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Original Research Article

A comparative study of ovulation induction with clomiphene versus clomiphene and bromocriptine in follicular phase of normoprolactinemic PCOS women

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ABSTRACT

Background: Hypothalamic pituitary axis dysfunction accounts for majority of ovulatory disorders and a predominant cause of women with PCOS. There is a dopaminergic control on gonadotropin secretion. In normoprolactinemic PCOS patients transient rise in serum prolactin can be observed during the late follicular phase and luteal phase. So, the aim of the study is to know the effect of bromocriptine and clomiphene in ovulation induction as compared to clomiphene alone.
Methods: Based on the various inclusion and exclusion criteria, seventy patients were randomly assigned into two groups. The patients in the first group were treated with tablet of clomiphene citrate (100 mg) from day 3 to day 7 of each cycle. The patients in the other group received 100mg of clomiphene citrate from day 3 to day 7 of each cycle and tablet bromocriptine (2.5 mg) from day5 to day14. Both groups were followed up with follicular study for three months. At the end of the three cycles the hormonal statuses of the patients were determined.
Results: There was no significant difference found in other hormones like serum FSH, LH and estradiol in both groups. The follicular diameter and the average endometrial thickness was increased to a significant level in the CC+Bcrt group as compared to the CC group. The rate of ovulation and pregnancy rate was higher in combination group.
Conclusions: Bromocriptine with clomiphene in follicular phase has an advantage of improving follicular diameter, endometrial thickness and hence ovulation and pregnancy rates.

Keywords: Bromocriptine, Clomiphene citrate, PCOS

INTRODUCTION

One of the major developments that have occurred in the last few decades is subfertility and its treatment.[1] Anovulation constitutes 40% of all female subfertility. Hypothalamic pituitary axis dysfunction (category II anovulation) accounts for 85% of ovulatory disorders. Category II consists predominantly of women with PCOS.[2] Clomiphene citrate is the first choice of treatment but approximately 20% of the PCOS patients do not ovulate despite higher dose of Clomiphene. About 30% of PCOS patients show mild hyperprolactinemia. In normoprolactinemic PCOS patients transient rise in serum prolactin can be observed during the late follicular phase and luteal phase.[3] There is a dopaminergic control on gonadotropin secretion.[4] Reduction of dopamine inhibitory effect causes abnormal Prolactin (PRL) and Lutenising hormone (LH) release. One of the available

options is addition of bromocriptine to clomiphene citrate. Use of bromocriptine in treatment of infertility in women is not associated with an increased risk of spontaneous abortion, multiple pregnancy or occurrence of congenital malformation in their progeny. Hence this study was planned to know the effect of bromocriptine in follicular phase and clomiphene in ovulation induction compared to clomiphene alone. So, the objective of the study was to determine and compare the follicular size, endometrial thickness and ovulation on induction and pregnancy rates with clomiphene citrate and clomiphene citrate with bromocriptine in follicular phase.

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), normal serum prolactin, normal tubal patency test, normal semen analysis. Women who did not fit into the above criteria were excluded from the study. Based on the various inclusion and exclusion criteria, seventy 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- CC group (n=35), were treated with tablet of clomiphene citrate (100 mg) of from day 3 to day 7 of each cycle. The patients in the other group - CC+Bcrt group (n= 35) received 100mg of clomiphene citrate from day 3 to day 7 of each cycle and tablet bromocriptine (2.5 mg) from day5 to day14. Both groups were followed up with follicular study for three months. 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- <20 ng/ml, FSH- 3-13 mIU/ml, LH- 1.5-12 mIU/ml, Estradiol -25-75 pg/ml) were considered as reference value. The final oocyte maturation was achieved with 1mg of Inj. Leupride ,5000 units of Inj. HCG after 12 hrs when follicle diameter reached 16 – 18 mm in size. A transvaginal ultrasonography (TVS) was done on day 9, day11, 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.

Statistical analysis

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

RESULTS

The mean age of the patients in the first group (CC group) was 25.08±3.2 years and in (CC+Bcrt) group was 26.4±3.3 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 24.4±2.82 kg/m^2 and 24.8±3.97 kg/m^2 respectively. The mean serum prolactin level was increased in the CC+Bcrt group as compared to the CC group but was not significant. There was no significant difference found in other hormones like serum FSH, LH and estradiol in both groups as shown in (Table 1).

Table 1: Hormonal levels in the clomiphene (CC) group and clomiphene + bromocriptine (CC+Bcrt) group after 3 months of treatment.

Parameters	CC group (n= 35)	CC+Bcrt group (n=35) in follicular phase	p value
S. Prolactin (ng/dl)	12.6±4.06	14.5 ±4.77	0.07
S. FSH (mIU/ml)	6.9±2.04	6.8±1.68	0.80
S. LH (mIU/ml)	6.1±2.81	6.05±2.67	0.91
S. Estradiol (pg/ml)	51.9±20.11	44.7±16.94	0.16

Table 2: Follicular diameter and endometrial thickness in the clomiphene (CC) group and clomiphene+bromocriptine (CC+Bcrt) group after 3 months of treatment.

	CC group (n= 35)	CC+Bcrt group (n=35) in follicular phase	p value
Follicular diameter (mm)	16.7±3.74	18.4±4.11	0.0031
Average endometrial thickness (mm)	7.94±1.902	8.4±1.581	0.1038

The follicular diameter was increased to a significant level in the CC+Bcrt group as compared to the CC group (P=0.003). The average endometrial thickness was increased in CC+ Bcrt group as shown in Table 2.

The rate of ovulation in Cc group was 62.85% as compared to 77.14% in the other group. Nine women in the CC group and sixteen women in the CC+Bcrt group became pregnant after treatment (Table 3).

Table 3: Ovulation and Pregnancy Outcome in the clomiphene (CC) group and clomiphene+bromocriptine (CC+Bcrt) group after 3 months of treatment.

	CC group (n= 35)	CC+Bcrt group (n=35) in follicular phase
Rate of ovulation	22/35 (62.85%)	27/35 (77.14%)*
Pregnancy outcome	9/35 (25.71%)	16/35 (45.71%)**

DISCUSSION

PCOS is a common reproductive endocrinopathy with biochemical, hormonal variation and dysfunction even in the presence of normal range of hormones. 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.[5-7] 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 present 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 is a dopamine agonist used to lower prolactin levels, increase GnRH secretion, and induce ovulation.[8] For this reason, bromocriptine has been studied as an adjunctive treatment to clomiphene for ovulation induction in anovulatory women. Bromocriptine as an adjuvant may have a role in decreasing this occult hyperprolactinemia. The mechanism of bromocriptine action may be due to enhanced follicular responsiveness, normalization of elevated nocturnal serum prolactin and suppression of LH in follicular phase.

In our study about 77.14 % women ovulated after combination treatment of clomiphene and bromocriptine. In the study by Porcile A et al, it was found that 50% of the women ovulated when bromocriptine was added to clomiphene citrate.[9] There was increased rate of pregnancy in the combination group. The study by Akhlagi and Hamedi, showed that treatment with clomiphene and bromocriptine resumed the regular menstrual cycle in 68.2% women and the pregnancy rate was 40%.[10] In another study, it was found that the pregnancy rates were 74.1% in women who were treated with a combination of clomiphene and bromocriptine.[11] In another study by Haixia et al found that 100 mg of clomiphene citrate in combination with 2.5mg of bromocriptine resulted in 85.2% of pregnancy rate.[12]

The increased pregnancy rate with addition of bromocriptine may be due to increased endometrial thickness and improved follicular responsiveness. The inhibitory role of dopamine and its agonists on LH secretion and androgen concentration in normal and hyperprolactinemic women have been demonstrated in many studies. Prolactin of an appropriate concentration is considered to be needed for maintenance of normal function of corpus luteum. Discontinuation of bromocriptine after ovulation might cause transient hyperprolactinemia during luteal phase but does not seem to interfere with establishment and maintenance of pregnancy.

CONCLUSION

Bromocriptine in addition to clomiphene in follicular phase has an advantage of improving follicular diameter, endometrial thickness and hence ovulation and pregnancy rates. Both bromocriptine and clomiphene citrate combination for ovulation induction is better than bromocriptine or clomiphene alone.

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