J Obstet Gynecol India Vol. 56, No. 2 : March/April 2006 Pg 159-161

ORIGINAL ARTICLE

The Journal of Obstetrics and Gynecology of India

Oral contraceptive pill pretreatment for clomiphene citrate resistant cases followed by repeat clomiphene citrate treatment

Goenka *Deepak*, Goenka *ML*

Institute of human reproduction, Bharalumukh, Guwahati - 781 009

OBJECTIVE(S) : To evaluate the effectiveness of 2 months oral contraceptive pill (OCP) pretreatment for clomiphene citrate (CC) resistant cases followed by repeat clomiphene citrate treatment.

METHOD(S) : In a prospective nonrandomized study at a private tertiary infertility center, 46 anovulatory women under the age of 36 years with CC resistance, were evaluated. Two months hypothalamic-pituitary-ovarian (HPO) axis suppression with OCP was followed by CC 100 mg from day 3 for 5 days.

RESULTS : Thirty-one (67.39%) patients showed dominant follicle ($\geq$ 20 mm) with 100 mg CC given for 5 days from day 3 of the cycle following two cycles of OCP.

CONCLUSION(S) : Suppression of the HPO axis for 2 months with OCP followed by 100 mg CC for 5 days results in good rates of folliculogenesis in women who had previously failed to develop a dominant follicle with similar dose of CC.

Key words : folliculogenesis, clomiphene citrate resistance, oral contraceptive pills

Introduction

Anovulation is one of the primary causes of infertility and clomiphene citrate (CC) is the first line drug for the treatment of anovulation. Almost 75% patients with anovulation are treated successfully with CC in doses of 50-150 mg [1]. Efficacy of doses above 100 mg per day is questionable [2]. Higher doses are also associated with more side effects like hot flushes and nausea.

In nonresponding patients, adjunctive therapies can be tried before moving on to gonadotropin therapy. Adjunctive therapies for CC resistant women include bromocriptine, dexamethasone, metformin, extended or higher doses of CC, and ovarian drilling.

Paper received on 29/03/2004 ; accepted on 15/09/2005

Correspondence :
Dr. Deepak Goenka
Institute of Human Reproduction
Bharalumukh, Guwahati - 781 009.
Tel. 0361-2544560, 2548767
Email : dgoenka@satyam.net.in

However usefulness of these adjunctive therapies is limited to specific abnormalities. Bromocriptine either alone or with CC is useful only if hyperprolactinemia is present [3,4]. Dexamethasone with CC is useful in hyperandrogenic women with DHEAS levels of > 300mg/dL [5,6]. Metformin increases the responsiveness only in polycystic ovarian syndrome (PCOS) cases with increased insulin resistance [7,8]. Dickey et al [2] had little success with higher or extended doses of CC and one or other side effects invariably start appearing with these doses. Finally, ovarian drilling is done for PCOS and offers time limited benefits. It is invasive, expensie and associated with risk of pelvic adhesions [9,10]. In addition the ovulation rate after ovarian drilling is comparable with ovulation rate with metformin [11,12] or gonadotropin [13] therapies.

The usual next step in these CC resistant cases is gonadotropins. Apart from its side effects like multiple pregnancy and risk of ovarian hyperstimulation syndrome (OHSS), one of the limiting factors associated with gonadotropin therapy is its cost.

In a group of CC resistant patients, we evaluated the

effectiveness of 2 months hypothalamic-pituitary-ovarian axis (HPO) suppression with oral contraceptive pill (OCP), followed by CC in a dose of 100 mg per day for 5 days from day 3 of the menstrual cycle.

Methods

CC resistance was defined as failure to show even a single dominant follicle ($\geq$ 20 mm) in two consecutive stimulated cycles. The first cycle was stimulated with 50 mg of CC per day for 5 days from day 3 and the second cycle was stimulated with 100 mg of CC per day for 5 days from day 3. Higher or extended dose of CC was not tried as it was found by us earlier (unpublished observation) and by Dickey et al [2] that optimum folliculogenesis can be obtained with a dose of 100 mg per day for 5 days in clomiphene sensitive patients. All these patients were also monitored for obesity (BMI >25 kg/m^2), galactorrhoea, hyperprolactinemia (serum prolactin level more than 30 ng/mL), increased DHEAS levels (>300 ?g/dL), increased insulin resistance (fasting glucose: insulin ratio < 3.0), and ovarian reserve using gonadotropin agonist stimulation test (GAST).

A total of 250 patients were stimulated in 4 months from April to July, 2003 for IUI. All those who failed to show a dominant follicle for two consecutive cycles with CC 50 mg per day for 5 days in the first cycle and 100 mg per day for 5 days in the second cycle were labeled as clomiphene resistent. All those who had galactorrhoea, hyperprolactinemia, increased DHEAS levels, and increased insulin resistance were excluded from the study and were treated with other adjunct therapies like bromocriptine, dexamethasone, and metformin. All patients having BMI > 25 were recruited in our weight reduction program. Those aged more than 36 years were also excluded from the study and were assessed for ovarian reserve using GAST and treated accordingly. The remaining were included in the study (Table 1).

Table 1. Clomiphene resistant cases.

Indications	Number	CC resistant
PCOS with anovulation	125	34
Male infertility (3-7 million sperm per ejaculate)	76	7
Endometriosis (confirmed on laparoscopy)	49	5
Total	250	46 (27.22%)

Out of 250 patients 46 (18.4%) showed CC resistance and were included in the study (Table-1). Table 2 gives the profile of these patients. They were given monophasic low dose oral contraceptive pill (OCP), which contained 0.03 mg ethinyl estradiol and 0.15 mg desogestrel for two cycles. Seven days no pill interval was used between two consecutive cycles to allow menstrual bleeding. CC 100 mg per day was repeated in the subsequent cycle for 5 days starting from day 3 of the menstrual cycle. Transvaginal ultrasound follicular monitoring was started from day 10 of the cycle and repeated every day until the mean diameter of the lead follicle was $\geq$ 20 mm. Thirty-one patients showed good folliculogenesis (lead follicle 20mm) and were given 10,000 IU of hCG as ovulation trigger.

In 15 patients in whom the follicular mean diameter failed to grow by a minimum of 1 mm per day after reaching a mean diameter of 14 mm was achieved, the monitoring was stopped and the cycle was cancelled. All ultrasound examinations were performed by the same operator (main author) using the same ultrasound machine (Aloka SSD 1700).

Results

The immediate post OCP suppression cycles were observed. The mean age of the patients was 28.8 years (range 21 to 36 years). Thirty-one (67.39%) patients showed a dominant follicle with 100 mg CC per day given for 5 days from day 3 in the cycle which followed the two cycles of OCP. Twenty-five patients showed monofolliculogenesis and six showed two follicles, one in each ovary (Table 2).

Table 2. Response to clomiphene citrate after pretreatment with oral contraceptive pill.

	Number	Percent	
Stimulated with CC	250		
CC resistant	46	18.4	(46/250)
Folliculogenesis by CC + hCG after OCP pretreatment.	31	67.39	(31/46)
Single follicle development	25	80.65	(25/31)
Development of two follicles	6	19.35	(6/31)

CC - clomiphene citrate OCP - oral contraceptive pill

Though our primary aim was to see the folliculogenesis in the subsequent cycle after stopping OCP, during follow-up we found that 16.13% (5/31) conceived with IUI in the first CC cycle following OCP pretreatment. All the remaining 26 patients showed good folliculogenesis in the second cycle too but did not conceive. In further studies it will be interesting to note for how long these patients continue to ovulate with CC after OCP ovarian suppression. The pregnancy rate was not the end point in the study as it depends on many factors such as semen quality and conditions like endometriosis.

Discussion

The suppression of the HPO axis for 2 months with OCP followed by CC treatment results in good rate of folliculogenesis. The treatment is much less expensive and is a low risk alternative in CC resistant patients before moving on to gonadotropin therapy or surgery. But it is important to counsel the patients that this involves 2 months of pretreatment (with OCP), during which pregnancy would not occur.

The lack of a uniform definition of CC resistance in the past has prevented the comparison between different protocols. We tried to define CC resistance. At our center we label CC resistant to only those who are resistant to CC for 5 days for at least two cycles, 50 mg in the 1st cycle and 100 mg in the 2nd, and are not having known disorders which can affect folliculogenesis such as obesity, hyperprolactinemia, hyperandrogenemia, and increased insulin resistance.

We could not measure serum gonadotropin levels, estrogens and androgens before and after the OCP suppression due to financial constraints. During the early development of OCPs in 1950s, the first combination of estradiol and progesterone pill was used, not for contraception but to treat infertility patients. The goal of treatment, at that time was the rebound effect after the pills were stopped. But now we understand that OCPs prevent ovulation by decreasing hypothalamic GnRH secretion, reducing pituitary responsiveness to GnRH, and thereby decreasing LH and FSH secretion. It is likely that the poor FSH:LH ratio is improved due to LH suppression with OCP [14]. There is also improvement in the adverse androgeneic microenvironment in the ovary [15]. The combination of these changes after OCP therapy, allows CC to work more effectively.

Conclusion

HPO axis suppression by OCP followed by CC treatment can successfully treat CC resistant cases. Compared with the usual alternative treatment of gonadotropins, it offers a low cost, safe, and effective alternative.

References

1. Imani B, Eijkemans MJ, Te Velde ER. A nomogram to predict the probability of live birth after clomiphene citrate induction of ovulation in normogonadotropic oligomenorrheic infertility. *Fertil Steril 2002;77:91-7.*
2. Dickey RP, Taylor SN, Curole DN et al. Relationship of clomiphene dose and patient's weight to successful treatment. *Hum Reprod 1997;12:449-53.*
3. Parsanezhad ME, Alborzi S, Jahromi BN. A prospective, double-blind, randomized, placebo-controlled clinical trial of bromocriptine in clomiphene-resistant patients with polycystic ovary syndrome and normal prolactin level. *Int J Fertil Womens Med 2002;47:272-7.*
4. Polson DW, Mason HD, Franks S. Bromocriptine treatment of women with clomiphene-resistant polycystic ovary syndrome. *Clin Endocrinol (Oxf) 1987;26:197-203.*
5. Keay SD, Lenton EA, Cooke ID et al. Low-dose dexamethasone augments the ovarian response to exogenous gonadotrophins leading to a reduction in cycle cancellation rate in a standard IVF program. *Hum Reprod 2001;16:1861-5.*
6. Lobo RA, Paul W, March CM et al. Clomiphene and dexamethasone in women unresponsive to clomiphene alone. *Obstet Gynecol 1982;60:497-501.*
7. Nestler JE, Stovall D, Akhter N et al. Strategies for the use of insulin-sensitizing drugs to treat infertility in women with polycystic ovary syndrome. *Fertil Steril 2002;77:209–15.*
8. Nestler JE, Jakubowicz DJ, Evans WS et al. Effects of metformin on spontaneous and clomiphene-induced ovulation in the polycystic ovary syndrome. *N Engl J Med 1998;338:1876-80.*
9. Saravelos H, Li TC. Post-operative adhesions after laparoscopic electrosurgical treatment for polycystic ovarian syndrome with the application of Interceed to one ovary: a prospective randomized controlled study. *Hum Reprod 1996;11:992–7.*
10. Gurgan T, Kisnisci H, Yarali H et al. Evaluation of adhesion formation after laparoscopic treatment of polycystic ovarian disease. *Fertil Steril 1991;56:1176–8.*
11. Pirwany I, Tuland T. Laparoscopic treatment of polycystic ovaries: is it time to relinquish the procedure? *Fertil Steril. 2003;80:241–51.*
12. Malkawi HY, Qublan HS, Hamaideh AH. Medical vs surgical treatment for clomiphene citrate resistant women with polycystic ovary syndrome. *J Obstet Gynaecol. 2003;23:289-93.*
13. Abdel Gadir A, Mowafi RS, Alnaser HM et al. Ovarian electrocautery versus human menopausal gonadotrophins and pure follicle stimulating hormone therapy in the treatment of patients with polycystic ovarian disease. *Clin Endocrinol (Oxf) 1990;33:585-92.*
14. Klein TA, Mishell DR. Gonadotropin, prolactin, and steroid hormone levels after discontinuation of oral contraceptives. *Am J Obstet Gynecol 1977;127:585-9.*
15. Branigan EF, Estes MA. Treatment of chronic anovulation resistance to clomiphene citrate (CC) by using oral contraceptive ovarian suppression followed by repeat CC treatment. *Fertil Steril 1999;71:544–6.*