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RESULTS OF DIAGNOSTICS AND TREATMENT OF WOMEN OF REPRODUCTIVE AGE WITH NON FUNCTIONING PITUITARY ADENOMA

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ABSTRACT

Relevance. Non functioning pituitary adenomas (NFA) are the most common pituitary lesions after prolactinomas. The absence of clinical symptoms of hormonal hypersecretion may contribute to the late diagnosis of the disease. Thus, most patients go to the doctor for signs and symptoms arising from massive exposure, such as neuro-ophthalmological symptoms and hypopituitarism, pituitary apoplexy.[3] Tumor mass effect and hypopituitarism cause high morbidity and mortality. However, early diagnosis and effective treatment minimize morbidity and mortality. In this article, our goal was to diagnose and treat patients with NFA in a timely manner, emphasizing that treatment should be carried out on an outpatient basis and in medical centers. This article is based on data published in the literature and on the experience of the authors.[4]

KEYWORDS: non functioning pituitary adenoma; transsphenoidal surgery; radiation therapy; cabergoline.

INTRODUCTION

Adenomas are the most common primary neoplasm of the anterior pituitary gland, accounting for 10-15% of all intracranial tumors.[1] They are benign neoplasms of monoclonal origin, and their pathogenesis is believed to mainly include inactivation of mutations in tumor suppressor genes or activation of mutations in protooncogenes, although in most cases specific mutations have not yet been identified.[2]

Pituitary adenomas are divided into active and non functioning, depending on the presence or absence of clinical syndromes resulting from hormonal hypersecretion. Once imaged, these tumors can be further classified as microadenomas (<10 mm) or macroadenomas (≥ 10 mm), depending on their size.[3] Approximately 30% of pituitary adenomas are clinically nonfunctioning, and most patients seek medical attention for signs and symptoms resulting from massive exposure to surrounding structures, that is, the optic chiasm, cranial nerves, and pituitary pedicle. However, some cases can be diagnosed incidentally with magnetic resonance imaging (MRI) and computed tomography (CT) brain examinations performed for other purposes.[4] This article is about the results of diagnosis and treatment of patients with non functioning pituitary adenomas (NFA), whose presentation was not accidental.[5]

In women, NFA is often combined with pathology of the reproductive system, and in 88% of women with NFA, PCOS is detected, in 23% - secondary hypogonadism with amenorrhea, which is why these patients often visit gynecologists.[6] These changes are often the result of compression or damage of gonadotrophs or pituitary lactotrophs by a growing tumor.[7]

The second of the possible reason for the violation of the pathology of reproductive function in NFA is the phenomenon of a crossed leg - compression of the macroadenoma of the portal vessels of the pituitary gland and a violation of the hypothalamic pituitary axis (HPA). Hypogonadism may be due to the inhibitory effect of PRL on the production of gonadotropins, progesterone and estrogens, as well as on the luteinization process.[8] After surgical removal of the NFA, the pituitary cells are decompressed and the hormonal status is often restored on its own. However, when changes in hormonal status are associated with ischemic necrosis of pituitary cells, recovery options after surgery are limited, because in the

tissue of the tumor itself apoplexy and sclerosis can also occur (often with prolonged therapy with bromocriptine drugs). In these cases, remission is clinically noted, and NFA is diagnosed on CT / MRI.[9]

Reproductive system dysfunctions in NFA may be caused by abnormal, non-cyclic production of gonadotropins or their subunits by adenoma cells. The physiological role of free gonadotropin subunits remains unclear. However, data appeared in the literature suggesting the possibility of an independent influence of the α-subunit of glycoprotein hormones on the reproductive system.[10]

A certain role in the pathogenesis of NFA may belong to peripheral links in the feedback system ovaries - hypothalamus - pituitary gland. It is known that chronic hyperestrogenism leads to hyperplasia of pituitary cells and can be a triggering mechanism for the development of adenoma. Probably, conditions accompanied by an increase in the content of estrogens in the blood (including PCOS) may contribute to the development of NFA.[11]

All types of physiological (menopause) or pathological (depleted or resistant ovary syndrome) ovarian hypofunction lead to stimulation of the secretion of pituitary gonadotropins, and such a load on the pituitary cells can cause compensatory cell hyperplasia and, possibly, contribute to the development of adenoma. In general, the analysis of the mechanisms of development of NFA and often associated with them violations of reproductive function, primarily PCOS, indicates the existence of a pathogenetic relationship between these types of pathology, which must be taken into account in their diagnosis and treatment.

Unlike hormone-active adenomas, NFAs do not have any specific clinical symptoms and are not manifested by the classic hormone hypersecretion syndromes (Cushing's disease, etc.). NFAs are more often detected as a finding on X-ray of the skull, and microadenomas, in contrast to macroadenomas, do not show symptoms of tumor compression of the surrounding tissues, however, as in large tumors, hyperprolactinemia (HP) can be observed, the origin of which is still hypothetical.[11] The endocrine manifestation of NFA can be partial or complete (with macroadenomas) hypopituitarism. This often results in menstrual disorders, anovulation and infertility, and decreased libido.[12]

Moderate hyperprolactinemia occurs in 48% of patients with NAH, which is often accompanied by galactorrhea-oligomenorrhea in women and sexual dysfunction in men.[13]

Hyperprolactinemia in NFA is of a functional nature (associated with a violation of the hypothalamic-pituitary relationship with large adenomas), which is confirmed by the results of the test with Parlodel, against the background of which in patients with NFA there is a decrease in the prolactin level by more than 50%, as in healthy people.[14]

In patients with NFA with both normo- and hyperprolactinemia, there is a decrease in the prolactin response to the stimulating effect of thyroliberin, which is more pronounced in hyperprolactinemia. The absence of the daily prolactin biorhythm was also revealed in patients with NFA, which was observed in large and giant adenomas.

When examining the hormonal status in the blood serum of patients with NFA, there may be a slight increase in the level of FSH, β-FSH, α-subunit, and less often LH.[15] LH-secreting tumors are rare, but in this case, an increase in testosterone levels may occur. The serum FSH level is elevated in about 15% of patients, which in 48% of cases is combined with the secretion of the α-subunit. Adenomas secreting only the α-subunit occur in 7% of cases.[16]

As shown by the results of multicenter studies (2020) conducted in 6 Endocrinological Centers in Italy (295 patients with NFA), the main clinical manifestations of NFA are visual impairments (67.8%), headaches (41.4%) and hypogonadism (43, 3%) in cases when we are talking only about macroadenomas. At the same time, the method of choice in their treatment is 98% - surgical treatment, which leads to improvement in 35.5%, and 41% of patients need additional radiation therapy. In patients without transphenoidal adenomectomy, recurrent growth is observed in 19.2% of cases within 7.5 ± 2.6 years. After surgical treatment, a relapse within 10 years occurs in 58.4% of patients, of which 18.4% require radiation therapy (RT), and the rest are reopirated.[17]

The next common pathology of the reproductive system in NFA is PCOS, accompanied by opsomenorrhea, infertility, hirsutism, and metabolic changes.[18] It should be noted that according to officially existing Russian health statistics, 4.3% of all cases of infertility develop due to PCOS, which occurs with a frequency of 60 women per 10,000 population of the Russian Federation.[19] Examination of such patients reveals chronic anovulation, an increased LH / FSH ratio (> 2), and hyperandrogenism. In recent years, it has been established that with PCOS insulin resistance and hyperinsulinemia often occur.[20]

At the same time, it is believed that PCOS accompanies about 75% of anovulatory infertility, thus being a non-specific manifestation of certain changes in the endocrine system. Moreover, in a number of women who have hyperandrogenic anovulation and have no signs of typical PCOS, the changes are of a functional nature (the so-called "functional ovarian hyperandrogenism" - FOH).[21] The evidence of the functionality of the changes are: 1) the absence of anatomical and morphological changes in the ovaries; 2) the

gonadotropin-dependent nature of the disorders (which can, in particular, be evidenced by the normalization of the level of androgens after the use of LH-RH analogs). There is a theory that PCOS is a form of FOG.[22] Modern ideas about the pathogenesis of PCOS are as follows. According to one theory ("estrone theory"), PCOS develops as a result of a "vicious" cycle of androstendione formation. The latter can be partially produced in the adrenal glands and is aromatized at the periphery into estrone.[23] An increase in estrogens has been found to increase the sensitivity of gonadotrophs, which leads to an increase in LH secretion, and the latter, in turn, induces or maintains an increased secretion of androstenedione.[24] The second, alternative, theory considers PCOS as a form of functional gonadotropin-dependent ovarian hyperandrogenism.[25] According to this theory, the basis of disorders in PCOS is an increase in the intra-ovarian concentration of androgens. The local increase in the level of androgens promotes follicular atresia and is responsible for anovulation as a result of the direct action of androgens on the ovary. Testosterone also, being an antiestrogen, inhibits ovulation and inhibits blastocyst development in the early stages of pregnancy.[26] Androgens, getting into the bloodstream, cause virilizing changes, the development of hirsutism. Processes that can lead to an increase in the level of androgens in the ovaries include: follicular atresia, which can be both the cause and the result of excess androgens; increased production of androgens outside the ovaries; defects in the biosynthesis of estrogens from androgens in the ovaries and dysregulation of androgen secretion, which may be the result of both excessive LH secretion by the pituitary gland and an increase in the action of LH by insulin, insulin-like and other growth factors.[27]

So, for the most part women with inactive pituitary adenomas suffer from reproductive disorders. Moreover, reproductive disorders in hypertension are associated with abnormal or acyclic production of gonadotropins (50%), pathological or functional hyperprolactinemia (75%), functional ovarian hyperandrogenism (up to 30%) and other reasons.[28] According to the literature data, hyperprolactinemia is the main pathogenetic mechanism among infertility in hypertension.

It is known that NFAs in size are microadenomas (up to 10 mm), macroadenomas (more than 10 mm), giant adenomas (3 cm or more). During the dynamic observation of patients with microadenomas, it was noted that their size increased in less than 25% of the examined patients and their spontaneous decrease was also possible. They only show signs of invasive growth in 2% of cases. In 80% of patients with microadenomas within 6 years of follow-up and in the absence of therapy, there was no increase in tumor size and an increase in the prolactin level, 10% showed tumor growth, and 10% of women showed spontaneous normalization of the prolactin level. At the same time, macroadenomas (more than 10 mm in diameter), in the absence of therapy, have a high growth potential, more often lead to narrowing of the visual fields and pituitary insufficiency.[29]

Primary hyperprolactinemia also develops when the pituitary pedicle is damaged and in such pathological processes in the sella turcica as NAG, craniopharyngioma, empty sella turcica, intrasellar cyst, Rathke's pocket cyst, and intrasellar meningioma.[30]

It is believed that in 11-30% of women with PCOS, an increase in PRL secretion may be associated with overproduction of estrogens, while in the rest of the patients it occurs as an independent endocrine disorder.[31]

Hirsutism, in combination with hyperandrogenism and its clinical manifestations, is diagnosed in almost every 4th patient with a frequency similar to that for a group of women with a normal level of prolactin.[32] PCOS is detected in 18-20% of patients against the background of impaired prolactin secretion. However, conditions such as hyperandrogenism, hirsutism, impaired fat metabolism, hypothyroidism, and PCOS are not mandatory clinical parameters of HP and most likely manifest themselves as an independent comorbid pathology.[33]

Adenomas of the pituitary gland, proceeding without clinical manifestations of hypersecretion of pituitary hormones, are called "inactive" pituitary adenomas (NFA). In the literature, the terms "clinically non-functioning adenomas or" silent "adenomas are also used. NFAs account for 25-30% of all pituitary tumors, while their suprasellar localization increases the frequency of nonselective adenomas to 70%.[34, 35] It is necessary to distinguish between the concepts of NFA and "incidentaloma", the latter is often found in foreign literature.[36] Incidentalomas - tumor formations found in any organ by chance during a more detailed examination of the patient. The variety of mechanisms of the effect of prolactin on a woman's body is due to the breadth of its biological action, active interaction with neurotransmitters, peripheral hormones, and the presence of prolactin receptors in many organs and tissues of the body. It is well known that pronounced ovarian hypofunction, which is most common in women with tumor genesis of hyperprolactinemia, aggravates the clinical picture of the disease, leads to disorders not only of the reproductive system, but also of other organs and systems.[37,38]

NFAs are uncommon during pregnancy because fertility is usually impaired. For patients wishing to become pregnant, tumor reduction is shown.[39] Pregnancy rarely increases the size of clinically nonfunctioning pituitary adenomas. An enlarged pituitary adenoma can occur due to tumor growth, heart attack, or hemorrhage into the tumor during pregnancy. Sometimes apoplexy of a pituitary adenoma with loss of visual fields may be the

first sign of the disease during pregnancy.[40] The risk of a visual field defect is increased in patients with tumors larger than 1.2 cm.[41] The increased size of the pituitary gland due to lactotroph hyperplasia can lead to a mass effect of pituitary adenoma during pregnancy with a rapid response to CD therapy.[42] If necessary, surgical treatment is possible in the second trimester of pregnancy. In the third trimester, bromocriptine treatment or conservative management may be preferred.

Based on the foregoing, the aim of our study was to study the spectrum of reproductive disorders in women with NFA, taking into account the size and duration of NAH, and to optimize their treatment.

MATERIALS

For the period from 2018 to 2020 on the basis of the Republican Specialized Scientific and Practical Medical Center of Endocrinology named after Academician Ya.Kh. Turakulova in the clinic and in the department of neuroendocrinology, 46 women aged 18-45 years with NFA were examined, who were subjected to a complete clinical-hormonal, imaging study.

The women studied by us were divided into 3 groups. The first group included 36 women with NFA with microadenomas. The second group consisted of 10 women with NFA with macroadenomas. The third group, the control group, included 20 healthy women.

Table 1.1: Distribution of patients by size of NFA (n = 46).

Typesofadenomas	Totalnumber	Microadenomas	Macroadenomas
NFA	46	36 (78,2%)	10 (21,7%)
Control group	20	20	20

Methods. Clinical research methods. When collecting anamnesis, working conditions, the presence of occupational hazards, bad habits (smoking, alcohol or drug abuse, treatment by a neurologist or psychiatrist, taking medications), heredity were determined. Clinical examination. When examining women, attention was paid to the length and weight of the body, physique, the development of adipose tissue and the peculiarities of its distribution. The method of anthropometry was used to estimate BMI, according to the WHO classification (2020). Gynecological status. The women were assessed together with the gynecologists of the maternity hospital No. 6 (Ph.D. Navruzova RS). When assessing the reproductive status, the following menstrual irregularities were taken into account: infrequent and absent menstruation, intermenstrual bleeding, and discharge before and after menstruation. In case of violation of the menstrual cycle, the following were specified: the time of the onset of the violations, the relationship with other diseases, surgical interventions, stressful situations, a change of residence, the onset of sexual activity or taking medications. It also took into account the history of pregnancies and their outcomes, the number and duration of marriages. 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 a biphasic nature of temperature with a decrease in ovulation on the day of 0.2-0.3 °C and a subsequent rise in phase II of the cycle by more than 0.5 ° C, compared with phase I of the menstrual cycle. The duration of the luteal phase, according to basal temperature, should normally be 12-14 days. A shortening of the second phase, as well as a slow, “step-like” rise, was regarded as an inferior luteal phase of the cycle. If the basal temperature curve was below 37 °C and had a monophasic character, the state was assessed as anovulatory cycle.[43,44]

Ultrasound of the ovaries and uterus with folliculometry (FM) was performed with a vaginal sensor (doctorMatchanova A.T.) on the basis of the Research Institute of Obstetrics and Gynecology of the Ministry of Health of the Republic of Uzbekistan according to the generally accepted method (Kulakov V.I. et al., 2002). FM was performed vaginally by ultrasound method, starting from 7-8 days MC.[45] The thickness of the endometrium, the size of the dominant follicle in the course of its development to the final stage - ovulation or anovulation, persistence or atresia were assessed. For completeness of information, FM data were compared with BT and hormonal indicators.

Neuro-ophthalmological examination was carried out in all patients on the basis of the RC of Neurosurgery (doctor Sharifullina F.K.). The fundus of the eye, visual fields and visual acuity were examined by methods of indirect ophthalmoscopy and fundoscopy.

X-ray method - a sighting image of the Turkish saddle, CT / MRI of the hypothalamic-pituitary region (in the clinic "JACKSOFT MEDICAL DIAGNOSTICS SERVICES").

The condition of the skin. Attention was drawn to the nature of body hair, especially excessive hair, the time of its appearance (before or after menarche). The assessment of the degree of hair growth, according to the scale of D. Ferriman, J. Galwey (1961), was carried out on a 4-point system on 11 areas of the body. For women, the normal hirsut number is 0-7 points. Based on the total number of points, which is 36, the patient's “hormonal status” indicator was calculated. The hirsut number of 8-12 points is borderline, and more than 12 points is increased. Registration of increased hair growth (hirsutism) was performed on the scale of D. Ferriman, J. Galwey (1961); (Table 1.2).

Table 1.2: The main clinical manifestations of NFA depending on the size of the formation.

Clinical manifestations	Microadenomas n=36	Macroadenomas n=10	Total n=46
Headaches	22(61,1%)	9(90%)**	31(67,4%)
Dizziness	17(47,2%)	2(20%)	19(41,3%)
Decreased vision	7(19,4%)	6(60%)*	13(28,3%)
Lactorrhea	22(61,1%)	8(80%)*	30(65,2%)
Amenorrhea	9(25%)	6(60%)*	15(32,6%)
Menstrual irregularities	31(86,1%)	8(80%)	39(84,8%)
Decreased libido	14(39%)	7(70%)*	21(45,6%)
Weight gain	19(52,7%)	4(40%)	23(50%)
Weakness	26(72,2%)	2(20%)**	28(60,8%)
Cardialgia	22(61,1%)	5(50%)	27(58,7%)
Puffiness	18(50%)	7(70%)	25(54,3%)
Hirsutism	18(50%)	5(50%)	23(50%)
Alopecia	6(16,6%)	2(20%)	8(17,4%)
Highbloodpressure	17(47,2%)	4(40%)	21(45,6%)
Sweating	12(33,3%)	2(20%)	14(30,4%)
Polyuria	4(11,1%)	7(70%)***	11(24%)
Polydipsia	6(16,6%)	7(70%)**	13(28,3%)
Drymouth	12(33,3%)	5(50%)	17(37%)
Acanthosis nigricans	16(44,4%)	2(20%)	18(39,1%)

Note: * - P <0.05; ** - P <0.01; *** - P <0.001 - statistical significance in relation to the group with microadenoma.

Further, we analyzed the range of reproductive indicators that allow us to clarify the possible mechanisms of the development of infertility in NFA.

It should be noted that while primary amenorrhea occurred only in 3 women with microadenoma, which accounted for 6.5% of cases, while secondary amenorrhea was the cause of infertility in 10 (21.7%). Among the patients of this group, 37 (80%) had newly diagnosed hypertension, 12 women diagnosed with hypertension were treated without effect. At the same time, violation of the menstrual cycle in 5 (10.8%) was of the oligomenorrhea type, in 12 (26.1%) opsomenorrhea and in 9 (19.5%) menometrorrhea.

A detailed analysis of the gynecological status revealed uterine hypoplasia of 1-2 degrees in 17 (36.9%), uterine hypoplasia of grade 3 in 2 (4.3%), chronic adnexitis in 26 (5.6%) patients. It is important to note that in patients with NFA, cases of PCOS were found quite often - in 27 (58.7%), reliable clinical and hormonal criteria for PCOS (clinically or hormonally confirmed hyperandrogenemia, violation of the menstrual cycle, primary infertility, hirsutism on a scale of ≥6, ultrasound picture of polycystic ovary).

Further, we analyzed the results of FM, which revealed anovulatory cycle in 25 cases (54.3%), follicle persistence in 15 (32.6%) cases and follicle atresia in 6 (13%) cases. BT results: normal, biphasic thermograms were found in only 4 (8.6%), shortening of the hyperthermic phase in 6 (13%) and in the overwhelming majority of 36 women (82.6%), the curve was monophasic. To clarify the causes and differences in the mechanisms of infertility in patients of 2 main groups, the results of FM were compared (Table 1.3).

As can be seen from the tables, in patients with NFA, cases of anovulation (87% each) with a monophasic curve significantly prevailed, and the frequency of follicle atresia increased (70%).

Table 1.3: Folliculometry results in the studied patients.

	NFA (n=46)	Control group n=20
Normal ovulation	6 (13%)	20
Anovulation	40 (87%)	20
Follicleatresia	28 (70%)	20
Follicle persistence	12 (30%)	20

Table 1.4. Comparative indices of basal thermometry in patients with NFA.

	Basal thermometry		
Study group	**Monophase curve**	**shortening of the hyperthermic phase**	**Biphasic curve**
NFA (n=60)	36 (60 %)	6 (10 %)	4 (6,6%)
Control group (n=20)	20	20	20

Moreover, folliculometry revealed the phenomena of chronic anovulation against the background of polycystic ovarian structure in 87% of patients (Fig. 1). It should be noted that, despite the same frequency of anovulatory infertility in women with NFA, the types of ovulation disorders differed significantly. The results indicate that if in general the ovulation process did not differ depending on the type of adenoma (48% - atresia and 52% - persistence), then with their separate analysis it was revealed that with prolactinomas chronic anovulation syndrome proceeded as atresia in 31.5% (17 cases) and 68.5% (37 patients) - by type of persistence. While with NFA, cases of follicle atresia occurred in 70% (28 patients) and follicle persistence in 30% (12 patients). All this indicates the presence of significant differences in the pathogenesis of the development of infertility in these forms of hypertension (Fig. 1).

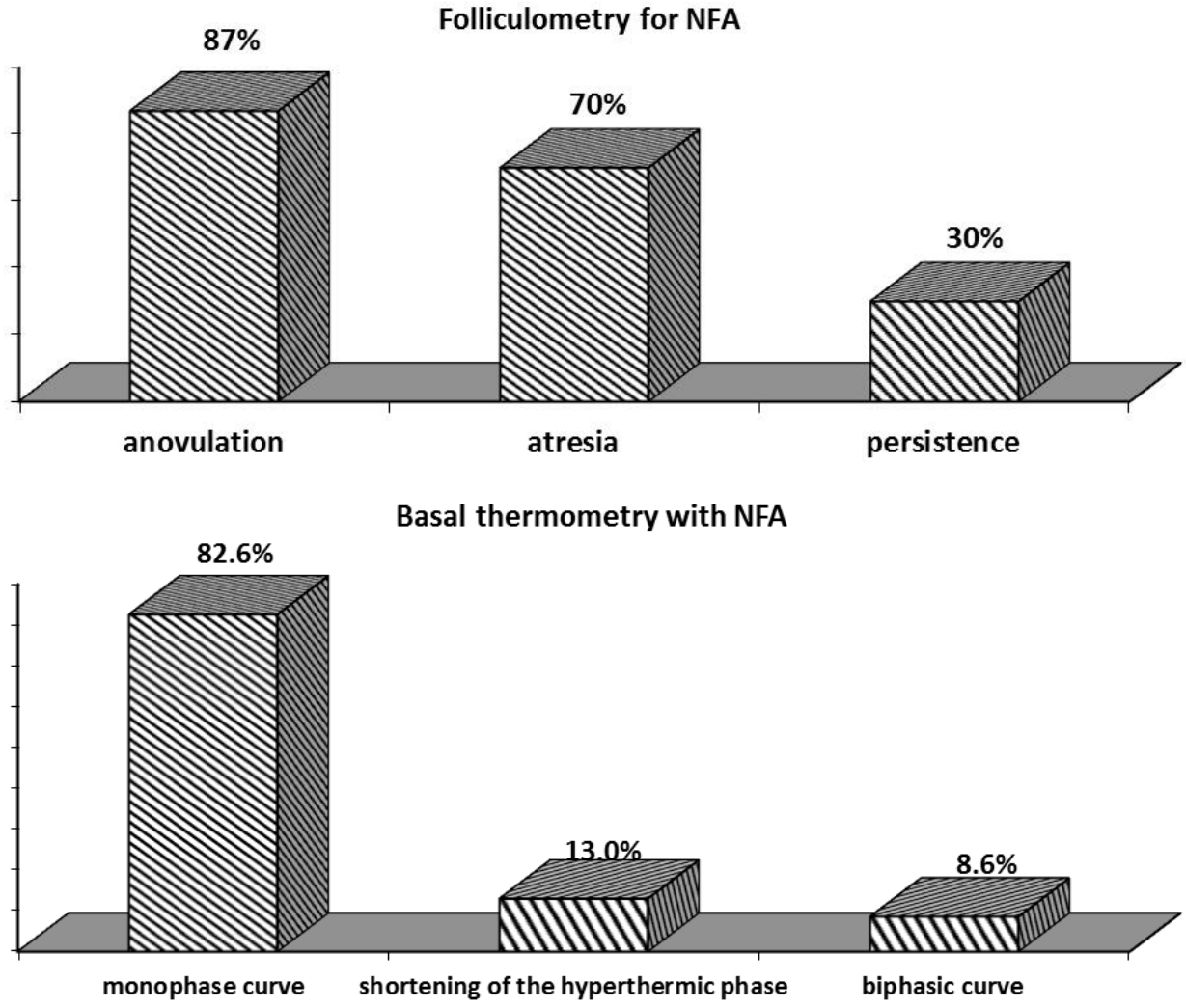

Figure 1: The results of folliculometry and basal thermometry in a comparative aspect.

Hormonal characteristics of women with NFA

Determination of the concentrations and rhythms of secretion of certain hormones can help in the diagnosis and differential diagnosis of the form of hyperprolactinemia. As a rule, with tumors of the pituitary gland, not only the quantitative parameters of hormones change, but also their response to a stimulus is damaged, the circadian rhythm is disturbed, and the degree of hormonal level disturbance depends on NFA, which can serve as an additional diagnostic criterion. In the group of patients with NFA, which consisted of 46 women aged 30.24 ± 0.88 years with a disease duration, on average, 4.47 ± 0.37 years, we investigated the levels of tropic hormones of the pituitary gland (LH, FSH, STH, TSH and prolactin) and hormones of the peripheral glands (estradiol, testosterone, progesterone and cortisol) (Fig. 2)

The results showed that the level of prolactin was within normal values in 34 (73.9%) patients and increased in 12 female patients (26.1%) with NFA, although the arithmetic mean values remained within the normal range and amounted to 8.61 ± 0, 76 (P <0.05), not significantly differing from the control group. It should be noted that the levels of prolactin significantly differed in patients depending on the size of the NFA. Thus, in women with microadenoma with intrasellar localization, the arithmetic mean values of the prolactin level amounted to 5.03 ± 1.06 ng / ml, and in patients with macroadenoma with a tendency to suprasellar growth, the concentration of PRL increased to 9.15 ± 0.78 ng / ml. That is, the levels of prolactin in NFA depend on the size and location of the formation.[47]

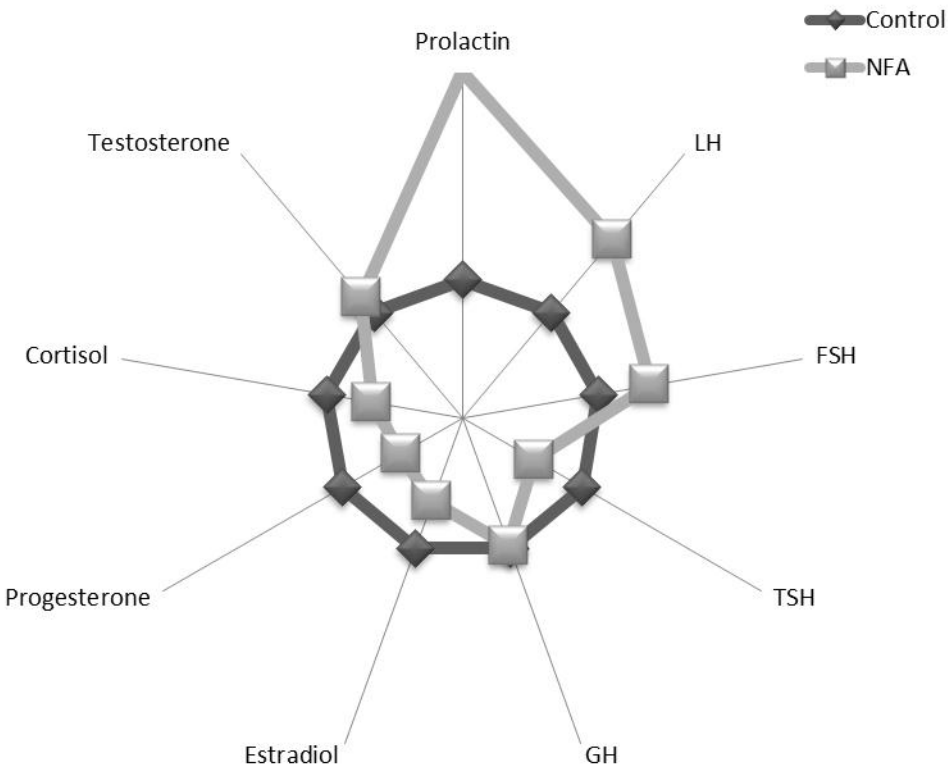

Figure 2: The state of pituitary hormones in NFA (n = 46) in patients with reproductive disorders, in relation to the data of the control group (n = 20).

Growth hormone in NFA is one of the most frequently disturbed hormones and is often clinically undiagnosed. In adults, there is a lack of growth hormone, especially when their slightly or significantly reduced levels are combined with a deficiency of other pituitary hormones.[48] This is due to the fact that in adults, the lack of GH has no specific clinical signs and, basically, resembles a picture of hypodynamia, hypotrophy, muscle hypotension and heart failure and, due to disorders of higher nervous activity, proceeds under the guise of chronic cerebrovascular accident. Thus, GH of the pituitary gland, in general, was reduced and the secretion of GH fluctuated in small variations from 0.3 to 4.3 ng / ml, on average, 3.45 ± 0.25 ng / ml. Among them, 16 women (34.6%) had normal GH levels and 30 patients had subnormal (low) GH levels (65.4%). Compared with the control group and patients with prolactinomas, the concentrations of GH were significantly lower (P <0.05 and P <0.0001), respectively.

The state of secretion of gonadotropins of the pituitary gland is of particular interest, since the main clinical manifestations of NFA and infertility (after hyperprolactinemia) are due to the violation of these

hormones. LH, FSH and prolactin carry out cyclical changes in the ovaries, provide ovulation and formation, the formation of the corpus luteum. The concentration of LH averaged 14.28 ± 1.12 mIU / L, which was 2 times significantly higher than the control values 6 ± 0.31 mIU / L (P <0.05) and 4 times higher compared to prolactin-secreting adenomas 3. 04 ± 0.98 mIU / L (P <0.0001). There was also a significant difference in LH values in patients with micro- and macroadenomas of the pituitary gland and, accordingly, ranged from 0.5 mIU / L to 28.56 mIU / L and averaged 12.0 ± 1.8 mIU / L. Of these, decreased LH levels were found in 6 (13%), increased in 21 (45.6%), and normal in 19 (41.3%). FSH ranged from 1.5 mIU / L to 13.6 mIU / L, with an average of 5.53 ± 0.44 mIU / L. Its levels were 2 times higher than the control group 3.14 ± 0.23 mIU / L (P <0.05) and 1.5 times lower than the values of the group of patients with prolactinomas 11.4 ± 0.83 mIU / L (P <0.0001) and averaged 6.75 ± 5.6 mIU / L. In general, in the group of patients with NFA, in 28 (60.8%) women, the FSH concentration was normal, and in 18 (39.1%) – decreased.[48]

Thus, the tropic function of the pituitary gland in women with NFA and infertility is characterized by a relative increase in the level of gonadotropins, depending on the size of the formation. As the size of the NFA increases, the levels of LH and FSH grow in parallel (Fig. 3). A number of data are presented in the literature[48], indicating the relationship between impaired fertility in NFA and the effect of "tumor mass", that is, with the development of hypopituitarism. But our studies indicate that at the stage of pituitary microadenomas, when the formation is small, infertility develops due to impaired hypothalamic regulation of gonadotropin secretion and inadequacy of feedback principles, as evidenced by a hypergonadotropic state with significant changes in LH, compared with FSH. Looking ahead, we can note one more fact that confirms this presentation - this is the effectiveness of dopamine agonists (CD and cabergoline) not only in terms of pathogenetic therapy, but also in fertility induction. This once again indicates the interest of the hypothalamic mechanisms in the development of hypertension and infertility.[48,49]

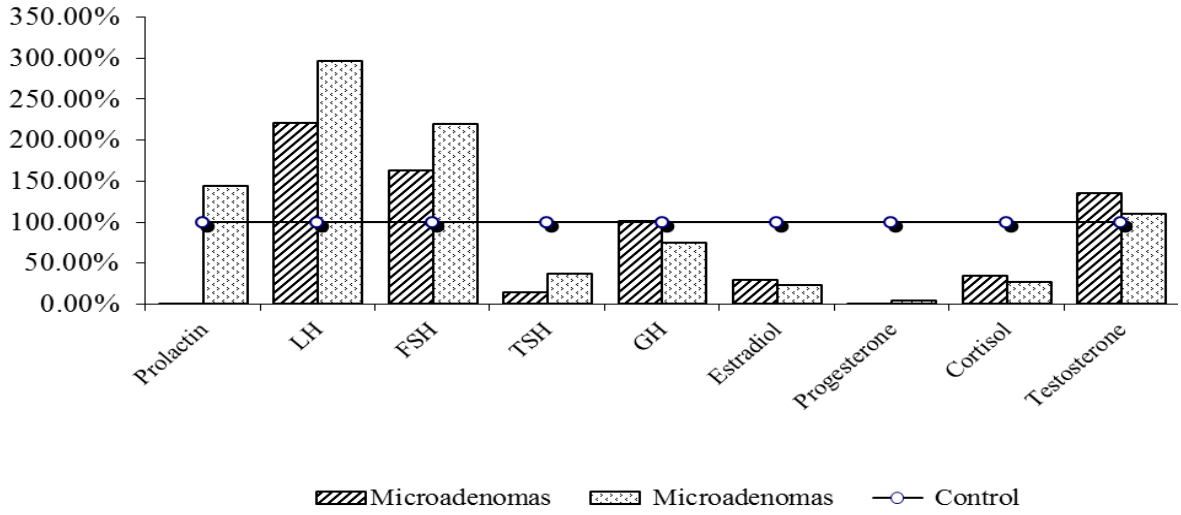

Figure. 3 Hormonal status of women with NFA and infertility (n = 46)

Table 1.4. Comparative levels of hormones in NFA, depending on the size of the formation.

Hormones	Control n=20	Microadenomas n=36	Macroadenomas n=10
Prolactin ng/ml	6,34 ± 0,35	5,03 ± 1,06*	9,15 ± 1,12*
LH mIU/l	6,0 ± 0,34	13,3 ± 1,16*	17,8 ± 2,91*
FSH mIU/l	3,14 ± 0,23	5,15 ± 0,4*	6,9 ± 1,36*
TSH mIU/l	3,74 ± 0,24	0,55 ± 0,15*	1,42 ± 0,19*
GH ng/ml	3,59 ± 0,35	3,65 ± 0,29	2,72 ± 0,37
Estradiol ng/ml	160,3 ± 7,43	47,39 ± 2,95*	38,32 ±9,11*
Progesterone pg/ml	21,36 ± 1,27	0,54 ± 0,05*	0,93 ± 0,16*
Cortisol nmol/day	345,67 ± 34,17	120,7 ± 9,84*	93,5 ± 14,96*
Testosterone nmol/l	0,53 ± 0,04	0,72 ± 0,06*	0,59 ± 0,07

Note: * - P <0.05 significant in relation to control.

As the analysis of the results showed, there is a significant change in the level of hormones with NFA. So, regardless of size, there is a tendency to an increase in the level of LH, testosterone, a significant decrease in

the levels of estradiol, progesterone, a tendency to a decrease in the levels of cortisol and growth hormone.

In comparison with the control, there was a significant increase in the levels of PRL, LH and testosterone and a decrease in the same hormones.

So, reproductive impairment in women with NFA develops against the background of an increase in BMI (67.4%), adnexitis (60.8%), inflammatory diseases of the brain (60.8%) and PCOS (54.3%); characterized by NMC (84.5%), hypertensive headaches (67.4%), lactorrhea (65.2%), in 45.6% with primary and 54.3% with secondary infertility. Violation of fertile function in 87% of cases developed into a syndrome of chronic anovulation, accompanied by a violation of ovulation by the type of atresia in 70% and by the type of follicle persistence in 30% of patients, which was due to a dysgonadotrophic state (an increase in LH and a decrease in FSH), inadequacy of feedback principles indicating the interest of hypothalamic regulation mechanisms both in the development of NFA and in the formation of infertility.[48,49]

Treatment. It is known that dopamine agonists are the treatment of choice for NFA.[49] Over the past 2 decades, bromocriptine (parlodel), despite a number of side effects and inconveniences in its use, has been considered as an effective tool not only for suppressing PRL levels, but also for restoring gonadal functions and adenoma shrinkage. Cabergoline is a new selective, potent and long-acting agonist that inhibits the secretion of prolactin for more than 21 days in 95% of patients after a 2-fold dose of 0.5 mg, restores the level of PRL to normal [49,50.] Based on this, we carried out a gradual and long-term combined use of these two drugs for the first preparatory stage of the treatment of infertility that developed against the background of NFA (46 cases) in women of fertile age. At the same time, cabergoline was prescribed by us at a dose of 3-4 mg / week with NFA, depending on the level of prolactin and the size of the adenoma for 1.5 years. In the next 6 months, we smoothly switched to bromocriptine (parlodel) at a dose of 2.5 mg at night. After 6 months, this dose was titrated individually in each case, and the patients were on it (1.25-2.5 mg / day) until pregnancy as a background (maintenance) treatment.[50]

The criteria for the effectiveness of treatment were the assessment of clinical indicators: restoration of menstrual function and ovulation, normalization of prolactin levels and reduction or stabilization (lack of growth) in the size of adenomas, pregnancy. The evaluation of the results of the study was carried out once every 3 months for 3 years.

Studies have shown that after 3 months of treatment, the normalization of clinical parameters was achieved by 21 (45.6%) women with NFA.

With NFA, the process of restoration of the menstrual cycle and ovulation proceeded relatively slowly: after 3 months of treatment with cabergoline, normalization of menstruation was observed in 17 (43.5%), after 6 months this figure increased to 28 (71.8%). And only a year after the start of treatment, we achieved recovery of menstruation in 34 (87.2%), and ovulation processes normalized only in 21 (53.8%) patients (Fig. 4).

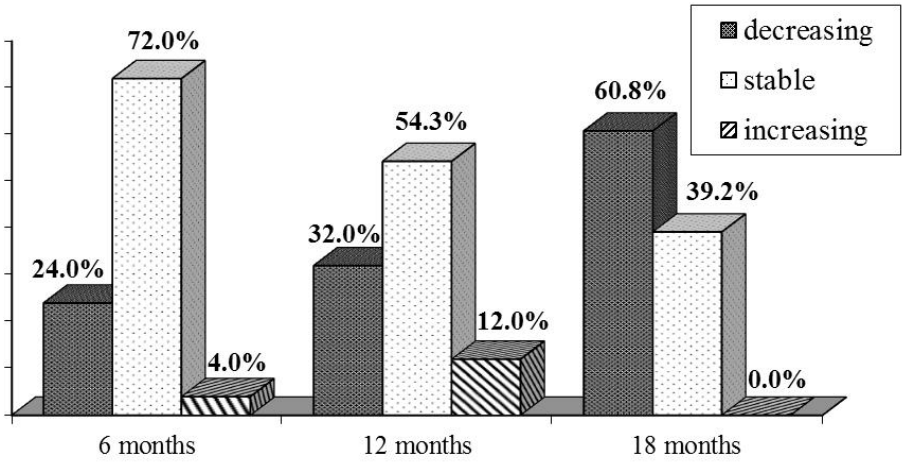

Figure 4. Dynamics of MRI indicators of NFA during treatment with cabergoline.

Women with inactive pituitary adenoma received 4 treatment regimens. (Figure 5)

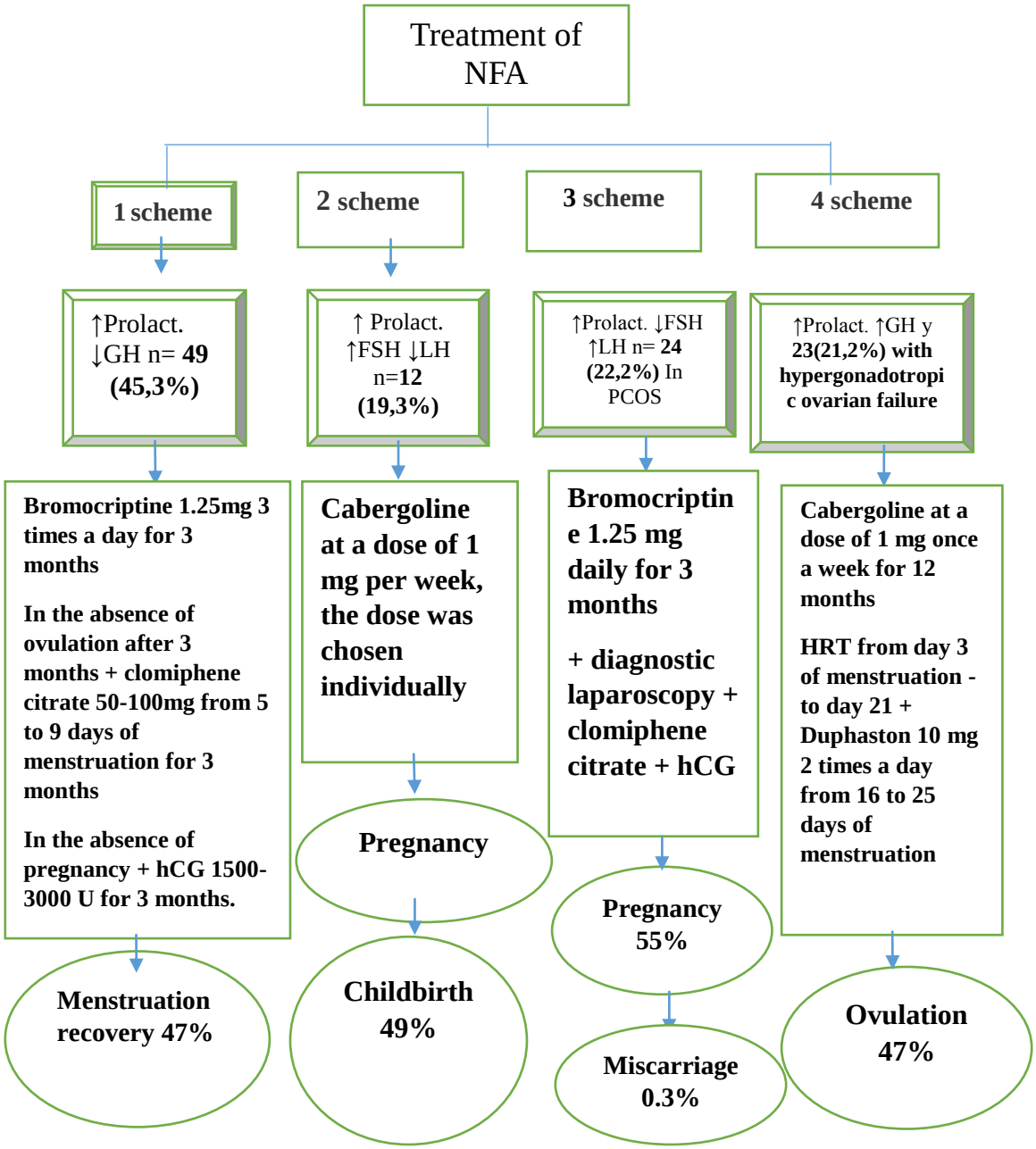

Figure 5. 4: treatment regimens.

RESULTS

According to the results of treatment within 36 months, it was found that in 47% of women clinical parameters were normal, 75% of patients recovered menstruation and ovulation, 55% of patients had pregnancy, 49% had childbirth, 0.3% had a miscarriage and 0.3% medical abortion.[50,51]

Thus, cabergoline was the drug of choice in the treatment of NFA in women with infertility. Cabergoline allowed us to manage not only biochemical, but also radiological and sonographic parameters in women with infertility. Patients with NFA showed a torpid reaction, 12% of cases (6 patients) were intolerant and characterized by continued growth of adenoma. Clinical-hormonal positive dynamic in patients with NFA was achieved in 60.8% of cases by the end of 18 months. In accordance with the study protocol, all patients after 12-18 months of cabergoline therapy were individually transferred to low maintenance doses of bromocritine gradually in order to induce fertility.[51]

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