Dexamethasone in unexplained infertility

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ABSTRACT

الأهداف: تحديد ما إذ كان استخدام عقار ديكساميثازون كدواء بديل و مناسب للمريضات اللواتي يعانين من عقم غير مفسر.

الطريقة: أجريت الدراسة في مستشفى أمير الجامعي بمدينة سيمنان بإيران، خلال الفترة ما بين أبريل 2001م إلى مايو 2008م. تم تقييم عدد 124 حالة تعاني من عقم غير مفسر واللواتي خضعن لتحفيز الإباضة والتخصيب داخل الرحم (IUI) (دورة واحدة فقط). تم استبعاد 16 حالة نتيجة لعدم استجابتهن لتحفيز الإباضة. بلغ عدد مجموعة الدراسة 42 حالة تلقت عقار كلوميفين سيتريت (CC) و عقار ديسكاميثازون، وبلغ عدد مجموعة التحكم 66 حالة تلقت عقار كلوميفين سيتريت لوحده. كانتا المجموعتين متساويتين بالنسبة للعمر وفترة العقم ومدخل كتلة الجسم. تم تقييم معدلات الحمل السريري في كلتا المجموعتين بواسطة استعمال الاختبارات الإحصائية.

النتائج: بلغ معدل الحمل السريري 21.4% و4.5% في مجموعة الدراسة ومجموعة التحكم على التوالي. كان هنالك فرقاً إحصائياً ملحوظاً بين المجموعتين (الخطر النسبي= 4.71, 95% التداخل الموثوق= 1.35-16.42 و p=0.0085).

خاتمة: بلغ مستوى الحمل لدى النساء اللواتي يعانين من عقم غير مفسر واللواتي خضعن لتحفيز الإباضة باستعمال عقار كلوميفين سيتريت CC و عقار ديسكاميثازون و التخصيب داخل الرحم (IUI) بشكل أعلى من النساء اللواتي خضعن لتحفيز الإباضة مع عقار كلوميفين سيتريت CC بمفرده.

Objectives: To determine if dexamethasone could be a suitable option in the treatment of patients with unexplained infertility.

Methods: This study was carried out in the Obstetrics Department of Amir University Hospital, Semnan, Iran, from April 2001 to May 2008. One hundred and twenty-four cases of unexplained infertility that underwent ovulation induction and intrauterine insemination (IUI) (only one cycle) were evaluated, and divided into 2 groups. Sixteen cases were excluded, as they were unresponsive to the induction ovulation regimen. Group I (n=42) received clomiphene citrate (CC) + dexamethasone, and the control group (group II, n=66) received CC alone. These groups were the same in age, duration of infertility, and body mass index. The clinical pregnancy rates were evaluated in 2 groups by using statistical tests.

Results: The clinical pregnancy rate was 21.4% in group I, and 4.5% in group II. There was a significant statistical difference between the groups (relative risk=4.71, 95% confidence interval=1.35-16.42, p=0.0085).

Conclusion: The pregnancy rate in women with unexplained infertility that underwent ovulation induction with CC + dexamethasone + IUI was significantly higher than those who underwent ovulation induction with CC alone + IUI.

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Infertility is a major distress of life, and approximately 15-30% of couples have unexplained infertility.[1] When the results of standard infertility evaluation including semen analysis, assessment of ovulation, hysterosalpingogram, test for ovarian reserve, and laparoscopy are normal, practitioners assign a diagnosis of unexplained infertility.[1] The treatments of unexplained infertility are empiric, and includes expectant observation with timed intercourse and lifestyle change.[1,2] Clomiphene citrate (CC) and intrauterine insemination (IUI),[1] controlled ovarian hyper-stimulation with IUI,[1,3] aromatase inhibitor,[4] *in-vitro* fertilization (IVF),[5] and laparoscopy are treatments[1] that enhance the fecundity in infertile women with a resection of minimal and mild endometriosis.[6] The likelihood of pregnancy in the untreated group is approximately 1.3-4.1% per cycle, and is lower than

most treatment intervention.[7] The pregnancy rate (PR) in treated groups are IUI = 3.8%, CC = 5.6%, CC+IUI = 8.3%, human chorionic gonadotropin (HMG) = 7.7%, HMG+IUI = 17.11, IVF = 20.7%, gamete intra-fallopian transfer (GIFT) = 27.[7] There are studies with regard to the use of drugs, such as danazole and bromcriptine in the treatment of unexplained infertility,[8,9] and in this study, we used dexamethasone as a drug in ovulation induction in combination with CC in patients with unexplained infertility that underwent IUI. Our aim was to determine if dexamethasone could be a suitable option in the treatment of patients with unexplained infertility .

Methods. This study included 124 cases of unexplained infertility that underwent IUI in the Department of Obstetrics and Gynecology, Amir Hospital, Semnan, Iran, from April 2001 to May 2008. A written informed consent was obtained, and the study was approved by the ethical committee of Semnan University of Medical Sciences. Sixteen cases were excluded because they were unresponsive to our induction ovulation regimen. The diagnoses of unexplained infertility were based on the evaluation of patients with sperm analysis, assessment of ovulation, and hysterosalpingogram. The patients that were infertile after one year unprotected intercourse, and the above diagnostic tests were normal were considered as unexplained infertility. One hundred and eight cases was divided in 2 groups. The study and the control groups were the same with regard to age, duration of infertility, and body mass index (BMI). In this study, in group I (study group), CC (50-150 mg/day) + dexamethasone (0.5 mg/day from the first day of menstruation-fourteenth day), and in the control group (group II) CC alone (50-150 mg/day from the third-seventh days of cycle) were used. Group I had no contraindication for dexamethasone use. One cycle of IUI was performed in all patients after ovulation induction. Transvaginal ultrasonography were performed in all patients in the twelfth day of the menstrual cycle, and among the patients with 1-3 follicles bigger or equal to 18 mm, and endometrial thickness larger than 7 mm, HCG (10000 IU) were injected, and IUI was carried out 36 hours after HCG injection. The exclusion criteria were; unresponsive to ovulation induction with the mentioned drugs in the first cycle in both groups, gastrointestinal ulcer, hypertension, diabetes mellitus, Cushing's syndrome, systemic tuberculosis, any acute infections, heart insufficiency, and proven osteoporosis in group I. The PR was evaluated between the 2 groups.

Statistical analyses of data were performed using Statistical Package for Social Sciences version 11.5 (SPSS Inc., IL., Chicago, USA), and EPI version 6, student t-test, Chi-square test, relative risk (RR), and 95% confidence interval. A $p<0.05$ was considered statistically significant.

Results. The mean ± Standard Deviation in age was 27.3 ± 5.8 in group I, and 27.5 ± 6.3 in group II, which was not statistically significant ($p=0.863$). The mean duration of infertility (group I - 4.5 ± 2.9 years, group II - 4.6 ± 3.7 years) was not statistically significant between the 2 groups ($p=0.919$), and with regard to BMI (group I - 20 [47.6%], group II - 31 [47%]) with normal BMI [18-25], it was the same in both groups ($p=0.947$). Pregnancy occurred in 9 cases (21.4%) in group I and 3 cases (4.5%) in group II. Statistical analyses showed that there were significant differences between the 2 groups with regard to PR, and the addition of dexamethasone to CC can increase the PR significantly (RR=4.71, 95% CI: 1.35-16.42, $p=0.0085$). The youngest pregnant woman was 23 years old, and the oldest was 35 years old. In 11 cases, pregnancy continued until full term with a normal and alive fetus, and in group I, one abortion happened in the first trimester (eight week of pregnancy). Twin pregnancy happened in one case in group I, and the result of this pregnancy was good with 2 normal, term, and alive fetus. All pregnant women had primary infertility except one case.

Discussion. Unexplained infertility is a cause of infertility in 13% of couples,[10] and irregular or low expression of integrins of endometrium that are cell adhesion molecules may be a cause of unexplained infertility,[11] and α (v) β3 integrin expression in endometrial stroma cell may be different in patients with unexplained infertility.[12] The other probable causes of unexplained infertility is incompetence of zone pellucida that is due to the malfunction of the gene that encodes the 4-glycoprotein, which compose the zone pellucida.[13]

In our study, the addition of dexamethasone to the usual regimen of ovulation induction was effective, but we cannot explain the mechanism of action in this study, however, it is an effective drug for ovulation induction.

In some studies, IUI + controlled ovarian hyperstimulation is as effective as expectant management in unexplained infertility.[14] And in a study by Battacharya et al,[15] CC or unstimulated IUI was found to be superior to expectant management. Usually, PR is different with different method, and to find more cost effective and accessible treatment is a medical practitioner's wish. In most studies, dexamethasone was used in polycystic ovarian syndrome (PCOS) patients who are resistant to CC even with normal dehydroepiandrosterone,[16,17] but in another study, this drug was used for ovulation

induction in patients without PCOS.[18] We decided to use it in our patients with unexplained infertility.

The optimal treatment of unexplained infertility is based on individual patient characteristics such as age, treatment efficacy, side effects, and cost consideration.[1] In this study, we used dexamethasone in the treatment of unexplained infertility that has low cost, and had no significant side effect, and noticeable efficacy.

In an unexplained infertility, ovarian stimulation resulting in 3 follicles is a significant prognostic factor with proper ovulation induction,[19] and having at least 3 follicles, the PR is higher. Adding dexamethasone to CC may improve the number of dominant follicle, and therefore, more pregnancy will occur.

The limitation of our study was the low number of cases with unexplained infertility, and the other was fair cooperation of patients. In future studies, more number of cases and cooperation of patients is recommended.

In summary, the addition of dexamethasone to CC may be an effective method in the treatment of unexplained infertility, and due to the small number of our study population, we recommend more and larger study number with regard to this subject.

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