

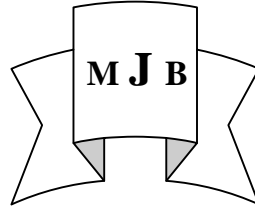
Prednisolone With Clomiphene Citrate in Ovulation Induction in Clomiphene Citrate-Resistant Polycystic Ovary Syndrome

Suhaila Fadhil Al-Shaikh

Ibtisam Fadhil

College of medicine, Babylon university, Hilla, Iraq.

Babil Teaching Hospital for Gyne. and Pediatric, Hilla, Iraq.



Abstract

The aim of this work was to evaluate the efficacy of adding prednisolone to clomiphene citrate (CC) in CC-resistant polycystic ovary syndrome (PCOS) in induction of ovulation.

Methods: forty three infertile women with CC resistant PCOS were randomly assigned into two groups. Group I (31 patients 72.09%): Clomiphene citrate 100 mg/day was given from day 2 to day 6 of the cycle and prednisolone 10 mg/day from day 2 to day 12 of the cycle. Group II (12 patients 27.9%): CC 150 mg/day was given from day 2 to day 6 of the cycle. The main outcome was ovulation. Secondary measures included endometrial thickness and pregnancy rate. Ovarian follicular response was monitored by transvaginal ultrasound.

HCG 10 000 U was given when at least one follicle measured 18 mm, and timed intercourse was advised.

Results: There were no statistically significant differences between groups regarding the age, duration of infertility, menstrual pattern, hirsutism, and PCO features by U/S. the mean endometrial thickness were significantly higher in the 1st group than in the 2nd group ($P < 0.05$). Similarly, there were significantly higher rates of ovulation (74.19 versus 16.66%) ($P < 0.001$) and pregnancy rate (54.84% versus 8.33%) ($P < 0.05$). Prednisolone was very well tolerated as no patients complained of any side effect.

Conclusion: Induction of ovulation by adding prednisolone to CC in CC-resistant PCOS is associated with no adverse anti-estrogenic effect on the endometrium and higher ovulation and pregnancy rates in a significant number of patients.

بردنيزولون مع كلوميفين سترت في تحفيز التبييض في متلازمة تكيس المبايض المقاومة
للكلوميفين سترت

الخلاصة

هذه الدراسة أجريت في مستشفى بابل للنسائية و الأطفال / وحدة تشخيص وعلاج العقم للفترة من ابريل 2008/ إلى أكتوبر /2009 و تم اختيار 43 مريضة مصابة بمتلازمة تكيس المبايض المقاومة للكلوميفين سترت (بعد فشل ثلاث محاولات لتحفيز المبايض بواسطة الكلوميفين بمفرده).

تم تقسيم المريضات إلى مجموعتين و بشكل عشوائي: المجموعة الاولى 31 (72.09%) مريضة و الثانية 12 (27.9%) مريضة

في المجموعة الأولى أعطيت المريضات كلوميفين 100 ملغم (من اليوم الثاني الى السادس للدورة الشهرية مع بردنيزولون 10 ملغم من اليوم 2 - 12 اما المجموعة الثانية فأعطيت كلوميفين 150 ملغم من اليوم 6-2 من الدورة.

المخرجات التي اعتمدت لنجاح الطريقة العلاجية كانت كالتالي:
أولا نسبة حدوث التبييض

ثانيا سمك البطانة الرحمية و نسبة حدوث الحمل

كان حدوث التبييض في المجموعة الأولى 74.19 % أما في المجموعة الثانية كان 66.66 % و نسبة حدوث الحمل كانت 54.84 % و في المجموعة الثانية كانت 8.33 %
الاستنتاج: من هذه النتائج يتضح إن الكلوميفين ستراتيت مع البردنيزولون يصلح أن يكون خيارا جيدا لعلاج الحالات المقاومة للكلوميفين ستراتيت لأنه علاج غير مكلف الثمن و ذو نتائج جيدة قبل اللجوء الى الطرق الاخرى التي يمكن استخدامها في هكذا حالات مثلا استخدام الهرمونات المنشطة (FSH) أو طريقة كي الأكياس المبيضية عن طريق الناظور (ovarian drilling).

Introduction

It has been suggested recently that, in some quarters, IVF be offered as 1st-line therapy to all infertile couples, regardless of the type of infertility. Hence, the time was thought right to scrutinize the results and complications of ovulation induction for anovulatory infertile couples. In addition to examining the outcome of conventional treatment with gonadotrophins and clomiphene citrate, special attention has been paid to the suggested improvement of results by taking into account the influence of obesity and the use of a low-dose gonadotrophin protocol. The possible contribution of more recent additions to the armamentarium such as insulin sensitizers and aromatase inhibitors, are promising. Attention has been given to the prevention and treatment of ovarian hyperstimulation syndrome. The use of intra-uterine insemination (IUI) as an adjuvant to induction of ovulation and controlled ovarian hyperstimulation (COH) is examined. The very firm conclusion has been reached that, taking into account efficiency, complication rate and cost of treatment, at this stage, women with hypogonadotrophic hypogonadism or polycystic ovary syndrome should be offered accepted methods of ovulation induction and that couples with 'unexplained' or

'multifactorial subfertility' should still be exposed to COH with IUI and only after the failure of these therapies, be offered IVF [1].

Clomiphene citrate (CC) is the traditional first-line treatment for chronic anovulation that characterizes polycystic ovary syndrome (PCOS) [2].

CC is accumulated in the body with low clearance rate and long half-life (5 days). Significant plasma concentrations of the active isomer of CC can be detected up to 6 weeks after administration. However, 20–25% of PCOS women fail to ovulate with incremental doses of CC. In addition, clinical data revealed a discrepancy between ovulation rates (75–80%) and conception rates (30–40%) during CC treatment [3].

The use of corticosteroid for the treatment of ovulatory dysfunction was first reported in 1953 by Jones *et al.* and Greenblatt [1]. Parsanezhad *et al.* (2002) had reported the novel use of the dexamethazone (DEX) (high dose, short course) for inducing ovulation in anovulatory women with PCOS and normal dehydroepiandrosterone sulphate (DHEAS) [4]. Dexamethazone therapy during the follicular phase has been described without any side effects or serious sequelae [5]. Our objective was to evaluate the efficacy of adding

prednisolone to CC in CC resistant PCOS in induction of ovulation.

Materials and Methods

Forty three infertile women their age range between (19 – 40) years were included from the patients attending the infertility clinic of Babil Hospital between April 2008 and October 2009. Patients were diagnosed as having PCOS according to the Rotterdam criteria for diagnosis of PCOS (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004) [6]. No patient showed hyperprolactinaemia, clinical evidence of hypercorticism or thyroid dysfunction. All patients had previously received CC 100 mg / day for five days and diagnosed as having CC resistance (failure of ovulation after three cycles of CC. Our inclusion criteria were: (i) age between 17 and 42 years; (ii) period of infertility >1 year; (iii) no treatment was taken during the last 2-3 months prior to the prednisolone co-treatment.

Exclusion criteria were infertility factor other than anovulation like tubal factor or of pelvic surgery or male factors. Hirsutism was diagnosed when the Ferriman and Gallwey score was >8.

Patients were divided into 2 groups 1st group (31 patients) received CC and co-treatment with prednisolone and the 2nd group (12 patients) received higher dose of CC 150 mg / day

Amenorrhic patients began treatment with induction of menstruation using Progesterone injection (100 mg). Ultrasonography was performed using a transvaginal transducer (6.5 MHz, endovaginal probe). On day 2, each patient underwent a baseline ultrasonographic examination. Clomiphene citrate, 100 mg for the 1st group and 150 mg for the 2nd group, was given from day 2 until

day 6. In addition to the CC each patient received prednisolone 10 mg/day orally, in two divided doses from day 2- 12 of the cycle in the 1st group. Transvaginal ultrasound examination was done 2 days after the end of CC and every other day according to the follicular size. HCG 10 000 U (Pregnyl) was given when at least one follicle measured 18 mm. Timed intercourse was advised 24–36 h after HCG injection. pregnancy was diagnosed by a positive pregnancy test and then when a gestational sac was detected on U/S. Each participant had only two treatment cycles.

Outcome measures

The primary outcome was the ovulation rate in the treatment cycle. Secondary outcome were the endometrial thickness and the pregnancy rate.

Statistical analysis

Data were collected and described by using number, percentage, minimum and maximum and mean +/- standard deviation, association between variables were measured by using t-test, chi square when appropriate. A *P*-level of <0.05 was considered statistically significant.

Results

As summarized in Table no. 1 there were no statistically significant differences between both groups regarding; age, duration of infertility, FSH and LH levels.

In table no. 2 it can be seen that there is no statistically significant difference between the two groups regarding the type of infertility, menstrual cycle pattern, hirsutism and PCO picture by U/S.

In table no. 3 it is evident that there is significantly higher rates of ovulation and pregnancy were seen in the 1st group as the endometrial thickness so.

In table no. 4 the distribution of the patients in relation to response to treatment is shown.

Prednisolone was very well tolerated as no patients complained of any side effect.

Table 1 Patients characteristics regarding the mean+/-SD of the age, duration of infertility, FSH and LH levels:

characters	N (MEAN+/- SD)	1 st group N(Mean +/- SD)	2 nd group N(Mean +/- SD)	P-value
Age (yr)	43 (27.54+/-6.31)	31(27.77+/- 6.41)	12(29.23+/-6.21)	NS
Duration of infertility	43 (4.33+/- 1.86)	31(4.34 +/- 1.91)	12(4.31+/-1.6)	NS
FSH mIU/ml	43 (8.21+/-4.19)	31(8.16+/-4.32)	12 (6.78+/-4.65)	NS
LH mIU/ml	43 (8.55+/-4.25)	31(8.74+/- 4.81)	12(8.16+/-4.32)	NS

Table 2 total no. of the patients and (%) of the type of Infertility, menstrual cycle history, hirsutism and PCO picture by U/S

Character		Total number (%)	1 st group N (%)	2 nd group N (%)
Type of infertility	primary	21(48.84%)	15 (48.39%)	6 (50%)
	secondary	22(51.16%)	16 (51.6%)	6 (50%)
Menstrual cycle	oligomenorrhoea	27(62.79%)	19 (61.29%)	8 (66.66%)
	amenorrhoea	6(13.95%)	4 (12.9%)	2(16.67%)
	Regular	10(23.26%)	8 (25.81%)	2(16.67%)
Hirsutism		12(27.91%)	8 (25.8%)	4(33.3%)
PCO (U/S)		36(83.72%)	26 (83.87%)	10 (83.33%)

Table 3 Outcome of treatment in both groups 1st group (clomiphene + prednisolone) and the 2nd group (clomiphene only)

Response to treatment	1 st group N=31	2 nd group N=12	P-value
Ovulation	23 (74.19%)	2 (16.66%)	< 0.001
Endometrial thickness (mm)	8.82+/- 1.49	7.03+/- 0.74	<0.05
pregnancy	17 (54.84%)	1 (8.33%)	< 0.05

Table 4 Ovulation and pregnancy in the subgroups (with primary and secondary infertility)

Response to R/ Patients subgroups		Ovulation	pregnancy
1 st group	Primary infertility (15)	11 (73.33%)	6 (40%)
	Secondary infertility (16)	12 (75%)	11 (68.75%)
2 nd group	Primary infertility (6)	---	---
	Secondary infertility (6)	2 (33.33%)	1 (16.66%)

Discussion

Parsanezhad *et al.* (2002) had reported the novel use of the Dexamethazone (high dose, short course) for inducing ovulation in anovulatory women with PCOS and normal androgen levels. Dexamethazone therapy during the follicular phase has been described without any side effects or serious sequelae [4, 5].

Azziz *et al.* (1999) found that there were no differences in ovulatory response to DEX therapy between women with and without androgen excess [1].

On the other hand, Daly *et al.* (1984) reported that the effect of steroids was largest in women with raised androgen levels [6]. The recent systematic review of the Cochrane library reported that the use of steroids like prednisolone or Dexamethazone as an adjunct to CC appears promising [7].

In this study, significantly higher rate of ovulation was reported in the prednisolone group 23(74.19%) vs 2 (16.66%), and in the Clomiphene plus prednisolone treatment group there is a significant improvement in the pregnancy rate when compared to CC alone 17 (54.84%) vs 1 (8.33%)

respectively, These results are in agreement with the results of Parsanezhad *et al.* (2002) [4].

There are a number of potential mechanisms by which steroids may affect ovarian function. Prednisolone acts directly on the pituitary gland to suppress the action of estradiol, which may be involved in the process of induction of ovulation by glucocorticoid-clomiphene treatment [8].

prednisolone enhances the FSH-stimulated follicular steroid production. The synergism of glucocorticoids with FSH in follicular progesterone production and its inhibition by transforming growth factor- β (TGF- β) indicate that glucocorticoid and TGF- β interaction may be necessary for granulosa cell differentiation as follicle matures through pre-antral stages [9].

The pregnancy rate in the 1st group were significantly higher than in the 2nd group. The endometrium was of adequate thickness to allow implantation. The adverse endometrial effect seen with CC, which is augmented by the relatively long half-life of CC (5 days), is not seen in the 1st group. This result is consistent with the results of other studies [4, 5]. They compared the effects of Dexamethason and CC on the endometrium.

Immunosuppression, leading to a favourable endometrial environment, was the rationale behind the administration of high-dose glucocorticoid from embryo transfer onwards, and higher implantation rates have been observed [10]. prednisolone predominantly influenced ovarian response, and a major endometrial effect is unlikely with the low dose used although a trend towards higher embryo implantation was observed. In this study, prednisolone use during the follicular phase resulted in a high rate of ovulation (74.19%) with a

pregnancy rate of 54.84%. All pregnancies were single. Parsanezhad *et al.* (2002) reported a higher ovulation rate (88%) [4]. This may be explained by the higher dose of CC (200 mg/day) given in their study. Compared to other methods of ovulation induction, the multiple pregnancy rates is approximately 10% with CC, almost entirely twins [11], 15–25% with gonadotrophins [12] and about 2% with laparoscopic ovarian drilling [13]. Comparing prednisolone with other medical methods of ovulation induction in cases of CC resistant PCOS, it is not as expensive as gonadotrophins and does not need intensive monitoring during and after treatment.

Thus, we can give prednisolone or dexamethazone to all patients with CC resistance, as its efficacy is not limited to a specific abnormality, and it can be used whatever the BM [14].

Some authors used low-dose DEX (0.5 mg/day) for 1 month [5; 6; 15; 16; 17; 18]. Ovulation rates ranged from 55 to 80%, and pregnancy rates ranged from 8.3 to 49%. The high-dose, short-course regimen is more convenient to the patient with higher ovulation (75–88%) and pregnancy rates (40–40.5%) according to the results of Parsanezhad *et al.* [4]. DEX 2.0 mg from day 2 to day 12 of the cycle would seem more appropriate than 0.5 mg until further data on 0.5 mg are available [7]. Further studies comparing the two regimens are required.

Conclusion

Induction of ovulation by adding prednisolone or dexamethazone to CC in CC-resistant PCOS is associated with no adverse anti-estrogenic effect on the endometrium and higher ovulation and pregnancy rates in a significant number of patients.

Induction with steroids appears to be independent on age, period of infertility.

Addition of prednisolone or Dexamethazone to CC is an effective, inexpensive and safe method for stimulating follicular development in CC-resistant PCOS and may be tried before gonadotrophins and laparoscopic ovarian drilling.

References

1. Azziz R, Black V, Knochenhauer E, Hines G and Boots L. Ovulation after glucocorticoid suppression of adrenal androgens in the polycystic ovary syndrome is not predicted by the basal dehydroepiandrosterone sulfate level. *J Clin Endocrinol Metab*: (1999); 84; pp 946–950.
2. Lidor AL, Goldenberg M, Cohen SB, Seidman DS, Mashiach S and Rabinovici J. Management of women with polycystic ovary syndrome who experienced premature luteinization during clomiphene citrate treatment. *Fertil Steril*: (2000); 74; pp 749–752.
3. Yen SS Chronic anovulation caused by peripheral endocrine disorders. In Yen SS and Jaffe RB (eds.) *Reproductive Endocrinology; Physiology, Pathophysiology, and Clinical Management*, 3rd edn. Philadelphia, Saunders: (1991); pp 576–630.
4. Parsanezhad ME, Albozi S, Motazedian S and Gholamhossein. Use of dexamethasone and clomiphene citrate in the treatment of clomiphene citrate-resistant patients with polycystic ovary syndrome and normal dehydroepiandrosterone sulfate levels: a prospective, double-blind, placebocontrolled trial. *Fertil Steril*: (2002); 78; pp 1001–1004.
5. Trott EA, Plouffe Jr L, Hansen K, Hines R, Brann DW and Mahesh VB. Ovulation induction in clomiphene resistant anovulatory women with normal dehydroepiandrosterone sulfate levels; beneficial effects of the addition of dexamethasone during the follicular phase. *Fertil Steril*: (1996); 66; pp 484–487.
6. Daly DC, Walters CA, Soto-Albors CE, Tohan N and Riddick DH. A randomized study of dexamethasone in ovulation induction with clomiphene citrate. *Fertil Steril*: (1984); 41; pp 844–848.
7. Beck JI, Boothroyd C, Proctor M, Farquhar C and Hughes E. Oral antioestrogens and medical adjuncts for subfertility associated with anovulation. *Cochrane Database Syst Rev*: (2005).
8. Terakawa N, Shimizu I, Aono T, Tanizawa O and Matsumoto K. Dexamethasone suppresses estrogen action at the pituitary level without modulating estrogen receptor dynamics. *J Steroid Biochem*: (1985); 23; pp 385–388.
9. Roy S, Wang J and Yang P. Dexamethasone inhibits transforming growth factor- β receptor (T β R) mRNA expression in hamster preantral follicles: Possible association with NF-YA. *Biol Reprod*: (2003); 68; pp 2180–2188.
10. Polak de Fried E, Blanco L, Lancuba S *et al.*. Improvement of clinical pregnancy rate and implantation rate of in-vitro fertilization-embryo transfer patients by using methylprednisolone. *Hum Reprod*: (1993); 8; pp 393–395.
11. Kousta E, White DM and Franks S. Modern use of clomiphene citrate in induction of ovulation. *Hum Reprod Update*: (1997); 3; pp 359–362
12. March CM. Human menopausal gonadotropins. *Infertil Reprod Mod Clin North Am*: (1990);1; pp 59–78.
13. Felemban A, Tan SL and Tulandi T. Laparoscopic treatment of polycystic ovary syndrome with insulated needle cautery, a reappraisal. *Fertil Steril*: (2000); 73; pp 266–269.

14. Kim LH, Taylor AE and Barbieri RL. Insulin sensitizers and polycystic ovary syndrome; can a diabetes medication treat infertility? *Fertil Steril*: (2000); 73; pp 1097–1098.
15. Diamant YZ and Evron S. Induction of ovulation by combined clomiphene citrate and dexamethasone treatment in clomiphene citrate nonresponders. *Eur J Obstet Gynecol Reprod Biol*: (1981); 11; pp 335–340.
16. Lobo RA, Paul W, March CM, Granger L and Kletzky OA. Clomiphene and dexamethasone in women unresponsive to clomiphene alone. *Obstet Gynecol*: (1982); 60; pp 497–501.
17. Hoffman D and Lobo RA. Serum dehydroepiandrosterone sulfate and the use of clomiphene citrate in anovulatory women. *Fertil Steril*: (1985); 43; pp 196–199.
18. Isaacs JD Jr, Lincoln SR and Cowan BD. Extended clomiphene citrate (CC) and prednisone for the treatment of chronic anovulation resistant to CC alone. *Fertil Steril*: (1997); 67; pp 641–643.