DOI: 10.5455/medarh.2013.67.181-184
Med Arh. 2013 Jun; 67(3): 181-184
Received: March 25th 2013 | Accepted: June 15th 2013

CONFLICT OF INTEREST: NONE DECLARED

ORIGINAL PAPER

Prolactinomas in Infertile Women: Clinical and Endocrine Characteristics Before and After 24 Months of Treatment with Bromocriptine

Midhat Hajder[1], Elmira Hajder[2], Melika Dervisefendic[3], Remzo Samardzic[4], Enisa Alic[1]
Department of Endocrinology, Internal Clinic, University Clinical Center Tuzla, Tuzla, Bosnia and Herzegovina[1]
PZU Institute of Human Reproduction, Obstetrics and Perinatal Medicine, "Dr. Hajder" Tuzla, Bosnia and Herzegovina[2]
Health Center Gracanica, Bosnia and Herzegovina[3]
Cazin Health Center with Outpatient clinic, Bosnia and Herzegovina[4]

Introduction: Prolactinomas are the most common tumors of the pituitary gland and cause of gonadal dysfunction and infertility. **Objective:** To determine the effects of bromcriptin to normalize prolactin, gonadal function more tumor mass and infertility. **Patients and Methods**: A prospective clinical study included 30 infertile women with micro-macro prolactinoma. We analyzed clinical parameters, the function of sex hormones, the maximum tumor diameter before and after 24-month therapy with bromocriptine. **Results:** Micro prolactinomas were significantly (66.3% vs. 33.7%, p <0.001) over-represented in infertile women compared to macro prolactinomas. Galactorrhea / amenorrhea, and infertility are common symptoms of macro-micro prolactinomas. Infertile women with present macro prolactinomas had significantly higher mean values of PRL (1900.3 vs. 7.8, p <0.001), significantly lower mean FSH (3.4 vs. 4.6, p <0.001), LH (2.9 vs. 5.2, p <0.001) , luteal progesterone (2.5 vs. 14.8, p <0.001) and estradiol (E2) (98.2 vs. 180.1, p <0.001) compared to the control group. Infertile women with micro prolactinomas had significantly higher values of PRL (170.4 vs. 7.8, p <0.001), significantly lower mean FSH (4.1 vs. 4.6, p <0.01), LH (3.8 vs. 5.2, p <0.01) luteal progesterone (2.7 vs. 14.8, p <0.001) and E2 (120.3 vs. 180.1, p <0.001) compared to the control group. After 24-month therapy bromocriptine in infertile women with micro-macro prolactinomas followed by a significant decrease in PRL (p <0.05), a significant reduction of the maximal tumor diameter (p <0.05), a significant increase in FSH, LH, E2 (p <0.05) compared to baseline values before treatment and a significant reduction in fertility (p <0.05). **Conclusion:** The syndrome amenorrhea / galactorrhea and infertility are the most common symptoms of prolactinomas. Micro prolactinomas are more frequent in women. Bromocriptine is an effective drug in the treatment of hyperprolactinemia with prolactinomas. It effectively normalize prolactin, establishing gonadal function and reduces tumor mass. Key words: Prolactinomas, Gonadal dysfunction, Maximal tumor diameter, Bromocriptine.

Corresponding author: Midhat Hajder, PhD. Department of Endocrinology, Internal clinic. University Clinical Center Tuzla, Tuzla, B&H.

1. INTRODUCTION

Hyperprolactinemia (HP) is the most common hypothalamic-pituitary problem in clinical endocrinology. Besides prolactinomas (macro-micro prolactinomas) hyper PRL can be caused by incidental thyroid (pseudohiper PRL) and functional hyper PRL (iatrogenic, primary hypothyroidism, PCOS, chronic liver and kidney stress). Hyper PRL direct effect on ovarian granulosa cells disrupts steroidogenesis and flavored androgens into estrogens, and directly inhibits GnRH and causes hypogonadotropy hypogonadism. The consequences are secondary amenorrhea/galactorrhea, infertility and habitual abortion (1). In 90% of women are micro prolactinomas tumor, while in men macro prolactinomas (2). Prolactinoma are the most common type of pituitary tumors and are associated with galactorrheom, amenorrhea and hyperprolactinemia. Size of serum prolactin is linearly correlated with tumor size. Diagnosis can be easily set up on the basis of elevated basal prolactin and using MRI pituitary region (3). Dopamine agonists (Bromocriptine, Cabergolin) are drugs of first choice in the treatment of prolactinomas and thus infertility treatment in infertile women. Dopamine agonists (Bromocriptine) normalized hyperprolactinemia in 72-92% of cases, normalized gonadal dysfunction in more than 90%, reduce the tumor mass in 60-70% of cases. Resistance to bromocriptine occurs in 10-20% of patients (4). The purpose of this study was to determine the effects of bromocriptine in normalizing prolactin, gonadal function, tumor mass and infertility.

2. MATERIALS AND METHODS

Patients: A prospective controlled clinical study included testing 30 infertile women with prolactinomas. The

study was conducted from January 2010 until January 2012 in outpatient polyclinics institutions TK. All infertile patients were determined factor infertility micro-macro prolactinomas. Criteria for inclusion were infertile women with clinical, hormonal and MRI demonstrated prolactinoma. The studies excluded infertile women with other causes hyper PRL (pseudo hyperprolactinemia and functional hyperprolactinemia) and infertile women with other infertility factors (uterine, tubal factor, male factor unexplained infertility). All infertile women have a certain baseline: TSH, prolactin, FSH, LH and estradiol. All patients underwent MRI the pituitary gland was scanned by camera 1.5 T before and 6, 12 and 24 months after treatment with bromocriptine. The maximal tumor diameter was obtained as the mean of all measurements and is expressed in millimeters. Primary objective was to determine the clinical signs and symptoms of hyperprolactinemia, the effect of prolactin on gonadal function and maximal tumor diameter. The secondary objective was to determine the effects of bromocriptine effects on the size of prolactin, gonadal function, and tumor size.

Definitions: Macroprolactinoma were define if the serum PRL levels > 200 μg/L, pituitary tumor with the largest diameter> 1 cm, measured with MRI. Micro prolactinoma defined if the serum PRL less than 200 μg/ L, a pituitary tumor less than 1 cm in diameter (5). Normal ranges are as follows: FSH and LH, 3-8 IU/L, estradiol, and PRL, 5-15 μg/L.

Study protocol: A total of 30 infertile women with hyper PRL covered in this study, aged 25-40 years, with an average duration of infertility of 4.5 ± 3.1.

Patients were randomized into two groups: Group A: 10 patients with macro prolactinomas, and Group B: 20 patients with micro prolactinomas. Both groups were treated with bromocriptine (Bromergon, 2.5 mg tablets, Lek, Ljubljana, Slovenia), at a dose of 2.5 to 20 mg/day to normalize prolactin (less than 10 μg/L). Prolactin level was measured baseline, then monthly for 24 months. FSH, LH, estradiol were measured baseline and quarterly intervals, for a period of 24 months.

Statistical analysis: Statistical analysis was performed by application of software called SPSS for Windows version 19 Numerical data are presented as mean ± SD, number %. To test the hypothesis between groups used Student's t-test (Mann-Wyitney test and Fisher exact test with a significance level of p <0.05).

3. RESULTS

From a total of 30 infertile women with tumor hiperPRL (macro-micro prolactinomas), 10 of them had macroadenomas, while 20 had microadenomas. Clinical signs and symptoms in patients with micro prolactinomas are: mean age 27.1 years, 20% had headache, BMI 26.6 kg/m^2, even in one patient was not observed visula field defects (0%) had galactorrhea, 85% galactorrhea / amenorrhea, 80 % irregular menstruation 80%, infertility 80%, 0% had hypopituitarism and duration of infertility was 4.2 years (Table 1). Clinical signs and symptoms in patients with macro prolactinomas: mean age 26.9 years, 40% had a headache, 50% of visula field defects, BMI 27.4 kg/m^2, 90% galactorrhea, 80% galactorrhea / amenorrhea, 90% irregular menstrual cycle, 90% infertility, 50% patients had hypopituitarism, duration of infertility amounted to 5.6 years (Table 1).

Comparison of basal values of PRL, FSH, LH, estradiol and progesterone are shown in Table 2. Infertile women with present macroprolactinoma and consequent hyper PRL had significantly higher mean values of PRL (1900.3 vs. 7.8, p <0.001), significantly lower mean FSH (3.4 vs. 4.6, p <0.001), LH (2.9 vs. 5.2 p <0.001), midluteal progesterone (2.5 vs. 14.8, p <0.001) and E2 (98.2 vs. 180.1, p <0.001) compared to the control group.

Comparing basal values of PRL, FSH, LH, estradiol and progesterone in infertile women with hyperprolactinemia conditional micro prolactinomas compared to the control group are

Parameters	Macropro lactinomas	Micropro lactinomas
Total number (№) Age (yr) No. of patients with headache (%) No. of patients with visual field defects (%)	 10/30 (33.3%) 26,9± 2.1 4/10 (40%) 5/10 (50%)	 20/30(66.7%) 27.1± 2.1 4/20 (20%) 0%
BMI (kg/m2)	27.4 ± 2.1	26.6 ± 2.1
F-G scor>7 %	2/10 (20%)	3/20 (15%)
Galactorrhoea (%)	9/10 (90%)	17/20 (85 %)
Irregular MC (%)	9/10 (90%)	16/20 (80%)
Infertility (%) Galactorrhea+ amenorrhea (%) No. of patients with hypopituitarism (%) Duration of infertility	 9/10 (90%) 8/10 (80%) 5/10 (50%) 5.6 ± 3.1	 16/20 (80%) 16/20 (80%) 0% 4.2 ± 2.4
Legend: The results are expressed as mean ± SD, percentage %, MC-menstrual cycle; FG score– Ferriman-Gallwey scores, BMI–body mass index.		

Table 1. Anthropometric and clinical characteristics of reproductive women with prolactinomas

Parameters	Macropro lactinomas	Controls	p – value
Total number (№ Serum PRL (μg/liter)	40 1900.3 ± 13.3	20 7.8 ± 2.4	- cp<0.001
*Serum FSH (IU/L)	3.4 ± 0.4	4.6 ± 0.1	cp<0.001
*Serum LH (IU/L)	2.9± 0.7	5.2± 0.6	cp<0.001
ΔSerum Luteal Progesterone (nmol/l)	2.5± 0.4	14.8± 2.3	cp<0.001
*Estradiole (pmol/l)	98.2± 20	180.1± 31	cp<0.001
Legend: The results are expressed as mean ± SD, percentage%, statistical significance p<0.05 level of significance, and ap<0.05, bP<0.01, cp<0.001, for the group with macrorprolactinomas Vs. control group, PRL – prolacti, *early follicular phase, Δmidluteal progesterone.			

Table 2. Basal endocrine characteristics of infertile women with hyperprolactinemia and makroprolactinomas and in comparison with the control group

Parameters	Micropro lactinomas	Controls	p – value
Total number (№ Serum PRL (μg/liter)	20 170.4 ± 65.3	10 7.8 ± 2.4	- cp<0.001
*Serum FSH (IU/L)	4.1 ± 0.3	4.6 ± 0.1	ap<0.05
*Serum LH (IU/L)	3.8± 0.7	5.2± 0.6	bp<0.01
ΔLuteal Progesteron (nmol/l)	2.7± 0.4	14.8±2.3	cp<0.001
*Serum Estradiole (pmol/l)	120.3± 20.9	180.1± 31	cp<0.001
Legend: The results are expressed as mean ± SD, percentage%, statistical significance p<0.05 level of significance, and ap<0.05, bP<0.01, cp<0.001, for the group with macroprolactinomas Vs. control group, PRL – prolactin, * early follicular phase, Δmiddle Luteal progesterone.			

Table 3. Basal endocrine characteristics of infertile women with hyperprolactinemia mikroprolaktinomom and in comparison with the control group

Parameters	Macroplacti nomas	p–value	
	Responsive	Resistant	
Total number (№	6/10	4/10	-
Basal serum PRL (μg/liter)	1290 ± 1342	2654 ± 1854	ap<0.05
*PRL levels after 2-yr bromcriptine (μg/liter)	5.9 ± 0.6	54.7 ±32.6	cp<0.001
Basal serum FSH (IU/L)	3.4 ± 0.4	2.8 ± 0.5	ap<0.05
*FSH (IU/L)	4.4 ± 0.2	3.1 ± 0.4	cp<0.01
Basal serum LH (IU/L)	2.9± 0.7	1.1± 0.8	bp<0.01
*LH (IU/L)	4.9± 0.7	3.1± 0.4	bp<0.01
Basal serum progesterone (nmol/l)	1.5± 0.4	1.2± 0.4	ns
*Progesterone (nmol/l)	12.5± 0.4	5.5± 0.6	cp<0.001
Basal serum estradiol (pmol/l)	98.2± 20	72.1± 21	ap<0.05
*Estradiol (pmol/l)	198.1± 20	102.2± 20	cp<0.001
Bazal maximal tumor diameter (mm)	23.5± 7.4	33.4± 6	bp<0.01
*Maximal tumor diameter (mm)	3.6± 2.5	21.4± 6.6	cp<0.001
% Decrease of maximal tumor diameter	83.3	49.8	cp<0.001
Maximal bromcriptine dose (mg/wk)	13.6± 2.5	25.6± 3.4	cp<0.001

Legend: The results are expressed as mean ± SD, percentage%, statistical significance p<0.05 level of significance, and ap<0.05, bP<0.01, cp<0.001, for the group with Responsive Vs. Resistant (bazal); ap<0.05, bP<0.01, cp<0.001, for the group with Responsive Vs. Resistant (*), PRL–prolactin. . * hormone levels after 2-year treatment bromocriptine.

Table 4. Response to bromocriptine in a 24–month treatment in infertile women with macroprolactinomas

given in Table 3. Infertile women with present micro prolactinomas and consequent hiperPRL had in the early follicular phase of the menstrual cycle significantly higher mean values of PRL (170.4 vs. 7.8, p <0.001), significantly lower mean FSH (4.1 vs. 4.6, p <0.05), LH (3.8 vs. 5.2, p <0.001) luteal progesterone (2.7 vs. 14.8, p <0.001) and E2 (120.3 vs. 180.1, p <0.001) compared to the control group.

Basal PRL value in infertile women with macro prolactinomas was 1900.3 μg /L. After treatment with bromocriptine, 60% (sensitive) had PRL value <15 μg / L, while 40% were (resistant), had drop PRL but not values <15 μg/L (Table 4). In the subgroup responsive patients had significantly lower mean basal PRL (1290 vs. 2654, p <0.05) * PRL (5.9 vs. 54.7, p <0.001), the maximal bromocriptine dose (13.6 vs. 25.6, p <0.001) compared to subgroup resistent. (Table 4). Hyperprolactinemia often lowered gonadotropins and ovarian hormones E2 and progesterone. Basal FSH values (3.4 vs. 2.8, p <0.05), * FSH (4.4 vs. 3.1, p <0.01), basal LH (2.9 vs. 1.1, p <0.01), LH * (4.9 vs. 3.1, p <0.01), luteal progesterone (12.5 vs. 5.5, p <0.001), basal E2 (98.2 vs. 72.1, p <0.05), * E2 (198.1 vs. 102.2 p < 0.001) were significantly higher in the subgroup responsive with respect to the subgroup resistant. Bromocriptine normalizes PRL values but also reduces the size of prolactinomas. Maximal basal tumor diameter (23.5 vs. 33.4, p <0.01) * maximal tumor diameter (3.6 vs. 21.4, p <0.001) and % decrease of maximal tumor diameter (83.3 vs. 49.8, p <0, 01), were significantly higher in the subgroup responsive in relation to the subgroup resistant (Table 4).

Basal PRL value in infertile women with micro prolactinomas was 170.4 μg/L. After treatment with bromocriptine 75% of them (sensitive) had PRL value <10 μg /L, while 25% (resistant) had decrease PRL but not in value <15 μg/L (Table 5).

In the subgroup (A) patients had significantly lower mean basal PRL (169.2 vs. 219.3, p <0.05) * PRL (5.6 vs. 32.5, p <0.01), taking the maximal bromocriptine dose (10.6 vs. 15.7, p <0.001) compared to subgroup (B) (Table 5). In mild hiperPRL value of FSH is normal. Basal LH (3.9 vs. 3.1, p <0.05), LH * (5.9 vs. 4.1, p <0.01), luteal progesterone (12.5. vs. 6.5, p <0.001) * E2 (298.1 vs. 192.3, p <0.001) were significantly higher in the subgroup of A with respect to the subgroup B. Bromocriptine not only to normalize PRL values , higher reduces the size of prolactinomas. Maximal basal tumor diameter (8.1 vs. 8.9, p <0.05) * maximal tumor diameter (1.5 vs. 5.3, p <0.01), and % decrease of maximal tumor diameter (80.2 vs. 34.6, p <0.001) were significantly lower the subgroup A in relation to the subgroup B (Table 5).

4. DISCUSSION

Prolactinomas are the most common tumors of the pituitary gland, leading to disturbances in the hypothalamic-pituitary-gonadal axes (3). Divided by the size of the macroprolactinoma and micro prolactinoma. Macro prolactinomas are defined if the serum prolactin is greater than 200 μg/L, a pituitary tumor with diameter greater than 1 cm, measured by MRI, while micro prolactinomas are defined if serum prolactin is less than 200 μg / L and pituitary tumor diameter measured MRI, less than 1 cm (5). Tumor size was a direct linear correlation with hyperprolactinemia (3) of the women at the time of diagnosis of hyperprolactinemia are detected in 90% of cases of micro prolactinomas, and in 10% of cases of macroprolactinoma, while men more often macroprolactinoma. Slightly higher frequency of micro prolactinoma in women is the cause of re-

Parameters	Microprola ktinomas	p–value	
	Responsive (A)	Resistant(B)	
Total number (№ Basal serum PRL (μg/ liter) *PRL (μg/liter)	15/20(75%) 169.2 ± 32.3 5.6 ± 3.6	5/20(25%) 219.3 ± 31.4 32.5 ±16.2	- ap<0.05 bp<0.01
Basal FSH (IU/L) *FSH (IU/L)	4.5 ± 0.4 5.3 ± 0.5	4.2 ± 0.5 4.9 ± 0.4	ns ns
Basal serum LH (IU/L) *LH (IU/L)	3.9± 0.7 5.9± 0.6	3.1± 0.8 4.1± 0.4	ap<0.05 bp<0.01
Basal serum progesterone (nmol/l) *Progesterone (nmol/l)	1.5± 0.4 12.5± 0.5	1.2± 0.4 6.5± 0.4	ns cp<0.001
Estradiol (pmol/l) *Estradiol (pmol/l)	98.6± 20.7 298.1± 20.8	88.1± 28.5 192.3±36.2	ns cp<0.001
Basal maximal tumor diameter (mm) *Maximal tumor diameter (mm) % Decrease of maximal tumor diameter Maximal bromcriptine dose (mg/wk)	8.1±1.4 1.5± 2.1 80.2 10.6±1.5	8.9±1.6 5.3±2.4 34.6 15.7± 1.4	ap<0.05 bp<0.01 cp<0.001 cp<0.001

Legend: The results are expressed as mean ± SD, percentag e%, statistical significance p<0.05 level of significance, and ap<0.05, bP<0.01, cp<0.001(basal), for the group with Responsive Vs. Resistant; ap<0.05, bP<0.01, cp<0.001, for the group with Responsive Vs. Resistant(*), PRL–prolactin. . * hormone levels after 2-year treatment bromocriptine.

Table 5. Response to bromocriptine in a 24–month treatment of infertile women with microprolactinomas

productive disorders (6, 7). Symptoms that occur with prolactinoma are galactorrhea, amenorrhea, gonadal dysfunction, infertility, and if present macroprolactinoma can occur and symptoms such as headache, visual disturbances, panhypopituitarism (1, 7). Prolactin direct effect on GnRH leads to dopamine blocking activity, and inhibition of the action of dopamine is absent, so that hyperprolactinemia, and further inhibition of GnRH leads to failure gonadotropin and estradiol. Prolactin direct effect on ovarian granulosa cells disrupts ovarian steroidogenesis, and it does not come up to the conversion of androgens to estrogens, and decreased estradiol (8, 9). The same mechanism leads to luteal phase defect, causing anovulation (10). Consequence of hyperprolactinemia in women's reproductive infertility, and the existence of occult hyperprolactinemia are recurrent abortions (1, 11). The first line of treatment micro prolactinomas are antagonists of dopamine (bromocriptine, cabergolin), are effective in the treatment of prolactinomas in both sexes (12). Bromocriptine was the first dopamine agonist to be introduced into clinical practice. It is a semisynthetic ergot derivatives of ergoline, a D2 receptor agonist with antagonist properties at D1 receptors. Its elimination half life is relatively short (3.3 hours), and therefore it usually has to be taken 2 or 3 times daily (13). Those in the 75-92% of normalized prolactin levels, establishing gonadal function in more than 90% of cases, reduce the tumor mass in 60-70% of cases and establish normal pituitary function. Approximately 10-26% of tumors develop resistance to therapy bromocriptine and 31-69% in the cabergolin therapy (4). In such cases prolactinoma require surgical treatment. Surgical resection of the adenoma is usually associated with a risk of recurrence in all patients. Hyperprolactinemia recurs one to five years after surgery in 10% -50% of patients with micro prolactinomas and in 20% -90% of patients with macro prolactinomas (14). Results of this study showed that the prevalence micro prolactinoma in reproductive women were 70% and 30% of macro prolactinomas. The predominant symptoms in existence macroprolactinoma were galactorrhea in 87.3%, galactorrhea-amenorrhea in 81.6%, panhypopituitarism in 52% of cases, irregular menstruation in 82% of infertility in 83% patients. In case of micro prolactinoma symptoms were galactorrhea in 83.3% of cases, galactorrhoea -amenorrhea in 82.3%, irregular menstrual periods were detected in 74.2% and 75.3% of infertility in women. The results are explained by hyperprolactinemia acts directly on the hypothalamus and pituitary gland and leads to secondary hypogonadism that causes these symptoms, while symptoms such as headache, visual disturbances and panhypopituitarism due to the pressure of the tumor mass on the surrounding structures in the hypothalamic-pituitary region. Our results are consistent with the results of other authors (15, 16). The results of our study indicate that the macro-and micro prolactinomas lead to significantly reduced ($p < 0.05$) values of FSH, LH, estradiol and luteal progesterone. The results of this study are consistent with results of other authors (11, 16). Results of this study indicated that bromocriptine therapy significantly reduced the prolactin $p<0.05$ in the macro-and micro prolactinomas. Bromocriptine therapy has significantly raised the value of FSH, LH, estradiol and luteal progesterone and led to the normalization of gonadal function in 90% of patients. After a 24-month treatment with bromocriptine there was a significant reduction ($p<0.05$), maximal tumor diameter in 83% of cases in sensitive prolactinomas and in 49.8% of cases of resistant prolactinomas. Results Colaoa and associates suggest that dopamine agonist (cabergolin) for a period of 24 months led to a significant reduction in the maximal diameter of the tumor ($p<0.01$) in micro-macro prolactinomas. Colao said that there were macro-micro prolactinomas that are sensitive and resistant to dopamine agonist therapy (16).

5. CONCLUSION

Micro-macro prolactinomas are cause of gonadal dysfunction, amenorrhea and infertility. Bromocriptine therapy is the first line of treatment micro prolactinoma and macroprolactinoma. Therapeutic effects are normalizing menstrual cycle in over 90% of cases and restore fertility in 60% of cases. Following the effect of therapy is to reduce the tumor mass. In 10-30% of infertile women with micro-macro prolactinomas there is resistance to therapy, bromocriptine, and such cases require surgical treatment.

RREFERENCES

1. Zargar AH, Laway BA, Masoodi SR, Bhat MH, Wani AI, Bashir MI, Salahuddin M,
2. Rasool R. Clinical and Etiological Profile of Hyperprolactinemia -Data from a Tertiary Care Centre. JAPI 2005;53:288-290.
3. Leung AK, Pacaud.D. Diagnosis and Management of Galactorrhea. American Family Physician 2004; 70:543-550.
4. Biller BM. Hyperprolactinemia. Int J Fertil Womens Med 1999; 44:74-7.
5. Losa M, Mortini P , Ribotto P,Giovanelli M. Therapeutic Options in Patients with Micro prolactinoma Businessbriefing:europeanendocrinereview2006;79-80.
6. Colao A, Di Sarno A, Cappabianca P, Briganti F, Pivonello R, Di Somma C, Faggiano A, Biondi B, Lombardi G. Gender differences in the prevalence, clinical features and response to cabergoline in hyperprolactinemia. Eur J endocrinol 2003; 148:325–331.
7. Delgrange E, Trouillas J, Maiter D, Donckier J, Tourniaire J. Sex-related difference in
8. the growth of prolactinomas: a clinical and proliferation marker study. J Clin Endocrinol Metab 1997; 82(7): 2102-2107.
9. Qari FA. Manifestations of Hyperprolactinoma and its Management by Bromocriptine and Cabergoline. JKAU: Med. Sci 2008; 15 : 51-62.
10. Kostal M, Tosner J. The influence of latent hyperprolactinaemia on the levels of LH, FSH, E2 and Tin the midfollicular phase of the cycle. Arch Gynecol Obstet 1997; 259: 65–68.
11. Kauppila A, Leinonen P, Vihko R, Ylöstalo P . Metoclopramide induced hyperprolactinemia impairs ovarian follicle maturation and corpus luteum function in women. J Clin Endocrinol Metab 1982; 65:955–960.
12. Kauppila A, Kirkinen P, Orava M, Vihko R. Effects of metoclopramide induced hyperprolactinaemia during early follicular development on human ovarian function. J Clin Endocrinol Metab 1984; 59: 875–881.
13. Hajder E, Hajder M, Zukic E, Samardzic R. Basal Hyperprolactinemia,Occult Hyperprolactinaemia and Gonadotropins secretion in infertile women. HealthMED 2010; 4 / Number 3 : 664-671.
14. Kars M, Souverein P.C., Herings M.C. et al. Estimated age- and sex-specific incidence and prevalence of dopamine agonist-treated hyperprolactinemia. Journal of Clinical Endocrinology and Metabolism 2009; 94, 2729–2734.
15. Webster J. A comparative review of the tolerability profiles of dopamine agonists in the treatment of hyperproloctinaemia and inhibition of lactation. Drug Saf 1996;14:228-38.
16. Losa M, Mortini P, Barzaghi R, Gioia L, Giovanelli M. Surgical treatment of rolactinsecreting pituitary adenomas: early results and long-term outcome. J Clin Endocrinol Metab 2002; 87(7): 3180-3186.
17. Zargar AH, Laway BA, Masoodi SR, Bhat MH, Wani AI, Bashir MI, Salahuddin M,Rasool R. Clinical and etiological profile of hyperprolactinemia-data from a tertiary care centre. J Assoc Phyicians India 2005; 53: 288-290.
18. Colao A, Vitale G, Cappabianca P, Briganti F, Ciccarelli A, De Rosa M, Zarrilli S, Lombardi G. Outcome of Cabergoline Treatment in Men with Prolactinoma: Effects of a 24-Month Treatment on Prolactin Levels, Tumor Mass, Recovery of Pituitary Function, and Semen Analysis. The Journal of Clinical Endocrinology & Metabolism 2004; 89(4):1704–1711.