Extended Clomiphene Citrate (CC) and Prednisone for the Treatment of Clomiphene-Resistant Anovulatory Women with the Polycystic Ovary Syndrome (PCOS)

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Abstract
Objective: To evaluate the effectiveness of a regimen of extended clomiphene Citrate (CC) and prednisone for the treatment of clomiphene-resistant polycystic ovary syndrome (PCOS) patients who had failed to ovulate on CC alone.

Design: Prospective interventional study.

Setting: Department of Obstetrics and Gynaecology/Al-Yarmouk Teaching Hospital during the period September 2001 through February 2002.

Patients & Methods: Twenty-one anovulatory (PCOS) patients who failed to ovulate after clomiphene citrate (CC) treatment administered for 5 days. Treatment consisted of CC, 100 mg, given on cycle days 3 through 9 (extended). Additionally, patients were given prednisone 5 mg orally each night throughout the cycle. Ovulation was confirmed by midluteal serum progesterone levels. Pregnancy was confirmed by serum hCG Levels and 7-week gestation ultrasound.

Results: A total of 21 patients completed 53 cycles of treatment with extended CC and prednisone (mean, 2.5 cycles; range 1-6 cycles). Sixteen (76%) of 21 patients became ovulatory and 40 (75%) of treatment cycles resulted in ovulation. Eleven of 21 patients, (52%) conceived with this therapy. In the conception group, one ended in spontaneous abortion.

Conclusion: The treatment with extended CC and prednisone is an economic, safe and effective alternative treatment for PCOS patients in whom the classical treatment with CC has failed.

Keywords: Clomiphene Citrate, Prednisone, Polycystic Ovary Syndrome (PCOS).

Introduction
The polycystic ovary syndrome (PCOS) is the most frequent endocrine disease in women of reproductive age. Hyperandrogenism, anovulation and metabolic syndrome are the cardinal features of PCOS. It affects approximately 5-10% of women of reproductive age. It is a common neuroendocrine cause of infertility. Pharmacological management of such condition includes the use of an escalating scale of an antiestrogen, clomiphene citrate (CC), which is the most utilized of the ovulation inducers [1]. However, 20%-25% of women are resistant to CC and do not ovulate [2].

Failure to ovulate in response to clomiphene has been approached by either medical or surgical treatment. An effective alternative medical treatment is gonadotrophin injections which increase costs and it is associated with the risk of ovarian hyperstimulation syndrome and multifetal gestation. Treatment with metformin and the new generation of insulin-sensitizing drugs is under evaluation [3].

Other investigators have described the use of aromatase inhibitor letrozole for inducing ovulation in anovulatory women with PCOS [4]. The most widely used surgical treatment is laparoscopic ovarian drilling (LOD), which appears to be as effective as gonadotrophin therapy but remains expensive and the ovary is at risk of postoperative adhesion formation [5].

Relatively inexpensive treatment alternative includes the concomitant use of dexamethasone (DEX) and CC. This alternative has improved the response to CC in this group of patients [6-8] but its use has been limited because, the side effects of this treatment overcome their benefits. Dexamethasone is a fluorinated glucocorticoid with extremely high potency and long pharmacologic duration of action. Given systemically for long periods, DEX can inhibit the return of adrenal function when therapy is discontinued [9]. Delayed adrenal recovery can impose serious risk for affected patients. Another alternative is the use of prednisone throughout the menstrual cycle together with CC administered in pre-established days. This treatment has improved the response without adding side effects [10].

The purpose of this study was to report our experience with a simple protocol of extended CC and glucocorticoids for the treatment of CC-resistant anovulatory patients. In an effort to reduce the potential for adverse effects from glucocorticoid therapy, we chose prednisone, a glucocorticoid with less potential for side effects than DEX.

Patients & methods
This study was conducted on a total of (21) CC-resistant patients with anovulatory infertility as a result of PCOS, who consented to be involved from September 2001 through February 2002.

We defined clomiphene citrate resistance as failure to ovulate or conceive during clomiphene treatment for up to six months. PCOS was diagnosed when the patients had one or more of the following features as indicated by menstrual
disturbances such as oligomenorrhea or amenorrhea; clinical evidence of hyperandrogenism, such as hirsutism; high LH-FSH ratios >2-3:1 and the typical appearance of polycystic ovaries observed on ultrasonography: ten or more cysts 2-8 mm in diameter, arranged peripherally “string of pearls sign” around an echodense stroma\cite{11,12,13}.

Participants were required to have tubal patency on hysterosalpingography or laparoscopy as well as a normal semen levels, and a partner with a normal semen analysis according to World Health Organization criteria\cite{14}.

The patients received CC 100 mg on cycle days 3 through 9. Additionally, prednisone 5 mg was administered each night at 11.00 p.m. during the cycle and continued until confirmation of pregnancy. Ovulation was confirmed by a midluteal serum progesterone levels ≥ 4 ng/ml. Serum hCG titers were obtained 14 days after the estimated day of ovulation in the absence of menses. Pregnancy was confirmed by serum hCG levels and 7 week gestation ultrasound. Ovulation and pregnancy rate were recorded for each patient and each treatment cycle.

Statistical Analysis
Data collected were entered in the computer and were analyzed using SPSS (Statistical Packages for Social Sciences, Version 10) and were presented in simple measures of mean, SD, and range. The correlation between cycle (in months) and the cumulative probability of conception was done by simple linear correlation and regression for calculation of maximum expected probability of conception.

Results
A total of 21 patients completed 53 cycles of treatment with extended CC and prednisone (mean, 2.5 cycles; range, 1-6 cycles). The mean female age was 26.5±6.1 years (mean±SD), and the range was 18-39 years. The mean weight was 73.6±11.8 kg with a range of 53-97 kg. The mean body mass index was 28.5±4.1 kg/m².

Sixteen (76%) of the 21 patients became ovulatory and 40 (75%) of 53 treatment cycles resulted in ovulation. There were eleven pregnancies in the 21 women during the treatment for a total cumulative pregnancy rate of 52%. In the conception group one ended in spontaneous abortion. No patients experienced side effects related to CC or prednisone.

Fig. 1 shows the monthly pregnancy rate. The maximum cumulative probability of conception as calculated by logistic regression analysis, would be expected to be 0.60 (Fig.2).
Clomiphene Citrate & Prednisone for treatment of Polycystic Ovary Syndrome

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Discussion

Clomiphene citrate is the drug most commonly prescribed for ovulation induction. It is the first choice medication in oligo/amenorrhoic infertility, essentially associated with polycystic ovaries. Clomiphene citrate resistant anovulatory women present a special problem to the clinician. Those are candidates to receive other alternatives. However, because of the cost and risk inherent to gonadotrophin therapy and laparoscopic ovarian drilling, alternative treatments are attractive.

Our experience with a regimen of extended CC and prednisone resulted in a high rate of ovulation (76%).

Additionally, spontaneous abortion, multifetal gestation, and medication-related side effects were uncommon in this small series. Our findings are similar to those seen by others using CC and Dex\textsuperscript{[7,8,15]} or CC and prednisone\textsuperscript{[10]} and are encouraging.

Although our study was not designed to examine the mechanisms involved in establishing ovulation, two known responses of the hypothalamic-pituitary-ovarian axis to glucocorticoids may be beneficial in CC-resistant patients. The first is that glucocorticoids reduce circulating adrenal androgens by approximately 40%\textsuperscript{[16]}; this marked reduction of the circulating androgen-burden on the ovary may allow escape from the androgen-estrogen-driven anovulatory state. The second effect may be modulation of GnRH pulsatility, specifically enhancing an episodic pattern that favors FSH release\textsuperscript{[17]}. These events may contribute to the unexpectedly high (76%) rate of ovulation. Previous reports of similar rates of ovulation and pregnancy in CC-resistant patients treated with Dex and CC\textsuperscript{[7,8,15]} stimulated our interest in this regimen.

We chose prednisone at the dose and timing used here suppresses adrenal androgens with minimal effects on adrenal corticosteroid reserve\textsuperscript{[18]}. Because the desired effect is reduction of adrenal androgens (and potential positive GnRH effects) and not complete adrenal suppression, we recommended use of an agent with minimal enduring adrenal suppression. Prednisone was empirically continued throughout the cycle to maintain its potentially beneficial effects on the Hypothalamic-Pituitary-Ovarian (HPO) axis throughout the luteal phase, including the critical period of late-luteal follicular recruitment.

Our report is a clear demonstration that clomiphene-resistant polycystic ovary syndrome (PCOS) patients can be successfully treated with extended CC and prednisone. This treatment offers an effective, reasonable, inexpensive, and low-risk alternative before gonadotrophin therapy or surgery.

Conclusion

The treatment with extended CC and prednisone is an economic, safe, and effective alternative method of management of PCOS patients in whom the classical treatment with CC has failed.

References

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