Journal of Pharmaceutical Research International

32(23): 71-77, 2020; Article no.JPRI.60864
ISSN: 2456-9119
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

Endocrine Markers of Fertility Potential in Reproductive Age Women with Idiopathic Hyperprolactinemia

Alina Valerievna Atalyan[1*], Leonid Fedorovich Shelokhov[1] and Lyubov Ilinichna Kolesnikova[1]

[1]FSBSI "Scientific Center of Family Health Problems and Human Reproduction", 664003, Irkutsk, St. Timiryazeva 16, Russia.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2020/v32i2330790
Editor(s):
(1) Dr. Rafik Karaman, Al-Quds University, Palestine.
Reviewers:
(1) Shashwati Sen, University of Delhi, India.
(2) Padam Raj Pant, Tribhuvan University, Maharajgunj Medical Campus, Nepal.
(3) Muhjah Falah Hassan, University of Kerbala, Iraq.
Complete Peer review History: http://www.sdiarticle4.com/review-history/60864

Original Research Article

Received 03 July 2020
Accepted 09 September 2020
Published 28 September 2020

ABSTRACT

Background: Hyperprolactinemia (HP) is a common endocrine gynecological disorder in women of reproductive age manifested with menstrual irregularity and sterility subfertility among the majority of women with this disorder.
Objective: The aim of this study was to assess the endocrinal markers of inferility in premenopausal women with idiopathic hyperprolactinemia.
Materials and Metahodology: The study included 82 women: 27 healthy women, 22 fertile women with idiopathic HP and 33 patients with endocrine sub fertility with idiopathic HP. All women underwent a standard history taking, clinical examinations. Lab tests were performed in all women and included the detection of the concentrations of prolactin, thyroid-stimulating hormone, thyroxine, triiodothyronine, cortisol, gonadotrophic hormones, testosterone, and estradiol by ELISA method.

E-mail: hr.testinghub@gmail.com;

Results: The study results demonstrated that subfertile women with HP are characterized by an increase of follicle-stimulating hormone and free triiodothyronine and a decrease of estradiol and cortisol when compared with fertile patients with HP and Healthy patients.
Conclusion: The better glucocorticoid and ovarian function of fertile women with HP supposed to be an essential issue in their reproductive ability.

Keywords: Prolactin; gonadotropins; thyroid-stimulating hormone; thyroid hormones; cortisol; sex steroids; idiopathic hyperprolactinemia; endocrine infertility.

1. INTRODUCTION

One of the most pressing problems in modern medicine is subfertility. In the majority of cases (42.6 – 65.3%), the cause of subfertility refers to female reproductive system disorders. The endocrine subfertility is widespread common and relates tocomprising 29-43% of the female subfertility sterile female population[1]. Hyperprolactinemia is traditionally considered as one of the major causes of female reproductive problems [2,3], and it is also a predictor of cardiovascular diseases, metabolic disorders, hormone-dependent gynecological diseases, and obstetric complications [4–6,7]. The frequency of hyperprolactinemiain patients, who suffer from gynecological disorders, is 11-47%. Some authors reported that, in the structure of female endocrine subfertility, hyperprolactinemia occurs in 18.9%-40% of all cases[8,9], and among young women with menstrual irregularities - in 5.5-13.8% [10].

The etiology of hyperprolactinemia allows the authors to classify this condition as physiological, pathological, including pharmacological[11,12]. The determination of the causes or their combinations requires a careful examination of the patient's medical history and clinical assessment[13]. Among pathological hyperprolactinemia, its idiopathic form is quite common and often has a genetic nature[14]. The key mechanism in the development of HP as a primary disease is the pituitary-hypothalamic-ovariandisfunction,impairment of tonic inhibitory of prolactin secretion by dopamine, and subsequent development inhibition of gonadotropins and sex hormones. The role of kisspeptin-1 in the genesis of anovulatory subfertility associated with HPwas demonstrated as well [15].

Prolactin secretion is controlled by prolactin inhibitor factor that is secreted from hypothalamus, other factors like vaso active inhibitory peptide (VIP) and Thyroid relising hormone (TRH) cause to increase prolactin secretion. In fact, TRH in addition to increasing TSH causes to rise prolactin level. In patients with primary hypothyroidism, increased levels of TRH can cause to rise prolactin levels and these patients may have galactorrhea. Different increased level of serum prolactin has been reported in 30% of patients with primary hypothyroidism [14].

Along with the pituitary-ovarian system (axis), thyroid hormones play an important role in the pathways of female reproductive disorders. The close relationship between the thyroid and reproductive systems was shown, and it's well known that the thyroid gland activity significantly changes during different periods of women'slife. Physiologically, TSH and prolactin act synergistically with FSH and LH, and they all have indirect effects on the growth and development of follicles. The disorders of the thyroid gland are frequent in patients with hyperprolactinemia, considered as an additional factor that determines the development of ovarian-menstrual function disturbences [16,3]. However, not all hyperprolactinmicpatients suffer subfertility. In addition, there is evidence that the frequency of menstrual function disorders can be comparable in the presence and absence of hyperprolactinemia[17]. However, it is not still clear whenhyperprolactinemia is the cause of endocrine, and in which cases this condition has no association with a reproductive disorders.

The objective of the study was to determine the endocrine features of fertile and subfertile women with hyperprolactinemia.

2. MATERIALS AND METHODS

Eighty-two women of reproductive age participated in the cross-sectional study from the Jan 2017- Nov 2019. All patients were examined at the outpatient department of the "Scientific Center of Family Health Problems and Human Reproduction" (Irkutsk, Russia). All the enrolled women were in the age between 22-25 years.

The control group (group 0) consisted of 27 practically healthy women without gynecological pathology who had a pregnancy the past 2 years without any lactation history (age 23.6±0.3 years). The first clinical group (group 1) included 33 subfertile patients in condition of stable hyperprolactinemia (age 24.4±0.3 years). The second clinical group (group 2) included 22 fertile women with idiopathic HP with preserved reproductive function (average age 23.5±0.4 years).

The inclusion criteria for both clinical groups were women with HP as follows: Group 1 included women with inability conceive alteast for two year of unprotected, timed intercourse, who had astable increase of serum prolactin level. A stable increase of serum prolactin concentration, the absence of pregnancy during at least for 2 years, having a regular sex without contraception (group 1). Group 2 included women who had any pregnancy 2 years back year but serum prolactin level was raised. The diagnosis of HP occurred within the second group before pregnancy and a year after child-birth.

The exclusion criteria were: the pituitary tumor, genital endometriosis, infectious and inflammatory conditions of the pelvic organs,(pelvic inflammatorydisease) ovarian and (or) adrenal hyperandrogenism, the male infertility factor, the use of dopamine agonists and medications that increase the concentration of prolactin (neuroleptics, antidepressants, monoaminooxidase inhibitors, oral contraceptives, antihistamines, opiates), Hyperandrogenism such as Polycystic ovarian syndrome (PCOS) has also been excluded.

After detail history taking and clinical examination,We conducted the blood sampling, blood sample was taken from the median cubital vein for hormonal studies ,from 8 to 9 am, within the early follicular phase (5-7 days of the menstrual cycle). The blood serum performed as research material.

To determine serumtriiodothyronine (T3), thyroxine (T4), thyroid-stimulating hormone (TSH), prolactin (PRL), luteinizing hormone (LH), follicle-stimulating hormone (FSH), cortisol, free thyroxine (free T4), testosterone ("Alcor Bio", Russia); free triiodothyronine (free T3) (XEMA); estradiol ("Elisas") we used immunoassay analyzer "Ultra Microplate Reader - Elx808" (USA).

The main criteria for laboratory and instrumental diagnostics of functional hyperprolactinemia were:

- prolactin increase in blood serum is higher than 680 mU/ml;
- computer or MR imaging to exclude micro -and macroadenoma, Empty sella syndrome (ESS); other tumors.

2.1 Statistical Data Analysis

In accordance with the data distribution type , we used various statistical analysis algorithms. We performed the descriptive statistics to represent quantitative data: average, standard deviation, median, 25th and 75th percentiles. We approached the Student's t-test to examine the statistical hypothesis for the equality of two independent samples. We approached the Mann-Whitney test as nonparametric alternatives for independent samples to the t-test. A p-value of < 0.05 was consideredstatistically significant. We performed all calculations by means of the Statistics package STATICTICA 10 StatSoft Inc. (USA).

2.1.1 Design of the study and estimation of sample size

The design of the study was a randomized, prospective, double-blinded, and controlled clinical study. The level of confidence in this study was taken 95% and by assuming that 30% of the population is exposed to a risk factor and assuming an equal number of cases and controls in matched study design hypothesized odds ratio of 2.0. Level of significance = 5%, Power = 80%, Type of test = two-sided.

Level of Significance: This is typically assumed as 5%. Type I error is inversely proportional to sample size. Power: Power was taken as 80% and Type II error is directly proportional to sample size.

3. RESEARCH RESULTS

Under the results of the physical examination, the study groups (Table 1.) are comparable in terms of body mass index (BMI) and blood pressure (BP).

In the group of sterile women in condition of hyperprolactinemia, 70% (n=23) had primary subfertility and 30% (n=10) had secondary

subfertility. The secondary subfertility had a history of childbirth with complications (10%; n=1), abortions (30%; n=3), and missed abortions (10%; n=1). The condition of menstrual irregularities in groups with hyperprolactinemia referred to 69.7% of cases with subfertility and to 59.1% - with preserved fertility (Fig. 1).

The subfertile women with diagnosis of Oligomenorrhea had an increased prolactin content in 6.1% of cases. The fertile women with hyperprolactinemiahad the same diagnosis in 9.1% of cases; The percentage of diagnosed polymenorrhea constituted 27.3% and 18.2% of cases, respectively. The condition of acyclic hemorrhages referred to the group of sterile women in 15.2% of cases against 9.1% in the group of fertile women with hyperprolactinemia. The menstrual irregularities ad modum dysmenorrhea in both groups with an increased content of prolactin occurred in 22.7% and 21.2% of cases, respectively.

In order to assess the state of the main links of the neuroendocrine system for women in condition of hyperprolactinemia, we determined the serum content of PRL, LH, FSH, estradiol, testosterone, TSH, T3, free T3, T4, free T4, cortisol, which characterize the pituitary-ovarian, pituitary-thyroid links and glucocorticoid function of the adrenal glands.

Table 1. Results of the female physical examination

Physical examination data	Control group N=27	Group 1 N=33	Group 2 N=22
	M±σ Me(25;75 percentiles)		
BMI	20,9±3,2 20,3 (18,3; 23,0)	22,1±4,7 20,9(18,7; 25,9)	22,2±3,3 21,9(19,1; 23,7)
BP systolic diastolic	115,5±12,7 120 (110; 120) 72,1±8,1 70 (70; 80)	110,6±11,1 110 (110; 120) 72,8±8,3 70 (70; 80)	112,3±8,4 120 (110; 120) 72,8±5,5 70 (70; 80)

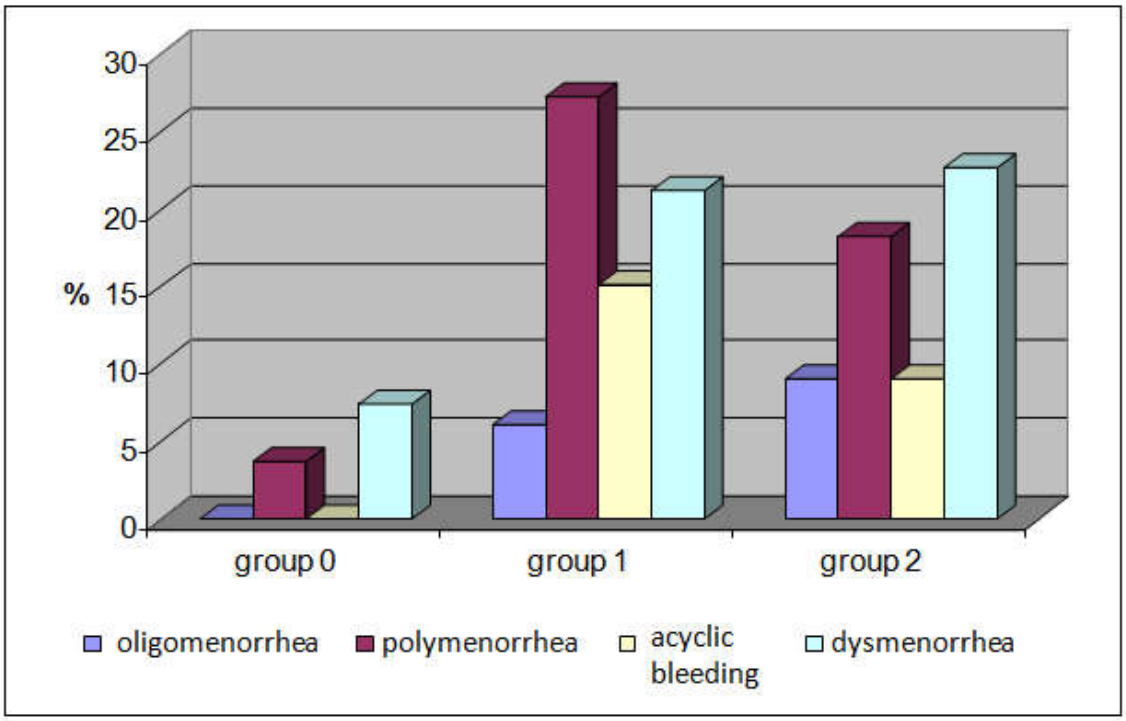

Fig. 1. The menstrual irregularities within groups under study

Table 2. The concentration of pituitary-ovarian hormones within the group of examined women

Indicators of	Group 0 (control) n=27	Group 1 n=33	Group 2 n=22	p
	M±σ Me (25th; 75th percentile)			
Prolactin, mU/ml	263,48± 99,35 247.0 (187,0; 337,0)	729,09±111,17 715.00 (657,00; 818,00)	935,46±292,64 844.50 (716,00; 1262,00)	P^1_{01}=0,001 P^2_{02}=0,0001 P^1_{12}=0,001
LH, mU/ml	4,47±2,21 4.3 (2,6; 5,4)	4,81±1,71 4.6 (3,7; 6,2)	5,29±2,27 5.5 (3,5; 7,0)	
FSH, mU/ml	4,60±2,15 4.80 (2,70; 5,90)	6,34±2,26 6.20 (4,70; 7,20)	4,78±2,28 4.45 (3,10; 5,60)	P^1_{01}=0,004 P^1_{12}=0,017
LH/FSH	0,88±0,44 0.75 (0,48; 1,13)	0,85±0,43 0.71 (0,53; 1,17)	1,17±0,56 1.04 (0,80; 1,69)	P^1_{12}=0,001
Estradiol, pmol/l	95,36±75,95 92.00 (22,00; 133,00)	73,30±64,87 53.00 (22,50; 105,00)	170,30±133,75 140.50 (92,0; 208,0)	P^2_{12}=0,033 P^2_{02}=0,006
Testosterone, pM/l	2,70±1,24 2.60 (1,70; 3,10)	2,75±1,31 2.80 (1,80; 3,50)	3,08±1,15 3.10 (2,30; 3,50)	

Note: [1] –Student's t-test; [2] – U-test

Table 3. Concentration of thyrotrophin, thyroid-stimulating hormones and cortisol within the group of examined women

Indicators of	Group 0 (control) n=27	Group 1 n=33	Group 2 n=22	P
	M± σ Me (25th and 75th percentile)			
TSH, mU/ml	1,53±0,58 1.40 (1,10; 1,90)	2,06±0,78 1.90 (1,60; 2,70)	2,07±0,90 2.00 (1,20; 2,70)	P^1_{01}=0,015 P^1_{02}=0,006
T3, nmol/l	2,2±0,1 2.2 (1,9; 2,8)	2,6±0,7 2.4 (1,9; 3,2)	2,2±0,2 2.3 (1,8; 2,7)	
Free T3, pmol/l	4,0±0,1 3.9 (3,7; 4,4)	5,1±1,9 4.5 (4,1; 5,3)	3,9±0,2 4.0 (3,4; 4,2)	P^1_{12}=0,010
T4, nmol/l	124,4±5,3 119.0 (104,0; 142,0)	129,5±9,6 136.0 (113,5; 148,5)	138,5±7,2 130.0 (116,0; 150,0)	
Free T4, pmol/l	15,87±0,71 15.9 (13,0; 18,0)	14,3±1,0 13.7 (12,3; 15,9)	15,8±0,8 15.2 (13,1; 17,6)	P^2_{01}=0,043
Cortisol, nm/l	475,27±140,59 446.0 (369,00; 649,00)	503,84±238,21 463.00 (368,00; 654,00)	700,18±352,59 601.50 (418,00; 950,00)	P^2_{02}=0,004 P^1_{12}=0,029

Note: [1] –Student's t-test; [2] – U-test.

Table 2 also shows that in the blood serum of subfertile patients, the content of PRL exceeds the control level by 277%; for fertile women, the concentration of PRL is 128% against the content of PRL within the group of subfertile patients.

In case of the LH indicators concentration analysis (Table. 2) within all clinical groups and in the control group, we can observe that these values do not exceed the reference range. As opposed to the concentration of LH, hyperprolactinemia of sterile women has a

symptom of a statistically significant increase (by 37.8%) of FSH content in comparison to the same value within the control group and by 32.6% in comparison to the concentration of fertile women. The estradiol concentration within the group of fertile patients with hyperprolactinemia exceeded the same value within the group of subfertile patients by 137%. The level of testosterone in all the groups of women under study (table. 2) was within the reference range without significant differences.

In accordance with the data of Table 3, the concentration of thyroid-stimulating hormone within groups of women with hyperprolactinemia, both fertile and sterile, is statistically much higher than within the control group.

We registered differences between groups of patients with hyperprolactinemia and other fertility state by the level of free T3 concentration. The content of free T4 revealed statistically significant differences between the control groups and subfertile patients in condition of hyperprolactinemia.

One can see the higher cortisol content in the group of subfertile patients in relation to its levels for fertile women in condition of hyperprolactinemia by 37%. (Table 3).

4. DISCUSSION AND CONCLUSION

The study revealed that the group of women in condition of hyperprolactinemia and subfertility in comparison with fertile patients with hyperprolactinemia have a characteristics of relative decrease in the level of estradiol under relatively higher FSH values. The elevated concentration of FSH, in accordance with our data, is a functional factor of subfertility indication as symptom of hyperprolactinemia. The molecular mechanisms in the basis of this phenomenon require further study.

A feature of the female pituitary-thyroid axis in cases of functional hyperprolactinemia and reproductive disorders is a relative decrease in the level of thyroxine free fractions. Despite the fact that these indicators occur within the range of reference values, the free T4 concentration decrease of sterile women may have some pathognomonic value. One can observe an increase in TSH in relation to control under condition of hyperprolactinemia without reference to the fertility state.

This could be characterized the state of glucocorticoid function in the adrenal glands of fertile women in condition of hyperprolactinemia as opposed to the group with subfertility by a significantly elevated cortisol concentration, which, evidently, has an adaptive character.

4.1 Conclusion

This study concluded that the women in condition of hyperprolactinemia and subfertility in comparison with fertile patients with hyperprolactinemia have a characteristics of relative decrease in the level of estradiol under relatively higher FSH values. So, this study determined the differences in the key links within the neuroendocrine system of women with hyperprolactinemia and different fertility state. The better glucocorticoid and ovarian function of fertile women with HP supposed to be an essential issue in their reproductive ability.

CONSENT AND ETHICAL APPROVAL

All women signed informed consent to participate in the study. The local Ethics Committee of the "Scientific Center of Family Health Problems and Human Reproduction" approved the course of the study.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Barren marriage: versions and contraversions / Edited by V. E. Radzinsky. M: GEOTAR-Media. 2018;404.
2. Pałubska S, Adamiak-Godlewska A, Winkler I, Romanek-Piva K, Rechberger T, Gogacz M. Hyperprolactinaemia - a problem in patients from the reproductive period to the menopause // Przeglad menopauzalny = Menopause review. 2017;16(1):1–7.
3. Shrestha S, Neupane S, Gautam N, Dubey RK, Jha AC, Doshi NR, Jayan A. Association of Thyroid Profile and Prolactin Level in Patient with Secondary Amenorrhea // The Malaysian journal of medical sciences : MJMS. 2016;23(5):51–56.
4. Suturina LV, Atalyan AV, Lazareva LM, Sholokhov LF, Rashidova MA, Kolesnikova LI. Infertility in women with idiopathic hyperprolactinemia is associated with oxidative stress // Reproductive sciences. 2019;26(1):281.

5. Adamyan LV, Andreeva EN, Artymuk NV, Belokrinickaya TE, Korzhenkova GP, Protasova AE, Rozhkova NI, Suturina LV, Filippov OS. BenignDysplasiaoftheBreast//Russian Journal of Human Reproduction. 2018;24(6):803-826.
6. Adamyan LV, Artymuk NV, Belokrinickaya TE, Petruhin VA, Smol'nova TYU, Suturina LV, Tetruashvili NK, Filippov OS, CHechneva MA, SHmakov RG. Miscarriage in early pregnancy: diagnosis and management tactics//Russian Journal of Human Reproduction. 2018;24(6):338-357.
7. Soto-Pedre E, Newey PJ, Bevan JS, Leese GP. Morbidity and mortality in patients with hyperprolactinaemia: the PROLEARS study // Endocrine connections. 2017;6(8):580–588.
8. Darzhaev ZYu, Atalyan AV, Rinchindorzhieva MP, Suturina LV. The frequency of infertility in marriage among the urban and countryfemale population of the Republic of Buryatia: the results of a population study // Fundamental and clinical medicine. 2017;2(4):14–21.
9. Soto-Pedre E, Newey PJ, Bevan JS, Greig N, Leese GP. The epidemiology of hyperprolactinaemia over 20 years in the Tayside region of Scotland: The Prolactin Epidemiology, Audit and Research Study (PROLEARS) // Clinical endocrinology. 2017;86(1): 60–67.
10. Lee DY, Oh YK, Yoon BK, Choi D. Prevalence of hyperprolactinemia in adolescents and young women with menstruation-related problems // American journal of obstetrics and gynecology. 2012;206(3):213:1-5.
11. Malik AA, Aziz F, Beshyah SA, Aldahmani KM. Aetiologies of Hyperprolactinaemia: A retrospective analysis from a tertiary healthcare centre // Sultan Qaboos University medical journal. 2019;19(2):129-134.
12. Melmed S, Casanueva FF, Hoffman AR, Kleinberg DL, Montori VM, Schlechte JA, Wass JAH. Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline // The Journal of clinical endocrinology and metabolism. 2011;96(2):273–288.
13. Samperi I, Lithgow K, Karavitaki N. Hyperprolactinaemia // Journal of clinical medicine. 2019;8:12.
14. Grattan DR. 60 YEARS OF NEUROENDOCRINOLOGY: The hypothalamo-prolactin axis // The Journal of endocrinology. 2015;226(2):101-22.
15. Bernard V, Young J, Chanson P, Binart N. New insights in prolactin: pathological implications // Nature reviews. Endocrinology. 2015;11(5):265–275.
16. Bassey IE, Udoh AE, Essien OE, Isong IKP, Gali RM, Archibong EE. Thyroid hormones and prolactin levels in infertile women in southern Nigeria // Journal of clinical and diagnostic research : JCDR. 2015;9(3):13-5.
17. Alpañés M, Sanchón R, Martínez-García MÁ, Martínez-Bermejo E, Escobar-Morreale HF. Prevalence of hyperprolactinaemia in female premenopausal blood donors // Clinical endocrinology. 2013;79(4):545–549.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdiarticle4.com/review-history/60864