

IMPROVED FERTILITY IN NORMOPROLACTINEMIC
WOMEN WITH OVULATION DEFECTS TREATED WITH
BROMOCRYPTINE

Jerome H. Check, M.D. and Harriet G. Adelson, B.S.
From the Department of Obstetrics and Gynecology, Division of Gynecologic Endocrinology and the Department of Medicine, Division of Endocrinology. Thomas Jefferson University Hospital and Medical School. Philadelphia, Pennsylvania.

ABSTRACT

Twenty-one normoprolactinemic women with long term infertility problems related to ovulation defects achieved pregnancies shortly after treatment with bromocryptine. These patients had been previously unsuccessfully treated with clomiphene citrate, human menopausal gonadotropins, estrogen, human chorionic gonadotropin, and other ovulation therapies.

The failure of the above therapy was attributed to the inability to establish good ovulation with good post-coital tests. In half of the cases a male factor contributed to the infertility.

The anti-estrogen properties of clomiphene citrate may cause associated hostile cervical mucus. In contrast, bromocryptine has no adverse effect on the mucus. Therefore it may be especially beneficial when the spermogram is at a borderline level where ideal mucus may be necessary.

INTRODUCTION

The use of bromocryptine for suppression of galactorrhea and restoration of menses and ovulation in women with elevated serum prolactins is well accepted and has

been clinically used for several years.¹ Bromocryptine has also been reported capable of treating secondary amenorrhea and restoring ovulation in post-pill anovulation in women with normal serum prolactins.²⁻⁴ Furthermore, pregnancies in euprolactinemic amenorrheic women have been achieved with bromocryptine.⁵

However, some doubt about the efficacy of bromocryptine's use in normoprolactin states was created by the study of Crosignani et al suggesting that the drug worked by a placebo effect.⁶ The cases presented below demonstrate many more cases of ovulation and pregnancies induced by bromocryptine in normoprolactinemic women. Furthermore, the details of these 21 cases suggest that the drug's action was not on a placebo basis in view of the patients' previous failure to respond to many months of other drug therapies.

METHODS

The patients selected all had an infertility duration greater than one year. In all cases clomiphene citrate was employed without success in achieving a pregnancy. Clomiphene was used for over five months in each case with 5 exceptions. Many patients had concomitant problems with endometriosis, tubal factor, or male factor.

They were started on 2.5 mg bromocryptine daily. If ovulation was not judged as adequate after two months treatment the dose was increased to 5 mg. If the endometrial biopsy or serum progesterone level were still too

low, but yet indicative of probable ovulation, luteal phase support with 50 mg/day of progesterone suppositories was used.

RESULTS

Twenty-one of 54 normoprolactinemic women treated with bromocryptine have conceived. They had an average infertility duration of 3.9 years. Nineteen of the 21 cases had successful ovulation with clomiphene citrate but poor sperm survival even despite supplemental estrogen. The conjugated estrogens employed were used in doses up to 5 mg daily. (Table 1)

There was an average of 12.8 months of prior treatment with other ovulation therapies before switching to bromocryptine. There was an average of 2.2 treatment cycles with bromocryptine before conception occurred.

The average prolactin level was 13.4 ng/ml prior to bromocryptine therapy and this level dropped to an average of 9.2 ng/ml after 2 months treatment. The highest prolactin level in this group of 21 patients was 20.6 ng/ml with the lowest baseline at 4.8 ng/ml. Eleven patients had serum prolactins under 11 ng/ml.

In 15 cases the dose of bromocryptine needed to achieve a pregnancy was 2.5 mg and in 6 cases the dose was 5 mg/day. The drug is taken continually without break. A male factor problem was present in 11 cases.

The details of one of the cases who was capable of achieving two pregnancies in a short period of time with

TABLE I
SUMMARY OF THE TREATMENTS IN THE TWENTY-ONE PATIENTS

Dur. of infert:	Age	LDP	DES & Pred	DES & Pred	Prog	DES Pred HCG	DES Prog	DES HCG	Pred Prog	DES HCG	Cl ¹	Cl ²	Cl ¹ Prm ¹
10	32	3	6				5				1	1	
10	32												
4	29										2	1	
3	27		1				3		4				1
2	30		2	3		2	2	3	3		1		
3.5	27										1	1	
2	31				5						1		1
2.5	25			3							2		1
4	24	2	2				6				1		
1.5	29		2										
4	23								5		1		
4	24		2						4				
3.5	28				16						2		
3	25										2	1	
6	32		4				1		1				
3.5	26				3						1*		3*
2	34										2		1
8	30		1	2		2		3					1
4	25										2	1	
2.5	27				6**						2		1
3	25		2	3					4				
3	29										1	2	
2	31										1	1	

ACHIEVING PREGNANCIES WITH BROMOCRYPTINE													
Cl ¹ Prm ²	Cl ¹ Prm ⁵	Cl ² Prm ¹	Cl ² Prm ²	Cl ² Prm ⁵	Cl ¹ Pred	Cl ¹ Prm ²	Cl ¹ Pred	Cl ¹ Prm ⁵	Cl ² HCG	Cl ² HCG	HMG	Brom ¹	Brom ²
		1	2	5							5		3
													2*
		1	1	2		1	2	4				2	
1	1											3	
			1	1			1					1*	1*
			1	2							2	2	
1	2											3*	
1	2										3	2	
	1										2	2*	
												2	
1	1											1*	
	5										2	2**	
												3	1
2											1	4*	
1				7							6	2	1
			2									1*	
1	3**											1	1
1*	2*											1	
			2	2						3		2*	
1	1										2	1**	
												1	1
		1	1	2	1	1	1	3				2*	
		2	1	1		2	3	4				1	

bromocryptine despite failures over several years with other ovulation regimes is presented below:

CASE REPORT

The patient is a 32 year old woman with a 10 year infertility history and she had been treated by three fertility specialists for seven years. Her problem was diagnosed as anovulation and azoospermia and she was interested in artificial donor insemination. She had been treated by two other fertility specialists with a combination of AID and either clomiphene citrate and/or HMG. She had had lysis of pelvic adhesions 9 years previously.

Her treatments in our office is summarized below.

(Refer to patient 1 in Table I)

1. Clomiphene citrate (up to 100 mg for 5 days) plus conjugated estrogens up to 5 mg/day from day 10 to day of ovulation. Results: failed because of poor cervical mucus and poor post-coital tests.
(10 cycles)
2. Low dose conjugated estrogens taken before, during and after clomiphene citrate. Results: still poor mucus.
(3 cycles)
3. Low dose estrogen therapy (diethylstilbesterol 0.2 mg days 5-16). Results: good mucus but poor ovulation.
(6 cycles)
4. Low dose estrogen therapy plus progesterone suppositories 25 mg 2 times per day beginning 3rd day of temperature rise.
(5 cycles)
5. Human menopausal gonadotropins 150 IU/day with an average of 12 ampules per cycle. Results: good mucus, good post-coital, but had spontaneous ovulation before HCG while serum estradiols were still low (under 400 pg.ml) and still

had an inadequate corpus luteum as evidenced by short luteal phase and low serum progesterone levels (under 10 at mid-luteal phase).

6. Treated with bromocryptine 2.5 mg first two weeks, then 5 mg daily. Results: good ovulation first cycle with mid-luteal phase progesterone level of 11.4 ng/ml. She conceived on the third treatment cycle.

Pregnancy was confirmed on her 21st day after ovulation. Vaginal cytology showed inadequate regression so 50 mg of progesterone suppositories was started per day.

The patient carried to 13 weeks gestation, then developed spotting a week after stopping progesterone suppositories. The ultrasound revealed a non-viable 12 week fetus and a spontaneous abortion occurred.

Three months after the spontaneous abortion the patient was placed back on 5 mg bromocryptine. She conceived on the second cycle. She was treated with 50 mg/day progesterone suppositories for her full pregnancy. She successfully delivered a viable full term infant.

The patient thus in our office had 29 treatment cycles with clomiphene citrate, HMG, low estrogen and HCG without success because of the inability to achieve the combination of good ovulation with good cervical mucus. Despite a serum prolactin level of only 13 ng/ml she was able to conceive quickly with bromocryptine; on her third cycle the first time and on cycle two in her second pregnancy. Her prolactin level after two months treatment was 8.6 ng/ml.

DISCUSSION

These cases demonstrate that bromocryptine has potential therapeutic benefit in infertility problems even in the absence of hyperprolactinemia. It especially appears to be efficacious when there is a mild ovulatory defect but where uncorrectable hostile mucus is produced when clomiphene citrate is used. This is best illustrated by the example case presented where despite nine years of treatment by fertility specialists with clomiphene citrate, low dose estrogen, progesterone suppositories, and even human menopausal gonadotropins, no pregnancy could be achieved. When bromocryptine was used, she was able to become pregnant once after three months treatment and again after only two months therapy.

In eleven of the cases there was an associated male factor treated with split ejaculate insemination and other treatment of the sperm. In many of these instances the cervical mucus, even despite clomiphene treatment, may have been of sufficient quality for survival of sperm with good concentration and motility but not for borderline quality sperm.

The mechanism of action is not known. It is possible that it works by reducing the prolactin level which was normal for the statistically average female but not for these patients. However, since in some patients the baseline prolactin levels were in the low normal range, the possibility exists that bromocryptine may induce ovulation

via direct stimulation of dopaminergic receptors of the gonad⁷ or the pituitary³.

The patients used in this study were all private patients and thus a true double blind study, where a placebo was given to half the patients, was not possible. Thus in a strict sense, these results cannot negate Crosignani's claim that the drug works merely as a placebo. However, these results provide much greater support for using bromocryptine in anovulatory normoprolactinemic women than the previous case reports not only because of the greater number of cases reported, but especially since bromocryptine was only started after many months of failures with other ovulation inducing drug regimes. The patients who became pregnant had a very significant infertility duration of 3.9 years. Furthermore, there certainly were enough placebo opportunities in the 12.8 months of failures with other drug therapies. In fact, the treatment cycles were not necessarily consecutive giving many of these patients opportunities to achieve pregnancies as a result of a clomiphene "rebound: (ie, persistent ovulation after stopping clomiphene without the adverse effect on the mucus).

There is some evidence that too low a prolactin might lead to a luteal phase defect. Therefore, in those patients whose prolactins dropped to under 7 ng/ml and/or if vaginal hormonal cytology showed inadequate regression, they were treated with progesterone vaginal suppositories 50 mg/day for 12 weeks. Nine of the 21 pregnant patients were so treated.

Only 2 of the 21 patients had any galactorrhea. There were no definite clues as to why some normoprolactinemic patients responded to bromocryptine whereas others did not except that if a requirement of over 100 mg for 5 days of clomiphene citrate was required to achieve ovulation then ovulation did not occur with bromocryptine. Eighteen of the 33 patients not conceiving on bromocryptine failed to ovulate. The remainder was composed of patients with various combinations of male factor, cervical factor, and tubal factor problems. Four patients failed to conceive despite what appeared to be good ovulation as measured by mid-luteal phase progesterone levels over 10 ng/ml and by appropriate endometrial biopsies and good post-coital tests of over 5 sperm per high powered field with good linear progressive motion.

The results with using bromocryptine to induce ovulation in normoprolactinemic women as a mode to achieve pregnancies, especially in patients who have failed to conceive with clomiphene because of associated hostile mucus, has been sufficiently encouraging to hopefully interest others to similarly try this drug. Perhaps, enough interest may be generated by some clinical research centers where a true double blind study can be set up to better evaluate the efficacy of this therapy.

ABBREVIATIONS

Dur of infertil= number of years of infertility

LDP= low dose premarin (0.3mg days 5-7; 0.6 mg days 8-10;
0.9 mg days 11-13)

DES= 0.1 mg day 5 to rise in BBT. If post-coital inadequate then increased to 0.2 mg days 5 to rise in BBT.

Prog= progesterone suppositories 25 mg 2x/day from 3rd day of rise in BBT to menses

DES+

prog+

HCG= DES and progesterone suppositories and 10,000 units HCG at nadir of BBT

Cl¹= clomiphene citrate 50 mg days 5-9

Cl²= clomiphene citrate 100 mg days 5-9

Prm¹= premarin 2.5 mg days 10 to rise in BBT

Prm²= premarin 2.5 mg days 10 to rise in BBT

HMG- human menopausal gonadotropins 1 to 2 ampules per day (75 IU FSH and LH per ampule) with serum estradiol level of 900-1800 ng/ml

Brom¹= bromocryptine 2.5 mg per day

Brom²= bromocryptine 5 mg per day

* = plus progesterone suppositories, 50 mg/day beginning 3rd day of temperature rise

** = plus HCG 10,000 units at mid-cycle

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