

**Research Article****Comparative study between bromocriptine and bromocriptine plus clomiphene citrate in cases of hyperprolactinemic infertility patients****<sup>1</sup>Zahra Zafar, <sup>2</sup>Abida Qadir****and <sup>3</sup>Muhammad Zeshan Aziz**<sup>1</sup>Women Medical Officer  
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BHU Tal Shumali Tehsile Jam Pur**ABSTRACT**

**Objective:** To compare the treatment success rate between bromocriptine and bromocriptine plus clomiphene citrate in cases of hyperprolactinemic infertility patients.

**Materials & Methods:** This comparative study was conducted at Department of Obstetrics and Gynecology, DHQ Teaching Hospital Dera Ghazi Khan from March 2017 to September 2017. Total 180 cases of hyperprolactinaemic infertility having age range from 20-40 years were selected.

**Results:** Mean age of the patients was  $29.68 \pm 5.45$  years, mean age of group A and B was  $28.47 \pm 3.22$  years and  $27.58 \pm 4.52$  years respectively. Comparison of treatment success rate between both groups was done. In study group A treatment success was noted in 56 (62.22%) patients. In study group B, treatment success was noted in 73 (81.11) patients. Statistically significant higher treatment success rate was noted in patients of study group B as compared to study group A with p value 0.0078.

**Conclusion:** Results of this study showed that bromocriptine plus clomiphene citrate is more effective than bromocriptine alone in the treatment of hyperprolactinaemic infertility. So, we recommend that these particular patients should be treated with bromocriptine plus clomiphene citrate instead of bromocriptine alone in order to achieve maximum number of pregnancies in hyperprolactinemic infertile women.

**Keywords:** Pregnancy, prolactin, female infertility, bromocriptine, clomiphene citrate.

**INTRODUCTION:**

Prolactin (PRL) is one of several hormones that are produced by the pituitary gland. PRL has many different roles throughout the body. Prolactin is a 198-amino acid protein (23-KD) produced in the lactotroph cells of the anterior pituitary gland. In individuals with pathological hyperprolactinaemia, glucose and fat homeostasis have been reported to be negatively influenced.<sup>1</sup> Hyperprolactinemia causes infertility in up to one-third of women with reproductive disorders.<sup>2</sup> Approximately 75% of patients

presenting with galactorrhea and amenorrhea have hyperprolactinaemia.<sup>3</sup> Prolactinomas are the most common type of functional pituitary tumours, with predictable incidence of 6–10 cases per million population per year and a prevalence of around 60–100 cases per million.<sup>1-2</sup> According to previous reports, it accounts for 40–45% of pituitary tumours.<sup>3,4</sup> Its occurrence varies with age and gender, developing more commonly in females of age between 20–50 years with the female-to-male ratio of around 10:1.<sup>5</sup>

In woman hyperprolactinemia can be defined as the presence of abnormally high level of prolactin in the blood. Normal levels are typically 10–35 ng/ml and 1 ng is equivalent to 21.2 mU/ml.<sup>6</sup>

Majority of patients with prolactinomas, both micro- and macroprolactinomas, can be successfully treated with dopamine D2 receptor agonists as first-line treatment, with normalization of prolactin secretion and gonadal function.<sup>7</sup>The most commonly used dopamine agonists are bromocriptine, pergolide, quinagolide and cabergoline. When comparing the plasma half-life, efficacy and tolerability of these drugs are different, there is also important to evaluate the risk/ benefits profile of each product. Nowadays, clomiphene citrate is also used with the bromocriptine in the treatment of hyperprolactinemic infertile women with menstrual irregularities and anovulatory cycles in order to achieve earlier pregnancies.<sup>8</sup>

This study was conducted to compare the treatment success rate between bromocriptine and bromocriptine plus clomiphene citrate in cases of hyperprolactinemic infertility patients so that some practical recommendations could be made to achieve maximum number of pregnancies in hyperprolactinemic infertile women with more efficacious treatment regime.

#### **MATERIAL AND METHODS:**

This comparative study was conducted at Department of Obstetrics and Gynecology, DHQ Teaching Hospital Dera Ghazi Khan from March 2017 to September 2017. Total 180 cases of hyperprolactinaemic infertility having age range from 20–40 years were selected. Patients with other causes of infertility i.e. tubal factors, male factor and unexplained infertility, polycystic ovarian disease, macroadenoma of pituitary gland, hyperthyroidism and h/o drugs like dopamine depleting, dopamine receptor blocking, H-2 blocker and verapamil intake were excluded. Written informed consent was taken from every patient. Selected patients were randomly divided into two groups A & B. A dose of 1.25 mg of bromocriptine was prescribed to patients of group A at bedtime with a snack and gradually increased

to 2.5 mg two times a day with food over 3–4 weeks and this treatment was continued for 6 months. Occurrence of pregnancy was awaited for one year after start of therapy. While in Group B, all patients were treated with bromocriptine with same dosage and methodology as was mentioned in group A. With the onset of menses, at day 2–6 of menstrual cycle, clomiphene citrate was started at initial daily dose of 50 mg two times a day for first two cycles, then 50 mg three times a day for third and fourth cycles and 100 mg two times a day for fifth and sixth cycles. Clomiphene citrate was stopped when ovulation was achieved which was confirmed by follicular tracking on transvaginal sonography at day 12 of each menstrual cycle. Occurrence of pregnancy was awaited for one year after start of therapy.

Final outcome was measured in terms that patient had reported back in OPD at monthly basis and pregnancy was confirmed by measuring serum  $\beta$ -HCG ( $\geq 5$  mIU/ml of  $\beta$ -HCG was taken as occurrence of pregnancy and level  $< 5$  mIU/ml was taken as absent pregnancy) every month for total duration of one year after start of therapy. All the collected data alongwith demographic profile of the patients were entered in predesigned proforma.

All the data was entered and analyzed by using SPSS version 18. Mean and SD was calculated for age and duration of infertility. Efficacy of the treatment regimens in both groups was presented by frequency and percentages. Efficacy of both treatment regimens was compared in two groups by chi square test. P value  $\leq 0.05$  was considered as statistically significant.

#### **RESULTS:**

Total 180 patients of hyperprolactinaemic infertility having age range from 20–40 years were selected for this study. Mean age of the patients was  $29.68 \pm 5.45$  years, mean age of group A and B was  $28.47 \pm 3.22$  years and  $27.58 \pm 4.52$  years respectively.

Patients of study group A were treated with bromocriptine alone and patients of study group B were treated with bromocriptine plus clomiphene citrate. Comparison of treatment success rate between both groups was done.

In study group A treatment success was noted in 56 (62.22%) patients. In study group B, treatment success was noted in 73 (81.11) patients. Statistically significant higher treatment success rate was noted in patients of study group B as compared to study group A with p value 0.0078. (Table 1)

Patients of both groups were divided into two age groups i.e. age group 20-30 years and age group 31-40 years. In study group A, out of 90 patients of group A, 53 patients belonged to age group 20-30 years and 37 patients belonged to age group 31-40 years. In study group B, out of 90 patients 56 patients belonged to age group 20-30 years and 34 patients belonged to age group 31-40 years. In age group 20-30 years, treatment success was noted in 40 (75.47%) patients and 48 (85.71%) patients respectively in study group A and B. Difference of treatment success rate was statistically insignificant with p value 0.2263. In age group 31-40 years, treatment success was noted in 16 (43.24%) patients of

group A and 25 (73.53%) patients of group B and the difference was statistically significant with p value 0.0157. (Table 2)

In this study, minimum duration of infertility was 1 year and maximum duration of infertility was 10 years. patients were divided into two groups according to duration of infertility i.e. 1-5 years and 6-10 years. Total 58 patients of study group A and 61 patients of study group B belonged to 1-5 years of infertility group. Treatment success rate was noted in 45 (77.59%) patients and 56 (91.8%) patients respectively group A and B. Difference of treatment rate between the both groups was statistically significant with p value 0.0405. In 6-10 years duration of infertility group, total 32 patients belonged to study group A 29 patients belonged to study group B. Treatment success was noted in 11 (34.38%) patients of group A and 17 (58.62%) patients of group B. Difference of treatment success rate between both groups was statistically insignificant with p value 0.0746. (Table 3)

**Table 1** Comparison of treatment success rate between the two groups

Study Group	Success rate		Total	P. Value
	Yes(%)	No(%)		
A (bromocriptine group)	56 (62.22)	34 (37.78)	90	0.0078
B (bromocriptine plus clomiphene citrate group)	73 (81.11)	17 (18.89)	90	

**Table 2** Comparison between Efficacy of both groups according to age.

Group	Treatment success		Total
	Yes(%)	No(%)	
20-30 years (P= 0.2263)			
A	40 (75.47%)	13 (24.53%)	53
B	48 (85.71%)	08 (14.29%)	56
31-40 years (P = 0.0157)			
A	16 (43.24%)	21 (56.76%)	37
B	25 (73.53%)	9 (26.470%)	34

**Table 3** Comparison between Efficacy of both groups according to duration of Infertility.

Group	Treatment success		Total
	Yes(%)	No(%)	
1-5 years (P= 0.0405)			
A	45 (77.59%)	13 (22.41%)	58
B	56 (91.8%)	05 (8.12%)	61
6-10 years (P = 0.0746)			
A	11 (34.38%)	21 (65.63%)	32
B	17 (58.62%)	12 (41.38%)	29

## DISCUSSION:

The purpose of this study was to compare the treatment success rate between bromocriptine and bromocriptine plus clomiphene citrate in cases of hyperprolactinemic infertility patients.

Mean age of the patients was  $29.68 \pm 5.45$  years, mean age of group A and B was  $28.47 \pm 3.22$  years and  $27.58 \pm 4.52$  years respectively.

In one study by Motazedian S et al<sup>9</sup> mean age of the patients of hyperprolactinemic infertility was 28 years which is comparable with our study. Similar mean age (29 years) of patients with hyperprolactinemic infertility was reported by Al-Husaynei AJ et al<sup>10</sup> in their study.

In present study, mean duration of infertility was  $5.69 \pm 3.47$  years which is higher than some previous studies.<sup>11-12</sup> The reason for this late presentation may be due to hakeem culture and lack of awareness in our society.

Patients of study group A were treated with bromocriptine alone and patients of study group B were treated with bromocriptine plus clomiphene citrate. Comparison of treatment success rate between both groups was done. In study group A treatment success was noted in 56 (62.22%) patients. In study group B, treatment success was noted in 73 (81.11%) patients. Statistically significant higher treatment success rate was noted in patients of study group B as compared to study group A with p value 0.0078.

Mahmood S et al<sup>13</sup> in their randomized study has compared the two regime i.e. bromocriptine alone versus bromocriptine plus clomiphene citrate in treating hyperprolactinemic infertility and found the bromocriptine combined with clomiphene citrate superior as compared to bromocriptine alone. He has found the efficacy of bromocriptine as 65% and bromocriptine plus clomiphene citrate as 75% in occurrence of pregnancy in hyperprolactinemic infertile women. These results are very much comparable to our results. Tripathy et al<sup>14</sup> reported also reported treatment success of clomiphene with bromocriptine as 75.8% which is also comparable with our results.

In another study done by AnateMet al<sup>15</sup> also showed better efficacy of bromocriptine plus clomiphene citrate in achieving pregnancy compared to bromocriptine alone. On the whole it is concluded that bromocriptine is effective in the treatment of hyperprolactinemic infertility. But bromocriptine plus clomiphene citrate has the advantage over bromocriptine alone in terms of both efficacy (achieving pregnancy) and tolerability. The efficacy of bromocriptine found in this study was 62.22% which is very much comparable with the studies of Sabuncu T et al<sup>16</sup> and Webster J et al<sup>17</sup> who had noted this as 59% and 58% respectively. But Motazedian S et al<sup>9</sup> and Mahmood IH et al<sup>18</sup> had found bromocriptine efficacy as 56% in their studies which is a little lower than our study.

## CONCLUSION:

Results of this study showed that bromocriptine plus clomiphene citrate is more effective than bromocriptine alone in the treatment of hyperprolactinemic infertility. So, we recommend that these particular patients should be treated with bromocriptine plus clomiphene citrate instead of bromocriptine alone in order to achieve maximum number of pregnancies in hyperprolactinemic infertile women.

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