

# Use of Bromocriptine in Mildly Hyperprolactinemic Women with Follicular Maturation Defects

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## *Abstract*

By means of pelvic ultrasonography to determine follicular maturation, the effects of bromocriptine 2.5 mg/day until conception were assessed in 23 women with luteal phase defects, mild hyperprolactinemia, and immature follicles (Group 1); 6 women with good estrogen levels and hyperprolactinemia (Group 2); and 10 women with normal follicular maturation and abnormal luteal phase (Group 3). Luteal phase defects were corrected in 20 of the 23 patients in Group 1, and 11 conceived (55%); in Group 2, infertility was corrected in 5 of the 6 patients, all of whom achieved pregnancy; in Group 3, 1 patient achieved pregnancy. It is concluded that with proper patient selection bromocriptine is effective in patients with infertility due to luteal phase defects and follicular immaturity even in the presence of only mildly elevated prolactin levels.

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**Keywords:** infertility; luteal phase defects; follicular immaturity; bromocriptine; hyperprolactinemia; prolactin

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## *Introduction*

In prudent medical practice one tries to choose the least risky, least expensive, and least complicated therapy that will accomplish the desired effect. There is little question that if pregnancy is desired, most physicians would use bromocriptine in a patient who is anovulatory and has elevated prolactin, low gonadotropin levels, and low estradiol, whether or not there is evidence of a pituitary micro- or macroadenoma.<sup>1</sup>

Clomiphene citrate would not be used in such situations because it would be ineffective in the presence of estrogen deficiency. Though human menopausal gonadotropins (HMG) could also induce ovulation, the risk of multiple births and the hyperstimulation associated with HMG, together with its expense, suggest that bromocriptine would be the better choice.

However, the role of bromocriptine in ovulation problems other than hypogonadotropic hypogonadism secondary to hyperprolactinemia is more debatable. For example, a recent study suggests that reducing the prolactin level concomitantly does not improve the response to HMG in a woman who has failed to conceive on bromocriptine alone.<sup>2</sup>

In women with luteal phase defects, progesterone alone may prove unsuccessful unless it can be demonstrated that mature follicles are being produced.

We recently described a method for determining the proper treatment of luteal phase defects with the use of pelvic sonography to determine the degree of follicular maturation, defining a size of 18 to 24 mm as mature.<sup>3</sup> We have also found that, in addition to size as a criterion for follicular maturation, a serum estradiol level of 200 to 500 pg/ml is necessary, and that some patients with mature-sized follicles fail to generate adequate serum estradiol levels. Followup ultrasonography to determine ovum release is also done in these patients.<sup>4</sup>

Based on our work in assessing follicular maturation, we designed the present study to determine the efficacy of bromocriptine in correcting abnormalities in luteal phase, estradiol level, follicular maturation, and ovum release in a series of patients. The effectiveness of this drug was also evaluated in patients who had anovulatory states in the presence of normal estrogen.

## *Patients and Methods*

Consecutive patients presenting for treatment, who had either a luteal phase defect or anovulation, were selected for the study. Patients were included in the study if their prolactin level ranged from 2 ng/ml below the upper limit of normal for the assay used, up to a value of 59 ng/ml. Maximum normal level in several assays used ranged from 18 to 25 ng/ml, with most assays having an upper limit of normal of 25 ng/ml. Very slight hyperprolactinemia was defined as within 2 ng/ml below or above the top normal level for the assay; slight

hyperprolactinemia as a range from 2 ng/ml above top normal value up to a value of 30 ng/ml; mild as levels from 31 to 40 ng/ml; and moderate as levels from 41 to 60 ng/ml.

Patients with associated infertility problems such as cervical factor or male factor problems (except very poor sperm quality) or slight adhesions were not excluded from the study, but those with tubal adhesions or very severe adhesive disease were excluded. This patient group was also mixed in terms of previous infertility therapy, and did not necessarily fail on other treatment.

Each patient was evaluated initially by serial pelvic ultrasound studies and serum estradiol and progesterone assays. A follicle was considered mature (versus premature or postmature) if the size of the dominant follicle was between 18 and 24 mm. Patients who met the study criteria started bromocriptine therapy with one-half of a 2.5-mg tablet with meals each night for the first three nights, then one 2.5-mg tablet with meals each night (to avoid nausea) until pregnancy occurred, or for a six-month trial.

### Results

The 39 patients included in the study were distributed according to three categories:

1. *Patients with luteal phase defects, mild hyperprolactinemia, and immature follicles.*

A total of 23 patients were evaluated. In 20 patients, bromocriptine corrected the follicular immaturity, promoting the formation of a mature follicle and increasing serum estradiol to  $\geq 200$  pg/ml. Eleven of the 20 (55%) conceived within six months of starting bromocriptine therapy. Three of the 11 women who conceived had first-trimester spontaneous abortions. Table 1 delineates the relationship between prolactin status and conception in the group.

Table 1 — Prolactin status and number of pregnancies among women in Group 1\* for whom follicular immaturity was corrected (n=20)

	Degree of Hyperprolactinemia			
	Very Slight	Slight	Mild	Moderate
No. of Patients	3	6	5	6
No. Pregnant	1	4	3	3

\* Patients with luteal phase defects, mild hyperprolactinemia, and immature follicles.

2. *Anovulatory patients with good estrogen and hyperprolactinemia.*

Of the six women in this group, five achieved pregnancy within six months after starting bromocriptine therapy. Included in the successful group were two women with mild and three with moderate hyperprolactinemia. The woman who failed to conceive had mild hyperprolactinemia.

3. *Hyperprolactinemic patients with normal follicular maturation and abnormal luteal phase.*

The prolactin levels in this group were not statistically different from those in the other groups. One of the ten patients in this group became pregnant after bromocriptine treatment. This patient had mild hyperprolactinemia and had been able to conceive in the past, but had suffered three spontaneous abortions. Therefore, in this case we felt obligated to add progesterone in the luteal phase to preserve the pregnancy.

In three of the patients in this group, including the patient who achieved pregnancy, endometrial biopsy demonstrated that bromocriptine alone had corrected the luteal phase defect.

*Associated Infertility Problems*

The three groups were well matched in terms of associated infertility problems (Table 2). Associated problems occurred in 7 of the 23 patients in Group 1 (35%), 2 of 6 in Group 2 (33.3%), and 3 of 10 in Group 3 (30%). In Group 3, two of the associated abnormalities occurred in women in whom bromocriptine had corrected the luteal phase defect.

Table 2 — *Associated infertility problems*

	Group 1 (luteal phase defects, mild hyper- prolactinemia and immature follicles)	Group 2 (anovulation, hyper- prolactinemia, and good estrogen)	Group 3 (hyperprolactinemia, normal follicular maturation, abnormal luteal phase)
Problem	No. (% of Group 1)	No. (% of Group 2)	No. (% of Group 3)
Cervical Factor	4 (17)	2 (33.3)	1 (10)
Male Factor	1 (4)	—	1 (10)
Adhesions	2 (9)	—	1 (1)
Total	7 (30)	2 (33.3)	3 (30)

*Discussion*

This study clearly demonstrates that bromocriptine can benefit many patients with luteal phase defects, follicular immaturity, and prolactin levels ranging from very slightly elevated to moderately elevated. The study also indicates the importance of patient selection and of evaluating the status of the endometrium and the follicle both before and during therapy.

When good estrogen levels coexist with ovulatory dysfunction, hyperprolactinemia, if present, is usually mild. However, hyperprolactinemia has been found in some patients with luteal phase defects.<sup>5,6</sup> Muhlenstedt<sup>6</sup>

reported slightly elevated prolactin levels in 70% of patients with a short luteal phase. Delvoye<sup>7</sup> demonstrated an inhibitory effect of elevated prolactin on luteal phase in normally menstruating women. Both Muhlenstedt<sup>6</sup> and Del Pozo<sup>8</sup> reported improved fertility after bromocriptine treatment in women who had luteal phase defects and slightly elevated prolactins.

In anovulatory states associated with good estrogen levels and mild hyperprolactinemia, some debate might arise regarding a choice between clomiphene citrate and bromocriptine. While the duration of therapy is shorter with clomiphene, its adverse effect on the cervical mucus is a major drawback, especially when borderline normal or slightly subfertile sperm quality are present.

Some authors have suggested the possibility of a placebo effect with bromocriptine.<sup>9</sup> However, normoprolactinemic women who conceived on bromocriptine in our previous series had been treated with other fertility drugs with no "placebo" effect.<sup>10</sup> Further, there is evidence that, in cases of very slight hyperprolactinemia or even euprolactinemia, bromocriptine may induce ovulation by directly stimulating dopaminergic receptors of the gonad<sup>11</sup> or the pituitary.<sup>12</sup> Moreover, the potential for bromocriptine to maintain hospitable cervical mucus, even in cases where oligospermia or asthenospermia are part of the problem, has been demonstrated.<sup>13</sup>

Criteria for hyperprolactinemia vary; there is no true marker for defining a normal prolactin level in an individual woman. If, for example, a woman has a prolactin level of 5 to 6 ng/ml for many years and suddenly develops a level of 19 ng/ml, her prolactin can be considered elevated even if it still falls within the normal range for a particular laboratory.

Our previous study<sup>10</sup> demonstrated the efficacy of bromocriptine in women with normoprolactinemia and either abnormal endometrial biopsies (indicating luteal phase defects) or mild ovulatory defects. These patients had failed to conceive on either clomiphene citrate or progesterone. Although we did not monitor follicular maturation in that study, we suspect that the successful pregnancies may have resulted from the fact that bromocriptine corrected follicular maturation as well as endometrial problems.

The present study evaluated the effect of bromocriptine in 23 women with luteal phase defects and poor follicular maturation as defined by ultrasound and estradiol levels. These patients were not necessarily failures on other fertility drugs. Furthermore, less than a third of the 20 patients in whom bromocriptine corrected follicular problems had moderate hyperprolactinemia. Yet 11 of the 20, or 55%, conceived within six months of starting bromocriptine therapy.

The three spontaneous abortions in this group occurred in women whose luteal phase defects had been corrected by bromocriptine. Because we were assessing the effect of bromocriptine alone in this group, we did not add

progesterone to the regimen. In these three cases, endometrial biopsies might have shown that, although the follicle had been corrected, addition of progesterone would have corrected the endometrial defect which was still present. Progesterone might also be added prophylactically in such cases to prevent luteal phase defects associated with subnormal prolactin levels. One would then follow up with endometrial biopsy to maintain the correct progesterone dosage.

In the group with anovulation and good estrogen, two women who conceived after bromocriptine had mild and three moderate hyperprolactinemia, an expected result. Cases of anovulation and very slight hyperprolactinemia may not respond to bromocriptine since they frequently have other problems such as polycystic ovaries.

Although only one of ten patients with hyperprolactinemia, abnormal luteal phase, and normal follicular maturation conceived on bromocriptine, we would not totally rule out a trial on the drug in such cases. If a patient has normal follicles with a progesterone deficiency in the second half of the cycle, she might benefit from an initial trial on progesterone alone. If results were poor, bromocriptine might then be added to the progesterone regimen. Indeed, a patient described in our previous study<sup>10</sup> conceived on bromocriptine after a diagnosis of anovulation with poor mucus. The pregnancy was maintained successfully with the addition of progesterone suppositories.

It should be noted that the patients in the present study had numerous associated infertility problems, including male factor, cervical factor, endometriosis, and tubal problems. Despite these additional difficulties, we achieved a gratifying success rate.

The central issue, we believe, is patient selection. Selecting a large number of cases with, for example, significant ovulatory dysfunction might perhaps demonstrate that a particular drug, such as bromocriptine, would not produce a large percentage of pregnancies. If patients have ovulatory defects, immature follicles, and prolactins at either borderline or upper normal levels, we would try clomiphene citrate first. In similar cases with poor mucus (which inhibits linear sperm movement) and a semen problem we have achieved very good results using bromocriptine, which corrects poor mucus (in contrast to clomiphene citrate, which does not correct such problems), together with a split ejaculate insemination technique.<sup>13</sup>

On the other hand, in a patient with mild hyperprolactinemia, normal follicular maturation and ovum release, and only a mild luteal phase defect, we might lean toward progesterone alone. If, however, the latter patient had improper follicular maturation, bromocriptine would be a clear first choice. Indeed, the present study showed that luteal phase defects were corrected in 20 of 23 such cases.

Certainly, in cases of poor follicular maturation there is a choice of fertility agents. However, HMG, which would likely be effective, is very expensive and

adds the risk of multiple births and hyperstimulation syndrome. Although clomiphene citrate could be another first choice, our series showed that bromocriptine corrected the abnormality in 20 of 23 cases, with 11 conceptions. The addition of progesterone would probably have improved the statistics considerably.

While the present study should be viewed as preliminary, it provides enough data to suggest a larger-scale blinded study of patients with follicular immaturity, to compare the effects of bromocriptine, bromocriptine plus progesterone, progesterone alone, and placebo. Nevertheless, these initial data suggest that, with proper patient selection, bromocriptine can be effective in a significant number of patients with prolactin levels ranging from very slightly to moderately elevated, and who also have follicular maturation problems with luteal phase defects.

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