Original Research Article

Endocrine markers of infertility in premenopausal women with idiopathic hyperprolactinemia

Abstract

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.

The purpose of the study was to determine the endocrine features of fertile and infertile women with hyperprolactinemia. (Not clear) ?The purpose of this study was todetermine the endocrine features hyperprolactenemia among fertile and infertile women.

The study involved included82 women: 27 healthy women, 33 patients with endocrine sterility infertility and idiopathic HP ?but were fertile or infertile, and 22 fertile women with idiopathic HP. All women underwent a standard history taking,clinical examination. 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.

The study results demonstrated that infertile 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. The better glucocorticoid and ovarian function of fertile women with HP supposed to be an essential issue in their reproductive ability.what about third group?

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

Introduction

One of the most pressing problems in modern medicine is infertility. In the majority of cases (42.6 – 65.3%), the cause of infertility refers to female reproductive system disorders. The endocrine infertility is widespread common and relates to comprising 29-43% of the female infertility sterile female population [16]. Hyperprolactinemia is traditionally considered as one of the major causes of female reproductive problems [8; 10], and it is also a predictor of cardiovascular diseases, metabolic disorders, hormone-dependent gynecological diseases, and obstetric complications [13–15; 12]. The frequency of hyperprolactinemia in patients, who suffer from gynecological disorders, is 11-47%. Some authors reported that, in the structure of female endocrine infertility, hyperprolactinemia occurs in 18.9%-40% of all cases [17; 11], and among young women with menstrual irregularities - in 5.5-13.8% [5].

The etiology of hyperprolactinemia allows the authors to classify this condition as physiological, pathological, including pharmacological[6; 7]. The determination of the causes or their combinations requires a careful examination of the patient's medical history (history should be before examination) and clinical assessment[9]. Among pathological hyperprolactinemia, its idiopathic form is quite common and often has a genetic nature[4]. The key mechanism in the development of HP as a primary disease is the pituitary-hypothalamic-ovarian disfunction, 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 infertility associated with HP was demonstrated as well [3].

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's life. 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 [2; 10]. However, not all hyperprolactinmic patients suffer infertility. In addition, there is evidence that the frequency of menstrual function disorders can be comparable in the presence and absence of hyperprolactinemia[1]. However, it is not still clear when hyperprolactinemia is the cause of endocrine infertility, 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 infertile women with hyperprolactinemia.

Materials and methods

Eighty-two women of reproductive age participated in the cross-sectional study. (Duration of study?)All patients were examined at the outpatient department of the "Scientific Center of Family Health Problems and Human Reproduction" (Irkutsk, Russia). 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. Case selection criteria?

The control group (group 0) consisted of 27 practically healthy women without gynecological pathology who had a pregnancy within the past year (age 23.6±0.3 years). (If the control had pregnancy within one year hyperprolactenemia may due to pregnancy or latetion. It should be cleared) The first clinical group (group 1) included 33 infertile patients in condition of stable hyperprolactinemia (age 24.4±0.3 years). The second clinical group (group 2) included 22 women with preserved reproductive function under hyperprolactinemia (average age 23.5±0.4 years). (Second clinical group selection is also not clear, who are the women in this group?)

The inclusion criteria for both clinical groups were women with HP as follows: Group 1 included women with inability conceive alteast for one 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 one year, having a regular sex without contraception (group 1), Group 2 included women who had any pregnancy during last one year but serum prolactin level was raised.any pregnancies during last year. But here question arises if they had pregnancy within last one year, the hyperprolactenemia may be due to pregnancy or lactation which is physiological. (group 2). The diagnosis of HP occurred within the second group before pregnancy and a year after child-birth.if she is lactating it is normal. If you have taken pre-pregnancy prolactin level what was the duration of study.

The exclusion criteria were: the pituitary tumor, hypothyroidism (you have mentioned TSH level was raised in hyperprolactenemia cases here you are excluding hypothyroidism? And you want to determine the endocrine dysfunction in case of hyperprolacetenemia. Its not clear), 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). What about tubal and endometrial factors of infertility?

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) or in case of amenorrhea. You mean Any day in case of amenorrhea? Make it clear The blood serum performed as research material.

To determine serum triiodothyronine (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.In all the cases or if prolactin level israised, if in case of raised prolactin level what was the cut off value for imaging?

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 considered statistically significant. We performed all calculations by means of the Statistics package STATICTICA 10 StatSoft Inc. (USA).

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).

Blood pressure, BMI is included in physical examination findings but important for hyperprolacetenemia thyroid examination and galactorrhea is not mentioned anywhere.

Examination fondings should be after the symptoms which is given below in bar diagram menstrual iggerularity.

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)

In the group of sterile women in condition of hyperprolactinemia, 70% (n=23) had primary infertility and 30% (n=10) had secondary infertility. The secondary infertility 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 infertility and to 59.1% - with preserved fertility (Fig. 1).

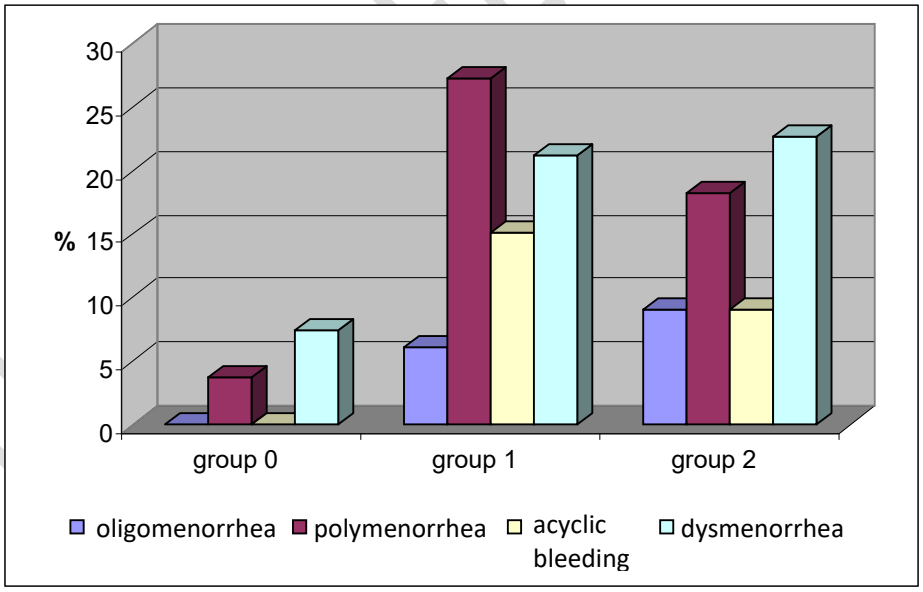

Fig. 1. The menstrual irregularities within groups under study

The infertile women with diagnosis of Oligomenorrhea had an increased prolactin content in 6.1% of cases. The fertile women with hyperprolactinemia

had 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 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 2 also shows that in the blood serum of infertile 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 infertile 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 infertile 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 infertile patients in condition of hyperprolactinemia.

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.

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

Discussion and conclusions

It should be better to write in passive form instead of we found,I did so on.

We found that the group of women in condition of hyperprolactinemia and infertility 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 infertility 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.

We can characterize the state of glucocorticoid function in the adrenal glands of fertile women in condition of hyperprolactinemia as opposed to the group with infertility by a significantly elevated cortisol concentration, which, evidently, has an adaptive character.

Thus, we 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.

Conclusion should be separately and clear

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