Original Article

Dexamethasone as a Supplement for Exogenous Gonadotropin to Improve Ovarian Response of Women over 35 Years Undergoing IVF/ICSI Cycles

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Abstract

Background: With aging, the ovarian reserve is decreased and that is a major contributor to poor ovarian response to exogenous gonadotropins. The aim of the present study is to evaluate the role of Dexamethasone on ovarian response in infertile patients aged over 35 years undergoing IVF/ICSI cycles.

Materials and Methods: In this triple blind placbo-control clinical trial study, a total of 72 infertile women over age 35, undergoing IVF/ICSI cycles, referred to Royan Institute from May 2000 to May 2002 were selected. Dexamethasone co-treatment (1mg/d) was started on the 21st of their preceding menstrual cycle and it was continued until oocyte aspiration. The main outcome measures were number of retrieved oocytes, number of fertilized and transferred embryos, number of used HMG, serum E2 level on HCG injection day, and pregnancy rate.

Results: There was no significant statistical difference in age, duration of infertility, Body mass index, hormonal tests, number of retrieved oocytes and transferred embryos. However, the number of used HMG was significantly lower in Dexamethasone group compared to placebo group (30.6±13.39 versus 41.64 ± 18.34) ($p<0.05$).

Conclusion: The addition of dexamethasone 1mg/d to standard long protocol decreased the number of HMG used in patients over 35 years who hold known risk of low ovarian response.

Keywords: Dexamethasone, Ovarian Response, IVF/ICSI

Introduction

Poor ovarian response to exogenous gonadotropins is one of the challenges of assisted reproductive technology that occurs in 9-26% of cycles (1) and may interrupt the cycle causing less available oocytes and an eventual decrease in pregnancy rate (2). Advanced age, prior ovarian surgery, pelvic adhesions, and high body mass index (BMI) are all associated with poor ovarian response; however, poor response is also noted in young women (1, 3). With aging, the ovarian reserve is decreased and that is a major contributor of poor ovarian response to exogenous gonadotropins (4). There are several reports about other potentially effective gonadotropin based treatment methods including high dose gonadotropin regimens (2, 5, 6) and cotreatment with growth hormone (GH) (7, 8) glucocorticoids (8-10), and low dose aspirin (11).

Moreover, it is possible to estimate the ovarian response by measuring the serum levels of GH during normal and ovulation induction cycles. Inadequate stimulation

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of the somatotropic axis may lead to poor ovarian response (12). The ovarian response to gonadotropins is regulated by IGF-1 (insulin-like growth factor 1) that has an in vitro positive feedback on FSH (13) via granulosa cell receptors (14). The effect of treatment with GH (15), L-Arginine (16) and pyridostigmine (17) as adjuvants in poor responders have been studied; all three act on the somatotropic axis. Both L-Arginine and pyridostigmine significantly improve ovarian and intrafollicular concentrations of IGF-1 (12). Glucocorticoids can indirectly improve the response of poor responders by increasing serum levels of GH (18) and IGF-1 (19) and by consequently increasing intrafollicular concentration of IGF-1. To date, the IGF-1 mRNA has not been detected in human granulosa cells prior to ovulation and it seems to be derived from circulation (19). In the study of Jenkins and colleagues, following pituitary suppression in IVF cycles, co-treatment with dexamethasone resulted in an increase in serum IGF-1 levels growing follicle (20). On the other hand, Dexamethasone impoved ovarian responsivenses by diminished effect of adrenal androgens on follicular growth (21). In another study Kemeter and colleagues found higher pregnancy rates in prednisolone group compared to control (22). Also, in a study by Keay et al, cotreatment with dexamethasone reduced the incidence of poor ovarian response (12). In the light of these results this study tries to compare the effect of dexamethasone on ovarian response in infertile women over 35 referring to Royan Institute with a control group.

Materials and Methods

In this randomized, triple-blind placebo-controlled trial that was approved in the medical ethic committee of Royan Institute (Infertility research center, Tehran-Iran) 72 infertile women over age 35 undergoing IVF/ICSI cycles were studied during 2000-2002.

The inclusion criteria comprised age over 35 and IVF/ICSI treatment candidacy. Women with endocrine disorders (thyroid, prolactin, etc), endometrioma and history of ovarian surgery were excluded. The patients were divided into two groups by Randomized permuted block. The conditions of the study and possible side effects were explained to all patients and the consents obtained. All patients received OCP-LD from 5th day of their preceding cycle. Then GnRH agonist (Suprefact Hoechst, Germany) 500µg/day, subcutaneously was prescribed from the 21st day of the cycle for 12-14 days to suppress ovarian function. In the treatment group, 36 patients received a daily oral dose of 1 mg of Dexamethasone (Tab, 0.5 mg, Daroo-pakhsh Co. Tehran, Iran) and the control group (36 patients) received placebo. Dexamethasone co-treatment was started on the 21st of their preceding menstrual cycle and it was continued until oocyte aspiration. After ovarian suppression which was confirmed by vaginal ultrasonography and serum Estradiol level on day 2 of cycle (LH≤5IU, E2≤50pg/ml) gonadotropin therapy was started using highly purified FSH (150-225IU/d; Menopur**,** Ferring Pharmaceuticals, Denmark) from the second day of cycle. GnRH analogue (200µg/day) was continued up to the day of hCG administration. Follicular development was monitored by serial transvaginal ultrasonography (Aloka 1000, Japan, 7.5 MHz probe) and serum E_2 levels. All of sonographic evaluations were done by one expert.

The number of oocytes, fertilized and transferred embryos, injected HMG ampoules, and the levels of estradiol on the day of HCG injection, and pregnancy rates were compared in the two groups. The data were analyzed using the two-tailed Student's *t*, Mann-Whitney rank-sum, and Fisher's exact tests. Data were expressed as means±SD and $p<0.05$ was considered as statistically significant.

Results

There were 36 women in the

dexamethasone group and 36 in the placebo group.

The mean age, duration of infertility, BMI, FSH, LH and estradiol of the third day of cycle as well as mean total testosterone and DHEA SO4 were compared between dexamethasone and placebo groups (Table 1). None of these variables showed significant difference between the two groups. The average concentrations of estradiol on HCG injection day were 486.85±271.17 pg/ml and 539.64±345.3 pg/ml in case and control groups, respectively. 55.6% of individuals in the dexamethasone group and 48.1% of the patients in the placebo group had estradiol levels lower than 500pg/ml on the day of HCG injection. However none of these differences reached tatistical significance.

The mean numbers of developed oocytes were 4.27±3.50 and 5.83±6.5 in case and control group respectively and the difference was not significant. 25.9% of cases and 33.3% of controls had 3 or less oocytes and an estradiol level<500 pg/ml; the difference lacked significance.

The difference in the percentage of formed embryos (2.13±1.67 in dexamethasone group vs. 2.58±2.03 in placebo group) was not also meaningful statistically.

Table 1: Demographic and clinical characteristics of the Dexamethasone treated patients and controls

Characteristic	Treatment group (n=36) (Mean±SD)	Color Group (n=36)	P Value
Age (Year)	36.55±4.54	37.44±3.53	NS
Duration of Infertility (Year)	12.55±6.29	15.2±6.75	NS
BMI (kg/m^2)	24.01±0.8	23.83±0.44	NS
Serum FSH level on day 3 (mlU/ml)	6.76±3.12	7.79±6.42	NS
Serum LH level on day 3 (mlU/ml)	6.12±2.73	4.66±3.67	NS
Serum Estradiol level on day 3 (Pg/ml)	32.6±22.1	41.5±27.4	NS
Total Testosterone level on day 3(ng/ml)	0.4±0.28	0.44±0.2	NS
DHA-S04 level on day 3 (mg/ml)	2.03±0.72	1.95±0.49	NS

Table 2: *In vitro* fertilization/embryo transfer outcomes in studied groups.

Characteristic	Treatment group (n=36)	Color Group (n=36)	P Value
Serum Estradiol level at the day of HCG injection (Pg/ml)	486.85±271.17	539.64±345.3	NS
Rate of Patients with serum Estradiol <500Pg/ml at the day of HCG injection	55.6%	48.1%	NS
No. of retrieved oocytes	4.27±3.5	5.83±6.4	NS
Rate of patients with <3 oocytes	50%	48.1%	NS
Rate of patients with (≥3 oocytes and Estradiol <500 Pg/ml) at the day of HCG injection	25.9%	33.3%	NS
Rate of fertiization oocytes	54%	55%	NS
Rate of transferred embryos	2.13±1.67	2.58±2.03	NS
No. of HMG ampouls used	*30.6±13.39	*41.65±18.34	NS

* p<0.05

However, the number of HMG ampoules used in two groups varied significantly (30.6±13.39 in case group vs. 41.65±18.34 in control group; $p<0.05$) (Table 2).

Discussion

Several studies have shown the effect of low dose dexamethasone on improvement of ovarian responsiveness at the initiation of induction of ovulation cycles (12, 23, 24). However, controversy still exists in this regard. In our study, the number of developed follicles and retrieved oocytes did not differ significantly between the dexamethasone and placebo groups. These findings are consistent with some prospective randomized trials performed previously (12, 24). Keay et al randomized 290 patients under 40 years undergoing IVF/ICSI cycles and reported that treatment with 1 mg dexamethasone daily could not improve the number of retrieved oocytes significantly (12).

In another study, Fridstrom et al. administered 10 mg prednisolone to PCOS patients treated with IVF and found no significant increase in the number of aspirated oocytes (24). In the current study, the number of HMG ampoules used in patients treated with dexamethasone was significantly lower than that of the placebo group; a finding not reported by Keay and Fridstrom. As mentioned earlier, glucocorticoids influence ovarian response through several mechanisms. In a different study, Keay and colleagues measured the ratio of cortisol (active glucocorticoid) to cortisone (inactive glucocorticoid) of the follicular fluid in IVF/ET cycles without ovulation induction and found that the level of cortisol leading to pregnancy was higher than its level in cycles where fertilization had occurred with an unsuccessful implantation. Furthurmore the ratio of cortisol to cortisone was higher in pregnancy associated cycles compared to cycles without fertilization; therefore it can be concluded that active glucocorticoid is responsible in final maturation of oocyte and implantation (25). Similarly, Harlow and colleagues showed that increase in intrafollicular cortisol occurring just before ovulation indicates the role of steroids in oocyte maturation and ovulation Although the number of fertilized oocytes in this study was similar in the two groups, the number of used HMG ampoules that is in turn a determining factor in the assessment of ovarian response to gonadotropins was significantly lower in dexamethasone group than placebo group. This can explain the role of dexamethasone in increasing ovarian response since follicular growth could be obtained with less amounts of gonadotropins. The reason for a lack of difference in the number of growing follicles and developed oocytes in two groups may be the fact that these numbers are directly related to the ovarian functional reserve and in aged women whose reserves have been reduced, one cannot reach a high number of oocytes despite the prescription of dexamethasone (26).

Conclusion

Although there was no statistical difference between number of retrieved oocytes and transferred embryos but the number of HMG ampoules used in Dexamethasone group was significantly lower than the placebo group. This difference may imply the positive effect of Dexamethasone on ovarian response to gonadotropins so that utilization of this drug as an adjuvant for standard treatment is recommended in patients over 35 years who hold known risk of low ovarian response. Further clinical trials are required to achieve more detailed results.

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References

1. Keay SD, Liversedge NH, Mathur RS, Jenkins JM. Assisted conception following poor ovarian response to gonadotrophin stimulation. Br J Obstet Gynaecol. 1997; 104: 521-527
2. Mahutte NG, Arici A. Poor responders: Does the protocol make a difference? Curr Opin Obstet Gynecol. 2002; 14(3): 275-281
3. Keay SD, Liversedge NH, Jenkins JM. Could ovarian infection impair the ovarian response to gonadotrophin stimulation. Br J Obstet Gynaecol. 1998; 105: 252-254
4. Beckers NGM, Macklon NS, Eijkemans MJC, Fauser BCJM. Women with regular menstrual cycles and a poor response to ovarian hyperstimulation for in vitro fertilization exhibit follicular phase characteristics suggestive of ovarian aging. Fertil Steril, 2002; 78: 291-297
5. Van Hooff MH, Alberda AT, Huisman GJ, Zeilmaker GH, Leeventuveld RA. Doubling the human menopausal gonadotropin dose in the course of an in vitro fertilization treatment cycle in low responders: a randomized study. Human Reprod, 1993; 8: 369-373
6. Karande V, Jones G, Veeck L, Muasher S. High dose follicule stimulating hormone stimulation at the onset of menstrual cycle does not improve the in vitro fertilization outcome in low responder patients. Fertil Steril, 1990; 53: 486-489
7. Adashi E, Rohan R. Intraovarian regulation. Peptidergic signaling systems. Trends Endocrinol Metab. 1993; 3: 243-248
8. Tarlatzis BC, Zepiridis L, Grimbizis G, Bontis J. Clinical management of low ovarian response to stimulation for IVF:a systematic review. Hum Reprod Update, 2003; 9(1): 61-76
9. Miell JP, Taylor AM, Jones J, Holly JM, Gaillard RC, Pralong FP, Ross RJ, Blum WF. The effects of dexamethasone treatment on immunoreactive and bioactive insulin-like growth factors (IGFs) and IGF-binding proteins in normal male volunteers. J Endocrinol 1993; 136(3): 525-533
10. Smith MP, Mathur RS, Keay SD, Hall L, Hull MG, Jenkins JM. Preovulatory human oocytes, cumulus cells and ovarian leukocytes express type 1 but not type 2 11-beta-hydroxysteroid dehydrogenase (11 ß-HSD) RNA. Fertil Steril 2000; 73: 825-830
11. Lok IH, Yip SK, Cheung Lp, Yin Leung PH, Haines CJ. Adjuvant low- dose aspirin therapy in poor responders undergoing in vitro fertilization:a prospective, randomized, double blind, placebo-controlled trial. Fertil Steril, 2004; 81(3): 556-561
12. Keay SD, Lenton EA, Cooke ID, Hull MGR, Jenkins JM. Low-dose Dexamethasone augments the ovarian response to exogenous gonadotrophins leading to a reduction in cycle cancellation rate in a standard IVF programme .Human Reproduction, 2001; 16(9): 1861-1865
13. Adashi EY, Resnick CE, D'Ercole AJ, Svoboda ME, Van Wyk JJ. Insulin-like growth factors as intraovarian regulators of granulosa cell growth and function. Endocr Rev, 1985; 6(3): 400-420
14. Gates GS, Bayer S, Seibel M, Poretsky L, Flier JS, Moses AC. Characterization of insulin-like growth factor binding to human granulosa cells obtained during in-vitro fertilization. J Recept Res. 1987; 7(6): 885-902
15. Homburg, R, Ostergaard, H. Clinical applications of growth hormone for ovarian stimulation. Hum. Reprod. Update 1995; 1: 264-275
16. Battaglia C, Salvatori M, Maxia N, Petraglia F, Facchinetti F, Volpe A. Adjuvant L-arginine treatment for in-vitro fertilization in poor responder patients . Hum. Reprod. 1999; 14(7): 1690-1697
17. Kim CH, Chae HD, Chang YS. Pyridostigmine cotreatment for controlled ovarian hyperstimulation in low responders undergoing in vitro fertilization embryo transfer. Fertil Steril, 1999; 71, 652-657
18. Casanueva FF, Burguera B, Muruais C, Dieguez C. Acute administration of glucocorticoids: a new and peculiar stimulus to growth hormone secretion in man. J Clin Endocrinol Metab, 1990; 70: 234-237
19. Zhou J, Bondy C. Anatomy of the human ovarian insulin-like growth factor system. Biol Reprod, 1993; 48: 467-482
20. Jenkins JM, Gadd SC, Anthony FW, et al. Corticosteroids may act via IGF-1 to improve the response to ovarian stimulation in IVF 'poor' responders. Br J Obstet Gynaecol, 1994; 101: 269-270
21. Isaacs JD, Lincoln SR, Cowan BD. Extended clomiphene citrate (CC) and prednisone for the treatment of chronic anovulation resistant to CC alone. Fertil Steril 1997; 67: 641-643
22. Kemeter P, Feichtinger W. Prednisolone supplementation to Clomid and/or

gonadotrophin stimulation for in-vitro fertilization a prospective randomized trial. Hum Reprod 1986; 1: 441-444
23. Keay SD. Poor ovarian response to gonadotropin stimulation the role of adjuvant treatment. Hum Fertil(Camb), 2002; 5 (1 Suppl): 46-52
24. Fridstrom M, Carlstrom K, Sjoblom P, Torbjorn H. Effect of prednisolone on serum and follicular fluid androgen concentrations in women with polycystic ovarian syndrome undergoing in-vitro fertilization. Hum Reprod, 1999; 14(6): 1440-1444
25. Keay SD, Harlow CR, Wood PJ, Jenkins JM, Cahill DJ. Higher cortisol:cortisone ratios in the preovulatory follicle of completely unstimulated IVF cycles indicate oocytes with increased pregnancy potential . Human Reproduction, 2002; 17(9): 2410-2414
26. Harlow CR, Jenkins JM, Winston RML. Increased follicular fluid total and free cortisol levels during the luteinizing hormone surge. Fertil Steril, 1997; 68: 48-53