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Clinical-hormonal aspects of women of reproductive age with prolactinomas

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Abstract. Introduction. Prolactinoma is the most common pituitary adenoma, constituting 40-66% of cases in epidemiological studies. Its prevalence ranges from 25 to 63 per 100,000, with incidence rates of 2.1 to 5.4 cases per 100,000 annually. The increasing detection of prolactinomas is attributed to advances in imaging techniques, such as computer tomography / magnetic resonance tomography, and to the improved laboratory techniques, such as Enzyme Linked Immunosorbent Assay or Immunoradiometric assay, enabling earlier diagnosis. Regardless of tumor size, reproductive dysfunction—ranging from reduced libido through infertility — is a common symptom of the condition. **The aim** of this study is to evaluate the clinical-hormonal profile of women of reproductive age with prolactinomas and to analyze the relationship between prolactin levels, clinical manifestations of the disease, and reproductive function disorders. **Material and Methods.** The study involved 185 women aged 17 to 37 with prolactinomas, divided into two groups based on tumor size: Microadenomas and macroadenomas. The methods included clinical (BMI, blood calcium, vitamin D3, general blood test), hormonal (Prolactin, Follicle-Stimulating Hormone, Luteinizing Hormone, progesterone, estradiol, testosterone, Thyroid-Stimulating Hormone, free T4, inhibin A/B, activin, anti-Mullerian hormone), instrumental (ultrasound with folliculometry), and neuroimaging (neuro-ophthalmological, computer tomography / magnetic resonance tomography) techniques, alongside with statistical analysis. **Results and Discussion.** The study of 185 women with prolactinomas revealed that 61.6% were diagnosed during pregnancy, with microadenomas being more common. Patients experienced reproductive issues, including infertility and menstrual irregularities, alongside with hormonal imbalances, such as elevated prolactin and reduced Follicle-Stimulating Hormone and Luteinizing Hormone. Early detection and tailored treatment are crucial for managing these complications. **Conclusions.** Prolactinomas in women of reproductive age are associated with significant reproductive and hormonal disturbances. Early diagnosis and personalized treatment are essential to manage symptoms, including infertility and menstrual irregularities, and to improve patients' outcomes.
Keywords: clinical-hormonal profile, women, reproductive age, prolactinoma.
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Клинико-гормональные аспекты у женщин репродуктивного возраста с пролактиномами

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Реферат. Введение. Пролактинома – наиболее распространенная аденома гипофиза, составляющая 40-66% всех случаев в эпидемиологических исследованиях. Ее распространенность колеблется от 25 до 63 на 100 000 населения, а заболеваемость составляет от 2,1 до 5,4 случаев на 100 000 в год. Увеличение частоты выявления пролактином связано с развитием методов визуализации (компьютерная томография/магнитно-резонансная томография) и усовершенствованием лабораторных методов (иммуноферментный анализ, иммуннорадиометрический анализ), позволяющих проводить более раннюю диагностику. Независимо от размера опухоли, репродуктивная дисфункция – от снижения либидо до бесплодия – является распространенным симптомом этого заболевания. **Целью** настоящего исследования явилось оценить клинико-гормональный профиль женщин репродуктивного возраста с пролактиномами и проанализировать взаимосвязь между уровнем пролактина, клиническими проявлениями заболевания и нарушениями репродуктивной функции. **Материал и методы.** В исследование было включено 185 женщин в возрасте от 17 до 37 лет с пролактиномами, разделенных на две группы в зависимости от размера опухоли: микроаденомы и макроаденомы. Методы включали клинические (индекс массы тела, кальций крови, витамин D3, общий анализ крови), гормональные (пролактин, фолликулостимулирующий гормон, лютеинизирующий гормон, прогестерон, эстрадиол, тестостерон, тиреотропный стимулирующий гормон, свободный Т4, ингибин А/В, активин, антимюллеровский гормон), инструментальные (ультразвуковое исследование с фолликулометрией) и нейровизуализационные (нейроофтальмологический, компьютерная томография /магнитно-резонансная томография) методы, а также статистический анализ. **Результаты и обсуждение.** Исследование 185 женщин с пролактиномами показало, что у 61,6% из них данное заболевание было диагностировано во время беременности, при этом преобладали микроаденомы. Эти пациентки сталкивались с проблемами репродуктивного здоровья, включая бесплодие и расстройства менструального цикла, а также гормональными

нарушениями, такими как повышение уровня пролактина и снижение концентрации фолликулостимулирующего гормона и лютеинизирующего гормона. Раннее выявление заболевания и индивидуализированный подход к лечению играют ключевую роль в эффективном преодолении этих осложнений. **Выводы.** Пролактиномы у женщин репродуктивного возраста приводят к выраженным репродуктивным и гормональным нарушениям. Для устранения симптомов, таких как бесплодие и расстройства менструального цикла, а также для улучшения состояния пациенток, необходимы ранняя диагностика и индивидуализированное лечение.
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Introduction. Prolactinoma is the most common type of pituitary adenoma, accounting for 40–66% in epidemiological studies [1]. Prevalence among different population groups ranges from 25/100,000 to 63/100,000 [2], with incidence rates ranging from 2.1 to 5.4 cases per 100,000 per year [1,3].

Mindermann and Wilson [4] reported that prolactinomas were the most common subtype among pituitary tumors (39%) with a female to male ratio of 10:1, whereas after this age the ratio is 1:1 [5]. Kars et al. [6], focusing on patients with hyperprolactinemia treated with dopamine agonists, reported a significantly higher incidence of prolactin-secreting pituitary adenomas at the ages of 25–34 years compared with men and a disappearance of this incidence difference after menopause [7].

Currently, there is a tendency to diagnosing more hypertensions, especially prolactinomas, due to the improved access to high-precision imaging methods, such as CT/MRI and new techniques of laboratory determination of hormones, such as ELISA, IRMA, and ICL, which improve the diagnosis of prolactinomas at the early stages of the disease [8]. Regardless of the nature and size of hypertension, one of the most common symptoms of manifestation is reproductive dysfunction of varying severity, from decreased libido through infertility [9].

Prolactinomas are a common cause of ovarian hormonal insufficiency, manifested by menstrual cycle (MC) disturbances, lactorrhea and infertility. Prolactinoma may be associated with menstrual cycle with multiple endocrine neoplasia type 1 (MEN1) and hereditary isolated pituitary adenoma (FIPA). The mechanism leading to benign growth of prolactin-secreting cells is not yet known. With hyperprolactinemia, the hypothalamus suppresses the release of gonadotropin-releasing hormone (GnRH), which leads to a decrease in the concentration of FSH and LH and a decrease in the concentration of estrogen in women [10-12].

Materials and methods. The present study comprised 185 women aged 17–37 years with prolactinomas, which were divided into two groups based on tumor size: microadenomas and macroadenomas. A comprehensive clinical and biochemical assessment was conducted, encompassing BMI, calcium levels in the blood, vitamin D3 levels, and a range of general blood parameters. Hormonal evaluations encompassed prolactin, FSH, LH, progesterone, estradiol, testosterone, TSH, free T4, inhibin A, inhibin B, activin, and anti-Mullerian hormone. Instruments were utilized for the purpose of conducting ovarian and uterine ultrasounds, in conjunction with folliculometry on days 11, 14, and 16 of the menstrual cycle. Furthermore, neuroimaging techniques such as neuro-ophthalmological exams, radiological imaging, and pituitary MRI/MSCT were employed. Statistical analysis was employed. Participants were required to have prolactinomas up to 20 mm without invasive growth, infertility for a minimum of 12 months, and no other identified causes, excluding those with healthy, fertile husbands. Exclusion criteria encompassed subjects aged >37 years, those with fertility-impairing endocrine or non-endocrine conditions, aggressive macroadenomas, couple infertility, and normal pregnancies.

Results and Discussion. The initial group under observation comprised 185 women diagnosed with prolactinomas, of which 71 (38.3%) patients exhibited EB and 114 (61.6%) patients were diagnosed with prolactinoma during pregnancy. The patients were divided into two groups depending on the size of the formation. Each group will be considered in turn. Of the 114 patients who were pregnant, microadenomas were present in 91 (79.8%) patients, macroadenomas in 23 (20.2%) women *(see Fig. 1)*. The size of prolactinomas before pregnancy ranged from 3 mm to 42 mm (9.2 ± 1.0 mm). The mean prolactinoma size was found to be 5.0 mm ± 0.3 mm in patients with pituitary microadenoma and 18.0 mm ± 1.8 mm in patients with macroadenoma.

The mean age of women with microprolactinomas was found to be 26.2 ± 5.5 years, with macroprolactinomas exhibiting a mean age of 26.7 ± 5.6 years. The mean age of menarche was determined to be 13.2 ± 1.14 years and 13.1 ± 1.14 years, respectively, in the microprolactinomas and macroprolactinomas groups. In the control group, the mean age was found to be 29.3 ± 4.8 years and 12.5 ± 0.9 years, respectively. With respect to gynecological age, no significant differences

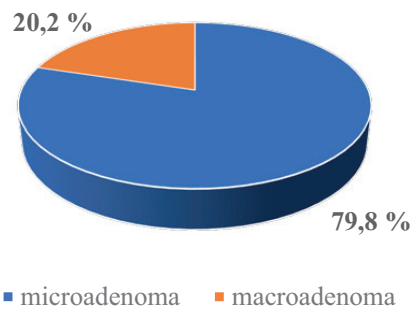

Fig.1. Structure of prolactinomas
Рис.1. Структура пролактиномы

were observed between the prolactinoma groups: 13.5 ± 0.4 years in women with microprolactinomas and 12.0 ± 0.7 years in women with macroprolactinomas, compared to 16.8 years in the control group.A number of characteristic features were identified when comparing the level of education of the examined individuals *(Table 1)*. The percentage of women with secondary and secondary specialised education was lower among patients with microprolactinomas, and the percentage of patients with higher education was higher among patients with microprolactinomas.

The largest proportion of women affected by micro- and macroprolactinomas, with approximately equivalent frequency, were employees. A comparative analysis of residential location reveals a nearly equal prevalence of micro- and macroprolactinomas among both rural and urban populations.

A high frequency of somatic diseases was observed among the prolactinoma patient cohort. The distribution of somatic diseases among the examined women is illustrated in *Figure 2*. The predominant percentage of concomitant somatic diseases was accounted for by the pathology of the thyroid gland and the presence of intracranial hypertension, which was found in almost every second woman with macroprolactinoma. Furthermore, two patients from the microprolactinoma group and two from the macroprolactinoma group had a history of traumatic brain injury, accounting for 2.2% and 8.7% of cases, respectively. It is also noteworthy to mention the presence of chronic gastrointestinal pathology in the subjects examined.

In the microprolactinoma group, gastrointestinal pathology was observed in 31.8% of cases, compared to 13.04% in the macroprolactinoma group. Long-term use of proton pump inhibitors, often prescribed for gastrointestinal conditions, may contribute to hyperprolactinemia and should be considered when assessing prolactinoma etiology.

A hereditary burden of menstrual function (MF) disorders was noted in 13.04% of patients with macroprolactinoma and 9.8% with microprolactinoma, with infertility being more common (21.7% and 18.6%, respectively). Additionally, 9.8% of microprolactinoma and 13.04% of macroprolactinoma cases had polycystic ovary syndrome (PCOS) among first- and second-degree relatives. Stress factors and complications

Table 1

Characteristic features of education level, social status, and place of residence of the subjects examined, (n=114), relative (%) / absolute (n)

Таблица 1

Характеристика уровня образования, социального статуса и места жительства обследованных, (n=114), относит (%) / абс (n)

Index	Microadenoma, n=91	Macroadenoma, n=23	P
Education			
Secondary	20.8 / 19	34.7 / 8	p=0.1
Secondary specialized	25.2 / 23	26.1 / 6	p=0.9
Higher	53.8 / 49	39.1 / 9	p=0.2
Social status			
Worker	15.4 / 14	17.4 / 4	p=0.8
Employee	31.8 / 29	30.4 / 7	p=0.8
Student	14.3 / 13	17.4 / 4	p=0.5
Other	38.4 / 35	34.7 / 8	p=0.6
Place of residence			
City	53.8 / 49	56.5 / 13	p=0.2
Village	46.1 / 42	43.4 / 10	p=0.9

during pregnancy or childbirth were reported in 26.3% and 26.08% of patients, respectively.

Reproductive system development was normal, with initial clinical presentations primarily involving opsomenorrhea (38.4% for microprolactinoma and 43.4% for macroprolactinoma). Oligomenorrhea occurred in 21.7% of macroprolactinoma cases and 14.2% of microprolactinoma cases (*Table 2)*.

During the analysis of reproductive function, the following results were obtained. There was a pregnancy in anamnesis in 74.7% of patients with microprolactinomas, in 69.5% with macroprolactinomas, 44.1% and 47.8% gave birth, respectively *(Table 3)*. Our data showed that 29.7% of patients with microprolactinomas had a miscarriage in anamnesis represented by spontaneous miscarriage in 26.4%, non-developing pregnancy in 19.7%, and ectopic pregnancy in 3.5% of cases. In those examined with macroprolactinomas, spontaneous miscarriage was noted in 13.04% of patients, non-developing pregnancy in 26% and ectopic pregnancy in 1.7%; in total, miscarriage in this group was 27.7%.

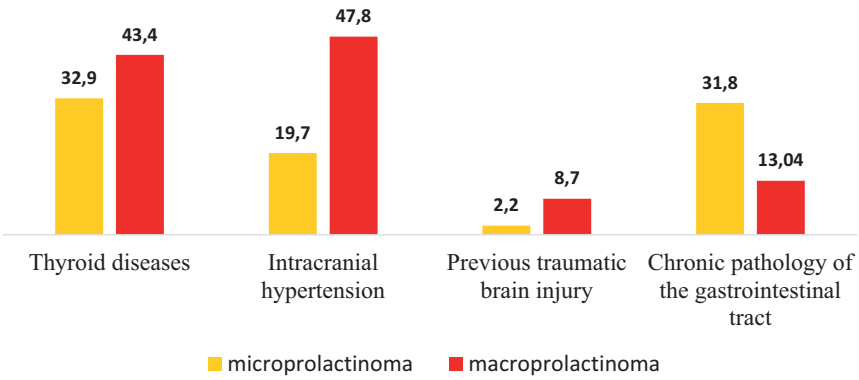

Fig. 2. Somatic pathology of those examined, %
Рис. 2. Соматическая патология обследованных, %

Table 2

State of menstrual function in women with prolactinomas, (n=114), relative (%) / absolute (n)

Таблица 2

Состояние менструальной функции у женщин с пролактиномами, (n=114), относит (%) / абс (n)

Menstrual cycle	Microadenoma, n=91	Macroadenoma, n=23	Total	P
Normal menstrual cycle	30.7/28	-/0	28(24.5%)	p<0.003
Dysmenorrhea	16.4/15	17.4/4	19(16.6%)	p=0.5
Oligomenorrhea	14.2/13	21.7/5	18(15.7%)	p=0.46
Opsomenorrhea	38.4/35	43.4/10	45(39.4%)	p=0.6
Amenorrhea I Amenorrhea II	5.5/5 9.9/9	4.3/1 17.4/4	6(5.2%) 13(11.4%)	p=0.5 p=0.6
Dysfunctional uterine bleeding	2.2/2	8.7/2	4(3.5%)	p=0.1

Table 3

Reproductive function of the examined patients, (n=114), relative (%) / absolute (n)

Таблица 3

Репродуктивная функция обследованных пациенток, (n=114), относит (%) / абс (n)

Index	Microadenoma, n=91	Macroadenoma, n=23	Total	P
Pregnancy	74.7/68	69.5/16	84(73.6%)	p=0.6
Childbirth	44.1/41	47.8/11	52(45.6%)	p=0.8
Spontaneous miscarriage	26.4/24	13.04/3	31(27.1%)	p=0.6
Non-developing pregnancy	19.7/18	26/6	24(21%)	p=0.5
Ectopic pregnancy	3.5/4	1.7/2	6(5.2%)	p=0.5
Infertility I	38.5/44	9.6/11	55(48.2%)	p=0.6
Infertility II	46.15/42	52.2/12	54(47,3%)	p=0.5

A study of gynecological diseases revealed that 7.7% of patients with microprolactinomas had endometrial hyperplasia, 5.5% had uterine fibroids, and 5.5% had endometriosis. Similarly, in the macroprolactinoma group, these conditions were observed in 8.7%, 8.7%, and 13% of patients, respectively (see *Table 4*). Furthermore, functional ovarian cysts were found to be significantly more prevalent in macroprolactinomas (21.7%) compared to microprolactinomas (12.1%), with a p-value less than 0.05. It is noteworthy that prolactin plays a certain role in the promotion of epithelial cell growth, which is associated with (BMH). The prevalence of BMH was observed to be 23.1% in microprolactinoma cases and 13% in macroprolactinoma cases.

Chronic salpingo-oophoritis was observed with similar frequency in both groups: 12.1% in microprolactinomas and 13% in macroprolactinomas. Hyperprolactinemia contributes to secondary PCOS development in patients with pituitary adenomas and infertility, with nearly one-fourth of macroprolactinoma patients presenting with secondary PCOS. Multifollicular ovaries were noted in 15.4% of microprolactinoma cases and 21.7% of macroprolactinoma cases.

Uterine hypoplasia was also observed, with microprolactinoma patients reporting grade I and II cases in 39.5% and 15.4%, respectively, while for macroprolactinomas, these rates were 34.8% and 26.1%.

At the initial visit, galactorrhea and menstrual irregularities were the primary complaints, reported by 81.3% of microprolactinoma patients and 86.9% of macroprolactinoma patients. Neuro-ophthalmological symptoms like blurred vision, headaches, and dizziness

Table 4

Characteristics of concomitant gynecological diseases in the examined patients, (n=114), relative (%) / absolute (n)

Таблица 4

Характеристика сопутствующих гинекологических заболеваний у обследованных пациенток, (n=114), относит (%) / абс (n)

Index	Microprolactinoma, n=91	Macroprolactinoma, n=23	Control group, n=20	p
Endometrial hyperplasia	7.7/7	8.7/2	-	p=0.8
Uterine fibroids	5.5/5	8.7/2	-	p=0.5
Functional ovarian cysts	12.1/11	21.7/5	25/5	p=0.6
Endometriosis	5.5/5	13.0/3	-	p=0.4
Benign mammary hyperplasia	23.1/21	13/3	-	p=0.2
Chronic salpingoopharitis	12.1/11	13.0/3	65/13	p=0.5
Polycystic ovary syndrome	10.9/10	26.1/6	-	p=0.6
Multifollicular ovaries	15.4/14	21.7/5	-	p=0.5
Hypoplasia of the uterus I degree	39.5/36	34.8/8	-	p=0.6
Hypoplasia of the uterus II degree	15.4/14	26.1/6	-	p=0.9

were also common, often leading patients to consult neurologists or ophthalmologists first.

Half of the patients with macro- and microprolactinomas initially sought help from gynecologists or ophthalmologists, while one-third with microprolactinomas consulted neurologists. Macroprolactinomas often presented with headaches (60.8%), dizziness (26.1%), and amenorrhea, while microprolactinomas showed similar trends, with headaches in 63.7% and dizziness in 13.2%. Vegetative-vascular dystonia symptoms were common in both groups (58.2% and 60.8%).

Obesity was prevalent in 50.5% of microprolactinoma and 56.5% of macroprolactinoma patients, while excess weight affected 32.9% and 21.7%, respectively ($p<0.05$). Decreased libido was reported by 47.2% of microprolactinoma and 43.5% of macroprolactinoma cases. Mood decline (51.6% vs. 43.5%), memory issues (32.9% vs. 34.7%), and anxiety and depression (34.1% vs. 21.7%, $p<0.05$) were common across both groups.

In macroprolactinoma patients, bitemporal hemianopsia and chiasmatic syndrome occurred in 73.4%, with 47.8% showing visual field narrowing and 13.04% having amblyopia. Optic nerve atrophy was more frequent in macroprolactinoma (28.7%) compared to microprolactinoma (2.7%), while retinal angiopathy rates were similar (13-14%).

Microprolactinomas accounted for 79.8% of cases, often linked to gastrointestinal diseases (31.8%) and pregnancy complications (25%). Delayed pathogenetic therapy was common as many patients first sought care from gynecologists or ophthalmologists. Secondary infertility affected 46% of microprolactinoma and 52.2% of macroprolactinoma cases, with high miscarriage rates (45% and 39%).

Anovulation was prevalent, affecting 68.1% of microprolactinoma and 78.3% of macroprolactinoma cases, linked to hormonal imbalances caused by hyperprolactinemia. Prolactin levels were significantly higher in macroprolactinomas (70.3 ng/ml vs. 32.2 ng/ml in microprolactinomas), with hypoestrogenism and hypoprogesteronemia observed in both groups. These findings highlight the need for timely diagnosis and tailored therapy.

We also found reduced levels of FSH and LH in patients with prolactinoma, but LH values were 0.7±0.2 IU/l in microprolactinoma and 0.8±0.38 IU/l ($p<0.001$ compared with control values) with macroprolactinoma correspond to the data of hypogonadotropic ovarian failure.

The level of total testosterone and cortisol was within the normative values in our examined patients with both micro- and macroprolactinoma (reference values for testosterone <0.60 ng/ml, cortisol 50-250 ng/ml).

In patients with prolactinomas, we observed a decrease in AMH levels compared to the control group, but the values were within the normogonadotropic state ($p_2<0.001$, $p_3<0.001$).

Patients with prolactinomas showed significantly reduced inhibin A levels (1.9±0.87 ng/ml in microprolactinomas, 1.7±0.8 ng/ml in macroprolactinomas, $p<0.0001$), over six times lower than controls, but within the reference limits. Inhibin B levels were also lower (47.1±3.2 pg/ml for microprolactinomas and 48.2±3.5 pg/ml for macroprolactinomas, $p<0.001$) compared to controls, but within the reference ranges. Activin was reduced by half versus controls ($p<0.001$), but it remained within the reference values with no significant differences between tumor types. AMH levels, though lower than controls, were within normal limits.

Conclusions. In conclusion, the majority of prolactinoma cases (79.8%) were microprolactinomas, often associated with gastrointestinal diseases (31.8%) and a history of complicated pregnancies or childbirth in 25% of patients. Common initial symptoms included menstrual dysfunction and neuro-ophthalmological issues, which resulted in a delay in pathogenetic therapy as many patients initially sought care from gynecologists or ophthalmologists. Secondary infertility was observed in 46% of microprolactinomas and 52.2% of macroprolactinomas, with miscarriage rates of 45% and 39%, respectively. Infrasellar growth was prevalent in both tumor types, with anovulation identified in 78% of macroprolactinoma and 68% of microprolactinoma cases. Hyperprolactinemia was observed in over 90% of patients, accompanied by hypoestrogenemia and hypoprogestonemia, indicative of the hypogonadotropic effects of hyperprolactinemia. The reduced secretion of inhibin A and activin underscores the necessity for further investigation, particularly concerning its impact on pregnancy outcomes and the need for treatment adjustments.

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Declaration of financial or other relationships. *All authors participated in the conception and design of the study and in the writing of the manuscript. The final version of the manuscript was approved by all the authors. The authors did not receive a fee for the study.*

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