Dexamethasone Supplementation to Gonadotropin Stimulation for In Vitro Fertilization in Polycystic Ovarian Disease

D. BIDER,[1,2] A. HOURVITZ,[1] I. TUR KASPA,[1] M. DIRNFELD,[1] and J. DOR[1]

Submitted: November 18, 1998
Accepted: December 9, 1998

Purpose: *This study was conducted to determine whether glucocorticoid supplementation for patients with polycystic ovarian disease during ovulation induction with gonadotropins for in vitro fertilization (IVF) therapy is beneficial.*
Methods: *Seventy-one cycles of patients undergoing first attempts at IVF, with classical polycystic ovarian disease and hyperandrogenemia, who enrolled in the IVF–embryo transfer program, were evaluated retrospectively. In 20 cycles (20 patients) glucocorticoid supplementation was noted and compared to 51 cycles (51 patients) without glucocorticoid as adrenal androgen suppression. Ovaries were stimulated by gonadotropin releasing hormone agonist, human menopausal gonadotropin, and dexamethasone. Ovarian responsiveness and IVF–embryo transfer outcome were analyzed and included the number of follicles >17 mm in diameter, serum estradiol concentration on the day of human chorionic gonadotropin administration, number of human chorionic gonadotropin ampoules administered, number of oocytes retrieved, percentage of oocytes fertilized, number of embryos transferred, implantation rate, and number of clinical pregnancies and their outcome.*
Results: *The results showed that the pregnancy rate in patients who received glucocorticoid was 22.1%, compared to 26% in the controls (statistically insignificant). The IVF cycle variables studied revealed no statistically significant differences.*
Conclusions: *Our observations did not support the notion that adrenal androgen suppression by glucocorticoid, or as an adjuvant therapy, is beneficial to patients with polycystic ovarian disease who enrolled in an IVF–embryo transfer program.*

KEY WORDS: glucocorticoid; IVF; ovulation induction; PCOD.

[1] IVF-ET Unit, Department of Obstetrics and Gynecology, The Chaim Sheba Medical Center, Tel Hashomer, and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel.
[2] To whom correspondence should be addressed at Department of Obstetrics and Gynecology, The Chaim Sheba Medical Center, Tel Hashomer, 52621, Israel.

INTRODUCTION

Polycystic ovarian disease (PCOD) is a chronic anovulatory entity. Most patients respond sufficiently to ovulation induction. However, some require alternative therapy [mainly in vitro fertilization–embryo transfer (IVF-ET)] after failed gonadotropin treatment. Once an alternative approach to these patients who had failed to conceive after the available treatment modalities had been proposed, the benefit of glucocorticoid (GC) as an adjuvant therapy was investigated (1,2).

The effect of adrenal suppression on ovarian follicular development remains unclear (2,3). Some investigators have shown that adrenal suppression by GC may be beneficial in certain anovulatory patients (4–9). Others have demonstrated no beneficial effects on ovarian responsiveness and IVF-ET outcome after suppression of adrenal androgens with GC (1,2).

This study was conducted to determine whether adrenal androgen suppression by GC during ovulation induction improves IVF-ET outcome in classical PCOD patients enrolled in an IVF program. Since glucocorticoid therapy in PCOD patients enrolled in IVF studies is rare, we felt the need for further investigation.

MATERIALS AND METHODS

Seventy-one first cycles of 71 patients aged 32.2 ± 4.57 SD who were diagnosed as having PCOD were enrolled in the study. All patients were counseled regarding ovum retrieval and advised to undergo the procedure under general anesthesia. All patients had irregular menstrual cyclicity, with amenorrhea of >8 weeks, and failed to conceive after clomiphene citrate or human menopausal gonadotropin(hMG)/human chorionic gonadotropin (hCG). The luteinizing hormone (LH)/follicle stimulation hormone (FSH) ratio

1058-0468/99/0500-0233$16.00/0

was >2; dehydroepiandrosterone sulfate (DHEAS) and testosterone were increased to ≥ 3.5 μg/ml and ≥ 1 ng/ml, respectively. In addition, all ultrasonographic scannings of the adnexa revealed polycystic ovaries, bilateral ovarian enlargement, and >10 follicles of 2–10 mm in diameter per ovary, with an increased density and area of the stroma.

The protocol of ovulation induction comprised 3.2 mg of gonadotropin-releasing hormone agonist [GnRH-a (D-TRP_6; decapeptyl depot, controlled release; Ferring, Malmö, Sweden)] given on day 1 of the cycle, followed 2 weeks later by 225 IU of hMG (Teva Pharmaceuticals, Kfar Saba, Israel) per day. After serum estradiol (E_2) concentrations reached >500 pg/ml and at least three follicles >18 mm in diameter were observed on vaginal ultrasound, 10,000 IU of hCG (Chorigon; Teva Pharmaceuticals, Petah Tikva, Israel) was injected. Oocytes were retrieved by ultrasonographically guided vaginal puncture and were cultured and maintained in human tubal fluid medium (Irvine Scientific, Irvine, CA) supplemented with 10% scientific serum (Irvine Scientific).

Dexamethasone (DEX), 0.5 mg, was supplemented (in 20 patients) each night, initiated on the first day of hMG stimulation and discontinued on the day after ET. The files of all patients were summarized. Differences in mean values between cycles were compared by Student's *t* and paired tests. The χ^2 test was used to compare fertilization and pregnancy rates.

RESULTS

Table I depicts the mean baseline endocrine profile of the patients studied during stimulation with and without DEX. Results are expressed as mean ± standard deviation (SD). There was no significant difference between the mean serum E_2 levels on the day of hCG administration. The number of hMG ampoules required for ovarian stimulation was not significantly different.

The pregnancy and implantation rates were not influenced by DEX administration. In all patients, a luteal phase of at least 12 days was noted (Table I).

The outcomes of IVF in 71 cycles with and without DEX supplementation are summarized in Table II.

DISCUSSION

In our study, enhanced androgen production by the adrenal gland was demonstrated in all patients with PCOD, but the role of these compounds as a cause for, or a participant in, the pathogenesis of PCOD remains controversial (3,10,11). There is no doubt that impaired reproductive function associated with adrenal activity is attributed to altered pituitary function. Several authors have indicated that adrenal hormones can have a direct effect on gonadal function (12–14). Moreover, others have suggested that suppression of the adrenal gland by DEX administration may be beneficial in patients who were previously unresponsive to ovulation induction with clomiphene citrate (CC) or hMG (4–6). Concomitant administration of GnRH-a and DEX during ovarian hyperstimulation delineates the contribution of the adrenal glands and the ovaries to abnormal steroidogenesis observed in PCOD patients (3). However, patients who did not receive DEX had similar IVF-ET outcomes. Our study and those of others (2,3) evoked questions regarding the role of adrenal function or contribution to stimulation failure seen in some patients (4–6,9). It is possible that during gonadotropin therapy, GC supplementation is unnecessary, because the action of gonadotropins eliminates the ovulation disturbances seen in PCOD.

Table I. Patients with PCOD: Baseline Hormonal Characteristics[a]

	Dexamethasone	Controls
Patients (No.)	21	50
Age (years)[a]	30.1 ± 2.99	32.2 ± 4.57[b]
Basal LH (mIU/ml)	10.9 ± 3.1	11.1 ± 2.9
Basal FSH (mIU/ml)	5.5 ± 2.2	4.9 ± 3.1
DHEAS (mg/ml)	2.9 ± 1.7	3.1 ± 1.3
Serum E_2 (pg/ml) on hCG day[a]	1736.5 ± 710	1616 ± 843
Luteal phase	14 ± 1	13 ± 1

[a] Values are means ± SD.
[b] No statistical differences.

Table II. Outcome of IVF Variable[a]

	Dexamethasone	Controls
Patients (No.)	20	51
No. of hMG ampoules[b]	32 ± 6	39 ± 11
No. of follicles on hCG day[b]	17.5 ± 1.5	16.2 ± 2.2
No. of oocytes retrieved[b]	18 ± 14	14 ± 10
Fertilization rate (%)	50	45
No. of embryos transferred[b]	3.8 ± 2.0	3.3 ± 2.2
Implantation rate (%)	12	13
Clinical pregnancy rate (%)	22	26
Live birth rate (%)	18	20
Ovarian hyperstimulation syndrome (No.)	2	4

[a] No significant differences between the groups.
[b] Mean ± SD.

Despite the large body of literature on ovarian stimulation for IVF-ET in patients with PCOD, most of the protocols lack the GC supplementation during ovarian hyperstimulation (15). Kemeter and Feichtinger (8) demonstrated that the pregnancy rate was higher in 77 non-PCOD patients who received 7.5 mg of prednisolone combined with CC and hMG daily during an IVF-ET cycle. The E_2 serum levels were significantly higher with GC supplementation.

We were unable to observe statistical differences in E_2 serum levels on the day of hCG administration and the pregnancy rate. Rein *et al.* (2) were unable to demonstrate any beneficial effect of DEX administration during ovarian stimulation for IVF-ET cycles. The outcome of IVF cycles in patients with a DHEAS concentration of >2.5 μg/ml and DEX supplementation for adrenal gland suppression showed no beneficial effects on ovarian responsiveness or pregnancy rate.

Therefore, the potential benefit of adrenal androgen suppression by GC during ovulation induction regimens used for IVF-ET has not yet been elucidated, since only a few studies (1,2,8) have evaluated the benefit of GC treatment. Because we used only 0.5 mg of DEX, it is possible that higher doses could be beneficial, especially for increasing the implantation rate (16).

In summary, our study, despite the small size of the group, did not support the assumption that GC had beneficial effects while the ovaries were hyperstimulated for IVF-ET therapy under GnRH-a suppression. There were no differences in either the pregnancy rate and its outcome or the cycle characteristics. Studies on the use of glucocorticoids in IVF patients, especially those with PCOD, should be elaborated on.

REFERENCES

1. Willman SP, Nass TE, Chetkowski RJ: A randomized trial of adrenal suppression for in vitro fertilization (IVF). Pacific Coast Fertil Soc Meet 1992;A23
2. Rein MS, Jackson KV, Sable DB, Thomas PP, Hornstein MD: Dexamethasone during ovulation induction for in-vitro fertilization: A pilot study. Hum Reprod 1996;11:253–255
3. Cedars MI, Steingold KA, de Ziegler D, Lapolt PS, Chang RJ, Judd HL: Long-term administration of gonadotropin-releasing hormone agonist and dexamethasone: Assessment of the adrenal role in ovarian dysfunction. Fertil Steril 1992;57:495–500
4. Lobo RA, Wellington P, March CM, Granger L, Keltzky OA: Clomiphene and dexamethasone in women unresponsive to clomiphene alone. Obstet Gynecol 1982;60:497–501
5. Evron S, Navot D, Laufer N, Diamant YZ: Induction of ovulation with combined human gonadotropins and dexamethasone in women with polycystic ovarian disease. Fertil Steril 1983; 40:183–186
6. Daly DC, Walters CA, Soto-Albors CE, Tohan N, Riddick DH: A randomized study of dexamethasone in ovulation induction with clomiphene citrate. Fertil Steril 1984;41:844–848
7. Haning RVJ: Role of dehydroepiandrosterone sulphate as a prehormone for ovarian steroidogenesis. Obstet Gynecol 1985;65:199–205
8. Kemeter P, Feichtinger W: Prednisolone improves the pregnancy rate of IVF. A prospective randomized study. Fertilat 1986;2:71–76
9. Petermann TS, Rabenbauer B, Wildt L: The effect of flutamide on pulsatile gonadotrophin secretion in hyperandrogenaemic women. Hum Reprod 1993;8:1807–1812
10. Kirschner MA, Jacobs JB: Combined ovarian and adrenal vein catheterization to determine the site of androgen over-production in hirsute women. J Clin Endocrinol Metab 1971;33: 199–209
11. Stahl NL, Teeslink CR, Greenblatt RB: Ovarian, adrenal and peripheral testosterone levels in the polycystic ovary syndrome. Am J Obstet Gynecol 1973;117:194–200
12. Hsueh AJW, Erickson GF: Glucocorticoid inhibition of FSH-induced estrogen production in cultured rat granulosa cells. Steroids 1978;32:639–648
13. Ben-Rafael Z, Benadiva CA, Garcia CJ, Flickinger GL: Cortisol stimulation of estradiol and progesterone secretion by human granulosa cells is independent of follicle-stimulating hormone effects. Fertil Steril 1988;49:813–816
14. Fateh M, Ben-Rafael Z, Benadiva C, Mastroianni L Jr, Flickinger GL: Cortisol levels in human follicular fluid. Fertil Steril 1989;51:538–541
15. Bider D, Levran D, Mashiach S, Ben-Shlomo I, Dor J: Polycystic ovarian disease (PCOD)—Pregnancy rate and outcome in in vitro fertilization. J Assist Reprod Genet 1993;10:11–14
16. Bider D, Amoday I, Yonesh M, Yemini Z, Mashiach S, Dor J: Glucocorticoid administration during transfer of frozen-thawed embryos: A prospective, randomized study. Fertil Steril 1996; 66:154–156