Pretreatment with an Oral Contraceptive Is Effective in Reducing the Incidence of Functional Ovarian Cyst Formation During Pituitary Suppression by Gonadotropin-Releasing Hormone Analogues

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Purpose: Our purpose was to assess the effect of pretreatment with oral contraceptives (OCs) on the formation of functional ovarian cysts during pituitary suppression with gonadotropin-releasing hormone (GnRH) agonists, subsequent follicular development, and pregnancy rates.

Methods: A retrospective case-controlled study of 31 in vitro fertilization (IVF) patients, all of whom in a previous cycle had commenced the long protocol of GnRH-agonist (Busereilin) in the early follicular phase and were pretreated in a subsequent cycle with 2 weeks of an OC containing 30 µg of ethinyl estradiol and 150 µg of desogestrel prior to GnRH-agonist administration, was undertaken. Follow-up visits were arranged after a minimum of 11 days of GnRH-agonist administration and weekly thereafter until pituitary suppression was achieved.

Results: Cysts were detected in 16 (51.6%) of the 31 patients not pretreated with OCs, and in 0 (0%) of the 31 patients pretreated with OCs (odds ratio = 67.1; 95% confidence interval = 5.6–350.7). Patients pretreated with OCs achieved pituitary suppression more rapidly (median difference = 4 days; 95% confidence interval = 2–7) and had comparable gonadotropin requirements and pregnancy rates.

Conclusions: Pretreatment with OCs prior to pituitary suppression in the early follicular phase decreases ovarian cyst formation, without an apparent effect on subsequent follicular recruitment or pregnancy rates.

KEY WORDS: oral contraceptive; long protocol; pituitary suppression; gonadotropin releasing-hormone agonist.

INTRODUCTION

Pituitary suppression with gonadotropin-releasing hormone (GnRH) agonists, starting in either the midluteal or the early follicular phase, has become a routine treatment prior to controlled ovarian hyperstimulation for in vitro fertilization (IVF) (1). This regimen minimizes the risk of a premature surge of luteinizing hormone (LH) and premature ovulation, simplifies treatment by reducing the need for close monitoring (2), and results in improved pregnancy rates (1). Unfortunately, pituitary suppression by GnRH agonists begun in the early follicular phase results in formation of functional ovarian cysts in up to 40% of patients (3). In patients who have ovarian cysts develop the administration of GnRH agonists generally has to be continued for a prolonged time before serum estradiol concentrations decrease to a basal level. This entails considerable inconvenience and expense for the patient because of additional ultrasound scans, blood tests, and prolonged GnRH agonist administration.

The administration of oral contraceptives (OCs) significantly suppresses the levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) (4). The administration of the OC pill could, therefore, reduce the incidence of cyst formation. However, the usefulness of OC administration in the prevention of ovarian cysts during pituitary suppression with GnRH agonists has not yet been adequately investigated.

In the present study, we compared the response of a group of patients who received a standard long protocol of GnRH agonists commencing in the early follicular phase in their first cycle of IVF treatment with the response in their second cycle of IVF treatment when they received 2 weeks of OC therapy before commencing

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ing GnRH agonist administration. We investigated the incidence of functional ovarian cyst formation and the length of time required to achieve pituitary suppression. We also compared subsequent follicular development, number of oocytes obtained, and fertilization and pregnancy rates.

MATERIALS AND METHODS

In the period between January 1997 and December 1997, 31 consecutive patients, all of whom in previous IVF cycles had achieved pituitary suppression with subcutaneous GnRH agonist (buserelin; Suprefact; Hoechst Rousell, Montreal) in a dose of 500 µg per day commencing on day 2 of the menstrual cycle before the administration of gonadotropins, and who had no absolute contraindications to use of OCs, were approached to take part in a study examining incidence of cyst formation during pituitary suppression. All 31 patients agreed to participate and subsequently received OCs containing 150 µg of desogestrel and 30 µg of ethinyl estradiol (Marvelon; Organon, Scarborough, Canada) pretreatment prior to commencement of GnRH-agonist. The OC was started on day 1 of the menstrual cycle for a period of 14 days. On the last day of OC pill administration, the first dose of buserelin was administered subcutaneously in a dose of 500 µg once a day. To confirm pituitary suppression, in both regimens, patients were recalled for an ultrasound examination and blood test on a Thursday, at least 11 days after initiation of buserelin treatment. Pituitary suppression was defined by the absence of any cystic structure 15 mm or greater in diameter and a serum estradiol concentration of 150 pM or less. If the criteria for pituitary suppression were not met, the dose of buserelin was increased to 500 µg twice a day, and an intramuscular injection of progesterone 100 mg was administered (5). If pituitary suppression was still not achieved after 3 weeks of buserelin administration, the ovarian cyst was aspirated under ultrasound control and ovarian stimulation started a minimum of 3 days later.

Following satisfactory pituitary suppression, ovarian stimulation was achieved with human menopausal gonadotropin (hMG) (75 IU FSH and 75 IU LH; Humegon; Organon) or with "pure" follicle-stimulating hormone (75 IU FSH; Fertinorm; Serono). The initial dose of gonadotropin was determined according to the patient's age, the basal FSH level, and the presence or absence of polycystic ovaries on ultrasound scan (6). Starting doses of gonadotropins were as fol-

lows: age in patients younger than 30, 150 IU of gonadotropins per day; age 30–37, 225 IU of gonadotropins; age 38–40, 300 IU of gonadotropins per day; and older than 40 years of age, 400 IU of gonadotropins. Patients with polycystic ovaries were started on 75 IU of gonadotropins, less for each age group. Patients with FSH levels greater than 10 IU/L were started on 75 IU of gonadotropins more than standard dose used for each age group. Subsequent adjustments were then made according to the follicular response as determined by serial ultrasound scans. Human chorionic gonadotrophin (hCG) (10,000 IU; Profasi; Serono, Oakville, Canada) was administered when there were at least three follicles with a mean diameter (measured in three planes) of at least 18 mm. Transvaginal oocyte recovery was performed 36 hr after hCG administration using an ultrasound scanner with a 5-MHz vaginal probe (Cheetah 2003, B&K Medical, Gentofte, Denmark). Oocyte recovery was performed using a double-lumen needle (16 gauge; K-OPSD-1635; W. A. Cook, Brisbane, Australia), a K-MAR 5000 vacuum pump (W. A. Cook) with an aspiration pressure of –100 mm Hg, and a K-MAR-4000 automatic follicle flushing system (W. A. Cook). Each visible follicle in both ovaries was aspirated. Oocytes were identified, washed in equilibrated Medicult universal IVF medium (Medicult; Hopkinton, USA), and then incubated in organ culture dishes (Falcon; VWR Canlab, Montreal) containing 0.9 ml of equilibrated Medicult medium. Insemination of 10 µl of prepared sperm, at a concentration of 5–7 mol/ml of motile sperm, took place 38–40 hr after hCG administration. Oocytes were examined for signs of fertilization between 18 and 21 hr after insemination. Depending on the patient's age and the quality of embryos, between one and four embryos were transferred approximately 48 hr after oocyte collection, by which time embryos had undergone at least one mitotic cellular division. Prior to embryo transfer (ET), all embryos were graded and the cumulative embryo score (CES) was calculated as described previously (7). In patients younger than 40 years of age, a maximum of three embryos was replaced. In patients older than 40 years of age, a maximum of four embryos was replaced. Fewer than the maximum number appropriate for the patient's age were transferred if there was an insufficient number of embryos available or the patient requested this.

The luteal phase was supplemented with 200 mg of micronized progesterone (Prometrium; Schering Canada Inc., Point-Claire, Canada), which was self-administered by patients vaginally, twice daily. A serum pregnancy test was performed 14 days following ET.

Statistics

Data were collected and analyzed using a scientific version of the McGill Infertility Database System infertility program. Double entry was used and all data were checked against manual entry in the case notes. As the results were found not to be normally distributed, statistical analysis was performed using χ^2 , Mann–Whitney, and Fisher–Irwin tests and odds ratios (ORs) and confidence intervals (CIs). CIs quoted are always 95%.

RESULTS

Thirty-one patients undergoing 62 cycles were included in the study. The median age of patients treated was 34.4 years (range, 27.7–44.8 years). The cause of infertility was attributed to male-factor infertility in 12 (30.9%) cases, tubal damage in 7 (20.9%) cases, unexplained infertility in 6 (20.1%) cases, anovulation in 6 (8.5%) cases, and endometriosis in 3 (7.7%) cases. The median interval occurring between two cycles of treatment was 161 days (range, 98–357 days). During the period of the study no significant changes in personnel or IVF protocols occurred.

On initial follow-up visit, at least 11 days following initiation of buserelin administration, functional ovarian cysts were detected in 16 (51.6%) of 31 cycles of patients not pretreated with OCs and in no cycle in patients pretreated with OCs (OR = 67.1; CI = 5.6–350.7) (Table I). Moreover, estradiol levels at this visit were significantly higher in cycles not pretreated (median difference = 86 pM; CI = 17–267 pM). Satisfactory pituitary suppression was achieved on the first visit in 29 (93.5%) of 31 cycles pretreated with OCs and only 16 (51.6%) of 31 non-pretreated cycles (OR = 11.1; CI = 2.5–99.0). Interestingly, the two patients pretreated with OCs who did not achieve pitu-

itary suppression on the first visit had both previously had cysts develop in nonpretreated cycles and had required prolonged suppression with buserelin. When pretreated with OCs, both patients had small cystic structures develop (11 and 12 mm in mean diameter, respectively). One of the two patients followed the standard protocol and achieved pituitary suppression 1 week later. The other patient decided to have the 11-mm cystic structure immediately aspirated, and she commenced gonadotropin therapy following satisfactory pituitary suppression 1 week later.

Ovarian cyst aspiration was required in three cycles in patients not pretreated with an OC. In two of these patients the principal cause of infertility was tubal damage, and in the third the cause of infertility was unexplained. None of these patients had polycystic ovaries.

While no difference in number of follicles recruited was observed between the two groups (median difference = 1; CI = –3 to 4), the growth of follicles was more rapid in the group pretreated with OCs (Table II). This resulted in significantly more follicles measuring more than 14 mm in diameter (median difference = 2; 95% CI = 0–5) and marginally higher serum estradiol levels on day 9 of ovarian stimulation (median difference = 1333 pM; CI = –63 to 2614 pM). However, by the end of ovarian stimulation this difference disappeared and on the day of hCG administration no difference in serum estradiol levels (median difference = 229 pM; CI = –1611 to 2448 pM) or number of follicles measuring more than 14 mm (median difference = 0; CI = –2 to 2) was observed. No difference in the quantity of gonadotropins required to achieve satisfactory ovarian stimulation was observed (median difference = 1; CI = –5 to 8). Similar numbers of oocytes were obtained (median difference = 1; CI = –2 to 4), and similar numbers of embryos (median difference = 0; CI = –2 to 2) of comparable quality

Table I. The Difference in the Length of Time Required to Achieve Pituitary Suppression with Buserelin Between Cycles Where Patients Were Pretreated with OCs Compared with Nonpretreated Cycles

	Pretreated with OC (n = 31)	Not pretreated with OC (n = 31)	P
Estradiol(pM) ^a	10 (10–512) ^b	113 (10–2106)	0.0005
No. patients with cyst >15 mm ^a	0	16	<0.0001
No. patients with confirmed pituitary suppression ^a	29	16	0.0006
Days on buserelin required to achieve pituitary suppression	14 (11–18)	17 (12–35)	<0.0001

^a On initial assessment after a minimum of 11 days of buserelin administration.

^b Median (range).

Table II. The Difference in the Response to Ovarian Stimulation Between Cycles Pretreated with OC and Cycles Where OC Was Not Administrated Prior to Commencement of Buserelin Treatment

	Pretreated with OC (<i>n</i> = 31)	Not pretreated with OC (<i>n</i> = 31)	<i>P</i>
Days on gonadotropins	10 (7–13) ^a	11 (9–13)	NS ^b
Total quantity of gonadotropins used (amp)	36 (20–110)	40 (22–96)	NS
Estradiol(pM) on day 9 of gonadotropin administration	4,356 (236–16,000)	2,358 (299–10,226)	0.06
No. of follicles on day 9 of gonadotropin administration	14 (2–27)	13 (4–25)	NS
No. of follicles >14 mm on day 9 of gonadotropin administration	5 (0–17)	2 (0–18)	0.016
Estradiol(pM) on day of hCG administration	6,057 (989–22,506)	6,605 (1,882–27,584)	NS
No. of follicles on day of hCG administration	15 (3–28)	16 (5–32)	NS
No. of follicles >14 mm on day of hCG administration	8 (1–23)	7 (2–18)	NS

^a Median (range).^b Not significant.

(median difference = 2; CI = -4 to 8) were replaced. Finally, although higher pregnancy rates were observed in the cycles pretreated with OCs, it did not reach a level of statistical significance (OR = 1.47; CI = 0.42–5.4) (Table III).

DISCUSSION

Over the past 15 years, IVF has become an established treatment for infertility. Its results compare favorably with those of spontaneous conception in the natural menstrual cycle in fertile women (8). In recent years, GnRH-agonists have become widely incorporated into ovarian stimulation regimens for IVF. Different protocols have been designed for the administration of GnRH-agonists. The long protocol is generally accepted to produce better results than the short protocol (9). It has also been shown that when the long protocol of GnRH-analogue is commenced in the early follicular phase with a depot preparation, the result is

less profound pituitary suppression, larger numbers of oocytes collected, and possibly higher pregnancy rates, compared with initiation of GnRH-agonist in the mid-luteal phase (10).

One disadvantage of early follicular over midluteal initiation of GnRH agonist is the generally increased incidence of ovarian cyst formation when GnRH agonist is started in the early follicular phase (10). We have previously investigated the effect of ovarian cysts formed during GnRH agonist administration. In that study, we found no decrease in either follicular recruitment or fertilization and pregnancy rates in patients who had cysts develop, provided that activity of the cyst has been suppressed prior to initiation of ovarian stimulation (11). However, the patients who had ovarian cysts develop required a significantly longer period of time to achieve ovarian suppression. We have also previously shown that the length of time for pituitary suppression can be somewhat shortened if an intramuscular injection of progesterone is administered in cases where no pituitary desensitization is achieved after 14 days of GnRH agonist administration (5). In spite of this modification, the period leading to ovarian suppression is frequently prolonged and unpredictable, requiring repeated blood tests and additional ultrasound scans. Moreover, a prolonged period of ovarian suppression causes additional stress and anxiety to the patients undergoing IVF treatment. It would, therefore, be of considerable interest to be able to reduce or abolish ovarian cyst formation during GnRH agonist administration. Previously, the formation of ovarian cysts prior to the administration of GnRH agonists in the midluteal phase had been successfully prevented by progesterone administration prior to analogue administration (12). However, to our knowledge, there have been no attempts to prevent cyst formation during

Table III. Comparison of Outcomes of Cycles Where Patients Were Pretreated with OC VA. Cycles Where OCs Were Not Administrated Prior to Commencement of Buserelin Treatment

	Pretreated with OC (<i>n</i> = 31)	Not pretreated with OC (<i>n</i> = 31)	<i>P</i>
No. oocytes collected	11 (3–28) ^a	10 (1–32)	NS ^b
No. oocytes fertilized	6 (0–22)	6 (1–20)	NS
Cumulative embryo score	30 (0–66)	29 (12–50)	NS
Pregnancy rate per cycle started	22.6%	16.1%	NS

^a Median (range).^b Not significant.

pituitary suppression commenced in the early follicular phase.

Functional ovarian cysts are probably formed by the transient initial stimulatory effect of GnRH agonist on gonadotropin release. Released gonadotropins in turn cause the rapid growth of primordial follicles. Owing to rapid pituitary suppression, however, continued follicular development and ovulation does not occur and follicular cysts are formed (13). The initial stimulatory effect of GnRH agonists increases the levels of both FSH and LH. However, early follicular development is caused primarily by FSH (14), and therefore, the surge of FSH, rather than LH, is probably responsible for functional cyst formation. Therefore, to abolish the formation of functional ovarian cysts in the follicular phase of the cycle, the initial FSH surge should be attenuated. Tzai and Yen (15) have previously shown that 0.2 mg of ethinyl estradiol given between day 3 and day 5 of the menstrual cycle significantly decreases FSH levels. In attempts to program IVF cycles and to abolish the occurrence of a premature LH surge, Templeton *et al.* (16) studied the effects of norethisterone and a combined OC on pituitary suppression. They reported a significantly slower response to combined treatment with clomiphene citrate and hMG in patients pretreated with the oral contraceptive pill and suggested that OCs cause a deeper pituitary suppression. In a separate study, Foreman *et al.* (4) reported a similar level of suppression of LH, but a significantly deeper suppression of FSH with the OC pill compared with norethisterone. A recent study comparing patients pretreated with norethisterone with controls showed a significant decrease in the initial rise of LH, but only a marginal reduction in the rise of FSH after initiation of GnRH agonists in the early follicular phase (17). From these studies, it seems that estrogen rather than progesterone is responsible for FSH attenuation in the early follicular phase and should, therefore, be more effective in the prevention of ovarian cyst formation. Strohmer *et al.* (18) prospectively compared patients treated with either the short protocol or the long protocol commenced in the early follicular phase. The early follicular-phase administration of GnRH analogues in the long protocol was preceded by pretreatment with the OC pill. They monitored hormonal and ultrasonic signs of pituitary suppression in the first 12 patients on the long protocol and found that, after 6 days of GnRH analogue administration, no patients had ovarian cysts develop. They concluded that 7 days of GnRH analogue administration invariably leads to satisfactory down-regulation if pretreatment with OCs has been used. The results of our study only partly confirm

their data. In a larger sample, we showed that pretreatment with OCs significantly decreases the length of time required to achieve pituitary suppression, but not all patients pretreated with OCs achieve pituitary suppression after 11 days of buserelin administration. In 6.5% of patients, a serum estradiol level of less than 150 pmol/ml was achieved only after 18 days of GnRH agonist administration. From our data it is, therefore, clear that before treatment with gonadotropins is started, ovarian suppression should be confirmed. If this is done at least 11 days after commencement of GnRH agonist therapy, 93.5% of patients are likely to have ovarian suppression confirmed. The remaining patients should continue with GnRH analogue use until ovarian suppression is confirmed.

An additional question involves the effect of pretreatment with OCs on subsequent follicular development, oocyte and embryo quality, and pregnancy rates. Tzai and Yen (15) showed that when ethinyl estradiol was given between day 3 and day 5 of menstruation and discontinued thereafter, folliculogenesis resumed, followed by ovulation and normal corpus luteal function. Pretreatment with OCs in IVF was first used more than 12 years ago to program IVF cycles and prevent a premature LH surge (16). Owing to deeper pituitary suppression, early reports suggested lower follicular recruitment and higher cancellation rates when pretreatment with OCs was used (19). However, when either the length of time between discontinuation of OCs and commencement of ovarian stimulation was extended to 3 days (20) or the dose of hMG was increased (21), comparable follicular recruitment was achieved. Moreover, Gonen *et al.* (20) have reported significantly better follicular recruitment and an absence of premature LH surge in patients pretreated with OCs containing 50 µg of ethinyl estradiol and 1 mg of ethynodiol diacetate. The data on the effect of sequential suppression with OCs and GnRH agonists are scanty. One retrospective study exists in which patients with a high response to gonadotropins in one cycle were pretreated in a subsequent cycle with an OCs (22). In that study, the authors reported a significant decrease in dehydroepiandrosterone sulfate and LH levels and higher fertilization and pregnancy rates in the patients pretreated with OCs. In our study, a significantly more rapid response to ovarian stimulation was observed in patients pretreated with OCs. This suggests that, perhaps, pretreatment with OCs results in less profound pituitary suppression. Additionally, a nonsignificant increase in pregnancy rates was observed in the cycles pretreated with an OCs. Both ours and previously reported data are based on

retrospective controls and, therefore, should be considered with some caution. However, it is quite unlikely that pretreatment with an OCs has any detrimental effect on pregnancy rates.

We conclude that pretreatment with an OCs, probably because of its estrogen component, results in a significant decrease in functional ovarian cyst formation during pituitary suppression by GnRH agonists initiated in the early follicular phase of the menstrual cycle. We also note a trend toward higher pregnancy rates. However, before introduction of this regimen can be widely recommended, it should be studied in a prospective randomized trial.

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