

A comparison of bromocriptine & cabergoline on fertility outcome of hyperprolactinemic infertile women undergoing intrauterine insemination

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Background & objectives: The aim of this study was to compare the effects of bromocriptine versus cabergoline on pregnancy in hyperprolactinaemic infertile women.

Methods: A total of 183 infertile women with hyperprolactinemia undergoing intrauterine insemination (IUI) were randomly divided into two groups. Group A: 94 with bromocriptine and group B:89 with cabergoline. The efficacy and safety was evaluated on the basis of normalization of prolactin levels, normalization of menstrual cycle, disappearance of galactorrhea, occurrence of pregnancy and adverse effects with each of these medications.

Results: The presence of galactorrhea and irregular menstruation were significantly lower in patients of group B than group A ($P<0.001$ and $P=0.011$, respectively) with a significant lower prevalence of side effects in cabergoline group. Pregnancy was significantly more achieved among the women with the treatment of cabergoline (82%) as compared to bromocriptine (56.4%) ($P<0.001$).

Interpretation & conclusions: Our results suggest that cabergoline treatment in infertile women with prolactinemia is more effective. It lowers prolactin with better tolerability and much more effective in the achievement of pregnancy.

Key words Bromocriptine - cabergoline - hyperprolactinemia - infertility

Prolactin is a pituitary-derived hormone that plays a pivotal role in a variety of reproductive functions. An excess of prolactin above a reference laboratory's upper limits, or "biochemical hyperprolactinemia" is the most common endocrine disorder of the hypothalamic-pituitary axis- up to 10 per cent of the population^{1,2}. The prevalence has been reported to range from 0.4 per cent in an unselected healthy

adult population in Japan to 5 per cent among clients at a family planning clinic¹. The rate is even higher among patients with specific symptoms that may be attributable to hyperprolactinemia: it is estimated at 9 per cent among women with amenorrhea, 25 per cent among women with galactorrhea and as high as 70 per cent among women with amenorrhea and galactorrhea¹.

The objective of hyperprolactinemia treatment is to correct the biochemical consequences of the hormonal excess³. Several dopamine agonists are currently available for the treatment of hyperprolactinemia, including bromocriptine and cabergoline in the USA and, additionally, quinagolide in the UK and most other European countries^{2,4}. Pergolide has also been used successfully in the USA to treat hyperprolactinemia⁵. A recently launched long acting dopaminergic drug, cabergoline, has been shown to have advantages over bromocriptine in terms of both efficacy and tolerability, and it is therefore an important advance in the treatment of hyperprolactinemia⁶.

On the other hand, hyperprolactinemia causes infertility in up to one-third of women with reproductive disorders⁷. Women with hyperprolactinemia are frequently prescribed dopamine agonists to reduce prolactin levels and restore normal menses. Bromocriptine has been used for a number of years for this purpose. However, patient compliance and its side effects led doctors to search for a better alternative.

The aim of this study was to compare the effects of bromocriptine versus cabergoline on pregnancy in hyperprolactinemic infertile women.

Material & Methods

Patients: This was a randomized controlled clinical trial to compare the effectiveness of cabergoline versus bromocriptine in hyperprolactinemic infertile women undergoing induction of ovulation for intrauterine insemination (IUI). This study was performed from March 2005 to March 2007 and finally 183 infertile patients undergoing IUI cycles, who referred to Infertility Clinic of Shiraz University of Medical Science and private clinics with hyperprolactinemia. A complete history and general physical examination were performed before basic investigation of infertility.

For all patients, semen analysis (SA), hormonal assay (HA) including: DHEAS, TSH, prolactin, FSH, LH and histerosalpingogram (HSG) with or without laparoscopy were done. The criteria for inclusion were as follows: (i) Primary or secondary infertility; (ii) Hyperprolactinemia with or without galactorrhea (prolactin > 20 ng/ml); and (iii) Normal HA except high prolactin level, normal HSG or laparoscopy and normal SA.

Patients with other causes of infertility such as tubal factor, male factor and unexplained infertility were excluded from the study. Women ones with nausea,

vomiting, orthostatic hypotension, chronic hypertension, headache, sensitivity to ergot derivatives, macroadenoma of pituitary gland and previous use of bromocriptine or cabergoline without effect were also excluded.

Prior to entering this trial, patients were fully informed of the conduct and consequences of the study and signed a consent form. This study was conducted following approval by institutional review board and ethics committee of Shiraz University of Medical Sciences and was in accordance with the ethical principles described in the Declaration of Helsinki (clinical trials registry NO.: IRCT138806142420N1).

Study protocol: A total of 183 women with hyperprolactinemia were recruited in this study with the mean duration of infertility of 4.5 yr (range 2-1 yr).

The patients were divided into two groups based on a computer-generalized random table:

(i) Group A: 94 patients under the treatment of bromocriptine 2.5 mg BID; (ii) Group B: 89 patients under the treatment of cabergoline 0.25 mg twice a week.

It is noted that the sample size was calculated using Altman's nomogram as 94 patients in each group, but 5 cases were excluded from group B (cabergoline) because they did not undergo regular visits and follow-ups and did not refer to our center again.

All the patients were asked about constipation, headache, nausea, vomiting and orthostatic hypotension. In addition, prolactin level was measured 4 wk after treatment.

Induction of ovulation was started when prolactin level became normal, and if it did not become normal, the patient was excluded from the study. Clomiphen citrate was administrated orally for 5 days with the dose of 100 mg/day from the 5th to the 9th day of cycle, and HMG (Merionol, IBSA, Switzerland) was injected intramuscularly with 2 Amp/day from the 8th day of cycle.

Vaginal sonography was performed on the day 10th or 11th of cycle and according to the size and number of stimulated follicles, HMG was continued till at least 2 dominant follicles with size of >18 mm were seen. If this condition was not achieved, HMG was discontinued and it was restarted from the next cycle. In addition, there was no cancellation due to hyperstimulation or excessive number of follicles in our patients. Then 5000-10000 IU HCG (Choriomon, IBSA, Switzerland)

was injected intramuscularly. Intrauterine insemination (IUI) was performed 24-36 h after swim-up method.

B-HCG was checked if the patient gave history of one week missed period. Medication was discontinued after positive B-HCG. Pregnancy was documented by transvaginal sonography, at 6-7 wk of gestational age. Main outcome measurements were serum prolactin level, disappearance of galactorrhea, regulation of menses, side effects of both medication and the occurrence of pregnancy.

Statistical analysis: Values are expressed as mean (\pm SD). To examine differences between patients of two groups, the Chi-square test with Yates' continuity correction and Student's t-test for categorical and quantitative data were employed, respectively. For further analysis, the logistic regression model was used to determine the factors significantly related to the occurrence of pregnancy. The SPSS software package v.13.0 (IL, Chicago, USA) was used for all analyses and all *P* values were two-tailed and a *P* value of <0.05 was considered significant.

Results

Of 183 patients, 159 (86.9%) had galactorrhea and 165 (90.2%) had irregular menstruation (mean age 28.89 ± 4.44 yr) (Table II), the mean duration of infertility of 4.50 (SD=1.88) yr and the mean baseline prolactin level of 64.65 (SD=17.40) ng/ml.

Group A (Bromocriptine): A total number of 94 women with hyperprolactinemia were recruited in this group. Of these 94 patients, 82 (87.2%) women had galactorrhea and 84 (89.4%) had suffered from irregular menstruation with the mean age of 28.62 (SD=4.42) yr, the mean duration of infertility of 4.52 (SD=1.71) yr and the mean baseline prolactin level of 64.02 (SD=18.64) ng/ml. After treatment with bromocriptine, the frequency of galactorrhea and irregular menstruation was reduced to 51.1 and 33 per cent, respectively. Moreover, the mean serum level of prolactin was decreased to 20.94 (SD=6.84) ng/ml.

Regarding the side effects of treatment, the most common adverse effect during the treatment period in group A was nausea and headache with the frequency of 43.6 and 26.6 per cent, respectively. In addition, vomiting, constipation and orthostatic hypotension were also seen in 20.2, 12.8 and 21.3 per cent, respectively (Table II).

Finally, after the study period, 58 (61.7%) of women of group A had a normal-range prolactin and the pregnancy was achieved in 53 (56.4%) patients.

Group B (Cabergoline): A total number of 89 women with hyperprolactinemia were recruited in this group. Out of these 89 patients, 77 (86.5%) women had galactorrhea and 81 (91%) had suffered from irregular menstruation with the mean age of 29.17 (SD=4.47) yr, the mean duration of infertility of 4.48 (SD=2.06) yr and the mean baseline prolactin level of 65.31 (SD=16.07) ng/ml. After treatment with cabergoline, the frequency of galactorrhea and irregular menstruation was reduced to 13.5 and 15.7 per cent, respectively. Moreover, the mean serum level of prolactin was decreased to 18.29 (SD=5.12) ng/ml (Table II).

The most common adverse effect during the treatment period in group B was nausea and orthostatic hypotension with the frequency of 18 and 18 per cent, respectively. In addition, vomiting, constipation and headache were also presented in 3.4, 14.6 and 9 per cent, respectively.

Finally, after the study period, 75 (84.3%) of women of group B had a normal-range prolactin and the pregnancy was achieved in 73 (82%) patients.

Comparison between groups: There was no difference between the baseline characteristics of the patients in two groups ($P>0.05$, Table I). Moreover, the mean serum level of prolactin at the beginning of the study was not statistically different between the two groups ($P=0.617$). Outcomes of the patients in two groups of the study are listed in Table II. The results of Student's t-test showed that the serum level of prolactin was significantly lower in patients who were given cabergoline ($P=0.003$).

The results of Chi² test demonstrated that the presence of galactorrhea and irregular menstruation

Table I. Demographic characteristics of the patients in two groups of study

Variable	A (Bromocriptine) n=94	B (Cabergoline) n=89	<i>P</i> value
Age (yr) range	19-38	20-37	0.403
mean \pm SD	28.62 \pm 4.42	29.17 \pm 4.47	
Duration of infertility (yr) range	2-10	2-10	0.493
mean \pm SD	4.52 \pm 1.71	4.48 \pm 2.06	
Serum level of prolactin (ng/ml) range	22-105	34-105	0.617
mean \pm SD	64.02 \pm 18.64	65.31 \pm 16.07	
Galactorrhea No. (%)	82 (87.2)	77 (86.5)	0.886
Irregular menstruation No. (%)	84 (89.4)	81 (91)	0.900

Table II. Outcomes of the patients in two groups of study after treatment

Variable	A (Bromocriptine) n=94	B (Cabergoline) n=89	P value
Serum level of prolactin (ng/ml) range	14-41	14-41	0.003*
mean \pm SD	20.94 \pm 6.84	18.29 \pm 5.12	
Normal-range prolactin level	58 (61.7)	75 (84.3)	0.001*
Galactorrhea	48 (51.1)	12 (13.5)	<0.001*
Irregular menstruation	31 (33)	14 (15.7)	0.011*
Nausea	41 (43.6)	16 (18)	<0.001*
Vomiting	19 (20.2)	3 (3.4)	<0.001*
Orthostatic hypotension	20 (21.3)	16 (18)	0.708
Constipation	12 (12.8)	13 (14.6)	0.883
Headache	25 (26.6)	8 (9)	0.004*
Pregnancy	53 (56.4)	73 (82)	<0.001*

*Statistical significant difference. Figure in parentheses are percentage values

were also significantly lower in patients of group B (Cabergoline) than group A (Bromocriptine) ($P<0.001$ and $P=0.011$, respectively).

Regarding the side effects of treatment, Chi² test showed that most of the adverse effects including: nausea ($P<0.001$), vomiting ($P<0.001$) and headache ($P=0.004$) were significantly less in patients who were treated with cabergoline. The only side effect in patients of group B (Cabergoline) was constipation which was not statistically significant ($P=0.883$).

The patients with normal-range prolactin were significantly higher in group B (Cabergoline) than group A (Bromocriptine) ($P=0.001$).

Additionally, pregnancy was significantly more achieved among the women with the treatment of cabergoline (82%) than the ones with bromocriptine (56.4%) ($P<0.001$).

More analysis with Logistic regression model showed that baseline and changes of serum level of prolactin ($P=0.001$ and $P=0.001$), after treatment galactorrhea ($P=0.005$) and after treatment irregular menstruation ($P=0.005$) were the significant variables to predict the achievement of pregnancy among these women ($P<0.001$, $R^2=0.523$).

Discussion

Cabergoline is one of several dopamine agonists that are currently available for the treatment of hyperprolactinemia but data on its exposure in early pregnancy are limited. In this study, pregnancy was occurred in 82 per cent of all infertile women who received cabergoline treatment at the time of study. Moreover, the level of prolactin was decreased to normal

range in 84.3 per cent of these women, and outcome significantly better than the group bromocriptine.

In a similar study by Colao *et al*⁸, 78 per cent of all the pregnancies in women who received cabergoline treatment at the time of conception and/or during pregnancy were followed by deliveries, with 97 per cent of these deliveries being live infants. Seventy-seven per cent of these live deliveries were term deliveries, and 62 per cent of the infants had normal birth weights that were distributed normally within the expected range.

Neonatal abnormalities were recorded for 9 per cent of the infants with no apparent pattern in type or severity. The rate of spontaneous abortions in this population was 9 per cent. This report reanalyses and extends by 154 pregnancies the results of an earlier study⁹.

Our data also confirm the interim analysis reported⁹ with no increase in miscarriage rates. In fact, the incidence of spontaneous abortions following cabergoline induced pregnancies in the study of Colao *et al*⁸ was 9.1 per cent (10.2% in study by Robert *et al*)⁹.

Colao *et al*⁸ also found no increase in the risk of low birth weight (< 2500 g) among infants of women treated with cabergoline prior to or during their pregnancy. The frequency of low-birth weight infants in their study was 6.6 per cent. Previous data from the initial study by Robert *et al*⁹ reported low birth weight in 6.8 per cent of neonates and is consistent with national and international data¹⁰.

However, regarding the mechanisms of their effects, inhibitors of prolactin secretion by the prolactin-producing cells of the anterior pituitary are thought to produce their effects by a direct agonistic

action on dopamine D2 receptors on lactotroph cells¹¹. Bromocriptine has been the most widely used prolactin-lowering agent since its introduction in 1972¹². Bromocriptine is highly effective for normalizing or reducing prolactin levels in hyperprolactinemic patients, and restores normal gonadal function in approximately 70-90 per cent of patients^{13,14}. However, the occurrence of side-effects and the need for two or three daily doses of bromocriptine remain important problems in the long-term management of hyperprolactinemic patients.

New dopaminergic ergoline derivative, cabergoline, has been found to suppress serum prolactin levels in hyperprolactinemic patients and several reports concerning women^{6, 15-18} have been published. But, only a few preclinical experiments have been reported so far. Furthermore, a few investigations have focused on the comparison between bromocriptine and cabergoline.

Our results show the better efficacy of cabergoline both on the pregnancy and lowering the serum level of prolactin. In addition, most of the side effects had significantly a lower incidence among the patients received cabergoline than those who were administered bromocriptine.

One of the limitations of this study is the lack of data on the outcome of pregnancies and our inability to evaluate fetal anomalies.

Our data suggest that cabergoline treatment in infertile women with hyperprolactinemia could lead to a positive impact on pregnancy. Worldwide, cabergoline treatment is considered to be a first-line treatment for hyperprolactinemic disorders because of its high efficacy and excellent tolerability. But more data on the long term safety of cabergoline are needed to be used in women with hyperprolactinemia who want to conceive.

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