Does Pretreatment with Progestogen or Oral Contraceptive Pills in Low Responders Followed by the GnRHa Flare Protocol Improve the Outcome of IVF-ET?

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Purpose: Women undergoing in vitro fertilization with low ovarian reserve and poor response to controlled ovarian hyperstimulation (COH) present a management dilemma. In a retrospective observational study, we compared the pretreatment use of the gestogen medroxyprogesterone acetate (10 mg twice daily from day 15 of the cycle for a minimum of 2 weeks) with an oral contraceptive pill (one tablet daily from day 4 of the cycle for a minimum of 3 weeks).

Methods: The criteria for inclusion in the study included one or more of the following: abandoned cycles due to poor response, fewer than four oocytes retrieved following a standard COH protocol, age >39 years, and elevated basal serum follicle-stimulating hormone (FSH). Thirty-eight women received pretreatment with gestogen, and a similar number of women received pretreatment with the pill. The flare protocol was used in all treatment cycles combined with an individualized dose of human menopausal gonadotropin (hMG) (4–8 ampoules/day of 75 units FSH/ampoule) depending on previous response, age, and early follicular serum FSH level. Both groups were similar in mean age, duration of infertility, early follicular FSH levels, and the distribution of various aetiologies.

Results: Twenty-nine cycles were abandoned before oocyte retrieval, 15 (39.5%) in the pill group and 14 (36.8%) in the gestogen group, because of an inadequate ovarian response. The mean ($\pm$ SD) number of ampoules (75 IU FSH/ampoule) of hMG used per cycle was similar in the pill and gestogen groups (59.7 ± 19.3 vs. 70.2 ± 29.4 , respectively). There also was no difference seen in the numbers of oocytes retrieved (4.4 ± 2.3 vs. 4.2 ± 2.5), total number of embryos (2.5 ± 2.4 vs. 2.2 ± 1.1), or the number

of embryos transferred (1.8 ± 1.2 vs. 2.1 ± 1.0) in the pill and gestogen groups, respectively. One pregnancy in each group resulted following embryo transfer in 22 women in the pill group and in 24 women in the gestogen group.

Conclusions: We conclude that pre-IVF treatment with oral contraceptive pill or gestogen combined with the flare protocol in women at high risk of or with a history of poor ovarian response, as defined in this study, did not appear to result in an improvement in outcome of IVF-embryo transfer.

KEY WORDS: In vitro fertilization; low responders; pre-in vitro fertilization treatment using oral contraceptive pill or gestogen; controlled ovarian hyperstimulation; “flare” protocol.

INTRODUCTION

The success of in vitro fertilization and embryo transfer (IVF-ET) is closely related to controlled ovarian hyperstimulation (COH) responsiveness (1), but this response can be highly variable and difficult to predict. Jones and colleagues (2) coined the phrase “low responders” to describe women who typically responded to COH with peak estradiol (E_2) levels of < 300 pg/ml, few oocytes retrieved, fewer embryos developed and transferred, and as a consequence, lower pregnancy rates. At present, this is one of the most challenging areas in assisted conception (2), since the prevalence of low responders is up to 18% according to the definitions used (3).

The definition of a low responder is controversial. There has been an abundance of criteria to identify low responders prior to COH, initially including advanced age >37 years (4), prior ovarian surgery (5), and women who, in previous COH, required markedly increased quantities of human menopausal gonadotropin (hMG) to obtain the required ovarian response (6). A raised level of early follicular phase (day 3 of cycle) plasma follicle-stimulating hormone (FSH) and estra-

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diol levels can predict those with poor response to COH irrespective of age (7,8). Others have introduced various dynamic tests to further identify low responders, such as the clomiphene citrate challenge test (9,10), gonadotropin challenge test, and gonadotropin-releasing hormone analogue (GnRHa) test (11). More recently, other tests to identify low response have been reported, such as measuring inhibin (12) and ultrasonographic ovarian volume measurement and examining the number of small follicles present before ovarian stimulation (13–15). A universally accepted definition of low responders certainly is not available; nevertheless, early follicular plasma FSH levels remain the most widely used test to predict a response to COH and identify patients with limited ovarian reserve (16).

Pretreatment with oral contraceptive pills before commencing COH is reported to improve the ovarian response (17,18). Pretreatment with progestogen has been claimed to improve IVF outcome generally (19). There are many COH protocols for low responders reporting varying degrees of success (20). We describe our experience in 76 patients who were considered to be low responders to COH by one or more of the above criteria following the use of a gestogen, medroxyprogesterone acetate (Provera, Pharmacia, and Upjohn, England) and an oral contraceptive pill (Marvelon, Organon, England) in the cycle preceding the IVF treatment.

MATERIALS AND METHODS

A total of 76 [IVF = 61; intracytoplasmic sperm injection (ICS) = 15] cycles were included in this nonrandomized, retrospective, observational study. Women having one or more of the following criteria were included: (1) a previous abandoned cycle following a standard COH protocol because of a very low response (fewer than three follicles >14 mm after 10–12 days of stimulation); (2) fewer than four oocytes retrieved following a standard COH protocol; (3) early follicular phase (days 2–4 of cycle) serum FSH >8 IU/liter; and (4) women aged >39 years. The majority of women had more than one of the above inclusion criteria. Ovum donation was discussed with all patients who had a low response in previous cycles, were >40 years old, and had high serum FSH. All patients included had early follicular phase FSH, luteinizing hormone (LH) and estradiol (E_2) plasma levels measured within 3 months before treatment. As the availability of donor oocytes is poor, patients were selected

for pretreatment with hormonal preparation, i.e., medroxyprogesterone acetate (gestogen) or oral contraceptive pill (OCP) based on the attending physician's choice. Initially, gestogen was used to facilitate cycle programs, but was prescribed subsequently as pretreatment. The OCP was considered an option for pretreatment more recently. Typically, OCP was given to start from day 4 of the menstrual cycle for minimum of 21 days to a maximum of 42 days, while the gestogen tablets were typically given at a dose of 10 mg twice a day from day 15 of the cycle preceding the IVF treatment for a period of 2–3 weeks. All patients had an ultrasound scan 1 week before completing their tablets to exclude the presence of large ovarian cysts. The patients were advised to stop the tablets, await withdrawal bleeding, and start the gonadotropin-releasing hormone analogue (Nafarelin acetate 200 μ g per nostril twice a day; Synarel, Searle Pharmaceutical Products, England) on the second day of the period.

The hMG dosage was individualized based on the previous response to COH, the early follicular phase serum FSH, age, and body mass index (BMI). A starting dose of 4–8 ampoules (75 IU FSH/ampoule) based on the criteria mentioned was started on the same day as the GnRHa. Monitoring of the ovarian response was performed by regular vaginal ultrasonography and human chorionic gonadotropin (hCG) 10,000 IU (Profasi; Serono, England) was administered when one or more leading follicles measuring >18 mm in diameter and an endometrial thickness $\geq$ 8 mm were seen. Both hMG injections and GnRHa were continued until the time of hCG administration. Cycles were abandoned if, after 10 days of COH, less than four mature follicles ($\geq$ 14 mm) were seen on ultrasonography. Transvaginal ultrasound-guided oocyte retrieval was performed 34–36 hr after the hCG trigger injection, in 61 cycles standard in vitro insemination was conducted and in 15 cycles, ICSI. A maximum of three embryos were transferred into the uterus 2 or 3 days after oocyte retrieval, and luteal support with vaginal pessaries containing 400 mg of progesterone was continued daily for at least 2 weeks after embryo transfer (ET). If pregnancy was determined 2 weeks after ET, ultrasound was performed to confirm the presence of intrauterine pregnancy typically 5 weeks after ET.

The Student's *t* test was used to compare the statistical significance of samples in the different group. The chi square exact probability test was used to compare percentages observed. Statistical significance was defined as $P < 0.05$.

Table I. Demographic Characteristics of Patients

	All (<i>n</i> = 76)	OCP (<i>n</i> = 38)	Gestogen (<i>n</i> = 38)
Age (years) ^a	36.7 (3.91)	36.4 (3.61)	36.7 (4.3)
Weight (kg) ^a	67.1 (16.2)	68.7 (17.6)	65.1 (19.6)
Duration of infertility: years ^a	7.2 (3.9)	6.9 (3.7)	7.1 (3.6)
Cycle day 2–4 serum FSH IU/Liter ^a	8.8 (3.7)	9.5 (4.3)	8.06 (2.9)
No. of patients with FSH >8 IU (%)	40 (52.6)	23 (60.5)	17 (44.7)
Causes of infertility <i>n</i> (%)			
Tubal	30 (39.5)	17 (44.7)	13 (34.2)
Male	17 (22.4)	7 (18.4)	10 (26.3)
Ovulatory	2 (2.6)	1 (2.6)	1 (2.6)
Unexplained	18 (23.7)	7 (18.4)	11 (29.0)
Endometriosis	9 (11.8)	6 (15.8)	3 (7.9)

^a Mean (SD).

RESULTS

Thirty-eight women had pretreatment with OCP and 38 patients had pretreatment with gestogen (Table I). Twenty-six women (34.2%) had had pelvic surgery of varying degrees and 43 (56.6%) were cigarette smokers. There were no statistically significant differences seen in any of the parameters studied between the two groups (Table I). Table II summarizes the outcome of the most recent IVF cycle in 63 patients who had previous treatment. Thirty-seven women (58.7%) reached oocyte retrieval and ET, while in 26 women (41.3%) the cycle was abandoned due to lack of or very low ovarian response. In the remaining 13 patients, the study cycle was their first IVF treatment.

The COH characteristics of the study patients are described in Table III. There were no statistically significant differences seen in mean number of ampoules of hMG used, the number of cycles abandoned, the mean number of oocytes collected, the number of total embryos available (as an indication of fertilization and cleavage), and number of embryos transferred (Table III). Although a larger amount of hMG was used in the gestogen group than the OCP, this difference was not statistically significant [95% confidence interval (CI): -0.87 to 21.87; *P* = 0.07]. A statistically sig-

nificantly larger total hMG dose was used in the index cycle than the previous cycle (64.4 ± 25.5 vs. 53.0 ± 21.7 ; 95% CI: 3.36 to 19.44; *P* = 0.006). The difference was statistically significant in the gestogen group (70.2 ± 29.4 ; 95% CI: 7.07 to 27.33; *P* = 0.001), but not in the OCP group (59.7 ± 19.3 ; 95% CI: -1.8 to 15.2; *P* = 0.12). One pregnancy was achieved in each group resulting in live births at term.

DISCUSSION

This study examined the possible beneficial effect in low responders of two preparations of synthetic steroids followed by a "flare" protocol of COH. There was no difference seen between the two groups with respect to their age, duration of infertility, early follicular phase FSH levels, or the cause of infertility. Both groups consisted of patients with the worst prognosis in our IVF program. A significantly higher dose of hMG was used in the index cycle of treatment when compared to the previous treatment cycle in those women who had previous IVF (64.4 ± 25.5 vs. 53 ± 21.7 ; *P* = 0.007). Despite this increase in hMG dose, the number of oocytes retrieved and the number of embryos generated did not show a corresponding rise. The rate of abandoned cycles was lower in the study cycle, but this was not statistically significant (38.2% vs. 41.3%). The parameters of COH and IVF treatment studied were similar in the oral contraceptive and gestogen groups despite the higher mean dose of hMG used in the gestogen group (70.2 ± 29.4) compared to the OCP group (59.7 ± 19.3), a difference that was not apparently statistically significantly different. Similar mean numbers of oocytes were retrieved and embryos developed and transferred in the two. Disap-

Table II. Features of Previous IVF Treatments in 63 Low Responders

No. of previous IVF treatment cycles ^a	1.80 (1.5)
Total no. of ampoules (75 IU) of gonadotrophins ^a	53.00 (21.7)
No. of abandoned cycles (%)	26.0 (41.3%)
No. of oocytes retrieved ^a	4.40 (2.5)
No. of embryos obtained ^a	2.40 (1.7)
No. of embryos transferred ^a	2.02 (1)

^a Mean (SD).

Table III. Clinical and Laboratory Features of IVF Cycles in 76 Women Who Had Received Pretreatment with OCP ($n = 38$) and Gestogen ($n = 38$)

	All patients ($n = 76$)	OCP ($n = 38$)	Gestogen ($n = 38$)	<i>P</i>
ICSI no. (%)	15.0 (13.7)	6.0 (15.8)	9.0 (23.7)	NS ^b
No. gonadotrophin ampoules started ^a	5.6 (1.6)	5.3 (1.4)	6.0 (1.7)	NS
Days of stimulation ^a	11.5 (2.2)	11.5 (2.5)	11.6 (1.8)	NS
Total no. of ampoules ^a	64.4 (25.5)	59.7 (19.3)	70.2 (29.4)	NS
Abandoned cycle no. (%)	29.0 (38.2)	15.0 (39.5)	14.0 (36.8)	NS
No. oocytes collected ^a	4.4 (2.4)	4.4 (2.3)	4.2 (2.5)	NS
Failed oocyte retrieved no. (%)	1.0 (1.3)	1.0 (2.6)	0.0	NS
Failed fertilization no. (%)	8.0 (10.5)	5.0 (13.2)	3.0 (7.9)	NS
Total no. of embryos ^a	2.5 (1.8)	2.5 (2.4)	2.2 (1.1)	NS
No. of embryos transferred ^a	2.1 (1.0)	1.8 (1.2)	2.1 (1.0)	NS
Clinical pregnancy rates (%)	2.0 (2.6)	1.0 (2.6)	1.0 (2.6)	NS

^a Mean ($\pm$ SD).^b NS, not significant.

pointingly, the pregnancy rate was very low (2.6%) in both groups, and for that reason we discontinued the whole trial. A weakness in this study is the lack of a control group. As this was an observational study examining clinical practice, we did not use a control group because our purpose was to try to determine whether either protocol would improve the outcome of these poor responder patients.

Improving pregnancy rates in low responders remains one of the biggest challenges that faces assisted conception treatment (21). The low pregnancy rate in this group was mainly attributed to serious oocyte factors. Previous studies have shown a favorable effect of the "flare" protocol in low responders (11,22) and pretreatment cycle with estrogen (23) and the use of the oral contraceptive pill before commencing COH (11,18) presumably by eliminating the existence of the corpus luteum, suppressing endogenous FSH to normal, and restoring the sensitivity in the ovarian follicle to exogenous FSH. Pretreatment with progesterone, apart from aiding in timing the start of COH, has been reported to improve IVF outcome in general, probably through a similar mechanism to estrogen pretreatment (19). IVF cycle pretreatment with progesterone is characterized by reduced gonadotropin flare-up response, no increase in corpus luteum rescue by GnRHa, and identical pregnancy rate to cycles without pretreatment (24). The reduced gonadotropin flare-up response to GnRHa may be a factor in the high hMG dose and the poor overall response in the gestogen group and very possibly may explain the same outcome in the OCP group. Keay and colleagues (20) suggested that by suppressing serum FSH to normal, and hence down-regulating the ovarian FSH receptors, sensitivity may be restored in the remaining

follicles. The use of the OCP in our study to suppress serum FSH did not support this concept.

Karande and colleagues (25) recently reported their experience with the "flare" protocol in low responders, describing an adequate ovarian response but a low ongoing pregnancy rate (6.5% per retrieval). Their study differed from ours in that they selected a group with an elevated day-3 FSH >12 IU/liter or a history of poor response and they only started the COH when the day-2 FSH was ≤ 12 IU/liter in the treatment cycle. The poor outcome in their study (6.5% pregnancy rate per retrieval) confirmed that patients with a history of elevated basal FSH do poorly with such subsequent stimulation (26). Our data expand on this information and confirm that using OCP or gestogen, which will lower the basal FSH, apparently does not improve the clinical outcome in low responders. Our findings also support other earlier reports that concluded that increasing the hMG dose does not improve the prognosis (3,27). Increasing the dose of gonadotropin may produce some benefits, but the saturation kinetic is reached as no further benefit was gained from further increase. The total hMG dose in the gestogen group was higher than in the OCP group by a mean total number of 10 ampoules (750 IU) possibly as a result of decrease in flare effect in pretreatment with gestogen (24). But, despite this increase, the stimulation and pregnancy outcome remained very low. Increasing the dose to more than 450 IU per day of FSH does not improve follicular recruitment or the pregnancy rate in low responders (28). As follicular recruitment starts before the index cycle by an unspecified time interval, Rombauts and colleagues (29) commenced the gonadotropin stimulation in the luteal phase in women with

suboptimal ovarian stimulation, but this strategy also did not improve the outcome.

The dose of GnRHa required to maintain pituitary suppression decreased with increasing length of treatment (30). By using a smaller dose of short-acting GnRHa (Triptorelin or leuprolide) to produce pituitary suppression; further reducing the dose at the start of COH produced better results for low responders (31–33). The flare-up regimen of GnRHa protocol is associated with early elevated level of progesterone due to corpus luteum rescue (34). Oral contraceptive and gestogen pretreatment can reduce the effect. The combination of oral contraceptive pretreatment and microdose GnRHa in a flare-up protocol has been reported to result in a higher estrogen peak, more mature oocytes, and increased numbers of embryos available for transfer (35).

Schoolcraft and colleagues (36) have examined the use of growth hormone as showing possible benefit to COH in low responders. In this study, pretreatment with OCP and the flare protocol with microdose GnRHa was used in conjunction with growth hormone, but the selection of patients differed from our study and others (3,27). The study also employed embryo-assisted hatching techniques. The evidence on the value of growth hormone remains controversial (22,37,38). The value of microdose GnRHa though is worthy of consideration in larger studies. The pretreatment of each cycle with oral contraceptive pill before commencing COH (17,18) presumably by eliminating the existence of the corpus luteum and so preventing the progesterone rise in the early follicular stage and suppressing endogenous FSH to normal will restore the sensitivity in the ovarian follicle to exogenous FSH. Pretreatment with progestogen apart from aiding in timing the start of COH has been reported to improve IVF outcome in general, probably through a similar mechanism to estrogen pretreatment (19). Pretreatment with progesterone was confirmed to eliminate corpus luteum rescue and progesterone rise, but it has been characterized by a reduced GnRHa flare-up and did not improve pregnancy rate (24).

The mechanism and the site of action of GnRHa is at several levels and is partly unknown. Following down-regulation, there may be residual gonadotropin secretion, depending on hypophyseal sensitization, and this may depend on the GnRHa protocol and which particular analogue is used. GnRHa also may affect the ovary directly and the endometrium receptivity. These concerns may explain the emergence of the microdose GnRHa protocol and the earlier cessation after down-regulation protocol (39). In the “cessation”

protocol, GnRHa luteal phase down-regulation is initiated, then discontinued with the start of the menses and COH initiation on day 3 of the cycle. In 224 cycles, there was a 12.5% cancellation rate and only one patient had a premature LH surge; a respectable 28% pregnancy rate per attempt was achieved in these low responders (39).

A decrease in ovarian volume measured by transvaginal sonography (TVS) was reported to be associated with poor response to ovarian stimulation (40). The number of small ovarian follicles (2–5 mm) detected by TVS after GnRHa and before COH was reported to give better prediction of number of oocytes retrieved than the woman's age or ovarian volume (15). If these findings are further confirmed and shown to be closely related to other ovarian reserve tests, surely they will lead to less costly and more easily accessible tests. The decline in ovarian reserve leads to a decline in reproductive potential. Even those with normal FSH but who do not respond to hMG stimulation are reported to be at risk of developing ovarian failure within several months (41). The decline in ovarian response is due to an ovarian or intraovarian cause. This decline could be influenced by genetic factors, surgical treatment (as ovarian or pelvic surgery), endometriosis, or immunological factors. Our group also has confirmed that cigarette smoking can adversely affect ovarian reserve (42).

Oocyte donation is the ultimate treatment for women who repeatedly fail to adequately respond to COH. In our experience, women are reluctant to take this option early in their fertility treatment. Furthermore, the legal restrictions on oocyte donation in Great Britain (i.e., no payment of donors) has resulted in a very long waiting list for anonymous oocyte donation and almost complete of known donation. Pressure is then placed on couples and on their fertility specialists to try other options in the hope of successful pregnancy with the full knowledge that some of these treatment options result in very low pregnancy.

We conclude that, as the pregnancy rate remained very low in women who are identified as low responders when using pretreatment OCP or gestogen in a flare protocol associated with a high gonadotropin dose, this strategy should not be used for this purpose. As the low responders group is very heterogeneous, management is difficult and needs to be individualized, and oocyte donation needs to be considered with the couple as an option if low response to COH is combined with other indicators of low ovarian reserve. More experience and research into alternative treatment strategies need to be considered urgently in these cases

and the temptation to use high doses of gonadotropin repeatedly should be resisted.

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