

# Bromocriptine Versus Progesterone Therapy for Infertility Related to Luteal Phase Defects in Hyperprolactinemic Patients

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**ABSTRACT:** Several anecdotal reports suggested an association of luteal phase defects (LPD) and hyperprolactinemia. Some physicians treat LPD with ovulation-inducing drugs, whereas others recommend progesterone support of the luteal phase. A study was thus initiated to evaluate in cases of LPD associated with hyperprolactinemia which therapy would be more efficacious—bromocriptine or progesterone (P). LPD was divided into two types based on follicle dynamic studies: (1) LPD associated with immature follicles and (2) pure LPD when the follicle was mature. The objective was to determine if P or bromocriptine would be more effective depending on the type of LPD. Randomized therapy with either bromocriptine (BCT) or progesterone vaginal suppositories (PVS) was given to 60 patients with pure LPD (established by endometrial biopsy in the late luteal phase) and similarly randomized therapy was given to 40 women with LPD and immature follicles. The incidence of pregnancies during an 8-month treatment period was as follows: pure LPD—23 of 50 women (77%) treated by PVS versus 5 of 30 women (17%) treated by BCT; LPD associated with immature follicles—3 of 20 women (15%) treated by PVS versus 14 of 20 women (70%) treated by BCT. Those women failing to conceive were now given the alternate therapy for the next 8 months. The pregnancies achieved were as follows: pure LPD—only 1 of 7 women (14%) who failed to conceive with PVS now conceived with BCT; but 20 of 25 women (80%) who failed with BCT now conceived with PVS; those with immature follicles—10 of 17 who failed with PVS now conceived with BCT; 1 of 6 who failed with BCT now conceived with PVS. The results suggest that both PVS and BCT can help establish pregnancies in hyperprolactinemic patients with LPD, but PVS is more effective when the follicle is mature and BCT more effective in LPD associated with immature follicles.

## INTRODUCTION

**T**HERE HAVE BEEN SEVERAL ANECDOTAL reports suggesting an association of luteal phase defects and hyperprolactinemia.<sup>1,2</sup> Some physicians treat LPD with ovulation-inducing

drugs,<sup>3-6</sup> whereas others recommend progesterone support of the luteal phase.<sup>7-9</sup> A study was thus initiated to evaluate in cases of LPD associated with hyperprolactinemia which therapy would be more efficacious—bromocriptine or progesterone.

We have previously demonstrated the importance of follicular maturation studies in determining the most effective therapy for LPD.<sup>10</sup> We divided these hyperprolactinemic patients into two categories, (1) LPD associated with immature follicles and (2) pure LPD (where the follicle was deemed mature), and attempted to determine whether progesterone vaginal suppositories (PVS) or bromocriptine was more effective for the two different types of LPD.

## PATIENTS AND METHODS

Therapy with either bromocriptine or PVS was randomized in 60 hyperprolactinemic patients with pure LPD according to the last digit of their social security number (evens receiving PVS, odds, bromocriptine). Similarly, 40 hyperprolactinemic patients with LPD and immature follicles had randomized therapy with PVS or bromocriptine. After 8 months, those patients not conceiving on their first therapy were now given the alternate therapy for another 8 months.

All patients were required to have a minimum of one year of infertility. All other infertility factors had to be deemed normal; that is, the sperm count was required to be a minimum of  $20 \times 10^6/\text{cc}$  with 60% motility—grade 3 of 4 motility quality—with 60% normal morphology. The postcoital test 8–10 hours after intercourse was required to show at least 5 sperm/high-power field with linear progressive motion. Tubal patency by hysterosalpingogram and/or laparoscopy was also a prerequisite.

A follicle was deemed mature if it attained a diameter of 18–24 mm and was associated with a serum estradiol level of at least 200 pg/mL. These measurements, though somewhat arbitrary, were established by evaluating over 1,000 cycles in fertile women. Patients with the luteinized unruptured follicle syndrome,<sup>11–13</sup> as evidenced by a follicle enlarging in size but associated with a drop in the

serum estradiol and a rise of the serum progesterone above 1.2 ng/mL in association with regression of the cervical mucus, were eliminated from this study.

The diagnosis of LPD was established by endometrial biopsies and dated according to Noyes et al.<sup>14</sup> The biopsy was performed in the late luteal phase and was dated according to the number of days from the biopsy to the onset of the succeeding menses. A biopsy that dated more than two days out of phase in both cycles was considered abnormal. The PVS treatment was started at 25 mg twice a day after the release of the ovum from the follicle as determined by pelvic sonography two or three days after the follicle was deemed mature. A repeat endometrial biopsy was performed, and was dated from the time of ovulation, since the PVS would delay the next menses. The biopsy was also repeated in patients treated with bromocriptine to see if this corrected the biopsy; and, if abnormal, the PVS was increased by 25 mg per day in the next cycle if the biopsy was out of phase until the biopsy finally dated appropriately.

Bromocriptine was started at 2.5 mg daily. If after a minimum of 30 days of therapy a mature follicle was not achieved, the dosage was increased to 2.5 mg twice a day.

A minimum prolactin level of 26 ng/mL was required for a diagnosis of hyperprolactinemia. All levels were obtained fasting in the morning during the follicular phase.

## RESULTS

### Study 1: Hyperprolactinemic Patients with Pure LPD

There were 23 pregnancies during 8 treatment cycles in the 30 women treated with PVS (77%), as compared with only 5 pregnancies in the 30 women

**TABLE I**  
**Study 1: Hyperprolactinemic patients with pure luteal phase defects.\***

No. of Patients	Treatment	No. of Pregnancies in 8 Months	1st-Trimester Abortions
30	Progesterone vaginal suppositories	23 (77%)	2 (8.7%)
30	Bromocriptine	5 (17%)	2 (40%)

\*Endometrial biopsy out of phase by more than 2 days; follicle size attained a minimum diameter of 18 mm associated with a serum estradiol ( $E_2$ ) level over 200 pg/mL.

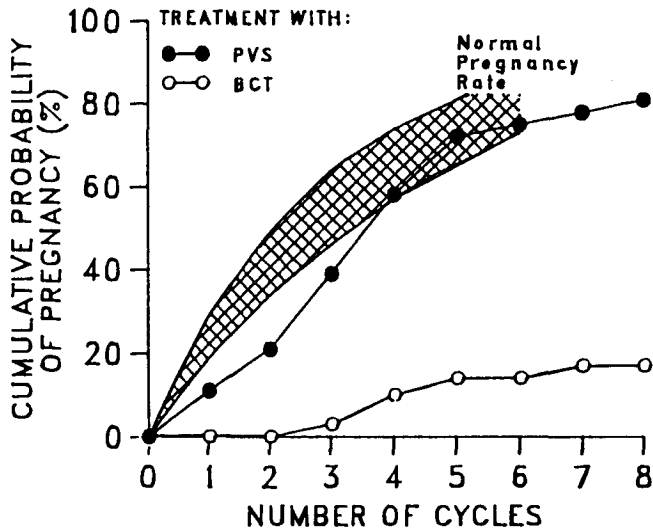


FIG. 1: Increased prolactin with pure luteal phase defect. The cumulative probability of pregnancy in patients with pure LPD treated by PVS approached the normal pregnancy rate, whereas the pregnancy rate in those treated with bromocriptine was far below the normal rate. BCT = bromocriptine.

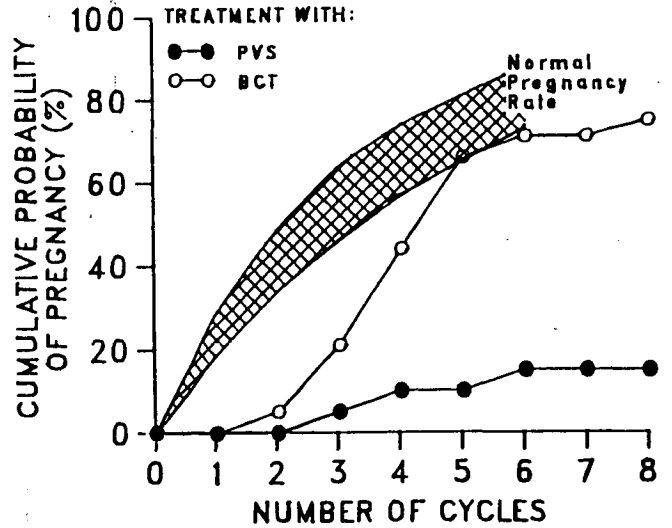


FIG. 2: Luteal phase defect associated with immature follicle and elevated prolactin. After a delay, the cumulative probability of pregnancy approached the normal pregnancy rate at 5 months in women treated with bromocriptine. Women treated with progesterone had pregnancy rates well below normal. BCT = bromocriptine.

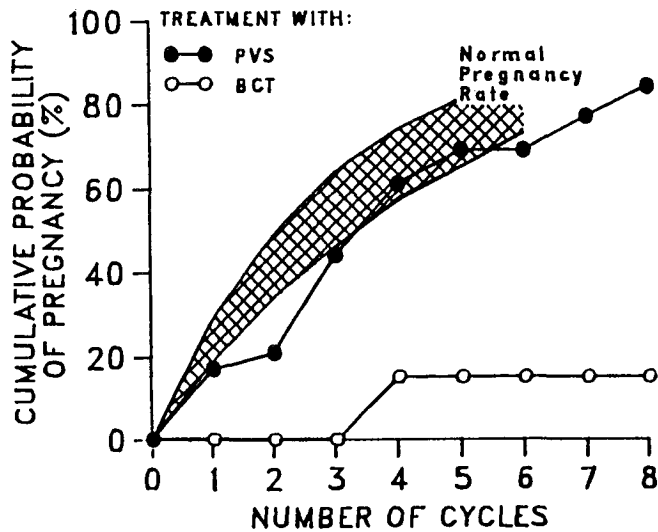


FIG. 3: Increased prolactin with pure luteal phase defect — cross-over study. Despite failing to conceive during the first 6 months with bromocriptine (BCT), women with pure LPD treated with PVS had a cumulative probability of pregnancy that approached normal. The pregnancy rate was poor for the next 6 months in those patients treated with BCT who had failed to conceive during the first 6 months with PVS.

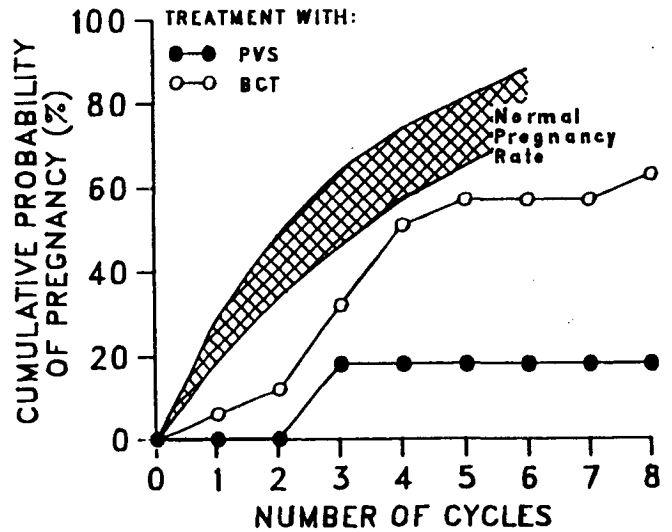


FIG. 4: Luteal phase defect associated with immature follicle and elevated prolactin — cross-over study. Patients with immature follicles and LPD who failed to conceive during the first 6 months with PVS did better with bromocriptine (BCT), but the cumulative probability of pregnancy did not quite reach the normal pregnancy rate. PVS was not effective during the second 6 months in those who had previously failed with BCT.

**TABLE II**  
**Patients with pure LPD—all follicles mature—first 8 months.**

	Treatment: Progesterone Vaginal Suppositories	Results	
		Pregnant	Aborting
Endometrial biopsy corrected	30	23 (77%)	2 (8.7%)
Inadequately corrected endometrial biopsy	0	0	0
<i>Bromocriptine</i>			
Endometrial biopsy corrected	6	4 (67%)	1 (25%)
Inadequately corrected endometrial biopsy	24	1 (4.2%)	1 (100%)

(17%) treated with bromocriptine. Chi-square analysis showed  $P < .001$  (see Table I). Life-table analysis comparing cumulative probabilities of pregnancy and further comparing them to normal pregnancy rates is seen in Figure 1.<sup>15</sup> There were only two first-trimester abortions in the 23 pregnancies achieved with PVS (8.7%), as compared with 2 of 5 losses in those treated with bromocriptine (40%). PVS corrected the endometrial biopsy in all cases, but the dosage had to be increased in 10 cases, whereas bromocriptine seemingly corrected the endometrial biopsy in 6 cases (20%). Four of the five women who conceived were in the group in which the biopsy was corrected (see Table II).

### Study 2: Hyperprolactinemic Patients with Immature Follicles and LPD

There was a total of 3 pregnancies out of 20 (15%) in

women treated with PVS, compared with 14 of 20 (70%) in women treated with bromocriptine (see Table III). Chi-square analysis showed  $P < .005$ . Life-table analysis comparing cumulative probabilities of pregnancy and further comparing them with normal pregnancy rates is seen in Figure 2. None of the three PVS pregnancies were aborted, whereas two were aborted (14%) in those treated with bromocriptine. PVS corrected the endometrial biopsy in all cases, but 12 of 20 (60%) required a dosage greater than 50 mg/day, whereas bromocriptine corrected the endometrial biopsy in 12 of the 20 cases (60%). Eleven of the pregnancies occurred in the group with the corrected endometrial biopsies; one spontaneous abortion occurred in this group (9%), compared with one loss in three (33%) among those conceiving with an uncorrected biopsy. Bromocriptine corrected follicular maturation in 17 of 20 cases (85%), and all 14 pregnancies occurred in women whose follicles were now mature (see Table IV).

**TABLE III**  
**Study 2: Hyperprolactinemic patients with Immature follicles\* and LPD.**

No. of Patients	Treatment	No. of Pregnancies in 8 Months	1st-Trimester Abortions
20	Progesterone vaginal suppositories	3 (15%)	0
20	Bromocriptine	14 (70%)	2 (14%)

\*Size <18 mm or serum estradiol <200 pg/mL.

**TABLE IV**  
**Patients with Immature follicles and LPD—first 8 months.**

	Treatment: Progesterone Vaginal Suppositories	Results	
		Pregnant	Aborting
Follicular maturation corrected	30	23 (77%)	2 (8.7%)
Inadequate follicular maturation	0	0	0
<i>Bromocriptine</i>			
Follicular maturation corrected—biopsy also corrected	12	11 (92%)	1 (9%)
Follicular maturation corrected—biopsy not corrected	5	3 (60%)	1 (33%)
Inadequate follicular maturation—biopsy corrected	0	0	0
Inadequate follicular maturation—biopsy not corrected	3	0	0

#### Crossover Data During the Second 8-Month Study: Patients with Pure LPD

Only seven patients treated with PVS failed to conceive during the first 8 months. One of these 7 (14%) conceived during the next 8 months following bromocriptine therapy (see Table I). However, 20 of the 25 patients (80%) who failed to conceive with bromocriptine now conceived with PVS. Chi-square analysis showed  $P < .005$ . Life-table analysis comparing cumulative probabilities of pregnancy and further comparing them with normal pregnancy rates is seen in Figure 3. Only one patient aborted (5%).

#### Crossover Data: Patients with Immature Follicles and LPD

Ten of the 17 (59%) patients who failed to conceive with PVS during the first 8 months now conceived with bromocriptine (see Table III). Only one patient aborted (10%). One of the six women failing to conceive during the first 8 months with bromocriptine did conceive during the second 8-month therapy period while treated with PVS; the patient did not abort. Chi-square analysis showed  $P < .1$ . Life-table

analysis comparing cumulative probabilities of pregnancy and further comparing them with normal pregnancy rates is seen in Figure 4. All 10 patients conceiving with bromocriptine demonstrated a mature follicle.

#### DISCUSSION

We have previously demonstrated the benefit of PVS therapy in women with LPD who seem to make mature follicles (70% pregnant in 6 months).<sup>16</sup> A similar success was demonstrated in this study in patients with pure LPD and hyperprolactinemia. Thus, the elevated prolactin did not inhibit the correction by PVS. However, bromocriptine does not appear to correct adequately the endometrial biopsy or result in significantly improved fertility in women with pure LPD.

Nevertheless, bromocriptine appears to be very efficacious in women with immature follicles, hyperprolactinemia, and LPD—whereas PVS is ineffective. Thus, both PVS and bromocriptine are effective in treating LPD resulting in pregnancies, but follicular dynamic studies should be performed to determine which therapy to employ. We cannot say whether clomiphene citrate or human menopausal gonadotropins might have been similarly effective in treating LPD with immature follicles despite hyperprolactinemia. A further study might compare the efficacy of clomiphene citrate versus that of bromocriptine. In our opinion, though, the adverse effect on cervical mucus would favor the use of bromocriptine.

There have been some reports of the efficacy of bromocriptine in women with normal prolactin levels.<sup>17-19</sup> We have previously published a paper reporting anecdotally the efficacy of bromocriptine in normoprolactinemic women with "ovulation defects" (most of which were LPD) who failed to conceive despite the use of other ovulation-inducing drugs or PVS.<sup>20</sup> We suspect that these women may have had follicular maturation defects corrected by bromocriptine despite euprolactinemia. We are now initiating a study to determine whether bromocriptine can correct LPD secondary to immature follicles in normoprolactinemic patients who do not respond satisfactorily to clomiphene citrate (e.g., hostile cervical mucus).

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