

## Bromocriptine Treatment in Infertile Population of Women with Galactorrhea

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### الخلاصة

ان نسبة افراز الحليب غير الوظيفي ( galactorrhea ) لدى النساء هي الثلث. وقد تترافق تلك الظاهرة مع ارتفاع هرمون الحليب في الدم ( hyperprolactinemia ) او قد لا تترافق معها. كان الهدف من الدراسه هو معرفه مدى الحاجه الى استخدام العقار الخافض لهرمون الحليب (bromocriptine) في علاج تلك الظاهره لدى من تعاني من مرض العقم او اضطراب الحيض ولكن لا تعاني من ارتفاع هرمون الحليب. تم جمع عينه 227 من النساء يعانين من ظاهرة ال ( galactohrea من عيادة العقم في مستشفى النسائية التعليمي ومن العيادة الخاصة منذ شهر تشرين اول 2009 وحتى شهر تموز 2011 ووفق ضوابط اختيارية واضحه تحدد من عدد المتغيرات التي يمكن ان تؤثر على نتائج الدراسة. تم الحصول على موافقة خطية من كل من المنخرطات في تلك الدراسه السريرية بعد شرح مفصل وتفصيلي للاعراض الجانبية الغير مرغوب بها. تم تقسيم المريضات الى كل من مجموعة A ومجموعة B ، تحتوي الاولى على ارتفاع هرمون الحليب مع ظاهرة ال ( galactorrhea ) وتحتوي الثانية على نسب هرمون حليب طبيعية مع ظاهرة ( galactorrhea ). خضعت كلا المجموعتين الى تعاطي جرعة صغيرة وثابتة من عقار البارلوديل او ( bromocriptine وتم مشاهدة التحسن السريري للاضرابات الحيضية وفحوصات الاباضة وحالات الحمل المتراكمة في كل مجموعة. كانت حصيله النتائج ان الدورة الحيضية قد انتظمت بمقدار 89,4% و 80,8% لكل من مجموعة A و B على التوالي. اما حالات الحمل السريري التي سجلت فكانت 90,8% و 76,6% لكل من المجموعتين على التوالي ايضا. ان هذا يدل على ان الاستجابة كانت بمقدار افضل لدى المجموعة A ولكن لازالت نتائج المجموعة B مهمة سريريا وبنسبة صدفة اقل من(0,007). ننصح باستعمال العلاج (bromocriptine) لحل المشاكل السريرية للنساء سواء كان لديهن ارتفاع في هرمون الحليب ام لا.

### Abstract

Galactorrhea ( a non-physiological production of milk) can be found with or without raised levels of serum prolactin . Prolactin is the hormone that stimulates milk secretion and cause luteal phase disturbance. Thus galactorrhea can lead to infertility which is one of the most common gynecological problems of women attending gynecological clinics .All patients included were showing galactorrhea and all were complaining of infertility.The patients were collected from the infertility clinic in the maternity teaching hospital in Al-diwaniah city ,and from private clinics from Oct 2009 to June 2001 and according to strict inclusion criteria, that eliminate other causes of infertility other than presence of galactorrhea and eliminate risky conditions that may exacerbate upon the use of the drug bromocriptine. The total number of patients was 227.

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Fasting serum prolactin was examined for each patient and all patients were started on treatment with Bromocriptine ( a dopamine agonist ) orally of 1.25 mg or at half tab a day on a fixed dose. The patients were grouped into two groups according to their levels of fasting serum prolactin, group A(G A) had high levels above normal serum prolactin gathering 87 patients and group B(G B) had normal serum prolactin levels gathering 120 patients. Twenty patients were out of the study being either missed from follow up or excluded for risk or for severe side effects. Each patient was followed up for 12 month from the initiation of the treatment or until appearance of response ,which one being earlier.Accumulative pregnancy rates were followed for the two groups in one year following treatment. The result was ( 89.8 % of patients of GA ), and 76.6% of patients of GB ).Although the difference is significant the accumulative pregnancy rate was significant in group B too. Conclusion: In infertile women with galactorrhea, we suggest treatment with bromocriptine in these patients regardless of serum prolactin level.

### **Introduction**

Galactorrhea ( a non physiological secretion of milk) can be found in up to a third of hyperprolactinemic patients(1). The secretion is watery or milky fluid that does not contain blood or pus, but multiple fat droplets seen by low power magnification microscopy(2). The level of serum prolactin is increased at late pregnancy, and during lactation (3).On the other hand hyperprolactinemia in women (which means level of circulating prolactin above 20ng/ml) is often associated with amenorrhea, oligomenorrhea , infertility and in 30-50% of patients with galactorrhea(4). The principal action of prolactin , a peptide hormone synthesized and released from the lactotrophs of anterior pituitary gland is to produce milk secretion and stimulate lactation(2)(5). It is 90-96% bound to protein and is completely metabolized. It is excreted mainly in feces and in little amounts in urine.In contrast many women with galactorrhea have normal serum level of prolactin(6). However, hypersecretion of prolactin leads to interruption of the release of gonadotropin-releasing hormone(6)(7), which in turn inhibits the release of FSH( follicular stimulating hormone) ,but mainly LH( luteinizing hormone) resulting in cycle disturbance and infertility. It may also act to reduce the granulosa cell number and FSH binding at the level of the ovaries(8). The primary influence on prolactin secretion is an inhibitory factor which is called dopamine(5) ,released from the hypothalamus. Any event that leads to decreased dopamine input can result in hyperprolactinemia and its consequences possibly galactorrhea(9).Prolactin is secreted episodically and serum levels fluctuate throughout the day and throughout the menstrual cycle ,with peak levels occurring at the midcycles(1).

On the contrary , .Bromocriptine myselate is semisynthetic ergot alkaloid derivative that stimulates dopaminergic receptors in the brain and anterior pituitary(1)(10) . It is classified as miscellaneous (9), and is rapidly absorbed and primarily metabolized by the liver with peak serum levels noticed after 3 hours(10).

### **Aim of the study**

In this study , the benefit of the drug bromocriptine is tested in the treatment of all cases of galactorrhea regardless of the serum level of prolactine hormone. The observation of the occurrence of pregnancy after a period of infertility or reversion of an abnormal menstrual cycle rhythm to a normal pattern in ladies whom bromocriptine myselate was prescribed to,led to this clinical trial. In those ladies ,although their serum prolactine hormone was not tested for , they succeeded to show a satisfactory response. In addition , the well known side effects and possible risks that occur due to the use of that medication raised the importance of establishing a clinical evidence for the benefit of that drug that should over weigh the harmful effects in women with possibly normal serum prolactine .

### **Materials and Methods**

The patients were collected from the infertility clinic in maternity hospital in Al-Diwaniah city as well as from the private clinic from Oct. 2009 to Jun.2011. The total number of patients collected was 227 over 21 months. All patients were infertile for different periods of time. All the patients had the presence of galactorrhea recovered by gently expressing milk from the nipple of one or both breasts by pressing on the periphery of the gland(s) towards the nipple. Each patient was informed about the mode of treatment that she will be offered, and a written consent was obtained after full explanation of side effects versus possible benefits.

#### **The Selection Criteria**

- \_Age of women ranged from 20 to 40 years.
- \_No clinical or lab evidence of genital tract infection.
- \_No leading clinical suggestion of possible bilateral Fallopian tube blockage.
- \_The semen analysis of the partner is normal , the test had been done within one year of the inclusion of the female partner in the study.
- \_The BMI was ranging from 20-29kg/m<sup>2</sup> ,patients were advised to keep their weights at approximately the same value throughout the time of the study or until they conceive.
- \_No history of diseases that may influence the results by adding more variables other than galactorrhea such as PCOS, hypothyroidism,...

\_Infertility whether primary or secondary( failure of the couple to have pregnancy after one year of unprotected intercourse taking place at about 2-3 times a week )

\_No history of diseases that add more risks to the patient on concomitant use of bromocriptine as severe or uncontrolled hypertension, seizures ,ischemic heart disease, renal failure, hepatitis ...

All patients had their fasting serum prolactine assessed and grouped into either Group A( with elevated fasting serum prolactine) or into Group B ( with normal fasting serum prolactine ). The test was done on fasting patients under physical and mental rest, at midmorning hours, without a preceding breast or pelvic examination. High levels were repeated one week later. Afterword , the medication was established regardless of the fasting serum prolactine level obtained. The drug given was Bromocriptine myselate by an oral tab, at a dose of 1,25 mg or half a tab. daily. The dose was fixed throughout the study time. The dose was given at night with the dinner and the patient was advised to lie down in the next few hours after its administration in anticipation of orthostatic hypotension. All patients were asked to notify any severe side effects like fainting or severe headache and were examined at each visit for their blood pressures, renal,liver and hemopoietic functions.

**Follow up of the response :\_**

1-regaining of the normal menstrual cycle rhythm in patients who started with irregular menstrual cycles.

2-establishment of menses in patients who started with secondary amenorrhoea

3-serial transvaginal U/S from day 7 up to day 21 trying to pickup a mature ovarian follicle.

4-ovulation test by urine detection of LH during LH surge that possibly assumes if it is positive that the patient is going to ovulate within 24- 36 hours

5-detection of pregnancy by ordinary urine pregnancy test followed by an early transvaginal U/S done at 5-6 weeks from the LMP.

All patients were instructed to stop the medication once pregnancy is diagnosed. All patients were instructed to have their coital activities during the whole length of the cycles, prohibited sensibly during menses

**Results**

The total number of patients included from October 2009 till June 2011 was 227. The number remained under the study was 207, 15 patients were missed from the follow up and one patient was excluded from the study because she was diagnosed later on as having pituitary adenoma. She was excluded because she needed larger doses of bromocriptine than the small fixed dose given in this study ,which makes the standardization of the dose of the drug in the clinical act impossible. Other four patients were excluded too .

**Table (1):-the number of patients including the different groups, the participating patients ,the follow-up missed patients and the dismissed from the study.**

Group	Number remained in study	Number missed from follow up	Number of patients excluded	Causes of exclusion	Total number
Group A( with elevated fasting serum prolactine)	87	11	2	Pituitary adenoma Severe side effects with increased BP	100
Group B( with normal fasting serum prolactine)	120	4	3	Severe headache, rise in BP, continuous vomiting	127
Total numbers	207	15	5		227

**Table (2):-shows the total number of patients who responded clinically in regulating or regaining their normal menstrual cycles upon administration of bromocriptine at 1.25 mg orally daily with the mean time duration in the hyperprolactemic galactorrheac patients group (A) and the euprolactenemic galactorreac**

Group	Number of patients with abnormal menstrual cycles	Duration of time until regulation of the cycle/ month				Total number responded	% in one year
		1-3	4-6	7-9	10-12		
A	85 out of 87	19	38	13	6	76	89.4
B	73 out of 120	16	39	4	—	59	80.8

**Table (3):-shows the total number of patients who achieved a positive ovulation tests upon administration of bromocriptine at 1.25 mg orally daily with the mean time duration in the hyperprolactemic galactorrheac patients group (A) and the normoprolactenemic galactorreac patients group(B).**

Group	Total Number of patients	Mean time duration/months				Number of responders	% per year
		1-3	4-6	7-9	10-12		
(A)	87	7	46	18	3	74	85.5
(B)	120	4	20	47	25	96	80

**Table (4):-shows the total number of patients who conceived upon administration of bromocriptine at 1.25 mg orally daily with the mean time duration and the accumulative pregnancy rates in the hyperprolactemic galactorrheac patients group (A) and the normoprolactenemic galactorreac patients group(B).**

Group	Total number of patients	Mean time duration / months				Number of pregnancies	% within one year
		1-3	4-6	7-9	10-12		
(A)	87	2	35	23	19	79	90.8
(B)	120	2	14	50	26	92	76.6

**Table(5) shows the causes of increased fasting serum levels in patients of group (A)**

Etiology of hyperprolactinemia	Number of patients	Percentage %
Pituitary adenoma	1 (excluded from the study)	1
Hypothyroidism	3	3
Chronic medications	15	15
Stressful life	43	43
Idiopathic	38	38
Total number	100	-

**Discussion**

Galactorrheawould point to hyperprolactinemia(11) ,but this is not the case in all of the patients. There is a proportion of ladies that show galactorrhea but still have normal fasting serum levels of prolactine. The fact that some patients who complain of subfertility have at the same time galactorrhea with no clinical , lab. or radiological evidence of any disease behind their subfertility. In addition , empirical treatment with antihyperprolactinemic drugs had shown good results in some patients. These two aspects raised the need for proper statistically based study to define the benefit of bromocriptine in non-hyperprolactinemic galactorrheac patients.

It was more difficult to convince women with normal levels of serum prolactine to participate in the clinical trial especially after fully informing them about the side effects of bromocriptine . However the fact that it may help them solve the problem of infertility could indeed help them give finally a written consent . In addition they were tell about some recent studies that showed that the number of the prolactine receptors are increased in the breast cancer which might point to the fact that prolactine could play a role in these tumor growth(8). That idea encourrged all of them to participate in the clinical trial.

It essential to clarify that only women with galactorrhea with clinical problems were selected to undergo the issues of the study ,while women with only raised levels of prolactine with no personal history of any confirmed clinical problem were not accepted. There is a biologically inactive complex of prolactine and immunoglobulin called big prolactine can give a physiologically insignificant elevation, therefore, the presence of a clinical problem should raise the decision to test for hyperprolactinemia (5).

The patients were instructed to be over-night fasting in order to test their serum prolactine to avoid the false positive high readings due to post-prandial rise in that hormone(5).

The patients were tested for serum prolactine at midmorning times to avoid the possible rise at early morning after the sleeping hours. The maximal rise in prolactine is detected during nighttime while asleep and a smaller increase occuring in early afternoon, nipple and breast stimulation, exercise ,stress can all to increased prolactine secretion(1).

Some patients were using drugs that the withdrawal of these medications was not the possible way of treating their hyperprolactenimic conditions because of the necessary and continuous need for these drugs, namely the psycotropic drugs. Any how the continued use of these druge with concomitant use of bromocriptine is not considered a contraindictaion(12).In fact in a study done in Korea university in Seol, Lee MS et al discovered that the use of bromocriptine for hyperprolactinemia caused by the antipschycotic drugs was not associated with any exacerbation of psychotic disorders.(13)

In 3 conditions ,hypothyroidism was the overt etiology behind the hyperrolactinemin state.this is because of the elevated thyrotrophic releasign hormone which is considered the prolacine releasing factor(5)(12).

In one case the level was more than 500 ng /ml, suggesting a pituitary tumor and the patient was subject to more imaging studies and was excluded from the study. The knowing of whether the patient has pituitary tumor is important because the tumor may enlarge during pregnancy(14).The exclusion was based on the assumption that she needs more increasing doses of the drug used in order to suppress the pituitary adenoma and this can not be put within the standardization of the dose used in the study. The other four excluded, had suffered form severe or intolerable side effects and could not could not continue their participation in the study. The usual normal range of serum prolactine is 5-20ng/ml. patients with a slightly high value reaching 40ng/ml were subject to second test to confirm the rise and to determine and treat the etiology(6).

Causes of hyperprolactenemia were diverse as shown by the table(5), but in quite big proportion they were unknown. The assumption of psychological stress or excitation is considered in those ladies and indeed they were of the most exploiters of the treatment given.

Because the basis of the study is empirical, it was necessary to use only small fixed doses of bromocriptine. In addition, it was necessary to restrict the dose due to the possible effect on the cardiovascular system as it was a similar study on the benefit of bromocriptine (15). The acquisition of written consent was necessary as it was the complete explanation of the distressing side effects prior to establishment of drug administration to each patient.

A small fixed dose was proposed too for the notorious side effects of the drug given. These include most commonly nausea and vomiting in 60% of the patients, but only 3-5% might discontinue the medication (10). Other side effects are orthostatic hypotension, nasal congestion and headache, but in most of the cases they disappear after few weeks of treatment. An alternative method to decrease the side effects is vaginal administration which is equally effective (16). Any way that way of administration was not advised for the standardization of the study structure so that all the patient under study took their medications right the same way.

Although bromocriptine does not pose a significant risk to the fetus, all patients were instructed to stop taking it whenever pregnancy is diagnosed. The pattern and incidence of anomalies were similar to those expected in non-exposed populations (17).

It was apparent that in all the tables the percentages of ladies responded in correcting their clinical problems were higher in group A than in group B. This may be explained in that the bromocriptine given had a strong inhibitory action to the prolactin hormone secreted in high levels in those ladies, the action being responsible about correction of the already disturbed hormonal pathways. On the other hand, in group B the serum prolactin is not elevated but still the women show galactorrhea which might be due to some increased sensitivity of the target tissues to the hormonal stimulation, so that the bromocriptine given was responsible about some extra-action to decrease the normal levels, so it might have had a longer time to correct the disturbance.

It was apparent that 3 ways were used to assess the response to treatment in all ladies, namely serial transvaginal U/S, detection of ovulation and occurrence of the pregnancy. That was not on the expense of effort or cost because none of the test used in center can prove that ovulation has actually occurred, and the occurrence of pregnancy is the only positive proof of ovulation (6). Any how, the two methods were used to only predict ovulation in order to time the most useful time for intercourse. All patients were asked to withdraw the medication once pregnancy is diagnosed yet, the drug is considered as category B during pregnancy (6)(18)(19)

In any way and at certain times the percentage of the women got pregnant was higher than the percentage of women with a positive ovulation test. This may be explained by the fact that some women have their ovulations occurring beyond the midcycle times, so that they showed negative ovulation tests when

tested at midcycle times then they got conceived shortly afterward in the same cycle. The test is based on the fact that the leutinising hormone reaches a high level in the urine about 24-36 hours prior to ovulation(20)(21).

The patients were advised not to restrict their sexual meetings to the midcycle times but to spread these activities to the whole length of their cycles, but with a bit more concentration on these midcycle days. This advice was to decrease the tension a woman might suffer from, during the midcycle times while she is thinking of how much successful her efforts are, to get pregnant. This tension indeed might raise her prolactine rendering the treatment less effective and delaying or inhibiting ovulation ,especially in sensitive women undergoing a stressful social life because of their subfertility problem. Spreading their sexual activities made those women more relaxed. In addition ,some women do ovulate in other times of their cycles making the chances of getting pregnant more if they spread their sexual activities over the whole cycle.

In a similar clinical trial by Eftekhari N et al found also that treatment of galactorrhoea whether or not associated with hyperprolactinemia is worthy to encourage the pregnancy rates in infertile women(22).

### Conclusion

It is worthy to treat patients with galactorrhea, who are complaining of chronic cycle irregularity and infertility by Bromocriptine mesylate .Although the success rates were higher in hyperprolactinemic patients , there is significant chance of benefit in patients with normal serum prolactine (p=0.007)

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