Gonadotropins and Glucocorticoid Therapy for "Low Responders"—A Controlled Study

D. BIDER,^{1,3} J. BLANKSTEIN,² J. LEVRON,¹ and I. TUR-KASPA¹

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Purpose: A randomized, nonplacebo controlled study was conducted to determine the effect of dexamethasone supplementation to a protocol of gonadotropin therapy in 42 "low-responder patients" aged 32 to 43 years.

Methods: All underwent at least two previous cycles treated by gonadotropins for unexplained infertility, or anovulation. Human menopausal gonadotropin was started on day 4 of the menstrual cycle combined with dexamethasone 0.5 mg administered nightly, as an adjuvant. A group of "low responders" who did not receive dexamethasone served as the controls. The number of follicles, total amount of gonadotropins used, time required for stimulation, fertilization, peak estradiol levels and pregnancy rate were evaluated.

Results: The number of developing follicles, estradiol levels, fertilization rate and pregnancy rate did not differ significantly.

Conclusions: Although certain beneficial effects were observed in the literature in some of the infertile patients treated with corticosteroids, the overall results did not support daily, low-dose dexamethasone (long-acting corticosteroid) as a clinically useful adjuvant therapy for "low responders" during gonadotropin therapy.

KEY WORDS: glucocorticoids; gonadotropins; low responders.

INTRODUCTION

Ovarian responsiveness to controlled ovarian hyperstimulation (COH) plays a major role in infertile patients, especially those enrolled in an in vitro fertilization-embryo transfer (IVF-ET) program. "Low" responders

to ovulation induction, even prior to IVF-ET therapy, represent an indirect sign of ovarian dysfunction due to aging and early evidence of reduction in the fertility potential due to decreased oocyte quality.

No consensus is available in the literature regarding the definition of "low responders" (1). However, when treatment by human menopausal gonadotropin (hMG) and human chorionic gonadotropin (hCG) lead to low E₂ levels despite a large amount of exogenous gonadotropin administration in combination with "poor" follicular development, we defined these patients as "low responders." Patients enrolled in IVF-ET programs are generally considered as "low responders" when E₂ levels are <1000 pg/ml at the end of COH with a daily dose of exogenous gonadotropins of at least 300 IU, the total amount of hMG exceeding 60 ampoules, and who have produced fewer than five oocytes (1). In our study, we enrolled patients defined as low responders because they were in greater need of hMG doses, and despite this, they did not develop more than one or two follicles with E₂ levels <250 pg/ml.

Different protocols such as GnRH-analogue (GnRH-a), follicle stimulating hormone (FSH), and hMG have been proposed for the treatment of "low responder" patients, or in combination with growth hormone (GH), as the "flare-up" effect protocols using daily low doses of GnRH-a (1–5).

Because glucocorticoids have a beneficial effect in selected patients during COH (6,7), we supplemented "low responders" during ovulation induction with hMG with dexamethasone, 0.5 mg daily, to determine whether this adjuvant would improve the outcome, especially the pregnancy rate.

MATERIALS AND METHODS

Forty-two "low-responder" patients, aged 33–41 years, participated in this study, after having given their informed consent. All had previously undergone

¹ Department of Obstetrics and Gynecology, The Chaim Sheba Medical Center, and Sackler Faculty of Medicine, Tel Aviv University, Israel.

² Department of Obstetrics and Gynecology, Mount Sinai Hospital Medical Center, Chicago, Illinois.

³ To whom correspondence should be addressed at Department of Obstetrics and Gynecology, The Chaim Sheba Medical Center, Tel Hashomer 52621, Israel.

at least two attempts of ovulation induction with gonadotropins alone after failed response to clomiphene citrate (CC) therapy. Before they enrolled in the study, all the files of the patients were evaluated. Assessment of general medical history, physical and gynecological examinations, laboratory tests, including hormonal profile of luteinizing hormone (LH), FSH, prolactin (PRL), and androgens, and ultrasound ovarian scanning were performed. Semen analysis of the partners of all the patients were normal according to the World Health Organization (8). The patients with primary or secondary infertility had normal periods or anovulatory cycles and underwent hysterosalpingography that proved normal. Furthermore, the mean serum E_2 levels in their previous cycle had been low (<250 pg/ml), despite the fact that they had received an initial dose of 3 ampoules per day of hMG. The number of growing follicles did not exceed one or two follicles greater than 17 mm. According to computerized randomization, patients had received a daily dose per os of dexamethasone 0.5 mg at night. Human menopausal gonadotropin, combined with dexamethasone, was started on day 4 of the menstrual cycle (group A) or without dexamethasone (group B). The previous cycle was also summarized (group C).

Monitoring of the stimulated cycle was performed by assessing serum E_2 levels and by transvaginal ultrasonographic scanning of the growing follicles. Human chorionic gonadotropin (10,000 IU) was administered when sonography provided at least one or two follicles measuring >17 mm in diameter in association with E_2 levels >200 pg/ml. Estradiol levels on the day of hCG injection, amount of hMG used at the time required for stimulation, and pregnancies were recorded after summarizing the files of the recent and previous cycles, in order to compare the results and to strengthen the study for statistical analysis. We used Student's *t* test.

RESULTS

Table I summarizes the outcome of ovulation induction in the two groups and compares them to the treatment cycles before patients enrolled in the study. The age of the patients did not differ between the groups (37.1 ± 2.9 and 36.1 ± 3.6 , respectively). No differences were observed in the E_2 peak levels on the day of hCG administration and in the number of follicles developed. The pregnancy rate was low and did not improve after dexamethasone supplementation, and one of the pregnancies in the dexamethasone group

ended in abortion. The number of ampoules and the time required to ovulation did not differ between the groups. Comparing the recent and the previous cycles, no improvement in the results was noted (Table I).

DISCUSSION

Our study was conducted to investigate whether any augmentation effect of dexamethasone on ovarian response described in earlier studies of infertile patients treated by exogenous gonadotropins for ovulation induction is beneficial (6,7,9). However, such adjuvant glucocorticoid therapy in a special group of "low responders" has not been evaluated in the past. Patients of advanced age and with elevated FSH levels were correlated with a "poor" ovarian response.

Follicular recruitment takes place in the late luteal and early follicular phase of the menstrual cycle. Therefore, high doses such as increased gonadotropins may lead to recruitment of new follicles (1). Nevertheless, this may stimulate the growth of recruited follicles unresponsive to lower doses of hMG. The supplementation of glucocorticoids theoretically could enhance the above physiologic events (10).

In "low-responder" patients the increase in gonadotropin doses did not always lead to an increase in follicle development and E_2 serum levels. Thus, an adjuvant corticoid might "improve" the overall results in these specially selected group of patients treated with hMG/hCG. However, our controlled study did not confirm a definite advantageous role of long-acting glucocorticoids at this dosage in such patients.

Ovarian receptors for glucocorticoids have been demonstrated and provided evidence that adrenal steroids affected ovarian function (11–13). Furthermore, cortisol was shown to be essential for granulosa cell (GC) cultures *in vitro* and effective stimulation of aromatase activity in other tissues (13,14). However, it is not known whether a local effect of corticosteroids on the ovaries is involved in the expression of their function. Different glucocorticoid levels have been shown to act on gonadotropins and to influence LH, FSH, E_2 , and progesterone (P) levels in humans and animals (14–16). For example, high levels of corticosteroids can inhibit FSH-induced E_2 production by GC. Progesterone secretion was not depressed. Moreover, GC obtained from patients treated with hMG responded to cortisol by E_2 and P secretion in a dose-dependent manner (10,14).

In animals, stimulation of the ovaries with corticosteroids is effective in facilitating the ovulatory

Table I. Outcome of Ovulation Induction in the Two Groups, Compared to Previous Treatment Cycles

	Group A (dexamethasone)	Group B	Group C (before dexamethasone)
Patients (No.)	20	22	42
Age	37.1 $\pm$ 2.9	36.1 $\pm$ 3.6	36.5 $\pm$ 3.0
Estradiol (pg/ml)	178 $\pm$ 52	196 $\pm$ 21	188 $\pm$ 42
No. of follicles $\geq$ 17 mm	1–2	1–2	1–2
Duration of human menopausal gonadotropin (days)	13 $\pm$ 2	14 $\pm$ 2	13 $\pm$ 2
No. of ampoules	37 $\pm$ 5	39 $\pm$ 4	38 $\pm$ 3
Endometrium (mm)	9 $\pm$ 2	8 $\pm$ 1	10 $\pm$ 3
No. of pregnancies	2	1	0

responses. Studies of patients enrolled in the IVF-ET program suggested an indirect effect of cortisol on the ovaries and an essential role of cortisol in the maintenance of GC cultures (17–19).

Two modes of action are proposed. The first is a direct action of glucocorticoids on the ovaries, and the second through suppression of adrenal androgens. A third mode of action was suggested by the effect of corticosteroids on the gonadotropin production at the pituitary level (10). Because patients treated for ovulation induction are under stress, therapy with adjuvant corticosteroids is beneficial, as demonstrated in the past (6,7,9). In our results we observed neither a non-beneficial effect of dexamethasone on the production of E₂ nor an increase in the number of growing follicles. The peak serum E₂ levels on the day of hCG administration did not differ even when compared to previous cycles. The pregnancy rate that is the goal of therapy was not influenced by the regular nightly suppression or supplementation of dexamethasone. We believe that gonadotropins act on the ovary without the need of adjuvant treatment to enhance their action. Despite the fact that patients treated by COH are under added stress, we did not observe a beneficial effect in this selected group of patients. “Low-responder” patients pose a great challenge to the field of reproductive medicine. Different protocols and adjuvant modes of ovarian stimulation have been proposed. However, in “low responders” adjuvant dexamethasone therapy to an increasing hMG dose for ovulation induction did not enhance the ovarian response, probably due to an unresponsive, a dysfunctional, or an aging ovary. From our experience and this present study, we observed that during gonadotropin treatment, adjuvant low doses of dexamethasone were almost-ineffective. The pregnancy rate did not improve. However, individual patients, such as those in a hyperandrogenemic state and patients in stress (including some “low responders”), may in specific circumstances benefit from glu-

cocorticoid supplementation due to its effect on the ovaries, adrenals, and pituitary glands.

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