Hypothalamic-Pituitary Suppression with Oral Contraceptive Pills Does Not Improve Outcome in Poor Responder Patients Undergoing In Vitro Fertilization-Embryo Transfer Cycles

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Purpose: *To evaluate and compare the use of OCP with GnRHa for hypothalamic-pituitary suppression in poor responder IVF patients.*

Methods: *Retrospective analysis of IVF-ET cycles of poor responders. Hypothalamic-pituitary suppression with OCP (Group I,* n = *29) or GnRHa (Group II,* n = *52), followed by stimulation with gonadotropin, oocyte retrieval, and embryo transfer. Baseline characteristics and cycle outcomes were compared.*

Results: *73 women underwent 81 cycles from 1/1/1999 to 1/1/2000. Baseline characteristics were similar. 31/81 (38%) cycles were cancelled (Group I, 14/29 (48%) vs. Group II, 17/52 (33%), NS). Cycle outcomes including amount of gonadotropin, number of eggs retrieved, number of embryos transferred, and embryo quality were similar. Patients in Group I required fewer days of stimulation to reach oocyte retrieval. Pregnancy outcomes were similar in the two groups.*

Conclusion: *Our retrospective analysis revealed no improvement in IVF cycle outcomes in poor responders who received OCPs to achieve hypothalamic-pituitary suppression instead of GnRHa.*

KEY WORDS: GnRHa; IVF cycle; OCP; poor responder.

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INTRODUCTION

During in vitro fertilization embryo-transfer (IVF-ET) cycles, most women undergo hypothalamic-pituitary suppression prior to the initiation of ovarian stimulation. This allows better scheduling of cycles, synchronization of follicular development, and prevents premature ovulation. Most of the time this gonadotropin suppression is achieved by the use of a gonadotropin releasing hormone agonist (GnRHa). However, it becomes challenging to utilize the benefits of hypothalamic-pituitary suppression in poor responders, that is, those with a poor response in previous stimulation cycle, or those with elevated baseline follicle stimulating hormone (FSH) levels.

Various suppression protocols have been used to treat these patients. Most of these protocols involve the use of a GnRHa (low-dose suppression, GnRHa flare, "GnRHa stop") (1,2). Hypothalamic-pituitary suppression can also be achieved with the use of oral contraceptive pills (OCP). The use of OCPs allows easy cycle scheduling, prevents endogenous luteinizing hormone (LH) surges as effectively as a GnRHa, might lead to "lighter" suppression, and could synchronize follicular development leading to a better response.

The purpose of this study was to compare the response to stimulation, and IVF cycle outcomes in poor responders, utilizing GnRHa or OCP to achieve hypothalamic-pituitary suppression.

MATERIALS AND METHODS

We reviewed all IVF cycles performed at the Montefiore Fertility and Hormone Center from

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1/1/1999 to 1/1/2000 in which the patient was identified as a poor responder. Patients were considered poor responders if they had elevated baseline (day 3) FSH (>9 mIU/mL) or had previous poor response (<3 mature follicles or a peak estradiol level <200 pg/mL after 8 days of stimulation). During the study period there were 93 cycles (22% of all fresh cycles) in which patients were idenified as poor responders. Twelve cycles are not included in this analysis because a GnRHa flare protocol was used or no suppression was used at all. The remaining 81 cycles (among 73 patients) are all included. Twenty-six patients received OCP (Demulen −35 μg ethinyl estradiol + 1 mg ethynodiol diacetate, Searle) for hypothalamic-pituitary suppression for at least 21 days. They participated in 29 cycles (Group I, $n = 29$). Forty-seven patients received GnRHa (Lupron, TAP Pharmaceutical) 0.5 mg daily to achieve suppression. They participated in 52 cycles (Group II, $n = 52$). Once suppression was achieved (estradiol <50 pg/mL) patients in both groups were stimulated with pure FSH (Gonal-F, Serono) and/or with HMG (Pergonal, Serono; Humegon, Organon or Repronex, Ferring). The proportion of women using pure FSH preparation, HMG, or both was comparable between the two groups. FSH levels were not measured at the time of suppression check. Prior to the gonadotropin stimulation, patients in Group II discontinued Lupron, once suppression was achieved ("Lupron stop"). From this point on all patients were managed similarly according to routine IVF protocol. When at least two follicles were greater than 17 mm, patients received 10000 IU hCG IM (Profasi, Serono). Thirty-four h after the hCG injection, oocytes were retrieved transvaginally, insemination was performed and the embryos were transferred 3 days after the retrieval. Patients with inadequate E2 response (<200 pg/mL after 8 days of stimulation) or with a dominant follicle were cancelled or converted to intrauterine insemination. All patients received luteal phase progesterone supplementation in the form of IM progesterone in oil (50 mg/day). Pregnancy was confirmed 12 days after the embryo transfer with a serum βHCG assay.

Data was collected including age, indication for IVF, presence or absence of severe male factor, baseline estradiol/FSH, peak estradiol, length of stimulation, amount of FSH used (IU), number of eggs retrieved, number of embryos available, quality of embryos based on cell number and fragmentation (mean cumulative score, MCS (3)), number of embryos transferred, and cycle outcome (cancelled vs. not cancelled and pregnant vs. not pregnant).

Statistical analysis was performed with the SPSS software and Student's t test and Fisher's exact test were used. $p < 0.05$ was considered statistically significant.

RESULTS

Among the 81 cycles studied, elevated baseline FSH (range 9–20 mIU/mL) was the indication in 66 cycles (Group I, 22/29 (76%) vs. Group II, 44/52 (85%), NS) and previous poor response in 15 (Group I, 7/29 (24%) vs. Group II, 8/52 (15%), NS). Age, baseline FSH, baseline estradiol, and the presence of severe male factor were similar in both groups (see Table I).

Cycle cancellation occurred in 31 cycles (31/81, 38%). There was a trend for higher cancellation rate in Group I (14/29 (48%) vs. 17/52 (33%), NS). All cycles were cancelled secondary to poor response, except for one that was cancelled secondary to premature ovulation, as evidenced by rising progesterone levels. This patient was in Group I.

The remaining 50 cycles, which reached oocyte retrieval and embryo transfer, were analyzed separately (15 in Group I and 35 in Group II). There was no difference between the groups regarding age, baseline FSH, baseline estradiol, peak estradiol, presence of severe male factor, amount of FSH used, number of eggs retrieved, number of embryos, and quality of embryos. Group I cycles were significantly shorter (10.5 days ± 0.47 SEM vs. 12.3 days ± 0.27 SEM, $p = 0.004$) (see Table II).

Clinical pregnancy was achieved in 3/15 (20%) patients in Group I versus 13/45 (25.7%) in Group II (NS). In addition there were two chemical pregnancies, one in each group. One pregnancy from Group II ended up in a spontaneous abortion of twins at 13 weeks. The remaining pregnancies progressed beyond the first trimester.

Table I. Characteristics of All Cycles Studied

	Group I ($N = 29$)	Group II ($N = 52$)	p value
Age	39.1 ± 0.67	38.0 ± 0.58	NS
Baseline FSH (mIU/mL)	9.1 ± 0.60	8.6 ± 0.24	NS
Baseline estradiol (pg/mL)	33.1 ± 4.05	36.6 ± 4.15	NS
Indication – high FSH	22/29 (76%)	44/52 (84.6%)	NS
Indication – previous poor response	7/29 (24%)	8/52 (15.4%)	NS
Severe male factor	5/29 (13%)	12/52 (23%)	NS
Cancellation	14/29 (48%)	17/52 (32.7%)	NS

Note. N = number of cycles in each group; NS = not significant; age, baseline FSH, baseline estradiol reported as mean value ± SEM.

Table II. Characteristics of Cycles That Reached Oocyte Retrieval and Embryo Transfer

	Group I ($N = 15$)	Group II ($N = 35$)	p value
Age	38.1 ± 0.99	37.8 ± 0.67	NS
Baseline FSH (mIU/mL)	9.4 ± 0.93	8.7 ± 0.25	NS
Baseline estradiol (pg/mL)	31.2 ± 3.67	30.2 ± 2.04	NS
Peak estradiol (pg/mL)	1470.5 ± 207.27	1410.8 ± 132.20	NS
Number of days of stimulation	10.5 ± 0.47	12.28 ± 0.27	0.004
Amount of FSH (IU)	5350.0 ± 521.45	5177.1 ± 269.74	NS
Number of oocytes retrieved	8.6 ± 1.20	9.0 ± 0.83	NS
Number of embryos on day of transfer	4.9 ± 0.82	6.2 ± 0.73	NS
Number of embryos transferred	2.8 ± 0.33	3.0 ± 0.16	NS
Embryo quality (MCS)	15.9 ± 2.24	16.1 ± 1.68	NS
Pregnancy rate	3/15 (20%)	9/35 (25.7%)	NS
Severe male factor	2/15 (13%)	10/35 (28.6%)	NS

Note. N = number of cycles in each group; NS = not significant; age, baseline FSH, baseline estradiol, peak estradiol, days of stimulation, amount of FSH, number of oocytes, number of embryos, embryo quality are reported as mean value ± SEM.

DISCUSSION

More and more women are delaying childbearing and are trying to conceive in their late thirties or early forties, when reproductive potential is declining. Many of these women initiate cycles with elevated baseline FSH levels and many end up with poor cycle outcomes. It is especially difficult to find an optimal stimulation protocol for them.

For various reasons, almost all IVF stimulation protocols involve hypothalamic-pituitary suppression. Without this suppression a high spontaneous ovulation rate (5–85%) is expected (4). Suppression also allows to conveniently schedule cycles. Some advocate that this suppression helps to synchronize follicular development and can lead to better cycle outcomes.

GnRHa can be used in different ways. To avoid excessive suppression, GnRHa can be initiated in the follicular phase with gonadotropins (2). When given this way, initially it contributes to ovarian stimulation while later in the cycle it prevents spontaneous endogenous LH surge. Published results in the literature are not consistent about the effect of these GnRHa flare protocols on cycle outcomes (2). If a GnRHa is started in the luteal phase, its use can be discontinued once suppression is achieved ("GnRHa stop" protocol) (1). It will still prevent the endogenous LH surge but will not contribute to further suppression. As an alternative, lower dose GnRHa can be used for suppression that is initiated in the luteal phase.

As an alternative to GnRHa, several investigators evaluated OCP use for hypothalamic-pituitary suppression (5–11). Gonen *et al.* studied the use of OCPs in patients undergoing IVF cycles and compared cycle parameters to previsously performed cycles where no suppression had been used. Patients who underwent OCP suppression required less gonadotropin to achieve optimal follicle maturation. They had more mature follicles as a result of ovarian stimulation and had more oocytes retrieved. There were no spontaneous LH surges in the OCP treated group. Despite these advances the pregnancy and miscarriage rates were similar between the two groups (5). Burry *et al.* reported their experience with OCP suppression in patients undergoing IVF cycles and they found a relatively high cancellation rate (36%) mainly due to dominant follicles and spontaneous LH-surges (6). Cohen *et al.* evaluated the effect of OCP pretreatment on IVF cycles and compared outcomes with cycles without pretreatment. Pregnancy outcomes were similar in the two groups, but significantly less patients were cancelled due to premature LH surges in the OCP group (7). Biljan *et al.* reported decreased need for gonadotropin and higher pregnancy rates in patients receiving OCP + GnRH suppression when compared with GnRH alone (8).

Several of the above mentioned protocols have been evaluated in poor responder patients. There is no uniformly accepted definition of poor or low responder, however, most studies identify these women based on previous poor outcome (low peak estradiol level or low number of follicles), elevated baseline FSH level, or increased need for gonadotropins during stimulation. Many studies use more than just one entry criteria (1,12–17). There is no universally accepted elevated baseline FSH level in these studies (range 6.5–15 mIU/mL). We followed similar criteria to identify our poor responder patients. We used a cutoff of 9 mIU/mL to determine low and high FSH. In our Center the experience is that women with baseline FSH levels >9 mIU/mL are more likely to have poor cycle outcome (cancellation, increased need for

gonadotropin, low number of follicles, low peak estradiol level). Only one previous study evaluated OCP use in poor responders undergoing IVF. Lindheim *et al.* reported their experience and compared outcomes of IVF cycles with either OCP or GnRHa. They reported lower cancellation rates and higher pregnancy rates with OCP use (9). After studying a similar number of cycles (84 vs. 81) our results show no beneficial effect of OCP use on IVF cycles in poor responders. Altogether we had a very high cancellation rate (31/81, 38%) among these poor responders. The mode of suppression (OCP vs. GnRH) had no effect on the cancellation rate. Patients in the OCP group had a shorter stimulation but still needed a comparable dose of gonadotropin. Both methods allow easy cycle scheduling and they prevent spontaneous LH surges with equal efficacy.

There are certain limits of our study. It is a retrospective analysis and because of this there are potential biases. Our patients were identified based on two different criteria, but either inclusion criteria is an accepted way of identifying poor responders. Patients were not randomly assigned to the medications, but it was the choice of the treating physician. There are no institutional guidelines for the selection of OCP or GnRHa use in such patients. Use of OCPs is an accepted alternative by all treating physicians. Only those cycles were included where suppression was discontinued when stimulation was started. Cycles with no suppression or with GnRHa flare use were not included to avoid another factor potentially influencing the outcome. Our results did not show any improvement in cycle outcomes or pregnancy rates, when OCP was used instead of a "GnRHa stop" protocol, questioning a beneficial effect of OCPs in IVF cycles of poor responders. To date there are no prospective studies evaluating the effects of OCP use on IVF cycle outcome in poor responder patients. The stimulation of poor responders remains a challenging task for the clinician.

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