Gonadotrophin-releasing hormone antagonists for assisted conception: a Cochrane review. Reprod Biomed Online 2007;14:640–9.
25. van Dongen AJ, Verhagen TE, Dumoulin JC, Land JA, Evers JL. Reasons for dropping out from a waiting list for in vitro fertilization. Fertil Steril 2010; 94:1713–6.
26. Mourad SM, Nelen WL, Akkermans RP, Vollebergh JH, Grol RP, Hermens RP, et al. Determinants of patients' experiences and satisfaction with fertility care. Fertil Steril 2010;94:1254–60.
27. Domar AD, Smith K, Conboy L, Iannone M, Alper M. A prospective investigation into the reasons why insured United States patients drop out of in vitro fertilization treatment. Fertil Steril 2010;94:1457–9.
28. Ombelet W, Campo R. Affordable IVF for developing countries. Reprod Biomed Online 2007;15:257–65.
29. Janssens RM, Lambalk CB, Vermeiden JP, Schats R, Schoemaker J. In-vitro fertilization in a spontaneous cycle: easy, cheap and realistic. Hum Reprod 2000;15:314–8.
30. Blockeel C, De Vos M, Verpoest W, Stoop D, Haentjens P, Devroey P. Can 200 IU of hCG replace recombinant FSH in the late follicular phase in a GnRH-antagonist cycle? A pilot study. Hum Reprod 2009; 24:2910–6.
31. Filicori M, Cognigni GE, Gamberini E, Parmegiani L, Troilo E, Roset B. Efficacy of low-dose human chorionic gonadotropin alone to complete controlled ovarian stimulation. Fertil Steril 2005;84:394–401.
32. Fabregues F, Penarrubia J, Creus M, Casamitjana R, Vanrell JA, Balasch J. Effect of halving the daily dose of triptorelin at the start of ovarian stimulation on hormone serum levels and the outcome of in vitro fertilization. Fertil Steril 2005;83:785–8.
33. Loumaye E, Vankrieken L, Depreester S, Psalti I, de Cooman S, Thomas K. Hormonal changes induced by short-term administration of gonadotropin-releasing hormone agonist during ovarian hyperstimulation for in vitro fertilization and their consequences for embryo development. Fertil Steril 1989;51:105–11.
34. Homburg R, Armar NA, Eshel A, Adams J, Jacobs HS. Influence of serum luteinising hormone concentrations on ovulation, conception, and early pregnancy loss in polycystic ovary syndrome. BMJ 1988;297:1024–6.
35. Tarlatzis BC, Grimbizis G, Pournaropoulos F, Bontis J, Lagos S, Spanos E, et al. The prognostic value of basal luteinizing hormone:follicle-stimulating hormone ratio in the treatment of patients with polycystic ovarian syndrome by assisted reproduction techniques. Hum Reprod 1995;10: 2545–9.