Effectiveness of Bromocriptine Monotherapy or Combination Treatment With Clomiphene for Infertility in Women With Galactorrhea and Normal Prolactin: A Systematic Review and Meta-Analysis

Tao Xue, MD; Shang-Wei Li, MD; and Yan Wang, MD
Reproductive Medical Center of West China Second Hospital, Sichuan University, Chengdu, China

ABSTRACT

BACKGROUND: Among women with unexplained infertility, 28% to 55% of patients with galactorrhea are normoprolactinemic. Bromocriptine, a common treatment for infertile women with hyperprolactinemia, has been used in the treatment of unexplained subfertility in women with galactorrhea and normal prolactin; however, its effectiveness and safety profile have never been determined.

OBJECTIVE: The aim of this study was to determine the relative effectiveness and safety profile of bromocriptine monotherapy or as an adjunct to clomiphene citrate in women with galactorrhea and normal prolactin levels.

METHODS: We conducted a search of the Cochrane Subfertility Review Group specialized register of controlled trials (March 2010), CENTRAL (The Cochrane Library, Issue 3, 2010), MEDLINE (1950–March 2010), EMBASE (1980–March 2010), and the China Biological Medicine Database (inception to March 2010) for relevant randomized controlled trials (RCTs) using the following terms: controlled, randomized, blinded, clinical trials, humans, galactorrhea, prolactin, bromocriptine, infertility, and subfertility. Additionally, reference lists of identified articles were searched for relevant articles.

RESULTS: Of the 8 studies identified, 5 were excluded after full-text review for the following reasons: lack of a placebo group (2); difference in cointerventions (1); difference in end points (1); and systematic review (1). Therefore, 3 RCTs were included in this review. Bromocriptine administered in combination with clomiphene was found to be associated with a higher accumulative pregnancy rate compared with clomiphene monotherapy (fixed odds ratio [OR], 5.33; 95% CI, 2.62–10.88), and a lower miscarriage rate (fixed OR, 0.20; 95% CI, 0.05–0.76). Only 1 trial reported live birth as an outcome, and multiple pregnancy rates were poorly reported. Patient-reported adverse effects were mentioned in the studies, but reports were often incomplete.

CONCLUSIONS: This review suggests the effectiveness of bromocriptine with clomiphene for infertility in women with galactorrhea and normal prolactin levels. Further RCTs of adequate power and of high methodologic quality are required.
INTRODUCTION

Infertility is defined as 1 year of unprotected coitus without conception. This is one of the most common reasons women are referred to gynecologic clinical centers. There are ~2.5 million infertile couples in the United States; that is, 10% to 15% of the world’s infertile population. Approximately 40% of infertility is due to female factors (e.g., salpingectomy, uterine malformation) and anovulation constitutes ~40% of all female infertility. Causes of anovulation are divided into 3 categories by the World Health Organization (WHO). Hypothalamic pituitary failure or hypogonadotropic hypogonadism (category 1) accounts for ~10% of ovulatory disorders. Hypothalamic pituitary or eugonadotropic dysfunction (category 2) accounts for ~85% of ovulatory disorders. The remaining 4% to 5% of ovulatory disorders are due to ovarian failure or hypergonadotropic hypogonadism (category 3). Category 2 consists predominantly of women with polycystic ovary syndrome (PCOS) but also may include hyperprolactinemia and women with unexplained anovulation. Here we noticed unexplained subfertility caused by unexplained anovulation of normal prolactin with galactorrhea.

Galactorrhea is a discharge of milk or a milk-like secretion from the breast in the absence of parturition, or beyond 6 months postpartum, in a nonbreastfeeding woman. The pathologic causes of galactorrhea include pituitary tumor, hypothalamic and pituitary stalk lesions, neurogenic stimulation, thyroid disorders, and chronic renal failure. Prolactin is secreted by the anterior pituitary and is a peptide protein hormone that plays an important role in reproduction. Normal prolactin levels are <20 ng/mL and abnormal levels have been found to induce galactorrhea and other adverse effects. Galactorrhea with hyperprolactinemia can lead to luteal phase dysfunction and, as a result, infertility. The main mechanism of action in hyperprolactinemia is the inhibition of pulsatile gonadotropin-releasing hormone (GnRH) secretion, which results in a hypoestrogenic state; galactorrhea is a common result in these cases. Galactorrhea present in a normal level of prolactinemia associated with ovulatory dysfunction may have similar abnormal patterns of pulsatile luteinizing hormone secretion.

The decision to treat patients with galactorrhea is based on the serum prolactin level, the severity of galactorrhea, and the patient’s fertility desires. The United Kingdom National Institute for Clinical Excellence guidelines state that first-line treatment for WHO-defined group 2 anovulation should be clomiphene (or tamoxifen) for up to 12 months. Clomiphene with or without adjunct medication is, at present, the first-line treatment for anovulatory women. Clomiphene is an antiestrogen and competes for receptor binding sites with endogenous estrogens. By blocking receptors in the hypothalamus and pituitary, clomiphene interferes with the feedback mechanism of endogenous estrogen on the pituitary and hypothalamus, resulting in increased follicle-stimulating hormone and luteinizing hormone secretion. Ovarian
hyperstimulation syndrome has been reported rarely following clomiphene use. However, clomiphene resistance (failure to ovulate after taking clomiphene) is common and occurs in ~15% to 40% of women with PCOS. Unexplained anovulation in patients who have galactorrhea with normal prolactin level often remains untreated. Alternative and adjunctive treatments have been sought due to the high incidence of this kind. Bromocriptine, which is used for ovulation induction, has been found to be effective in hyperprolactinemic women.

Bromocriptine is a dopamine agonist used to lower prolactin levels, increase GnRH secretion, and induce ovulation. For this reason, bromocriptine has been studied as an adjunctive treatment to clomiphene for ovulation induction in anovulatory women. It has been reported to induce a return to cyclical ovarian activity in normoprolactinemic women with PCOS. It has been suggested that the presence of normoprolactinemic galactorrhea in patients with ovulatory dysfunction may represent a covert disorder of prolactin-related physiologic factors, and may also respond well to bromocriptine. The effect of treatment with bromocriptine in women with primary or secondary infertility and normal prolactin serum level with galactorrhea has been investigated. An implicit treatment mechanism is currently not very clear; the use of bromocriptine for galactorrhea or luteal phase dysfunction can inhibit galactorrhea and induce ovulation.

Whether bromocriptine has beneficial effects in the ovulatory dysfunction associated with galactorrhea even with normal prolactin levels is not known. We reviewed the available literature in an attempt to establish the effectiveness and safety profile of bromocriptine monotherapy or in combination with clomiphene in ovulation induction on this kind of patient.

Symptoms of patients with ovulatory dysfunction include galactorrhea, irregular menstruation, and infertility. Bromocriptine may be worthwhile for women with unexplained subfertility who also have expressible galactorrhea.

**METHODS**

**Selection Criteria**

We conducted a search of the Cochrane Subfertility Review Group specialized register of controlled trials (March 2010), CENTRAL (The Cochrane Library, Issue 3, 2010), MEDLINE (1950–March 2010), EMBASE (1980–March 2010), and the China Biological Medicine Database (inception to March 2010) for relevant randomized controlled trials (RCTs) using the following exploded (exp) medical subject heading terms: exp (controlled OR randomized, OR blinded AND clinical trials) AND humans AND (galactorrhea and prolactin and bromocriptine) AND (infertility or subfertility). The search strategy was developed by database specialty personnel not associated with the study. Reference lists from pertinent reviews and retrieved articles were also checked to identify additional studies. In addition, we attempted to find data from poster presentations and by consulting several experts in the field.

In the systematic review, the following inclusion criteria were established: each trial should (1) be a prospective clinical RCT; (2) report on bromocriptine monotherapy or with adjuncts; (3) enroll women with unexplained subfertility and galactorrhea.
with normal prolactin levels; (4) be a randomized comparison of bromocriptine versus
placebo or blank control, regardless of the initial time of treatment, treatment dura-
tion, dose and administration route of the drug; and (5) report concomitant inter­-
ventions (including treating complications) if administered equally to all intervention
groups. Two reviewers (T.X. and Y.W.), who worked independently, used these criteria
to review each article identified.

A study was excluded if: (1) it was quasi randomized or nonrandomized; (2) patients
with hyperprolactinemic infertility, breast disease, or conditions not suitable for bro-
ocriptine were excluded; (3) the patients used metformin or other insulin-sensitizing
agents; (4) there were differences in the concomitant interventions between study groups;
(5) the report was repetitive (if > 1 version of the same study was retrieved, only the
most recent was used).

DATA EXTRACTION

The two reviewers applied the eligibility criteria and assessed trial quality indepen­
dently. Inconsistencies between reviewers’ data were resolved through discussion until
a consensus was reached. Each RCT was scored for quality to assess validity using the
Jadad Quality Score system. If the score of a study was > 3, it was considered a high-
quality study. The extracted data included characteristics of the trial, patients, inter­
ventions, and outcomes. The primary outcome was pregnancy rate; secondary out­
comes were ovulation, miscarriage, and patient-reported adverse events (AEs).

QUALITY ASSESSMENT

Trials were screened and analyzed for the following quality criteria: (1) method and
timing of randomization: randomized (eg, by computer, random number tables, or
drawing lots), quasi-randomized (eg, hospital number, date of birth), unclear (eg, ran­
domization claimed but not further described); (2) concealment of allocation: adequate
(eg, third party, sealed opaque envelopes), inadequate (eg, open list of allocation
codes), unclear (eg, not stated, or ‘envelope method’ stated without further descrip­
tion); (3) study blinding; (4) whether an intent-to-treat analysis was performed; and
(5) whether a power calculation was conducted a priori. Trials rated as quasi-random­
ized were excluded from this review.

STATISTICAL ANALYSIS

Meta-analysis was performed according to recommendations from The Cochrane
Collaboration and the quality of reporting of meta-analyses guidelines. The effect
measures estimated were odds ratio (OR) for dichotomous data and weighted mean
difference for continuous data, both reported with 95% CIs. The OR represented the
odds of an AE occurring in the bromocriptine group versus the comparator. An OR
of < 1 favored the latter group. The point estimate of the OR was considered statisti­
cally significant at P < 0.05 if the 95% CI did not include the value 1.

Studies that contained a zero in 1 cell for the number of events of interest in 1 of
the 2 groups resulted in problems with the computation of ratio measurement; there­
fore, on the recommendation of a statistician, a value of 0.5 was added in both groups
for those studies. Heterogeneity between the results of different trials was examined by inspecting the scatter of data points on a graph and the overlap in their CIs and, more formally, by a $\chi^2$ test. $P < 0.1$ was considered statistically significant in regard to heterogeneity. Fixed-effects models were used throughout, unless statistical heterogeneity was significant, in which case a random-effects model was used. Analysis was performed using the statistical software Intercooled Stata version 8.2 (Stata Corp, College Station, Texas) and Review Manager version 4.2 (The Cochrane Collaboration, Oxford, United Kingdom).

If a clinically important difference in drug regimen (outside of normal clinical practice) had occurred between trials an attempt to form dose subgroups for analysis would have been made.

**RESULTS**

The search strategy initially generated 8 studies (Figure 1); no further studies were found beyond the database search. After full-text review, 5 trials were excluded: 2 did not consider a placebo group; 1 had a difference in cointerventions between treatment groups; 1 was a systematic review; and 1 had differing end points. Therefore, 3 RCTs were identified that satisfied all of the inclusion criteria for this review (Table I and Table II).

![Figure 1. Identification of eligible randomized controlled trials. CBM = China Biological Medicine Database.](image-url)
Table I. Randomized controlled trials of bromocriptine treatment with or without clomiphene in infertile women with galactorrhea and normal prolactin levels.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Method</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Notes</th>
<th>Allocation Concealment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akhlaghi and Hamedi²²</td>
<td>Randomized controlled trial</td>
<td>44</td>
<td>Clomiphene (100 mg/d from the 5th through the 9th days of the menstrual cycle) with bromocriptine (2.5 mg BID for 3 months) or bromocriptine monotherapy</td>
<td>Regular menstrual cycle resumed in 68.2% of clomiphene users and 50.0% of bromocriptine users</td>
<td>Pregnancy rates were 40.0% and 22.7%, respectively</td>
<td>Adequate</td>
</tr>
<tr>
<td>Anzhen and Liang²³</td>
<td>Randomized controlled trial</td>
<td>53</td>
<td>Clomiphene (50 mg/d from the 5th through the 9th days of the menstrual cycle) with bromocriptine (1.25 mg/d for 3 months) or bromocriptine monotherapy</td>
<td>Pregnancy rates were 74.1% and 34.6%, respectively</td>
<td>Adequate</td>
<td></td>
</tr>
<tr>
<td>Haixia²⁴</td>
<td>Randomized controlled trial</td>
<td>57</td>
<td>Clomiphene (50–100 mg/d from the 5th through the 9th days of the menstrual cycle) with bromocriptine (2.5–5 mg/d for 3 months) or bromocriptine monotherapy</td>
<td>Pregnancy rates were 85.2% and 33.3%, respectively</td>
<td>Adequate</td>
<td></td>
</tr>
</tbody>
</table>
Table II. Jadad Quality Score\textsuperscript{16} of randomized controlled trials included in the meta-analysis.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year of Publication</th>
<th>Randomization</th>
<th>Withdrawals/Jadad Blinding</th>
<th>Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akhlaghi and Hamedi\textsuperscript{22}</td>
<td>2004</td>
<td>Centralized randomization schedule</td>
<td>Only mentioned/double-blind</td>
<td>5</td>
</tr>
<tr>
<td>Anzhen and Liang\textsuperscript{23}</td>
<td>2006</td>
<td>Randomization mentioned, but method not specified</td>
<td>No withdrawals/double-blind</td>
<td>4</td>
</tr>
<tr>
<td>Haixia\textsuperscript{24}</td>
<td>2002</td>
<td>Randomization mentioned, but method not specified</td>
<td>No withdrawals/blinding unclear</td>
<td>3</td>
</tr>
</tbody>
</table>

\textbf{Included Studies}

No RCTs were found for the following interventions: bromocriptine monotherapy versus placebo and bromocriptine monotherapy versus clomiphene monotherapy. Three RCTs compared bromocriptine plus clomiphene versus bromocriptine monotherapy (Table I).

The study by Akhlagi and Hamedi\textsuperscript{22} was an RCT of 44 women with galactorrhea, normal serum prolactin and dehydroepiandrosterone sulfate levels, normal coned-down view (in the radiographic evaluation of sella turcica), normal hysterosalpingogram, normal spermiogram, and a failure to ovulate. Patients were administered a high dose of clomiphene citrate (100 mg/d from the 5th through the 9th days of the menstrual cycle) or bromocriptine (2.5 mg BID for 3 months). Regular menstrual cycles resumed in 68.2\% of the clomiphene group and 50.0\% of the second group. The pregnancy rates were 40.0\% and 22.7\%, respectively. No AEs were reported.

Anzhen and Liang\textsuperscript{23} conducted an RCT in 53 patients with galactorrhea, normal serum prolactin, normal hysterosalpingogram, and normal spermiogram. Patients received clomiphene (50 mg/d from the 5th through the 9th days of the menstrual cycle) or bromocriptine (1.25 mg/d for 3 months). Pregnancy rates were 74.1\% and 34.6\%, respectively. No AEs were reported.

The study by Haixia\textsuperscript{24} was an RCT in 57 patients with galactorrhea and normal serum prolactin. Depending on other etiologic factors, patients received clomiphene (50–100 mg/d from the 5th through the 9th days of the menstrual cycle) and/or bromocriptine (2.5–5 mg/d for 3 months). Pregnancy rates were 85.2\% and 33.3\%, respectively.

\textbf{Outcomes}

All 3 included trials reported pregnancy rate; 2 reported miscarriage rate.\textsuperscript{23,24} Live birth was reported in 1 trial.\textsuperscript{24} Patient-reported AEs were mentioned in studies but reports were often incomplete.
Primary Outcome

Pregnancy rate analysis suggested a large and consistent benefit of bromocriptine plus clomiphene (154 patients; fixed OR = 5.33; 95% CI, 2.62–10.88) (Figure 2).

Secondary Outcomes

Miscarriage rate analysis suggested lower incidence in the bromocriptine plus clomiphene group (62 patients; fixed OR = 0.20; 95% CI, 0.05–0.76) (Figure 3). Ovulation rates were not reported. Patient-reported AEs were so poorly reported in the trials that we were unable to analyze them.

Publication Bias

Publication bias was assessed for all pooled ORs with 95% CIs using the Begg test. The results presented the treatment effects estimated from individual studies plotted on the horizontal axis (OR) against the SE of the estimate shown on the vertical axis (SE [log OR]). All of the studies lay within the 95% CI and were uniformly distributed around the vertical axis, suggesting a low likelihood of publication bias.

Discussion

This review shows some evidence supporting the effectiveness of the current first-line treatment in this kind of patient, clomiphene citrate in combination with bromocriptine.

In infertile patients with galactorrhea and normal prolactin levels, application of low-dose bromocriptine for ovulation-induction treatment may improve pregnancy rates and lower miscarriage rates. However, the published evidence is limited. This review included only 3 trials with a total of 154 participants. The inclusion and exclusion criteria were dissimilar, there was discordance among the heterogeneity of the study populations, and differences in experimental design.

Most previous studies focused on prolactin serum levels rather than galactorrhea. It was found that infertile patients with galactorrhea and normal prolactin levels had a significant response to bromocriptine treatment. This suggests that galactorrhea should be assessed by obstetricians and gynecologists in infertile patients. And, in cases positive for galactorrhea, treatment with bromocriptine should be initiated and followed up for ≥6 months before any other evaluations and treatments. Clomiphene is now widely accepted as an effective treatment but further trials on bromocriptine alone or in combination with clomiphene citrate should be conducted.

Limitations

All of the trials included in this review had methodologic flaws, which weakens the results found. More rigorous RCTs are required for all the interventions. Live birth rate is the gold standard in primary outcome for RCTs of this nature, and only 1 of the trials reported this and follow-up to delivery was not complete.

RCTs of the treatments, such as bromocriptine monotherapy or as an adjunct, for unexplained subfertility in women with galactorrhea but normal prolactin levels that are adequately powered and of high methodologic quality are needed.
Figure 2. Forest plot of pregnancy rates in infertile women with galactorrhea and normal prolactin levels taking bromocriptine monotherapy or in combination with clomiphene. OR = odds ratio.
### Table 1: Forest plot of miscarriage rates in infertile women with galactorrhea and normal prolactin levels taking bromocriptine monotherapy or in combination with clomiphene.

<table>
<thead>
<tr>
<th>Study</th>
<th>Bromocriptine and Clomiphene, n/N</th>
<th>Bromocriptine Monotherapy, n/N</th>
<th>OR (fixed) 95% CI</th>
<th>Weight, %</th>
<th>OR (fixed) 95% CI</th>
<th>Year</th>
<th>Jadad Quality Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haixia\textsuperscript{24}</td>
<td>6/20</td>
<td>5/9</td>
<td>0.34 (0.07–1.74)</td>
<td>50.67</td>
<td>2002</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Anzhen and Liang\textsuperscript{23}</td>
<td>0/23</td>
<td>3/10</td>
<td>0.05 (0.00–0.99)</td>
<td>49.33</td>
<td>2006</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>43/23</td>
<td>19</td>
<td>0.20 (0.05–0.76)</td>
<td>100.00</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 6 (bromocriptine and clomiphene), 8 (bromocriptine)

Test for heterogeneity: $\chi^2 = 1.32, df = 1 (P = 0.25)$, $I^2 = 24.1$

Test for overall effects: $z = 2.36 (P = 0.02)$

---

**Figure 3.** Forest plot of miscarriage rates in infertile women with galactorrhea and normal prolactin levels taking bromocriptine monotherapy or in combination with clomiphene. OR = odds ratio.
CONCLUSIONS

Bromocriptine taken concomitantly with clomiphene might be effective in increasing accumulative pregnancy rates and lowering miscarriage rates of infertility in women with galactorrhea and normal prolactin levels. Further studies are needed to confirm these results.

ACKNOWLEDGMENTS

The authors wish to thank Wen Jin, MD, for his help in developing the search strategy. The authors have indicated that they have no conflicts of interest regarding the content of this article.

Dr. Li wrote the initial version of the protocol and commented on drafts of the review. Dr. Xue performed the primary literature search, initial assessment of trials and quality analysis, data collection and analysis, and wrote the initial draft of the review. Dr. Wang checked the literature search, reviewed quality analysis and data collection, checked and revised the initial draft of the review, and provided clinical input for the review.

REFERENCES


**Address Correspondence to:** Li Shang-Wei, MD, Reproductive Medical Center of West China Second Hospital, Sichuan University, Chengdu, 610041 China. E-mail: lishangwei_huaxi@yahoo.cn