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Infertility predictors for prolactin-secreting pituitary adenomas

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Abstract: Purpose of research - To improve reproductive outcomes of women with prolactinomas by evaluating fertility predictors. Material and methods. We examined 250 women aged 17-35 years (average age 30.5 years) with endocrine infertility (EI) and hyperprolactinemia. Of these, 71 (28.4%) patients with prolactinoma and endocrine infertility were selected for an in-depth study. All patients underwent a complete clinical - hormonal and visualization examination and were divided into patients with EI with pituitary microprolactinomas (64.7%) and patients with EI with macroprolactinomas (35.2%). Clinical, imaging, and hormonal studies have been performed. The basal levels of the pituitary gonadotropic hormones — LH, FSH, as well as PRL, TH, peripheral gland hormones cortisol (C), estradiol (E) and total testosterone (T), dehydroepiandrosterone sulfate (DHEA-S), progesterone, inhibins A and B were determined , activin, antimuller hormone. The research materials were subjected to statistical processing using the methods of parametric and non-parametric analysis. Results. According to the objectives, the functional state of the HPO system and the clinical characteristics of infertility in prolactinomas were studied, an analysis of complaints and anamnestic data of patients with EI with prolactinomas was made, depending on the size of the formation in a comparative aspect. The state of ovarian reserve was assessed, with the determination of FSH, activin, AMH, inhibin A and B in the blood serum. The inhibin A level in both Me groups was 1.30 ng/ml, which significantly differed from the control group (p_2 <0.0001, p_3 <0.0001). The level of inhibin B underwent significant changes in both groups. A decrease in inhibin B and an increase in FSH can prove a decrease in ovulatory ovarian reserve. The studied women with EI in both groups showed a decrease in AMH, in the group with microadenomas ranged from 0.12 to 2.1 and averaged 0.75 ± 0.27 ng/ml, and in the group with macroadenomas ranged from 0.09-2.2 and averaged 0.97 ± 0.49 ng/ml, which significantly differed from the control group (p_1 <0.05, p_2 <0.001 p_3 <0.001). The conducted Spearman correlation and regression analysis showed that between prolactin and AMH (r = -0.4; p<0.01), between prolactin and progesterone (21dMC) (r = -0.576; p<0.0001) as well as between prolactin and inhibin B (r = -0.67) there is a strong "-" negative relationship and all indicators were statistically significant. Conclusions: Endocrine disorders in women with prolactinomas are significantly increased in patients with macroadenoma compared with microadenoma. Correlation-regression analysis found a negative relationship between PRL and AMH (r = -0.4, P <0.0001), PRL and progesterone (r = -0.57, P <0.0001). With an increase in PRL by 1 unit, there is a decrease in AMH by 0.008 units (P <0.001), a decrease in inhibin B by 0.11 (P <0.001), progesterone by 0.04 units (P <0.0001) and the degree of hyperprolactinemia and this all can predict EI development.

Keywords: Prolactinoma, infertility, inhibin, activin.

Introduction. Among primary intracranial tumors, pituitary adenomas (AH), ranging from 7.3% to 18%, take third place in frequency after gliomas and meningiomas [3].

Standardized incidence rates (SIR) for hypertension range from 4 to 7.39 [39]. Until 2006, data on the prevalence of hypertension in the clinical setting was insufficient and one of the pioneering epidemiological studies conducted in Liège in Belgium in 2006 covering 71,972 people in rural, suburban and urban populations. The authors revealed 1 case per 1064 population, of which 66.2% were prolactinomas, and 80% of them were women with microprolactinomas [5]. According to Fontana and Gaillard [7] in Switzerland, the prevalence of hypertension was 1 case per 1241 population of which 56% was prolactin, in the United Kingdom -1 per 1289 population, of which 57% prolactin, respectively (Fernandez et al.), in Iceland the prevalence was the highest - 1 per 865 population, with 40% prolactinomas [18]. Other studies from Finland [11] and Malta [6] show similar results and the same ratios for prolactinomas. Moreover, Swedish scientists with a similar frequency of hypertension, indicate a low representation of prolactin -32% among them - and a higher frequency of functionally inactive formations-54%. This imbalance is due to differences in the criteria used for consideration by prolactin, so they adopted a prolactin level exceeding the upper limit of the norm by 3 times. Of all neoplasms of the pituitary gland to adenomas with hyperproduction of prolactin (PRL), i.e. Prolactin accounts for about 40% [4]. The prevalence of prolactin varies from 100 to 755 cases per 1 million adults and the incidence varies from 6 to 10 new cases per 1 million adults per year [3,4]. In general, women suffer more often, especially their predominance evident in the reproductive period. Thus, the ratio of men and women aged 20 to 50 years is 1:10, although after 50 years, such a gender difference is leveled [4]. An in-depth meta-analysis of prolactin prevalence by Ezzat et al. [10] showed that prolactinomas were the most common subtype of pituitary tumors, occurring in 25–41%, 22.5% in radiological studies and 14.4% in a series of autopsy studies. Moreover, the results of immunohistochemical staining of tissue of pituitary formation on prolactin in the autopsy material of patients without a diagnosis of pituitary adenoma not only confirmed, but also revealed an even greater frequency of 39.5% [9]. Mindermann and Wilson [14] reported that prolactinomas were the most common tumor subtype (39%) with a 10: 1 ratio of women to men aged 18 to 50 years, whereas after this age the ratio was 1: 1 [15]. Kars et al. [16], focusing on patients with hyperprolactinemia who received dopamine agonists, reported a significantly higher incidence of prolactin at the age of 25–34 years compared with men and the disappearance of this difference in incidence after menopause [18]. Currently, there is a tendency to increase AH, especially prolactin, in view of improving access to high-precision imaging methods, CT/MRI, new laboratory methods for determining (ELISA, IRMA, IHLA) hormones that allow better diagnosis of prolactin in the early stages of the disease. Regardless of the nature and size of hypertension, one of the most common symptoms of manifestation, as a rule, is reproductive dysfunction of varying severity - from decreased libido to infertility [1]. So, with Cushing's Syndrome, 30% of women have menstrual dysfunction (MD), including in 75–80% of cases, from painful cycles and oligo-, opsomenorrhea to persistent amenorrhea [20,42,44]. Atrophic changes, cystic degeneration, sclerosis, and a significant decrease in follicular activity are often found in the ovaries. After successful treatment of Cushing's syndrome (as the level of cortisol in the blood normalizes), generative function is restored in many women [43]. Despite clinical and biochemical remission, menstrual irregularities persist for 41% of patients [19]. The restoration of menstrual and childbearing function in women with SC indicates that these disorders are not organic, but only functional in nature [20]. Reproductive system disorders in patients with acromegaly occur from 40 to 89% [21], which develop in 30–40% due to hyperprolactinemia. In women with NAH, up to 88% of women may have polycystic ovary syndrome (PCOS), 23% have secondary hypogonadism with amenorrhea [2.41].

The influence of the pituitary adenoma on menstrual irregularities and reproductive function remains an urgent problem in modern gynecology [22,38]. More often, patients who have pituitary microadenomas contact a gynecologist, since with large tumor sizes, the leading ones are neurological and ophthalmic disorders, and reproductive system disorders are fading into the background. Prolactinomas can cause hypogonadism, menstrual irregularities (oligomenorrhea or amenorrhea) and infertility (luteal phase disturbances or anovulation) in premenopausal women [23]. When pregnancy is excluded, hyperprolactinemia in approximately 10-20% of patients leads to amenorrhea. Women with untreated prolactinomas, as a rule, cannot achieve pregnancy, since hyperprolactinemia affects the pulsating ability of gonadotropin releasing hormone (GnRH) and reduces the secretion of follicle-stimulating hormone (FSH), as well as the secretion of luteinizing hormone (LH) [24]. It is known that infertility is a polyetiological disease and requires the development of modern universal markers, the study of the level of which would determine the appropriate tactics of managing patients with impaired fertility, assessment of the prognosis and the prospects of treatment [25]. In recent years, a significant role has been given to the role of a new class of peptides that transform growth factors — inhibin, activin, and AMH. Moreover, the American Society for Reproductive Medicine, as well as a number of researchers indicate the presence of additional factors involved in the complex mechanism of regulation of reproductive function [40]. According to them, activin and follistatin are produced in the ovaries and the pituitary gland and are likely to act on FSH secretion through autocrine and paracrine mechanisms. So, activin stimulates the production of FSH, while follistatin suppresses the action of activin. Yding Andersen C et al. emphasize the role of inhibin, consisting of two subunits and having two forms - inhibin A and inhibin B. [34]. It is synthesized in women in follicles and placenta, in men - in Sertoli cells. Inhibin A is found mainly in women (its function in men is unknown). Inhibin B is the main indicator of the EFORT test (Exogenous FSH Ovarian Reserve Test) - a test for the functional reserve of the ovaries) [35]. These factors are produced in the pituitary gland, in the ovaries and, through autocrine and paracrine mechanisms, are involved in the regulation of reproductive disorders. For a long time, AMH function in the female body was unknown [36]. This is due to the fact that only the follicle granulosa cells from the preantral stage to the large antrum stage can produce this hormone [36]. In the ovaries of a girl, the first signs of AMH production appear in the prenatal period (32–36 weeks of pregnancy) and the level of this hormone in the blood slowly rises with age. The maximum level of AMH reaches a woman aged 20-30 years, after which it gradually decreases and is zero at menopause [28, 29]. Moreover, AMH in women correlates with the number of antral follicles, with age, which best reflects a decrease in reproductive function in healthy women with proven fertility [28,30]. According to studies by R. Fancin et al. [37] the endocrine effects of FSH, LH, estradiol, progesterone, inhibin A, and inhibin B depend on changes in their serum levels during the menstrual cycle. Determination of the combination of inhibin B, AMH, and FSH markers on the 3rd day of the cycle can be a reliable test for assessing the ovarian reserve, that is, reflect the number of functionally active follicles in the woman's ovaries [31, 32]. Thus, due to the high incidence of reproductive disorders in women with hypertension, the presence of a number of contradictions in their correction, the possibility of therapy, contraindications, and the impossibility of radical removal of the tumor pose serious problems for endocrinologists, neurosurgeons and gynecologists. There are constant contradictions in the management of pregnancy, childbirth, the postpartum period, lactation and breastfeeding. In this regard, we faced the task of an in-depth study of the pathogenesis of reproductive disorders and infertility in hypertension, the possible search for sensitive tools for early diagnosis, and determination of predictors of infertility in patients with prolactinomas.

The aim of the study was to improve reproductive outcomes in women with prolactinomas by evaluating fertility predictors.

Materials and research methods. For the period from 2015 to 2020, based on the clinics of the Republican Specialized Scientific and Practical Medical Center Endocrinology named after Y.Kh. Turakulova (Department of Neuroendocrinology) and RSSPMC OaG examined 250 women aged 17-35 years (average age 30.5 years) with endocrine infertility (EI) and hyperprolactinemia. Of these, 71 (28.4%) patients with prolactinoma and endocrine infertility were selected for an in-depth study. The control group consisted of 20 healthy women of a similar age. All patients underwent a complete clinical - hormonal and visualization examination and were divided into 2 groups: group 1 - 46 (64.7%) patients with EI with pituitary microprolactinomas and group 2 - 25 (35.2%) patients with EI with macroprolactinomas .

The inclusion criteria were: age from 17 to 35 years; prolactinomas up to 20 mm in size without signs of invasive growth; infertility for 12 months or more with the exclusion of all other causes; a healthy fertile husband and a normal physiological pregnancy in the control group. Exclusion criteria: age over 35 years; the presence of any concomitant endocrine pathology that aggravates fertile function (hypothyroidism, chronic heart failure, diabetes), etc.; the presence of non-endocrine causes of infertility (tubal, peritoneal, uterine, cervical, immunological, psychosexual, inexplicable); the presence of a formation of any origin with invasion into nearby structures; pair infertility;

The design of the study of patients with primary infertility with prolactinom is illustrated in Fig. 1.

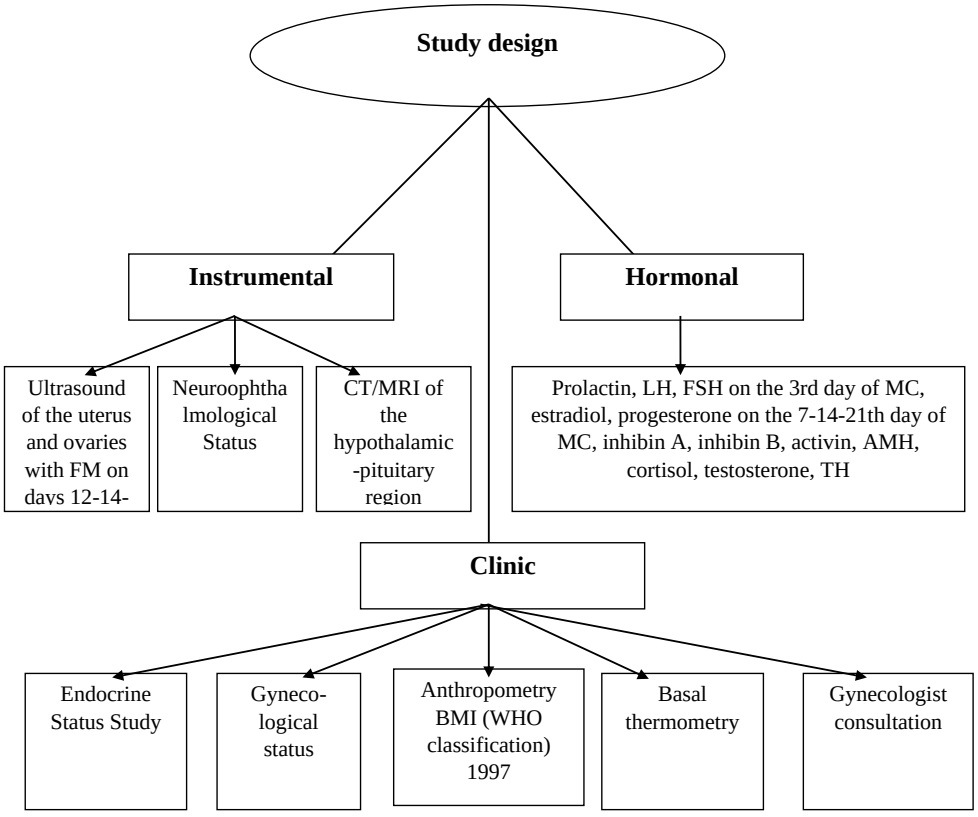


Fig. 1. Study design of patients with primary infertility in prolactinomas

The age of women ranged from 17 to 35 years and averaged 27.37 + 0.79 years. The observation period was 0-3-6-12 months, the duration of the disease averaged 8.44 + 0.52 years, while with the duration of the disease from 1 to 5 years - 49.2%, from 5 to 10 years - 40, 8%, more than 10 years - 9.8% (Fig. 2).

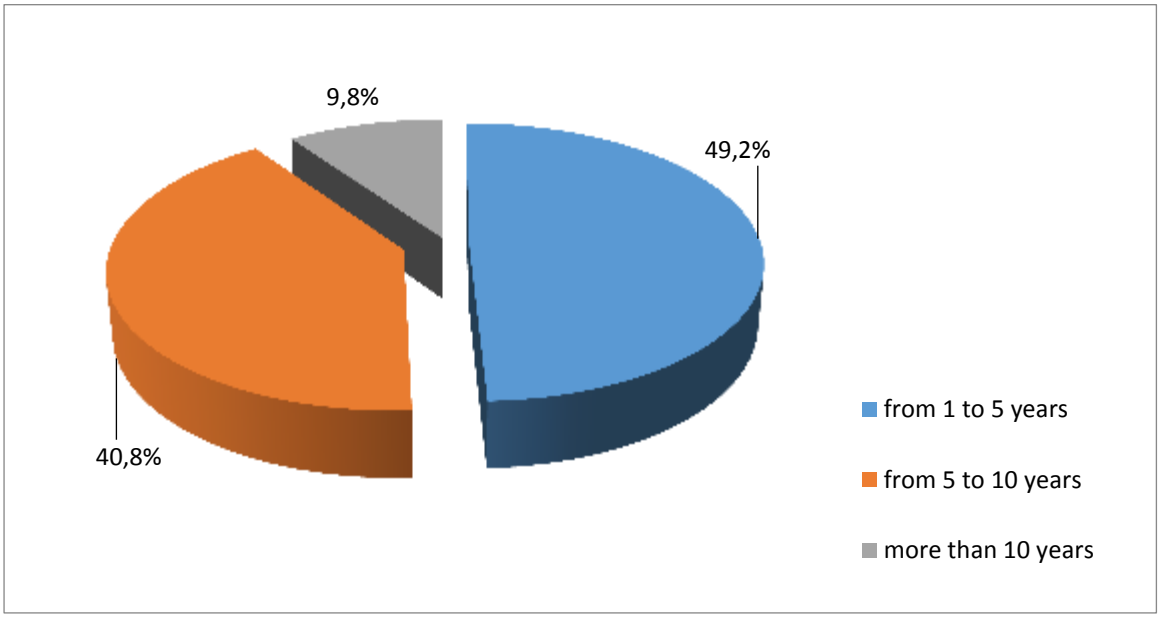


Figure 2. The duration of the disease in women with primary infertility with prolactinomas (%) (n = 71)

Clinical research methods. When examining women, they paid attention to the length and body weight, physique, development of adipose tissue and the features of its distribution. The method of anthropometry was used to assess body mass index (BMI), according to the WHO classification (2014). ***The gynecological status*** of women was assessed jointly with a gynecologist (Central Clinical Hospital of Uzbekistan Temir Yullari JSC, candidate of medical sciences A. Kasymova). When assessing reproductive status, the following NFMs were taken into account: rare menstruation and their absence, intermenstrual spotting, as well as discharge before and after menstruation, were specified: the time of onset of disorders, communication with other diseases, surgical interventions, stressful situations, change of residence, the beginning of sexual activity or taking medications. The history of pregnancies and their outcomes, the number and duration of marriages were also taken into account. Basal thermometry was carried out in the morning, at the same time, without getting out of bed, with the same thermometer for 5-7 minutes. A sign of the ovulatory cycle was considered the two-phase nature of the temperature with a decrease in the day of ovulation by 0.2-0.3 ° C and a subsequent rise in the second phase of the cycle by more than 0.5 ° C, compared with the first phase of the menstrual cycle. Ultrasound of the ovaries and uterus with folliculometry (FM) was performed with a vaginal probe (doctor A. Matchanova) on the basis of the RSNPMC Obstetrics and Gynecology of the Ministry of Health of the Republic of Uzbekistan and in the Horev clinic (doctor Tashmatova I.D.) and according to the generally accepted methodology (V. Kulakov. et al., 2002). FM was performed vaginally by ultrasound on days 12-14-16 of the MC [33]. The thickness of the endometrium, the number of antral follicles, the size of the dominant follicle during its development to the final stage — ovulation or anovulation, persistence or atresia were evaluated. For completeness, FM data were compared with BT and hormonal indices. ***A neuroophthalmological study*** was performed in all patients on the basis of the RSNPMC Neurosurgery (doctor Rakhmatullaeva D.S.). The fundus, visual fields, and visual acuity were studied using indirect

ophthalmoscopy and fundoscopy. ***The condition of the skin.*** They drew attention to the nature of hair growth, especially excess, the time of its appearance (before or after menarche). Assessment of the degree of hair growth, according to the scale of D. Ferriman, J. Galwey (1961), was carried out according to a 4-point system in 11 areas of the body. For women, the normal hirsut number is 0-7 points. ***Mammary glands***. Inspection of the mammary glands was carried out in a standing position and lying with sequential palpation of the external and internal quadrants of the gland. They drew attention to the structure of the mammary glands, their sizes (hypoplasia, hypertrophy, trophic changes). All patients were determined by the absence or presence of discharge from the nipples, its color, texture and character. The state of pigmentation of the nipple areola was also evaluated.

Gynecological research methods. One of the objective indicators of reproductive dysfunction was the assessment of MC. NMC included the absence of menstruation in girls or women of reproductive age, violations of the duration and intensity of bleeding and the intervals between them. ***Hormonal studies*** included determining basal levels of the pituitary gonadotropic hormones - LH, FSH, as well as PRL, TH, peripheral gland hormones cortisol (K), estradiol (E) and total testosterone (T), dehydroepiandrosterone sulfate (DHEA-S), progesterone, inhibins A and B, activin, antimuller hormone. With preserved menstrual function, LH and E levels were examined on 7.14 or 21 days, and progesterone (P) - only on day 21 by the RIA method. The levels of inhibin A and B, activin, AMH, and FSH on the 3rd day of the menstrual cycle were determined by ELISA using the corresponding test systems on the MINDRAY MR-96 A semi-automatic analyzer in the Dior Medikal Centr clinic (Ph.D. Fusailova Sh. .Sh.). Evaluation of the ovarian reserve using passive methods (determination of the levels of inhibins A and B, activin, antimuller hormone) was carried out using test systems from DSL (USA) by ELISA. ***X-ray method*** - an aim picture of the Turkish saddle, CT/MRI of the hypothalamic-pituitary region was carried out (in the Dior Medikal Centr clinic, doctor A. Khadzhemetov, Jacksoft clinic, doctor H. Shamirzaev).

The statistical method. The research materials were subjected to statistical processing using the methods of parametric and non-parametric analysis. Systematization of the initial information and visualization of the obtained results was carried out in Microsoft office Excel 2006 tables. Statistical analysis was performed using the free statistical software “R” version 3.5.2. When comparing the mean values (M (SD)) in normally distributed and the median (Me [IQR]) in abnormally distributed sets of quantitative data, the Student t-test was calculated. When comparing the nominal data, a correlation method was used according to the Pearson² criteria. Differences were considered statistically significant at a significance level of $p<0.05$. Sample characteristics are presented as mean ± error of the mean. When testing statistical hypotheses in computer software packages, not only the value of the statistical criterion (Student's t-test, Fisher's criterion, etc.) was calculated, but the achieved (critical) significance level was directly calculated to evaluate the criterion used. Using correlation and regression analysis, we determined the necessary inclusion of certain factors in the multiple regression equation, and also evaluated the resulting regression equation for compliance with the identified relationships using the coefficient of determination.

The results of our own research and discussion.

According to the task, the first stage of research was the study of the functional state of the HPO system and the clinical characteristics of infertility in prolactinomas. For this, 71 women with prolactinomas were examined. Patients vigro intacta and EI, which developed against the background of other endocrine diseases, were excluded from the study. At the stage of evaluating fertile function, we excluded all cases of paired infertility. For this, the husbands of the women studied had a spermogram and a Shuvarsky test (for biological

compatibility). Fertility in husbands was considered not rejected in the absence of a concomitant inflammatory process in the urogenital system, with a spermogram with actively motile spermatozoa of more than 70% and a negative result of the Shuvarsky test.

Of the examined patients, 45 (63.3%) were women with newly diagnosed hypertension. 32 (45%) women received various types of treatment, but without effect, including 20 (28.1%) patients were treated only by a gynecologist for infertility. 18 (25.3%) patients received conservative treatment with various drugs that act on the level of PRL, 11 of them took Dostinex, 4 - bromergon and 3 women - other drugs. Two patients (2.8%) received radiation therapy, and 3 patients (4.2%) received TAG on the background of drug therapy.

The next stage of our research was the analysis of complaints and anamnestic data of patients with EI with prolactinomas, depending on the size of the formation in a comparative aspect (Table 1).

Table 1: The frequency of clinical manifestations of patients with EI with prolactinomas, depending on the size of the formation (n=71)

Symptoms	Microadonoma n=46		Macroadenoma n=25		P
	Абс	%	Абс	%	
NMC	32**	69%	25**	100%	**0.003**
Miscarriage	12	26%	8	32%	0.312
Stillbirth	4	8%	3	12%	0.6
Non-developing pregnancy	11*	24%	4*	16%	**0.04**
Abortion	10	21%	3	12%	**<0.001**
HRT	30	65%	15	60%	0.663
BPH	9	19,5%	5	20%	0.963
Galactorrhea	30***	65%	25***	100%	**<0.001**
Visual impairment	0	0%	25***	100%	**<0.001**
Headaches	28	61%	20	80%	0.100
Decreased libido	13***	28%	21***	84%	**<0.001**
PMS	37*	80%	14*	56%	**0.02**
ICH	27	58%	16	64%	0.663
ICG syndrome	1***	2%	8***	32%	**<0.001**
Inflammation brain disease	3	5%	1	4%	0.660
Primary infertility	27	58%	15	60%	0.915
Secondary infertility	18	39%	10	40%	0.943

Note: * -P <0.05, ** - P <0.01, *** P <0.001– statistical significance in relation to the group with macroadenoma.

This scheme clearly illustrates that in women with microadenoma, compared with macroadenoma, MCFs were significantly more common in 69% (P = 0.003) and primary (58%) and secondary infertility (39%) with microadenomas and macroadenomas were found with the same frequency -60% and 40%, respectively, ICP in 80% (P = 0.02) (tab. 1). At the same time, in patients with pituitary macroadenoma prevailed: impaired vision in 100% (P <0.001), headaches (80%), decreased libido in 80% (P <0.001) and MCF in 100% of cases. In women with pituitary macroprolactinomas, the nonspecific effects of prolactin and signs associated with the mass effect of formation were relatively more common. Galactorrhea, as

the main manifestation of the disease, occurred in 65% (P <0.001) of patients who suffered from microadenoma and 100% (P <0.001) from macroadenoma. Infertility was primary in 42 women (59.1%) and secondary in 28 (39.4%) women, and secondary infertility in 20 cases (28.1%) ended in miscarriages in the early stages of pregnancy, stillbirth in 7 (9.8 %), medical abortion in patients with microadenomas in 21% (P <0.001), and in patients with macroadenomas in 12% (P <0.001), non-developing pregnancy in 24% (P = 0.04) and only in 2 cases (2.8%) - by the birth of a child. One of the common manifestations of hyperprolactinemia is dishormonal breast hyperplasia (DBH), which is characterized by a wide range of proliferative and regressive changes in breast tissue. 19.7% (14 patients) had DBH, which was characterized by pain in the mammary gland, pain and engorgement, palpation and discharge. Further, in view of the multifaceted influence of prolactin, we evaluated the functional state of the central nervous system. To distinguish between symptoms caused by mechanical compression of nearby structures with the formation of the effect of "tumor mass", we separately analyzed patients with micro and macroadenomas. The following syndromes were distinguished in the group of patients with microadenoma: intracranial hypertension syndrome in 27 (58%), PMS syndrome in 1 (2%) (P <0.001), and in patients with macroadenoma in 8 (32%) (P <0.001) cases, inflammatory diseases of the brain in 4 (5.6%).

Analysis of hormonal indicators revealed (Table 2) significantly high levels of PRL in both groups relative to the control group (healthy patients) (p1 <0.001, p2<0.0001, p3<0.0001). The LH level in patients in the group with microadenomas averaged 0.82 ± 0.92 IU/L, and in the group with macroadenomas the average values were 0.62 ± 0.18 mIU/L, i.e. LH levels were significantly reduced in both groups relative to the control (p_2 <0.0001, p_3 <0.0001). Estradiol levels underwent various fluctuations in both groups, in the group of patients with microadenomas ranged from 21.47 to 75.3 ng/ml and Me was 38.20 ng/ml, and in the group with macroadenomas ranged from 20.40 to 32.40 ng/ml and Me was 27.50 ng/ml , which was significantly lower in comparison with the control group. The progesterone levels on day 7 in both groups were significantly reduced relative to the control (p_2 <0.001, p_3 <0.001), and the progesterone level on the 21st day of the menstrual cycle ranged from 1.10 to 3.98 pg/ml and Me was 2.75 pg/ml, and in the group with macroadenomas ranged from 0.42 to 3.30 pg/ml and in Me amounted to 1.20 pg/ml, which were significantly reduced in relation to the control group (p2 <0.0001, p3<0.0001). So, in both groups there was a deficiency of the luteal phase. TH levels fluctuated within normal values, ranged from 0.7 to 4.1 IU/l and averaged 2.64 ± 0.76 mIU/I in the group of patients with microadenomas and 2.50 ± 0.69 mIU/I in the group with macroadenomas. Testosterone levels between patients with macroadenomas were significantly significant in relation to the control group (p_2 <0.01), and cortisol levels were within normal limits. Next, the state of the ovarian reserve was assessed — FSH, activin, AMH, inhibin A and B in serum were determined. As can be seen from table 2, the level of FSH in the group of women with microadenomas ranged from 7.20 to 18.12 U/l and Me was 11.8 U/l, which was significantly different from the group of patients with healthy control (p_3 <0.001) and with macroadenomas (p_1 <0.0001) , where the level of FSH Me was 2.60 units/liter. The inhibin A level in both Me groups was 1.30 ng/ml, which significantly differed from the control group (p_2 <0.0001, p_3 <0.0001). The level of inhibin B underwent significant changes in both groups. In the group of patients with microadenomas, it ranged from 32 to 47 and averaged 42.17 ± 2.91 pg/ml, and in the group with macroadenomas, inhibin B ranged from 32.8 to 48.2 and averaged 42.10 ± 3.06 pg/ml, which significantly differed from the control group (p_2 <0.001, p_3 <0.001). A decrease in inhibin B and an increase in FSH can prove a decrease in ovulatory ovarian reserve. If we consider activin, then in patients with microadenomas it ranged from 0.05 to

11.20 pg/ml and Me was 9.15 pg/ml, and in the group with macroadenomas, Me was 0.07 pg/ml, which did not differ from the control group. The studied women with EI in both groups showed a decrease in AMH, in the group with microadenomas ranged from 0.12 to 2.1 and averaged 0.75 ± 0.27 ng/ml, and in the group with macroadenomas ranged from 0.09-2.2 and averaged 0.97 ± 0.49 ng/ml, which significantly differed from the control group (p_1 <0.05, p_2 <0.001 p_3 <0.001).

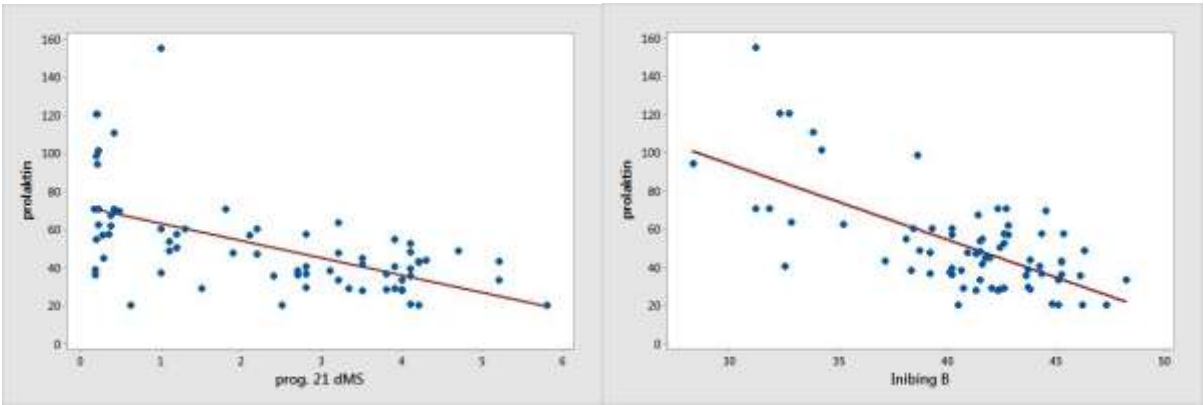
Table 2: Comparative hormone levels in women with EI with prolactinomas depending on the size of education.

Hormon (un)	Macroadenoma (n=25)	Microadenoma (n=46)	Control (n=20)	P
Prolactin (Me [IQR]) ng / ml	60.20 [54.30-70.20]	38.00 [28.73-46.53]	7.5 [5.5-8.2]	**p_1 <0.001** **p_2 <0.0001** **p_3 <0.0001**
Progesterone 7 DMC (Me [IQR]) mg / ml	0.48 [0.28-1.00]	0.76 [0.22-1.10]	1.3 [1.1-1.2]	p_1 ≤0.749 **p_2 <0.001** **p_3 <0.001**
Progesterone 21 DMC (Me [IQR]) mg / ml	1.20 [0.42-3.30]	2.75 [1.10-3.98]	9.6 [6.5-12.8]	p_1 = 0.109 **p_2 <0.0001** **p_3 <0.0001**
Estradiol 7 DMC (Me [IQR]) pg / ml	27.50 [20.40-32.40]	38.20 [21.47-75.3]	59.45 [49.3-69.25]	p_1 =0.5 p_2 =0.13 p_3 =0.34
LH 3 DMC (M (SD)) u / l	0.62±0.18	0.82±0.92	5.8±0.42	p_1 =0.270 **p_2 <0.0001** **p_3 <0.0001**
FSH 3 DMC (Me [IQR]) u / l	2.60 [2.20-12.90]	11.8 [7.20-18.12]	6.35 [5.5-7.3]	**p_1 <0.0001** p_2 =0.53 **p_3 <0.001**
Inhibin A (Me [IQR]) ng / ml	1.30 [1.00-2.60]	1.30 [1.10-2.08]	6.4 [5.35-7.3]	p_1 =0.699 **p_2 <0.0001** **p_3 <0.0001**
Inhibin B (M (SD)) pg / ml	42.10 ±3.06	42.17 ±2.91	62.06±8.2	p_1 =0.934 **p_2 <0.001** **p_3 <0.001**
Activin (Me [IQR]) pg / ml	0.07 [0.04-10.07]*	9.15 [0.05-11.20]*	5.2 [4.2-6.2]	p_1 <0.04 p_2 =0.11 p_3 =0.18

Hormon (un)	Macroadenoma (n=25)	Microadenoma (n=46)	Control (n=20)	P
AMG (M (SD)) ng / ml	0.97 ±0.49	0.75 ±0.27	3,26±0.53	**p_1 < 0.05** **p_2 <0.001** **p_3 <0.001**
Cortisol (Me [IQR]) ng / ml	102.00 [95.3-128.00]	99.80 [83.2-102.5]	88 [75.6-97.53]	p_1 =0.947 p_2 =0.14 p_3 =0.21
Testosterone (M (SD)) ng / ml	0.4 ±0.18	0.34 ±0.18	0.3±0.02	p_1 =0.223 **p_2 < 0.01** p_3 =0.35
TTH (M (SD)) mIU / I	2.50 ±0.69	2.64 ±0.76	2.4±0.5	p_1 =0.464 p_2 =0.07 p_3 =0.062

Note: * - P <0.05, ** - P <0.01, *** P <0.001, **** P <0.001 statistical significance in relation to the group with macroadenoma and to the control group.

It is known that hyperprolactinemia both directly and indirectly disrupts the processes of ovulation and gestation. But does PRL affect a woman's ovarian reserve? How do transforming growth factors change under the conditions of tumor hyperprolactinemia? In this regard, we carried out separate correlation studies depending on the level of PRL. Correlation and regression analysis was performed according to the Spearman method between prolactin and such hormones as estradiol, LH, FSH, activin, AMH, Inhibin A, inhibin B in groups of patients with EI with prolactinomas (n = 71) (Fig. 3) and separately in depending on the size of hypertension: micro and macroadenomas of the pituitary gland (table. 3).



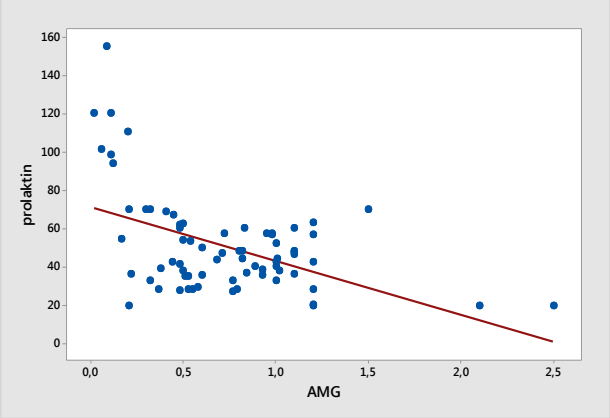


Fig. 3. Spearman correlation and regression analysis depending on the level of PRL in women with EI with prolactinomas (n=71).

As can be seen from Figure 3, Spearman correlation and regression analysis showed that between prolactin and AMH (r = -0.4; p<0.01), between prolactin and progesterone (21dMC) (r = -0.576; p<0.0001) a between prolactin and inhibin B (r = -0.67) there is a strong "-" negative relationship and all indicators were statistically significant. Our regression analysis showed that with an increase in prolactin by 1 unit, AMH decreases by 0.008 units (p<0.001), inhibin B decreases by 0.11 units (p<0.001), progesterone (21dMC) decreases by 0.04 units (p <0.001). Correlation analysis between prolactin and estradiol (r = -0.01) (p = 0.9), LH (r = -0.3; p = 0.01), FSH (r = -0.3; p = 0.01), activin (r = -0.2; p = 0.1) showed a weak - negative relationship, and between prolactin and inhibin A (r = 0.2; p = 0.04) a weak positive relationship was found.

Table 3: Correlation analysis of hormones in patients with EI with prolactinomas depending on the size of the formation (n=71)

	Estra-diol	**Progesterone (21dMC)**	**LH**	**FSH**	**Activin**	**AMG**	**Inhibin A**	**Inhibin B**
PRL micro-adenoma (n = 46)	r=0,159	r=(-) 0,501 ***	r = (-) 0,254	r=0,3	r=0,076	r=0,057	r=(-) 0,2	r=(-) 0,626 ****
P-value	0,29	**0,001**	0,08	0,07	0,618	0,707	0,429	**0,0001**
PRL macro-adenoma (n = 25)	r=(-) 0,214	r=(-) 0,530 ***	r=(-) 0,548 **	r=(-) 0,4 *	r=(-) 0,267	r=(-) 0,567 **	r=0,605 ***	r=(-) 0,702 ****
P-value	0,3	**0,001**	**0,005**	**0,05**	**0,1**	0,003	**0,001**	**0,0001**

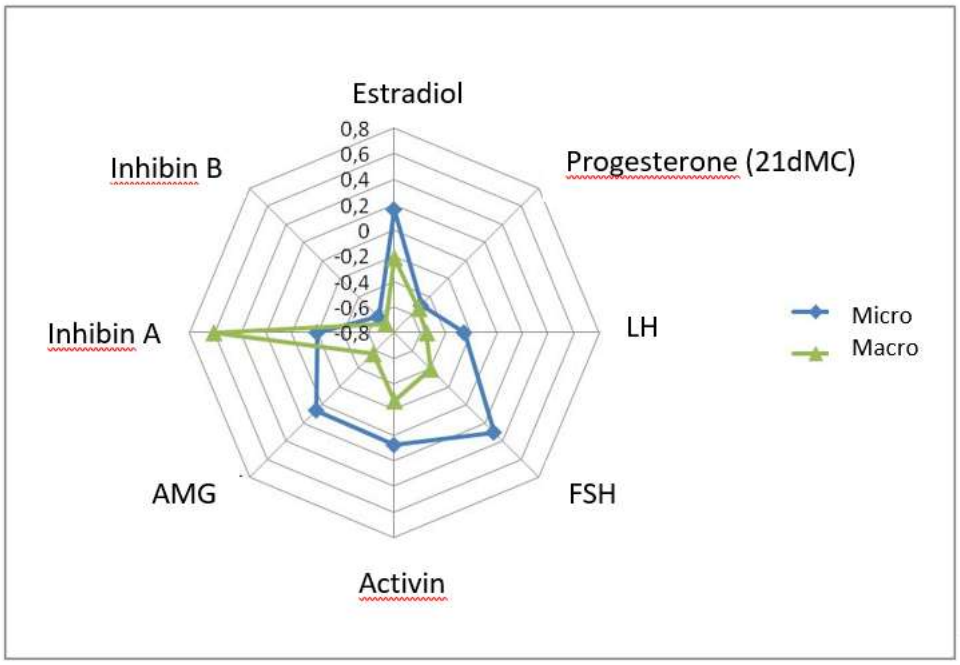


Fig. 4. Correlation analysis in patients with EI with prolactinomas depending on the size of the formation (n=71)

According to the correlation results, it can be said that a strong negative correlation was between PRL and progesterone (at 21dMC) (r = -0.501) and inhibin B (r = (-) 0.626) in the group with micro PA ($p<0.0001$). Between PRL and hormones such as estradiol (r = 0.159), FSH (r = 0.3), AMH (r = 0.057), activin (r = 0.076), there was a weak positive relationship. We determined a weak negative relationship between PRL and LH (r = (-) 0.254), PRL and inhibin A (r = (-) 0.2) and these connections were not statistically significant. If we consider a group of patients with macro-hypertension, you can see a strong negative relationship between PRL and FSH (r = (-) 0.4; $p<0.05$), PRL and inhibin B (r = (-) 0.702; p<0, 0001), PRL and AMH (r = 0.567; $p<0.003$), PRL and LH (r = (-) 0.548; $p<0.005$) and PRL and progesterone (21dMC) (r = (-) 0.530; $p<0.001$) and the indicators were statistically significant. These connections prove that with an increase in the level of PRL in patients with macroAG, the levels of FSH, AMH, LH, and inhibin B are significantly reduced. The correlation also showed that with an increase in the level of PRL, the level of inhibin A also increases and there was a strong positive correlation between the two hormones (r = 0.605) and this was statistically significant ($p<0.001$). And between PRL and estradiol, PRL and activin, there was not a strong negative relationship and these indicators were not statistically significant (Fig. 4).

Further, in accordance with the objectives, we investigated the quality of the menstrual cycle, which was assessed by basal thermometry and folliculometry (Table 4).

The results of basal thermometry (BT) showed deviations from the norm in both groups, which were characterized by the following violations: monophasic temperature in 56 (78.8%), shortening of the hyperthermic phase in 10 (14%), two-phase curve in 5 (7.04%).

Folliculometry and BT in patients with EI with prolactinomas in two groups (n=71)

Table 4

	Folliculometry			Basal Thermometry		
Researched groups	Anovul	atresia	persistent	monophase	Shortened Hyper.	Biphasic

MacroPA (n=25)	18 (72%)	4 (16%)	3 (12%)	20 (80%)	4 (16%)	1 (4%)
MicroPA (n=46)	31 (67,3%)	6 (13%)	9 (19,5%)	36 (78,2%)	6 (13%)	4 (8,6%)
P	0,131	0,295	0,274	0,3	0,877	0,297

Folliculometry, as a method of objectifying the ovulation process, revealed anovulation in 49 cases (69%), follicle atresia, and follicle persistence in 12 (16.9%) (Table 4). As can be seen from the table, in patients with infertility with prolactinomas, anovulation cases (69%) with a monophasic BT curve (78.8%) predominated significantly. We also performed a correlation analysis of BT indices with the results of FM with anovulation, follicle artesia and follicle persistence, and in the group with macroadenomas we found a positive correlation ($r = 0.503$) between monophasic BT and anovulation ($p = 0.005$), follicular atresia and shortening of the hyperthermic phase ($r = 0.522$, $p = 0.478$), the follicle persistence and the two-phase BT curve ($r = 0.607$, $p = <0.0001$). And in the group with microadenomas, the following occurred: a positive average relationship between anovulation and monophasic BT ($r = 0.554$, $p = 0.003$). Between monophasic BT and anovulation ($r = 0.554$, $p = 0.002$) and atresia with a shortening of the hyperthermic phase of BT ($r = 0.6$, $p = 0.002$), follicle persistence, and a two-phase BT curve ($r = 0.62$, $p = 0, 0001$). Moreover, in patients with monophasic BT and anovulation with FM, there was an inverse correlation with the level of progesterone ($r = 0.550$, $p = 0.004$) and ($r = -0.388$, $p = 0.050$), respectively. A similar analysis conducted in women from the healthy control group found interesting data. That is, normal increase in follicle size by 1 mm is accompanied by an increase in BT by 0.12 C^{O} ($r = 0.872$, $p = <0.0001$).

Conclusions

1. Endocrine disorders in women with prolactinomas consists of NFM (69%), miscarriage and non-developing pregnancy (52%), decreased libido and PMS (80%) and endocrine infertility (primary in 58% and secondary infertility in 39%). The frequency of occurrence of which is significantly increased in patients with macroadenoma compared with microadenoma ($p<0.03$: $p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$), respectively.

2. Infertility was primary in 42 women (59.1%) and secondary in 28 (39.4%) women, and secondary infertility in 20 cases (28.1%) ended in miscarriages in the early stages of pregnancy, stillbirth in 7 (9 , 8%), medical abortion in patients with microadenomas in 21% ($P <0.001$), and in patients with macroadenomas in 12% ($P <0.001$), non-developing pregnancy in 24% ($P = 0.04$) and only 2 cases (2.8%) - by the birth of a child.

3. The study of the indicators of FM and BT in patients with EI with prolactinomas, depending on the size of the formation, revealed a significant violation of ovulation processes by the type of anovulation (67.3% and 72%), atresia (13% and 16%) and follicle persistence (19 5% and 12%) with a monophasic BT curve (78% and 80%) with micro- and macroadenomas, respectively. There was a positive correlation between monophasic BT and anovulation ($r = 0.554$, $p = 0.002$) and follicular atresia with a shortening of the hyperthermic phase of BT ($r = 0.62$, $p = 0.002$).

4. Spearman correlation and regression analysis found a negative relationship between PRL and AMH ($r = -0.4$, $P <0.0001$), PRL and progesterone ($r = -0.57$, $P <0.0001$). That is, with an increase in PRL by 1 unit, a decrease in AMH by 0.008 units ($P <0.001$), a decrease in

inhibin B by 0.11 (P <0.001), progesterone by 0.04 units (P <0.0001), and the degree of hyperprolactinemia can predict EI development.

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