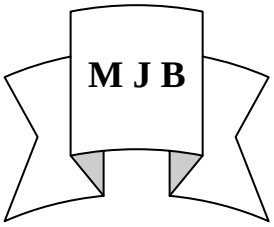
Dexamethasone Improve Ovarian Response to Ovulation Induction Drugs in Women Over 35 Years

Suhaila F. Al-Shaikh
College of Medicine, University of Babylon, Hilla, Iraq.



Abstract

Background: With aging, the ovarian reserve is decreased and that is a major contributor to poor ovarian response to ovulation induction treatment. The aim of the present study is to evaluate the role of Dexamethasone on ovarian response in infertile patients aged over 35 years.

Materials and Methods: In this study, a total of 36 infertile women over age 35, referred to Babylon hospital-infertility clinic from May 2010 to may 2011 were selected. Ovulation induction was initiated for them using HMG (human menopausal gonadotrophin) for 2 consecutive cycles then after excluding 10 women Dexamethasone co-treatment (1mg/d) was started (in 26 women) in their next menstrual cycle. It was started on the 21st day of the menstrual cycle and continued until CD12 together with the HMG (from CD 2-12) of the next cycle. The main outcome measures were number of mature follicles detected by U/S, number of used HMG ampoules/cycle , and serum E2 level on HCG injection day.

Results: There was no significant statistical difference in age, duration of infertility, hormonal tests, and number of mature follicles. However, the number of used HMG ampoules was significantly lower in Dexamethasone used cycle compared to non-dexamethasone cycles ($p<0.05$).

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

الديكساميثازون عند اضافته الى ادوية تحفيز الاباضة يحسن استجابة المبايض عند النساء فوق سن الخامسة والثلاثين

الخلاصة

مع تقدم العمر بالمراة ينضب لديها احتياطي البيوض في المبايض و هذا يؤدي بالنتيجة الى قلة خصوبتها و ضعف استجابتها للادوية المحفزة للاباضة

في هذه الدراسة تم تقييم دور دواء الدكساميثازون عند اضافته للادوية المحفزة للاباضة

تم اختيار ٣٦ امراة فوق سن ال ٣٥ عام ممن يراجعن استشارية العقم في مستشفى بابل للنسائية و الاطفال للفترة من مايو ٢٠١٠ الى مايو ٢٠١١

في البدأ و بعد اجراء الفحوصات اللازمة واخذ موافقتهن تم اعطاءهن المحفزات الهرمونية (الهرمون المحفز للبويضة)ابتداء من ثاني يوم للدورة الشهرية مع مراقبة الاستجابة للتحفيز عن طريق مراقبة حجم البويضة بواسطة جهاز الفحص بالامواج فوق الصائتة المهبلي وفحص نسبة هرمون الاستراديول.

و تم تكرار نفس العلاج للشهر الثاني على التوالي و بزيادة جرعة الهرمون المحفز للبويضة.

و بعد استثناء ١٠ نساء (٦ بسبب نجاح الحمل و ٤ لم يتابعن العلاج) أي ان المجموعة الجديدة ٢٦ امرأة تم اخضاعهن للطريقة العلاجية الاخرى باستخدام الدكساميثازون مع الهرمون المحفز للبويضة مع الاستمرار بمراقبة الاستجابة للعلاج بواسطة فحص حجم البويضات بجهاز الفحص بالامواج فوق الصائتة المهبلي وفحص نسبة هرمون الاستراديول.

النتائج: لم يكن هناك فرق احصائي واضح في عدد البيوض الناتجة من التحفيز و لكن كان عدد الحقن المستخدمة من الهرمون المحفز للبويضة اقل في المجموعة التي استخدم فيها دواء الدكساميثازون مع عملية التحفيز و بشكل مهم احصائيا

الاستنتاجات: عند اضافة الدكساميثازون لعملية تحفيز الاباضة بواسطة الهرمون المحفز للبويضة يؤدي الى الحصول على عدد جيد من البيوض ولكن بعدد اقل من حقن الهرمون المحفز مما يدل على استجابة المبايض بشكل افضل بعد اضافة دكساميثازون لعملية التحفيز وكذلك تكون التكلفة لعملية التحفيز (أقل) نظرا لارتفاع ثمن الهرمونات المحفزة للبويضات.

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 co-treatment 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 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 via granulosa cell receptors [13, 14]. The effect of treatment with GH, L-Arginine and pyridostigmine as adjuvants in poor responders have been studied [15-17]; 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 and growing follicle [20]. On the other hand, Dexamethasone impoved ovarian responsivness 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, co-treatment 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 with a control group.

Materials and Methods

In this study a total of 36 infertile women over age 35 years were studied during may 2010- may 2011.

The inclusion criteria comprised age over 35 , Women with endocrine disorders (thyroid, hyperprolactinemia, etc), endometrioma and history of ovarian surgery , women with tubal factor and couples with male factors infertility were excluded. oral consents obtained from all patients. All patients (36 women (control group)) received HMG injections from cycle Day 2 (1 ampoule/day 75 IU) with u/s

monitoring of the follicles on every other day until a leading follicle of 16 mm was detected and the process was repeated with higher doses of HMG in the next cycle (2 ampoules 150 IU / day) . then the ovulation induction was repeated for the same women with addition of dexamethasone (10 women are excluded in this treatment because 6 get pregnant and 4 women were lost from follow up) so 26 patients (treatment group) received a daily oral dose of 1 mg of Dexamethasone (Tab, 0.5 mg). Dexamethasone co-treatment was started on the 21st of their preceding menstrual cycle and it was continued until CD12. gonadotropin therapy (HMG) 2 ampoules 150 IU/ day) from the CD2 was continued up to the day when a leading follicle of 16 mm detected then hCG was administered. Follicular development was monitored by serial transvaginal ultrasonography.

The number of mature follicles, injected HMG ampoules, and the levels of estradiol on the day of hCG injection, were compared in the two groups. The data were analyzed using the two-tailed Student's *t*, and Fisher's exact tests. Data were expressed as means ± SD and $p<0.05$ was considered as statistically significant.

Results

There were 26 women in the(1st) treatment group (when dexamethasone was added to the treatment) and 36 women (2^{nd}) (control group) (non dexamethasone treatment group). The mean age, duration of infertility, FSH, LH and estradiol and testosterone of the second day of cycle (Table 1). None of these variables showed significant difference between the two groups.

The mean numbers of mature follicles were 2.27 $\pm$ 1.5, 1.83 $\pm$ 1.4 in 1st and 2nd group respectively

However, the number of HMG ampoules used in two groups varied significantly (20.6 $\pm$ 5.39 in 1st group vs. 26.65 $\pm$ 6.34 in 2nd 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]. However, controversy still exists in this regard. In this study, the number of mature follicles did not differ significantly between the dexamethasone and non dexamethasone groups. These findings are consistent with some prospective randomized trials performed previously [12, 23]. 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, they administered 10 mg prednisolone to PCOS patients treated with IVF and found no significant increase in the number of aspirated oocytes [23]. In the current study, the number of HMG ampoules used in patients treated with dexamethasone was significantly lower than that of the non-dexamethasone group.

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 the second 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 mature follicles in two groups may be the fact that these numbers are directly related to the ovarian

functional reserve and in aged women (> 35 years) whose reserves have been reduced [3], one cannot reach a high number of oocytes despite the prescription of dexamethasone.

Conclusion

Although there was no statistical difference between number of mature follicles but the number of HMG ampoules used in Dexamethasone group was significantly lower than the non-dexamethasone 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 and also yield lower cost for the treatment cycles.

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

Characteristic	Dexamethasone Treatment group (n=26) (Mean±SD)	Control Group (n=36) (Mean±SD)	P Value
Age (Year)	38.55±3.54	36.55±4.54	NS
Duration of Infertility (Year)	13.55±7.29	12.55±6.29	NS
Serum FSH level on day 2 (mlU/ml)	8.76±3.12	7.79±3.42	NS
Serum LH level on day 2 (mlU/ml)	5.12±2.73	6.66±3.67	NS
Serum Estradiol level on day 2 (Pg/ml)	100.6±22.1	95.5±27.4	NS
Total Testosterone level on day 2 (ng/ml)	0.4±0.38	0.44±0.2	NS

Table 2 treatment outcomes in studied groups.

Characteristic	Treatment group (n=26) (Mean±SD)	Control Group (n=36) (Mean±SD)	P Value
Serum Estradiol level at the day of HCG injection (Pg/ml)	486.85±271.17	539.64±345.3	NS
No. of mature follicles	2.27 ± 1.5	1.83 ± 1.4	NS
No. of HMG ampouls used	20.6±5.39	26.65±6.34	<0.05

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