

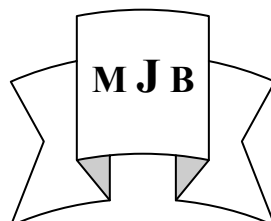
Physiological Study of Some Hormonal Parameters in Infertile Hyperprolactinemic Women in Pre and Post-Treatment with Cabergoline and Bromocriptine

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Abstract

Hyperprolactinemia is the most common endocrine disorder. It occurs more frequently in women than in men. The clinical symptoms of hyperprolactinemia are amenorrhea, oligomenorrhea infertility, and galactorrhea in women; decreased libido and impotence in men.

The aims of the study are to estimate some possible risk factors for hyperprolactinemic infertile women and to assess some hormonal and hematological changes to these women. And also to reveal the role of two types of dopamine agonist drugs (cabergoline and bromocriptine) in treatment of hyperprolactinemia and restoring normal ovulation.

This study consists of a total number of 100 married women in the reproductive age (their age ranged between 18 and 42 years), seventy women were in patient's groups and thirty healthy women were regarded as a control group. Thirty five from seventy patients were given cabergoline and other thirty five of patients were given bromocriptine drug.

The results were obtained from the study found that most age group was 28-32 years. The percentage of patients who had positive family history of hyperprolactinemia was significantly more than those in control group. The percentage of patients and control who living in urban areas were significantly more than those living in rural areas. In addition to that, The percentage of patients who had primary infertility more than those who had secondary infertility.

Regarding the percentage of pre-treatment patients who had irregular menstrual cycle and galactorrhea, there was highly significant increase compared with control group and post-treatment patients while there was less significant decrease in patients after cabergoline drug therapy compared with patients treated with bromocriptine drug regarding the presence of these signs and symptoms.

Regarding hormonal assay, the study showed highly significant increase in serum prolactin hormone and testosterone hormone levels and high significant decrease in serum FSH, LH, and progesterone hormone levels in pre-treated patients compared with control group. Furthermore; there was high significant decrease in serum prolactin hormone level, and less significant decrease in serum testosterone hormone level, and high significant increase in serum FSH, LH and progesterone hormone levels in post-treatment patients in compared with pre-treated patient's groups.

Additionally; there was highly significant decrease in serum prolactin, low significant increase in LH and progesterone, and there was no significant difference in serum FSH and testosterone level in post-treated patients with cabergoline drug compared with post-treated patients with bromocriptine drug.

To conclude, hyperprolactinemia associated with increased and decreased in some hormonal parameters and the dopamine agonist agents are effective in correcting the disturbance in these parameters.

الخلاصة

زيادة هرمون البرولاكتين (هرمون الحليب) في الدم هو أكثر اضطرابات الغدد الصماء شيوعاً. هو يحدث في النساء أكثر من الرجال. الاعراض السريرية لزيادة هرمون الحليب في الدم هي انقطاع الطمث، قلة الطمث، والعقم، وأفراس الحليب من الثدي عند النساء؛ قلة الشهوة الجنسية والعجز الجنسي عند الرجال.

الاهداف من هذه الدراسة هي تقييم بعض عوامل الخطورة الممكنة لدى النساء العقيمات المصابات بزيادة هرمون الحليب في الدم ومعرفة التغيرات لبعض المعايير الهرمونية لهذه النساء أيضا لظهور دور نوعين من الادوية المعززة للدوبامين (الكبرجولين و البروموكريتين) في معالجة زيادة هرمون الحليب في الدم واستعادة التبويض الطبيعي.

شملت الدراسة كعدد كلي ١٠٠ امرأة متزوجة في عمر الانجاب (اعمرهن تتراوح بين ١٨ -٤٢سنة) . ٧٠ امرأة ضمن مجموعة المرضى وثلاثين امرأة متمتعته بالصحة اعتبرت ضمن مجموعة السيطرة . ٣٥ من ٧٠ مريضه اعطيت علاج كبركولين (cabergoline) و ٣٥ مريضه الاخرى اعطيت علاج بروموكريتين(bromocriptine)

أوجدت النتائج التي تم تحصيلها من الدراسة ان أكثر مجموعة عمرية عند المريضات كانت ٢٨-٣٢ سنة .نسبة المريضات التي كانت لديها تاريخ عائلي لزيادة هرمون الحليب في الدم اكثر من اللاتي في مجموعة السيطرة . نسبة المريضات ومجموعة السيطرة التي تسكن في المدينة اكثر من اللاتي تسكن في المناطق الريفية. اضافة الى ذلك ،نسبة المريضات التي تعاني من عقم أولي اكثر من الاتي تعاني من عقم ثانوي.فيما يتعلق بنسبة المريضات قبل العلاج التي كانت تعاني من عدم انتظام الدورة الشهرية،وافراز الحليب من الثدي،هناك زيادة معنوية كبيرة مقارنة بالنساء في مجموعة السيطرة وعن المريضات بعد العلاج بينما كان هناك نقصان معنوي طفيف بين المريضات بعد علاج cabergoline مقارنة بالمريضات بعد علاج bromocriptine فيما يتعلق بوجود هذه العلامات والاعراض

فيما يتعلق بالتحليل الهرموني ،أظهرت الدراسة أن هناك زيادة معنوية كبيرة في مستويات هرمون الحليب(prolactin) والهرمون الذكري (testosterone) في مصل الدم مع نقصان معنوي كبير في مستويات الهرمون المحفز للحوصلات المبيضة(FSH)،الهرمون المحفز للجسم الاصفر (LH)، وهرمون الحمل(progesterone) في مصل الدم لدى المريضات قبل العلاج مقارنة بمجموعة السيطرة. علاوة على ذلك هناك نقصان معنوي كبير في مستوى هرمون الحليب ،نقصان معنوي طفيف في مستوى الهرمون الذكري في مصل الدم ،مع زيادة معنوية كبيرة في مستويات الهرمون المحفز للحوصلات المبيضة ،الهرمون المحفز للجسم الاصفر ،وهرمون الحمل في مصل الدم لدى المريضات بعد العلاج مقارنة بمجاميع قبل العلاج .اضافة الى ذلك؛ هناك نقصان معنوي كبير في هرمون الحليب،زيادة معنوية طفيفه في مستويات الهرمون المحفز للجسم الاصفر وهرمون الحمل ، مع عدم وجود فرق معنوي في مستوى الهرمون المحفز للحوصلات المبيضة والهرمون الذكري بين المريضات بعد علاج cabergoline مقارنة بالمريضات بعد علاج bromocriptine.

استنتجت الدراسة، بان زيادة هرمون الحليب في الدم يصاحبه زياده أو نقصان في بعض المتغيرات الهرمونية وأن العناصر المعززة للدوبامين فعاله في تصحيح الخلل في هذه المتغيرات.

Introduction

Hyperprolactinemia is the most common endocrine disorder of the hypothalamic-pituitary axis, up to 10 percent of the population [1]. It is a condition of elevated serum PRL. Normal PRL levels in both women and men are <25 nanograms/ml (25 micrograms/l or 500 milliunits/l) and 20 nanograms/ml (20 micrograms/l or 400 milliunits/l) respectively [2].

Hyperprolactinemia occurs more commonly in women. Its prevalence ranges from 0.4% in an unselected normal adult population to as high as 9 to 17% in women with reproductive disorders. It was found to be 5% in a family planning clinic, 9% in women with adult-onset amenorrhea, and 17%

among women with polycystic ovary syndrome. It is present in 25% women with galactorrhea [3] and as high as 70% in women with amenorrhea and galactorrhea [4]. Hyperprolactinemia can produce a variety of reproductive dysfunctions in women including inadequate progesterone production during the luteal phase after ovulation, irregular ovulation and menstruation, absence of menstruation, and galactorrhea (breast milk production by a woman who is not nursing). In men, hyperprolactinemia may be associated with impotence and can affect fertility [5].

Prolactin secretion may increase with sleep, stress, coitus, exercise, nipple stimulation, ingestion of certain foods, and pregnancy. Elevated

prolactin levels can result from physiological causes, such as pregnancy and stress, and pharmacological causes, including the use of neuroleptics, estrogens, opiates, antihypertensive drugs or calcium channel blockers [6]. Once physiological, pharmacological, and iatrogenic stimuli have been eliminated as causes of elevated prolactin levels, the presence of a micro- or macroprolactinoma is the most likely cause of persistent pathological hyperprolactinaemia.

Hyperprolactinemia could also be because of hypothyroidism, polycystic ovarian syndrome, chronic renal failure and hepatic insufficiency [7].

Treatment of choice for hyperprolactinaemia is mostly with dopamine agonists such as cabergoline, bromocriptine, and less frequently lisuride. A new drug in use is norprolac with the active ingredient quinagolide. Extract can be tried in some cases of persistent hyperprolactinemia [8,9].

The Aims of Study

1. Studying the effect of high levels of serum prolactin hormone on female fertility and assessing the etiology and the risk factors that lead to irregularities in the levels of serum prolactin hormone.
2. Demonstration of the correlation between the serum levels of prolactin hormone and the serum levels of other hormones (follicle stimulating hormone (FSH), luteinizing hormone (LH), progesterone, testosterone, and thyroid-stimulating hormone (TSH).
3. Comparing the effects of cabergoline and bromocriptine on progression of signs and symptoms between two samples of hyperprolactinemic patients (compare the efficacy cabergoline versus bromocriptine in the treatment of women with hyperprolactinemia).

Materials and Methods

The study was conducted during the period from November 2010 to June 2011 at Babylon Maternity and Pediatric Teaching Hospital. The study consisted of a total number of 100 women in the reproductive age. Their age ranged between 18-42 years. The seventy infertile patients with hyperprolactinemia were diagnosed by specialist doctors whose chief complaints were infertility and/or menstrual disturbances and/or galactorrhea and high serum prolactin levels in two separated measurements (The upper range of normal serum prolactin level was considered 23ng/ml); where as the control group included thirty healthy married women. The patients were allocated randomly to one of two groups:

Group 1. (n=35) received cabergoline (dostinex, 0.5 mg tablets, manufactured by Pharmacia Italia S.P.A., Italy).

Group 2. (n=35) received bromocriptine (Parlodel, 2.5 mg tablets, manufactured by Novartis Pharma AG., Basle, Switzerland).

Women assigned to the cabergoline group received 1 (0.5 mg) tablet of cabergoline weekly; where as the women assigned to the bromocriptine group received half (2.5 mg) tablet of bromocriptine daily for the first week, one tablet daily for the second week and then two tablets for the remaining weeks of treatment to reduce the incidence and severity of side effects. All patients enrolled in the study fulfilled the exclusion criteria as following:

Patient's refusal, history of recent administration of hormonal therapy, male factor infertility, other causes of female infertility, the women who show the presence of a pituitary tumor or presence of local lesions of the breast, hyperprolactinemia related to

polycystic ovary disease or thyroid disorders, history of renal or hepatic disease, and history of allergy to ergot derivatives. Some patients were excluded prematurely from the study in case of diagnosis of pregnancy or because of loss to follow up.

All the patients and the control (who fulfilled the selection criteria) underwent clinical evaluation at base line and at the end of treatment period of 3 months.

Blood samples were obtained from the patients and control at baseline and at 12 weeks after the initiation of therapy (at the end of the trial)for hormonal (prolactin, FSH, LH, testosterone and TSH) assay by minividas. Another blood samples were obtained from the patients and control at day 21 of cycle for measurement of serum levels of

progesterone hormone. All the hormonal assays were performed according to the procedure recommended by the company (Biomerieux, France) by minividas instrument which is an automated computerized quantitative test for use on the vidas analyzer for the enzyme immunoassay determination of human serum or plasma using enzyme linked fluorescent assay (ELFA) technique[10].

Results

Distribution According to Age Groups:

As shown in table (1),the most common age group was (28-32) years which represents the highest percentage of total hyperprolactinemic patients.

Table 1 Shows the distribution of all pre-treatment infertile hyperprolactinemic patients (70) according to age groups:

patient's groups	Number of patient in each Age group with percentage.				
	(18-22) years	(23-27) years	(28-32) years	(33-37) years	(38-42) years
Patients assigned to cabergoline (group1)	4(11.4%)	7(20%)	14(40%)	7(20%)	3(8.6%)
Patients assigned to bromocriptine (group2)	3(8.6%)	7(20%)	13(37.1%)	8(22.9%)	4(11.4%)
Total number of patients	7(10%)	14(20%)	27(38.6%)	15(21.4%)	7(10%)

Residence

Figure (1) revealed there was no significant difference ($p>0.05$)

between patients and control groups regarding to their residence in urban or rural areas.

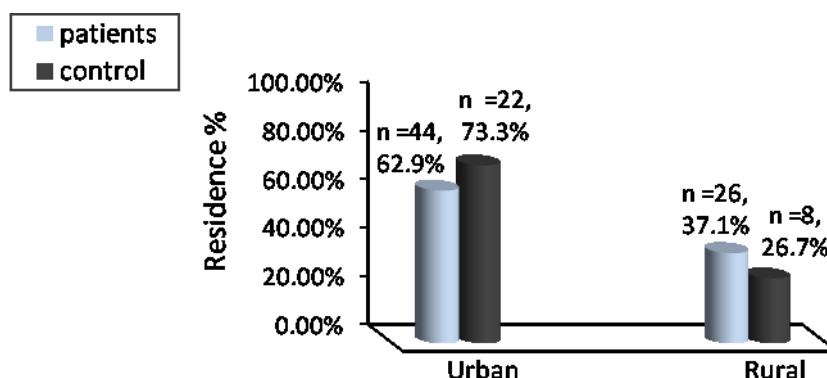


Figure1 Demonstrates the distribution (number, n and percentage,%) of pre-treatment infertile hyperprolactinemic patients and control groups according to their residence.

Family History:

The study showed low significant difference ($P < 0.05$) between patients

and control groups regarding to their family history of hyperprolactinemia (Fig. 2).

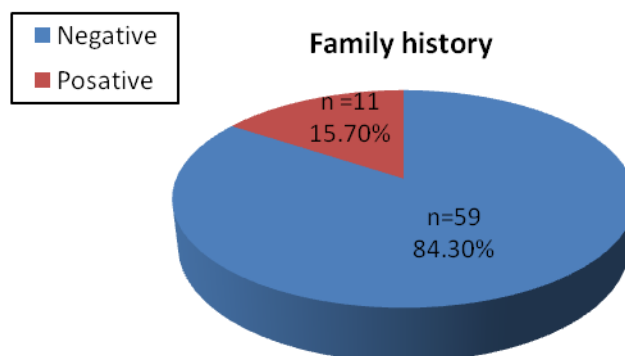


Figure 2 Demonstrates the distribution (number (n) and percentage (%) of pre-treatment infertile hyperprolactinemic patients and control groups according to their family history.

Type of Infertility

Thirty nine patients out of 70(55.7%) had history of primary infertility while

the other 31(44.3%) had history of secondary infertility (Fig. 3).

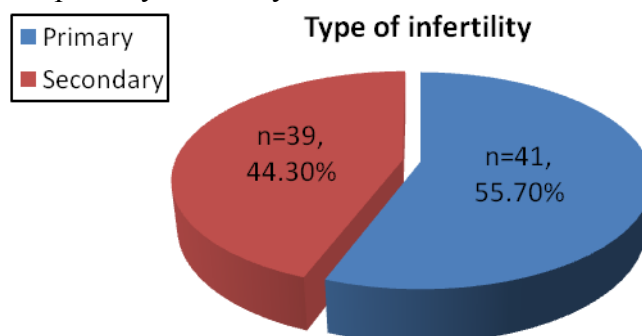


Figure 3 Distribution (number, n and percentage,%)of pre-treatment infertile hyperprolactinemic patients according to the type of infertility.

Menstrual Cycle Regularity and Galactorrhea:

There was high significant increase ($P<0.01$) in pre-treatment patient's groups compared with the control group regarding the presence of irregular cycle and galactorrhea. Statistical analysis showed high

significant decrease ($P<0.01$) in post-treatment patients compared with pre-treatment groups as well as low significance decrease ($P<0.05$) in post cabergoline treatment group compared with post bromocriptine treatment group regarding presence of these signs and symptoms (table.2).

Table 2 Represent the percentage,% of irregular cycle and galactorrhea among all studying groups.

parameter	Pre	Post	Pre	Post	control
	cabergoline	cabergoline	brmocriptine	brmocriptine	
Irregular cycle %	A 85.7 %	**a 11.4%	A 82.9%	**b 34.3%	B 8%
Galactorrhea %	A 48.6%	**a 2.9%	A 57.2%	**b 17.1%	B 3.3%

Values with different capital letters indicate significant difference at 0.01 level between groups.

Values with different small letters indicate significant difference at $p<0.05$ between groups.

** indicate significant difference at $p<0.01$ level between the pre and post- treatment of same patients group.

Hormonal Investigations:

The Table (3) shows the difference between pre-treatment infertile hyperprolactinemic patient's groups and control group and also between pre-treatment and post-treatment patients groups as well as between

two post treatment patients groups regarding mean values of serum prolactin, follicle stimulating hormone (FSH), luteinizing hormone (LH), progesterone ,testosterone , and thyroid stimulating hormone (TSH).

Table 3 mean values of serum prolactin, follicle stimulating hormone (FSH), luteinizing hormone (LH), progesterone, testosterone, and thyroid stimulating hormone(TSH) among all studying groups.

parameter	Pre cabergoline	Post cabergoline	Pre brmocriptine	Post brmocriptine	control
Prolactin (ng/ml)	A 52.1±2.7	**a 10.5±0.47	A 50.14±2.3	**b 16.4±0.59	B 8.3±0.29
FSH (mIU/ml)	A 3.5±0.21	** 5.9±0.28	A 3.8±0.17	** 5.6±0.27	B 6.3±0.32
LH (mIU/ml)	A 2.95±0.13	**a 4.85±0.18	A 2.67± 0.14	**b 4.3±0.17	B 5.1± 0.23
Progesterone (ng/ml)	A 5.1±0.59	**a 15.9±0.42	A 5.4±0.74	**b 13.7±1.2	B 17.5±0.61
Testosterone (ng/ml)	A 0.42±0.05	* 0.29±0.06	A 0.4±0.04	* 0.25±0.03	B 0.23±0.02
TSH(mIU/ml)	1.67±0.22	1.77±0.16	1.74±0.24	1.79±0.19	2.1±0.10

Values with different capital letters indicate significant difference at 0.01 level between groups.

Values with different small letters indicate significant difference at $p < 0.05$ between groups.

** indicate significant difference at $p < 0.01$ level between the pre and post- treatment of same patients group.

Discussion

The age of hyperprolactinemic infertile patients was classified into five groups. (table 1) demonstrated that the most common age group among infertile patients was the age group 28-32 years. This result was in agreement with the [11], who observed that among infertile hyperprolactinemic women, the most common age group was 25-34. Although the hyperprolactinemia can occur at any age group , the majority of patients were young and this is probably due to their great concern regarding getting pregnancy which made them consult the fertility specialist at earlier time . Regarding the residence, in both infertile and fertile women , the present study observed that urban proportion was higher than rural one (fig. 1). The result of this study was consistent with that of other study [12], who said that the prolactin levels significantly higher

for females in the informal settlements compared with the rural strata. The high prevalence of hyperprolactinemic infertile women in urban community is possibly due to wide-spread environmental pollutants exposure as well as the type of lifestyles and habits. The percentage of patients who had positive family history of hyperprolactinemia was significantly more than those in control group(fig. 2). This finding may be due to environmental factors such as, diet, sedentary lifestyle and stress. This result go in line with [13], who thought that hyperprolactinemic infertility may run in families and there is evidence of effect of life events in pathogenesis of hyperprolactinemia.

The percentage of infertile hyperprolactinemic patients with primary infertility was significantly higher than those with secondary type (fig.3).This result was in accordance

with those of [14], who found that the 60% of infertile hyperprolactinemic women had primary infertility and 40% had secondary infertility. This is probably due to that the patients with secondary infertility consult a specialist less frequently than others because they are in less urge for seeking medical help since they already got children.

In present study, the percentage of patients who had irregular cycle in pre-treatment hyperprolactinemic groups was highly significant increase than control women (table.2). This is may be due to most patients presented with irregular menstrual cycles as a consequence of disturbance in the main hormones which regulate the menstrual cycle. this result near to result of [15], who confirmed that percentage of menstrual irregularity in hyperprolactinemic women was 90.2%. The data obtained from the present study revealed that cabergoline and bromocriptine are both effective in restoring regular menstrual cycles. This data was in agreement with those of other study [16-18], who stated the efficacy of both cabergoline and bromocriptine in treatment of menstrual disorders in hyperprolactinemic women. The present study also demonstrated that cabergoline is more effective than bromocriptine in restoring regular cycle (table.2) and this result was supported by [18,19], who revealed that cabergoline are more effective than bromocriptine in restoring regular menstrual cycle.

The percentage of patients who had galactorrhea in pre-treatment hyperprolactinemic groups was high significantly increased than in control women (table.2). In post-treatment with cabergoline and bromocriptine, the percentage of patients who still had galactorrhea about 2.9% and 17.1% respectively with high significantly

decrease than pre-treatment groups (table.2) Galactorrhea was defined as in appropriate lactation and the most important hormones that regulate the process of lactation are prolactin, estrogen and progesterone. High levels of estrogen and progesterone inhibit lactation during pregnancy while in hyperprolactinemia, the high level of prolactin with low levels of estrogen and progesterone lead to galactorrhea [20]. The incidence of galactorrhea in hyperprolactinemic patients is between 30% and 80%, depending on the skill of the examiner and the degree of estrogen deficiency [21]. Present findings were consistent with that of [22], who stated that the percentage of hyperprolactinemic women with galactorrhea pre and post-treatment with dopamine agonist drugs were 54% and 9% respectively. This study also demonstrated that cabergoline is more effective ($P < 0.05$) than bromocriptine in treatment of galactorrhea and this in agreement with [23], who concluded that the cabergoline has more efficacy than bromocriptine in treatment of hyperprolactinemic galactorrhea.

Regarding the mean values of serum prolactin, there were highly significant increase in pre-treatment hyperprolactinemic patients compared with the control group (table.3). This result agreed with those of the [24, 25] these studies also got high levels of serum prolactin in hyperprolactinemic women. This finding is due to that the hyperprolactinemia is a condition in which too much prolactin is present in the blood of women who are not pregnant and in men [6, 26]. Also this study found that there was high significant decrease in post-treatment with cabergoline or bromocriptine drugs compared with pre-treatment groups regarding the mean values of serum prolactin hormone (table.3). This result matches with the results got by

[15,27], who mentioned that the dopamine agonist agents have become the treatment of choice for the majority of patients with hyperprolactinemic disorders this is because the dopamine agonist agents have a similar mode of action to dopamine in stimulating dopamine receptors on the prolactin-secreting pituitary cells and the stimulation of these receptors leads to inhibition of both prolactin secretion and synthesis [28]. In addition, the present result shown the serum prolactin level was less significantly decrease in patients who treated with cabergoline than those whom received bromocriptine (table.3). This finding have been well supported with data published by other studies [22,29], who demonstrated that cabergoline is more effective than bromocriptine in normalizing serum prolactin levels.

Regarding the mean values of FSH and LH hormones, this study found highly significant decrease in pre-treatment patient's groups compared with the control group (table.3). These results were agreed with others [25, 30, 31], who reported the decrease in serum LH, FSH levels in hyperprolactinemic women compared to normoprolactinemic women. The decrease in serum levels of FSH and LH hormones in hyperprolactinemic infertile women probably due to the high level of prolactin can work at both central and ovarian sites. In presence of high levels of prolactin, the ovulation may be suppressed due to the suppression of secretion of gonadotropins releasing hormone (GnRH) because the high levels of prolactin interference with hypothalamic-pituitary-gonadal axis through a positive feed back effect on dopamine secretion. Increase dopamine reduce GnRH secretion by suppressing arcuate nucleus function [3]. This leads to reduction in pulsatile

secretion of LH and FSH hormones. Also the high circulating levels of prolactin hormone interfering with the action of the gonadotrophins at the ovarian level and impairing normal gonadal steroid secretion, which in turn alters positive feedback effects at the hypothalamic and pituitary levels. This leads to lack of gonadotrophins cyclicity and to gonadal dysfunction in women including amenorrhea, oligomenorrhea with anovulation or infertility [23]. On the other hand, we observed that there was high significant increase in the serum levels of FSH and LH hormones of post-treated with cabergoline or bromocriptine drugs compared with pre-treated groups (table.3). This finding was appeared in close relation with that study [33], who described that the increase in serum FSH and LH during treatment with dopamine agonist drugs.

The results of this study revealed that highly significant decrease in pre-treatment hyperprolactinemic patients compared with the control group regarding serum level of progesterone hormone (table. 3). This is thought to be due to the production of progesterone hormone from corpus luteum within the ovary could occur in luteal phase of the menstrual cycle and the production of this hormone is dependent on continued pituitary LH secretion [34]. We can considered that the hyperprolactinemia is a cause of inadequate progesterone production during luteal phase after ovulation because of it is associated with luteal phase insufficiency and decrease pulsatile secretion of LH hormone [35]. This finding was in agreement with the finding of other study [25], who found that the serum level of progesterone was decreased in hyperprolactinemic patients. Moreover, the level of serum progesterone was highly significant

increase in post-treatment with cabergoline or bromocriptine drugs compared with pre-treatment groups as well as the level of progesterone hormone in patients who received cabergoline drug was higher than those patients who treated with bromocriptine (table.3). This result can be explained by that after treatment the serum level of prolactin of first group was lower than that of the second group so this lead to increase the serum progesterone level of first group more than of second one. These findings were supported by the study of [36], who stated that the dopamine agonist drugs have been reported to correct luteal phase defect associated with hyperprolactinemia. As well as other study was observed that there was an inverse relationship between the serum level of prolactin and progesterone hormone in hyperprolactinemia [37].

There was highly significant increase in serum testosterone level in pre-treatment hyperprolactinemic patients compared with control group (table. 3), while there was low significant decrease in post treatment with cabergoline or bromocriptine drugs compared with pre-treatment groups regarding the serum level of testosterone hormone (table. 3). In reproductive-aged women, 25% of the circulating testosterone comes from the adrenals; the ovaries contribute with another 25%. The rest of the testosterone is produced by the peripheral conversion of androstenedione in adipose tissue [38]. The testosterone that is produced in women is converted into the female reproductive hormone, estrogen [39]. In hyperprolactinemia, one of the major cause of this increment in serum testosterone can be low estrogen levels so the testosterone and androgens are circulated more freely in the body. Furthermore a role of PRL

on the human adrenal gland has been postulated in various clinical studies who have demonstrated for the first time the expression of the PRL receptor in the human adrenal gland and the high level of prolactin is a possible cause of adrenal over production of androgen [40]. This result also was mentioned by [41], who said that the serum testosterone level was higher and estradiol level lower in hyperprolactinemic patients than in control women. The decrease of serum testosterone after treatment with dopamine agonist drugs in the present results was an agreement with [42], who suggested that the dopamine agonist drugs reduces PRL and serum androgens and results in a significant clinical improvement in acne and hirsutism therefore, dopamine agonist drugs are recommended as monotherapy for hyperandrogenic and hyperprolactinemic women.

The present study shown there was no significant difference between all studying groups regarding the means of TSH (table.3). This result was in parallel with study of [43], who demonstrate that hyperprolactinemia suppresses pulsatile LH secretion but not TSH secretion and suggest that GnRH secretion is sensitive to hyperprolactinemia, but that TSH secretion is not.

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