Evaluation of a combined therapy of clomiphene citrate (incremental) and dexamethasone in resistant anovulatory patients with polycystic ovaries

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Summary: This study was designed to evaluate the efficacy of a combined therapy of an incremental dose of clomiphene citrate, and dexamethasone in resistant anovulatory patients with polycystic ovaries. Eighty two cycles of ovulation were induced in 28 patients as a part of the treatment protocol. Twenty two (78.5%) of the patients ovulated of which 16 (57%) conceived. The study shows significant improvement in ovulation and conception with a combined clomiphene (incremental) and DEX (follicular phase) treatment in anovulatory patients shown to be previously resistant to conventional clomiphene therapy. In lieu of its economic efficacy and safety advantages over alternative treatment of gonadotrophin stimulation or surgery, further research to define the role of glucocorticoid therapy in this category of patients could be of value.

Introduction:

About two-thirds of patients with anovulation (prolactin levels normal) ovulate or show evidence of an ovarian follicular response when treated with clomiphene in standard dosage (upto 200mg/day for 5 days). Most of the patients are treated successfully with an escalating scale of clomiphene citrate (CC). However, upto 25% of patients fail to ovulate after administration of CC 150mg and 15% of patients remain anovulatory despite treatment with CC in doses upto 200 mg for 5 days.

Alternatives for women with CC-resistant anovulation include menotropin regimens and ovarian wedge resection or diathermy. Gonadotropin therapy is expensive and associated with a risk of multiple pregnancy and ovarian hyperstimulation syndrome.

Additionally, patients with PCOD have a per cycle fecundity of < 10% and a cumulative probability of pregnancy of 50% after 12 cycles of gonadotrophin therapy (Dor et al, 1980). GnRH also recently has been used regularly, the degree of monitoring required being considerably less than gonadotrophin therapy. In addition, the incidence of multiple pregnancy is lower (5 to 8%) and significant ovarian hyperstimulation has been reported (Martin et al, 1990). While wedge resection of the ovaries is no longer used as a treatment option, electrocautery of the ovaries has been introduced (Abdel et al, 1990).

However, surgical therapy remains expensive and the ovary is at risk of post operative adhesion formation (Farhi et al, 1995). Because of the lack of ideal and more economical alternatives to the therapy, the use of clomiphene citrate with dexamethasone (DEX) has been employed in an effort to improve the response to CC in this group of patients (Trott et al, 1996). This study was designed to evaluate this simple protocol of clomiphene (incremental dose) with glucocorticoid for the treatment of CC-resistant anovulatory patients.

Materials and Methods:

Patients treated with CC for anovulation and infertility at the I.V.F Unit, Mahavir Hospital and Research Centre, Hyderabad, were identified from our data base. We defined clomiphene citrate resistance as failure to ovulate at a dosage of 200mg over 5 days. Identified patients had a normal hysterosalpingogram or diagnostic laparoscopy as well as normal thyroid and prolactin (PRL) levels. Semen analysis was normal in all male partners. A total of 28 patients were studied, all having provided fully informed consent. Ten patients were oligomenorrhoeic, the remaining 18 had secondary amenorrhoea.

All the patients received CC (300mg) in 3 divided doses given on cycle days 2 through 7. Dexamethasone (0.5 mg) was administered at bed time (10pm) during the follicular phase of the cycle for 15 days, hCG (10,000 IU) given when the dominant follicle was greater than 18mm in diameter.

Serum hCG titres were obtained 14 days after the estimated day of ovulation in the absence of menses. Clinical pregnancy was confirmed by vaginal ultrasound at 6 to 7 wks. of gestation. Incremental clomiphene regimen was repeated in 3 subsequent cycles in patients initially responsive. During treatment, patients were instructed to report any abnormal symptoms such as abdominal pain or blurring vision.

Monitoring was done by serial vaginal ultrasound and serum estradiol (E2).

A postcoital test was performed on day 12, 14 and 16. Satisfactory result was characterized by i) good sperm density ii) adequate forward progressive motility and, iii) a cervical score of 6 or more.

Treatment was discontinued if conception had not occurred within 4 cycles.

Re-evaluation consisting of laparoscopy and semen analysis was performed prior to treatment with hMG or pure FSH and LHRH analogue.
Statistical analysis was performed using Student's t-test.

Results:

Twenty eight patients had 82 cycles of ovulation induction. 22 patients were responsive, 5 remained unresponsive. The mean number of cycles per patient was 2.5 with a range of 1 to 8 cycles. Twenty two (78.5%) patients became ovulatory and 67 of the 82 cycles (82%) resulted in ovulation ($p<0.05$). Sixteen of 28 patients (57%) conceived with therapy ($p<0.05$). In the conception group 3 pregnancies resulted in spontaneous abortion and one gestation was twins. Only one patient reported side effects related to clomiphene or dexamethasone and had to be abandoned from the study.

Table – 1
Results of the combined therapy of clomiphene citrate (incremental) and dexamethasone.

Characteristics	No.	Percentage
No. of patients	28	
Mean age	35	
Total No. of cycles	82	
Ovulatary (responsive) patients	22	78.5
Anovulatory (unresponsive) Patients	5	17.85
Ovulatory cycles	67	82*
Conceptions	16	57*
Abortions	3	11

** P<0.05*

Discussion:

The results of this study show that by incremental and extended clomiphene therapy, ovulation has been induced in a majority of patients previously unresponsive to clomiphene in standard dosage. These results contrast sharply with the not so encouraging results seen in CC-resistant patients after treatment with hMG (Dor et al, 1980).

In addition, other complications like spontaneous abortions, 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 (Lobo et al, 1982).

In the mechanisms involved in establishing ovulation to 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% (Loughlin et al, 1986). 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 on the modulation of GnRH pulsatility specially enhancing an episodic pattern that favours FSH release (Ringstom and Schwartz, 1987). These events may contribute to the unexpectedly high (82%) rate of ovulation.

Dexamethasone is a fluorinated glucocorticoid with extremely high potency and long duration of action. A dose of 0.5 mg at bed time could consistently diminish ACTH-stimulated cortisol response (Rittmaster et al, 1985). Given systematically for long periods, DEX can inhibit the return of adrenal function when therapy is discontinued. Therefore, in one study, DEX was given from D3 to D12 of the period.

The pregnancy rate of 57% observed in our studies using

the combined regimen along with minimal adverse effect is extremely encouraging considering the very economical cost of the therapy compared to gonadotrophins. There might be additional mechanisms for this beneficial combined therapy of the effect of DEX on follicular development. We speculate that DEX treatment during the follicular phase enhances follicular development based on previous animal studies demonstrating enhancement of FSH synthesis and secretion by short term DEX treatment (Brann et al, 1992). Although this speculation needs further validation, the present results provide preliminary evidence supporting the utility of adding follicular phase DEX therapy as an adjunct to extended and incremental CC regimen for the induction of ovulation in the CC resistant anovulatory patient.

This therapy offers economic efficacy and safety advantages over alternative treatment of gonadotrophin stimulation or surgery and further important studies should be initiated to define the role of glucocorticoid therapy in these patients.

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