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Original Article

Obstetrics & Gynaecology Section

Induction of Ovulation with Clomiphene Citrate Versus Clomiphene with Bromocriptine in PCOS Patients with Normal Prolactin: A Comparative Study

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ABSTRACT

Introduction: Polycystic ovarian syndrome (PCOS) is the main cause of anovulatory infertility. Various combination of drugs have been tried to induce ovulation in PCOS patients with varied result. So, this study was planned to compare the effect of bromocriptine combined with Clomiphene Citrate and Clomiphene Citrate alone, in patients of polycystic ovarian syndrome with normal prolactin level.

Materials & Methods: On the basis of inclusion and exclusion criteria, seventy four PCOS patients with normal prolactin level (< 20 ng/ml) and BMI between 20-30 were randomly assigned into two groups. One group (n=38) received 50 mg clomiphene citrate (CC) from day3 to day7. The other group (CC+Bcrt) was given 50 mg of clomiphene citrate from day3 to day7 along with 0.8mg of bromocriptine daily for full cycle (n=36). Both the groups were treated for 3 cycles. The outcomes were measured by the hormonal status, follicular size, ovulation rate and pregnancy outcomes.

Results: The serum prolactin level was normal in both the groups before treatment. After 3 cycles the prolactin level decreased in (CC+Bcrt) group ($p< 0.01$). Follicular development (size >15mm) was observed in 30 patients (78.9%) in CC group and 28 patients (82.3%) in CC+Bcrt group. There was no significant change in hormonal status (LH, FSH and Estradiol) of both the groups. The rate of ovulation was 69.4% in CC group and 75.8% in CC+Bcrt group. During the treatment period, nine patients in CC group and seven patients in CC+Bcrt group became pregnant.

Conclusion: There is no added benefit of bromocriptine with clomiphene citrate as compared to clomiphene alone in ovulation induction as well as pregnancy outcomes in PCOS patients with normal prolactin.

Keywords: Prolactin, Clomiphene citrate, Bromocriptine

INTRODUCTION

Infertility and its treatment options are one of the major developments that have occurred in the last few decades [1]. Polycystic ovarian syndrome (PCOS) is the commonest cause of Anovulatory Infertility. Women with PCOS have an increased incidence of World Health Organization (WHO) group II anovulatory infertility [2]. Ovulation induction is done to achieve repeated unifollicular ovulation [3].

Clomiphene citrate (CC) is available as one of the first line treatment options, for women with PCOS related anovulatory infertility. More than 80% of the women, ovulate when they are treated with clomiphene citrate. However some (15-20%) women remain anovulatory despite higher dose of Clomiphene [4,5,6]. Mostly, patients who are hyperandrogenic, overweight and hyperinsulinemic do not respond to clomiphene [7]. In majority of the cases, the reason for the lack of response to CC is unknown [8]. So, for these patients, a few adjunctive therapies like glucocorticoids, extended dose of CC, aromatase inhibitors and insulin sensitizers can be advriced [9]. Majority of the PCOS patients (17-43%) are hyperprolactinemic [10,11,12,13] and Bromocriptine induces ovulation in these patients by reducing the serum prolactin level. It also, induces ovulation in some anovulatory patients with normal prolactin level [14]. The reason for this induction may be due to reduction of occult hyperprolactinemia in PCOS patients [15]. The possible explanation for this includes – excess production of biologically active forms of prolactin not detected in all immunoassay system and transient but exaggerated nocturnal prolactin secretion that goes unrecognized in randomly drawn blood sample. Studies on the use of bromocriptine as an adjunctive therapy to clomiphene in PCOS are limited. So, this study was done to compare the effect of clomiphene citrate and bromocriptine as an adjuvant to clomiphene citrate in PCOS patients with normal prolactin level.

MATERIAL AND METHODS

A prospective randomized study was done in the infertility outpatient department of a tertiary care teaching hospital, South India. The study was undertaken with a prior approval of the Institutional Ethical Committee. The selection of the patients was done by inclusion and exclusion criteria.

The inclusion criteria were being infertile female diagnosed with PCOS (at least fulfilling 2 out of 3 criteria for PCOS), serum prolactin level ≤ 20 ng/ml, age < 35 years and body mass index (BMI) between 20-30. Patients with hyperprolactinemia (> 20 ng/ml), other causes of infertility (tubal, uterine) and patients with comorbid diseases, (tuberculosis, abnormal GTT) were excluded from the study. Based on the various inclusion and exclusion criteria, seventy four patients were randomly assigned into two groups. The age of the patients was noted and the body mass indices were determined in both the groups. The basal values of serum prolactin, serum hormonal levels like LH, FSH and estradiol were measured. The hormonal assays of prolactin, LH, FSH were done by FEIA (Fluorescent Enzyme Immunoassay) method and the serum estradiol level was measured by ECLIA (Electrochemiluminescence Immunoassay) method. This measurement was done on the day 2 of the first cycle in each group. The patients in the first group (n=38), were treated with tablet of clomiphene citrate (50mg) from day3 to day7 of each cycle. The patients in the other group (n=36) were given the same 50 mg tablet of clomiphene citrate from day3 to day7 and tablet bromocriptine (2.5mg) from day1 to day30 of each cycle. All the drugs were given to each group for three consecutive cycles. At the end of the three cycles i.e. on day2 of the fourth cycle, again the hormonal status (Serum Prolactin, LH, FSH, Estradiol) of the patients were determined. The normal levels of serum hormones

(Prolactin- 80-500 ng/ml, FSH- 3-13 mIU/ml, LH-1.5-12 mIU/ml, Estradiol -25-75 pg/ml) were considered as reference value.

A transvaginal ultrasonography (TVS) was done on different days like day 9, day1 1, day 13 and day 15th of each cycle to determine the follicular size, endometrial thickness and evidence of follicular rupture. The rate of ovulation (two out of three cycles) and the pregnancy outcome were noted for the comparison of the different treatment modalities.

The data obtained were expressed as mean ± SD. The statistical analysis was done for t-test, chi square test. p value less than 0.05, was considered as statistically significant.

RESULTS

The mean age of the patients in clomiphene (CC) group was 25 ± 4.2 years and in (CC+Bcrt) group was 25.13 ± 3.5 years. Similarly, the body mass index (BMI) of each patient was determined in both the groups. The mean BMI in (CC) treated group and in (CC + Bcrt) group were 24.43 ± 2.57 kg/m^2 and 25.36 ± 2.34 kg/m^2 respectively, which were not significantly different. Most of the patients in treatment group with bromocriptine had experienced some kind of adverse effects like nausea, vomiting, dizziness, confusion, fainting and insomnia. These side effects were not strong enough to stop medication in this group. The serum hormone levels like prolactin, LH, FSH and estradiol were determined on the day 2 of the fourth cycle as depicted in [Table/Fig-1]. The serum prolactin level was within normal limit for all patients in both the groups before treatment. But, there was a significant decrease in serum level of prolactin in CC+Bcrt group after 3 cycles of treatment (p< 0.01). The follicular development was considered when the follicular size became more than 15 mm. Thirty women (78.9%) in CC group and twenty-eight women (82.3%) in CC + Bcrt group, had follicular development (p = 0.71). In patients who received clomiphene alone, 69.4% ovulated, whereas 75.8% women ovulated when bromocriptine was combined with clomiphene. The rate of ovulation (2/3 cycles) was 41.7% and 33.3% in CC and CC+Bcrt group respectively. Nine women (23.6%) in the (CC_ group and seven women (19.4%) in CC+Bcrt group, became pregnant during the study period (p = 0.657).

Serum hormone levels	Before treatment		After treatment	
	CC group (n= 38)	CC+Bcrt group (n=36)	CC group (n= 38)	CC+Bcrt group (n=36)
Prolactin (ng/ml)	12.87 ± 4.0	14.8 ± 4.1	11.96 ± 3.89	10.51 ± 3.75*
LH (mIU/ml)	6.21 ± 3.15	9.91 ±4.7	5.01±2.49	5.02 ± 1.32
FSH (mIU/ml)	7.08±3.07	6.10±2.12	6.12±2.06	4.94±1.16
E2 (picogm/ml)	59.23±20.61	59.6±32.6	46.56±17.34	53.91±14.10

[Table/Fig-1]: Hormonal levels (day 2 of cycle) in the clomiphene (CC) group and clomiphene + bromocriptine (CC+Bcrt) group after 3 months of treatment

Mean ± SD, * p < 0.01, FSH, Follicular stimulating hormone; LH, luteinizing hormone; E^2 ,Estradiol

DISCUSSION

Clomiphene citrate is the main treatment for women with anovulatory infertility due to polycystic ovarian syndrome. But, about 15-20% of PCOS patients do not respond to clomiphene therapy [4–6]. Various factors like, associated hyperandrogenemia, hyperprolactinemia, insulin resistances have been proposed as possible explanations. Different combination regimens have been tried to overcome this resistance like dexamethasone, bromocriptine and metformin along with clomiphene.

In the current study, the serum prolactin level was normal in all the patients. Prolactin is said to have diurnal variation and molecular heterogeneity which may lead to occult hyperprolactinemia. Bromocriptine as an adjuvant may have a role in decreasing this occult hyperprolactinemia.

The study done by Kubato et al., had shown that combined treatment of clomiphene and bromocriptine resulted in ovulation rate of 57.3% and pregnancy rate of 26.7%. They also reported significant decrease in serum prolactin and LH level [16]. In our study, there was no significant change in hormonal status (LH, FSH and estradiol). Though, the prolactin level significantly decreased in CC+Bcrt group, we could not demonstrate any remarkable change in ovulation as well as pregnancy rate. Studies done by Steingold et al., [17] and Takakura et al., [18] showed various changes in hormonal levels. Buvat et al., observed that there is no significant changes in hormonal profile and clinical characteristics after treatment, with the combination of bromocriptine and clomiphene citrate [19].The study done by Mohammad et al., had shown that the only significant long term bromocriptine therapy in clomiphene citrate resistant polycystic ovarian patients was to lower the serum prolactin concentration, which is similar to our study [20]. The only limitation of our study is the shorter duration of treatment (three months) and small sample size. But, studies have shown the effect of bromocriptine within this time period [20].

CONCLUSION

The theory of occult hyperprolactinemia may not have a role in inducing ovulation and therefore in the overall pregnancy rate. In the present study, we conclude that there is no added benefit of bromocriptine with clomiphene citrate as compared to clomiphene alone in ovulation induction, as well as, pregnancy outcomes in PCOS patients with normal prolactin.

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