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Programming of ovarian stimulation with norethindrone acetate in IVF/GIFT cycles

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Twenty patients were given norethindrone acetate (NET) to program the initiation of controlled ovarian hyperstimulation and to coordinate follicular aspiration with surgery to obtain spermatozoa from the husband. Patients received NET, 10 mg/day orally, starting between days 2 and 4 of the cycle. The duration of NET therapy varied from 9 to 37 days. The mean time of onset of vaginal bleeding, after cessation of NET, was 2.9 ± 0.7 days. Ovarian stimulation was carried out with a combination of a luteinizing hormone releasing hormone analog, follicle-stimulating hormone and human menopausal gonadotrophin. The day of human chorionic gonadotrophin (HCG) administration ranged from day 8 to day 15 of the cycle (10.1 ± 1.7). On the day of HCG injection, the mean E_2 level was 2188 ± 1126. The mean number of follicles aspirated was 18.4 ± 9.9 per cycle. The mean number of oocytes collected per cycle was 15.5 ± 8.5. There was no correlation between duration of NET suppression and the number of days of gonadotrophin therapy needed to reach HCG administration. The large number of oocytes retrieved is probably related more with the fact that the patients represented a group with a purely male factor of infertility, than by the specific drug protocol utilized. Our results demonstrate that the ovarian response to gonadotrophin stimulation was not affected by NET administration. The main advantages of the use of this drug for cycle control are that its administration is oral, simple and inexpensive.

Key words: IVF/GIFT/ovulation induction/ovulation programming

Introduction

Follicular aspiration and embryo transfer require a complete availability of staff facilities and equipment involved in IVF/gamete intra-Fallopian transfer (GIFT) programs. For this reason, it might be preferable to avoid the coincidence of such procedures with weekends and holidays, when the routine activity of the operating theatre and outpatient surgical facilities are reduced (Zorn *et al.*, 1987).

Thus, programming of controlled, ovarian hyperstimulation around the week's calendar has been proposed in order to allow a suitable timing of oocyte collection and transfer (Wardle *et al.*, 1986; Thatcher *et al.*, 1988). Several drugs have been utilized with different protocols for cycle programming and synchronization, but their influence on multiple follicular development is still not completely understood (Frydman *et al.*, 1986, 1988; Patton *et al.*, 1988).

We have studied the effectiveness of a progestin, norethindrone acetate (NET), to control the onset of menses in a group of patients undergoing control ovarian hyperstimulation.

Materials and methods

The study group consisted of 20 couples in whom the only cause of infertility was a severe male factor due to obstructive azoospermia. There were no infertility factors identified in the female partners, all of whom experienced regular menses with normal intervals.

Each female partner (mean age 31.6 ± 4.4 years) underwent controlled ovarian hyperstimulation with subsequent oocyte recovery. On the same day of ovum collection a surgical epididymal aspiration (Silber *et al.*, 1988) for the possible recruitment of motile spermatozoa was performed on the husband. Oocytes and spermatozoa were then incubated for 48 h and, in the case of fertilization, embryos were transferred to the uterus or to the Fallopian tubes (Balmaceda *et al.*, 1988). Data on fertilization and pregnancy rates are presented elsewhere (Silber *et al.*, 1988).

To satisfy the specific needs of the laboratory and the clinical staff, all the follicular and sperm aspirations were programmed to be performed within a period of 7 days. To control the onset of menses of the treated cycle and to achieve an equal distribution of surgical procedures during such a short period of time, all the patients received oral norethindrone acetate (NET) (Norlutate®, Parke-Davis, Morris Plains, NJ), 10 mg daily, starting between days 2 and 4 of the previous cycle.

The treatment was continued for 9–37 days, depending on the number of days between the prior menses and the desired data for the initiation of controlled ovarian hyperstimulation. We projected a time interval of 3 days, most likely to occur between discontinuation of NET and the onset of next menses (= day 1 of the treated cycle).

Ovarian stimulation was carried out with a combination of a luteinizing hormone releasing hormone analog (LHRHa), leuprolide acetate (Lupron, TAP Pharmaceuticals, Chicago, IL), pure follicle-stimulating hormone (FSH) (Metrodin, Serono

Table I. The effect of NET administration on the response to controlled ovarian hyperstimulation in IVF/GIFT cycles

Patient	Duration of NET treatment	Day HCG	E_2 level day HCG	No. of follicles	No. of oocytes (mature)
1	30	8	2819	33	24 (15)
2	37	8	1586	11	9 (7)
3	9	8	2388	18	18 (3)
4	14	9	2014	15	12 (11)
5	20	9	5017	35	33 (16)
6	29	9	3352	14	12 (12)
7	14	9	2939	28	24 (18)
8	23	10	3623	38	35 (19)
9	35	10	1933	22	13 (8)
10	18	10	3122	24	18 (13)
11	14	10	2076	13	11 (8)
12	29	10	559	5	4 (4)
13	19	10	2763	20	10 (9)
14	33	11	632	4	4 (2)
15	23	11	1817	17	13 (13)
16	21	11	1320	21	21 (20)
17	21	11	3007	39	23 (16)
18	32	11	766	13	9 (5)
19	28	14	1122	12	9 (4)
20	19	15	928	12	9 (8)

Results:	
Day HCG	10.1 ± 1.7
E_2 level day HCG	2188 ± 1126 pg/ml
Follicles aspirated per patient	18.4 ± 9.9
Oocytes recovered per patient	15.5 ± 8.5
Mature oocytes	67.8%[a]
Cancellations	None
Side effects with NET	None

[a]Mean ± standard deviation of the total oocytes recovered.

Laboratories, Randolph, MA) and human menopausal gonadotrophins (HMG) (Pergonal, Serono Laboratories, Randolph, MA). The LHRHa was given s.c., 1 mg (0.2 ml) daily from day 1. Two ampoules per day (150 IU) of FSH and HMG were administered from day 3 to day 6. Individualized injections of HMG (150 IU/day) were continued from day 7 until the day of human chorionic gonadrotrophin (HCG) (Profasi, Serono Laboratories, Randolph, MA) administration, according to the follicular development and the serum level of oestradiol (E_2). Patients were given HCG, 10 000 IU, when two or more follicles had reached a diameter of 18 mm on vaginal ultrasound (RT 3000, General Electric Co., Milwaukee, WI) and the serum E_2 level had reached >300 pg/ml for each main follicle (≥ 18 mm in diameter). Injections of LHRHa were then discontinued. An ultrasonographic, needle-guided, transvaginal aspiration of the follicles was performed 34–36 h after administration of HCG.

Results

No cancellation in response to the norethindrone-controlled programmed ovarian stimulation was observed in the study group and no adverse effects were reported during NET treatment. Data regarding NET administration and its effect on the response to controlled, ovarian hyperstimulation in each patient are shown on Table I. The duration of NET therapy was 23.7 ± 7.6 days (range 9–37). The onset of menses occurred 2.9 ± 0.7 days after discontinuation of NET (range 1–4 days). Patients received HCG administration on day 10.1 ± 1.7 of their treatment cycle (range 8–15 days). The serum E_2 level was then 2188 ± 1126 pg/ml. The mean number of follicles aspirated was 18.4 ± 9.9 per patient. A total of 311 oocytes was retrieved (15.5 ± 8.5 per patient) (the oocyte recovery rate/follicle was 85%). Of these, 211 oocytes were mature (67.8%) (Asch *et al.*, 1986).

Discussion

The possibility of applying a fixed schedule of ovulation induction for research purposes has already been demonstrated (Templeton *et al.*, 1984).

These results allowed the initiation of controlled ovarian hyperstimulation to be manipulated in order to program IVF or GIFT procedures (Wardle *et al.*, 1986; Patton *et al.*, 1988).

Our study has confirmed the reliability of NET in cycle synchronization, as 100% of the patients studied started their menses within 4 days after the discontinuation of NET. Suppression of ovarian function was maintained for periods ranging from 9 to 37 days, but no differences were noted in terms of the number of days required for follicular development in response to stimulation in the next cycle. The prolonged NET suppression did not influence stimulation and all the patients satisfied the criteria for HCG administration. In contrast, a relevant percentage of cancellations was reported during ovarian stimulation after cycle synchronization with oral contraceptives (Benadiva *et al.*, 1988).

Analogs of LHRH have been utilized also in programming such patients, prolonging the 'medical hypophysectomy' until the required date of initiation of controlled ovarian hyperstimulation (Frydman *et al.*, 1988; Lewinthal *et al.*, 1988).

According to Frydman *et al.* (1988), the absence of an endogenous LH peak provided also the possibility of advancing or delaying the HCG administration by day, allowing a better manipulation of the day of ovum collection.

On the other hand, LHRHa presents some inconveniences, e.g. side effects, the need for injectable administration and greater cost (Lewinthal *et al.*, 1988).

A recent study by Thatcher *et al.* (1988) demonstrated that premature endogenous LH peaks do not occur during ovarian stimulation of patients previously suppressed with NET. It is theoretically possible that the NET-induced hypogonadotrophism may block follicular development and synchronize the maturation of a particular cohort of oocytes. Thus, excluding the presence of one or more leading follicles, the possibility of a premature LH surge appears to be reduced (Cohen *et al.*, 1987).

In our study, the high number of oocytes retrieved per patient and the elevated percentage of preovulatory oocytes obtained (67.8%) might confirm this theory. Nevertheless, it has also to be considered that we studied patients who underwent ovarian stimulation for the first time and in which the etiology of infertility was a severe male factor.

In conclusion, NET has been shown to be reliable in cycle synchronization, not influencing the subsequent controlled ovarian hyperstimulation. In addition to its efficacy, the simplicity in its use, the absence of side effects and its low cost clearly demonstrate an important role in programming IVF and GIFT cycles.

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