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OPTIMIZATION OF THE TREATMENT OF WOMEN WITH PROLACTINOMAS SUFFERING FROM ENDOCRINE INFERTILITY

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Fertility is a person's ability to reproduce, in accordance with the UN international demographic dictionary.[2,8] Infertility is the absence of pregnancy with regular sexual intercourse during the year, without observing any contraceptive measures.[3,5] Despite active scientific activity aimed at developing various schemes for the treatment of infertility, the development of assisted reproductive technologies, its prevalence is quite high, according to various authors, 12-18%.[2,11] The highest rates of primary infertility (inability to give birth to a first child) - over 2.5% of all women - were obtained for a number of developing countries and for Moldova. The lowest - 0.5-0.7% - for the countries of South America (Peru, Bolivia, Venezuela, Ecuador) and Poland. In Russia, secondary infertility covers 3.2% of all women aged 20-44 (for comparison: in the USA, Norway and Finland, this share is 1%, that is three times lower). Primary infertility in Russia is 1.9%, which coincides with the global average.[5] According to various studies conducted in Uzbekistan, the proportion of women suffering from primary infertility, from among the married, is from 4.9% to 5.3%. Residents of African countries (9-12% of all women) suffer the most from secondary infertility. At least this problem characteristic to the highly developed countries. So, in Finland, Norway and the USA, this figure does not exceed 1% of women. At the global level, the number of infertile couples in 2010 was estimated at 48.5 million. Of these, 29.3 million cannot give birth to another child, in addition to existing children. In 2010, 1.9% of women aged 20-44 years "at risk of pregnancy" in the world were unable to give birth to their first child (primary infertility), according to a study by Victoria Sakevich. And 10.5% of women who already have children could not give birth again (secondary infertility). Coverage of primary infertility ranges from a minimum of 1.5% in Latin America to a maximum of 2.6% in the North Africa / Middle East region. Experts note a high level of primary infertility in Eastern and Central Europe and Central Asia - 2.3%. In the same region, the most depressing situation with secondary infertility is 18%. There are many causes of infertility, for each woman they are individual, often have a combined character. Therefore, the treatment of a patient with infertility is long, accompanied by high material costs.[7,16] The influence of the pituitary adenoma on menstrual irregularities and reproductive function remains an urgent problem of modern endocrinology and gynecology.[2,15] The pituitary adenoma is a benign neoplasm originating from the glandular tissue of the adenohypophysis, which can cause hyper- or hyposecretion of hormones.[13,22] Between all intracranial tumors it is the third most common after gliomas and meningiomas.[1,4] The percentage of this disease between all primary CNS tumors is from 7.3 to 18% and is detected at the age of 20 to 50 years. It is more common in women 20-30 and 50-60 years old.[2.21] In addition to serious neurological disorders, this pathology can lead to no less serious violations of the reproductive function of women. Prolactinomas are most common among pituitary adenomas and make up 40-50% of them. This is a hormonally active tumor that secrets an increased amount of prolactin.[8,12] It is observed in women of childbearing age 6-10 times more often than in men. Normally, prolactin, along with follicle-stimulating (FSH) and luteinizing hormones (LH), has a regulatory effect on the fertile function of women. The functions of prolactin include: - synchronizes follicular maturation and ovulation together with LH; - supports the existence of the corpus luteum and the formation of progesterone through participation in the synthesis of cholesterol; - prepares the mammary glands for lactation; - regulates the volume and composition of amniotic fluid.[10,19]

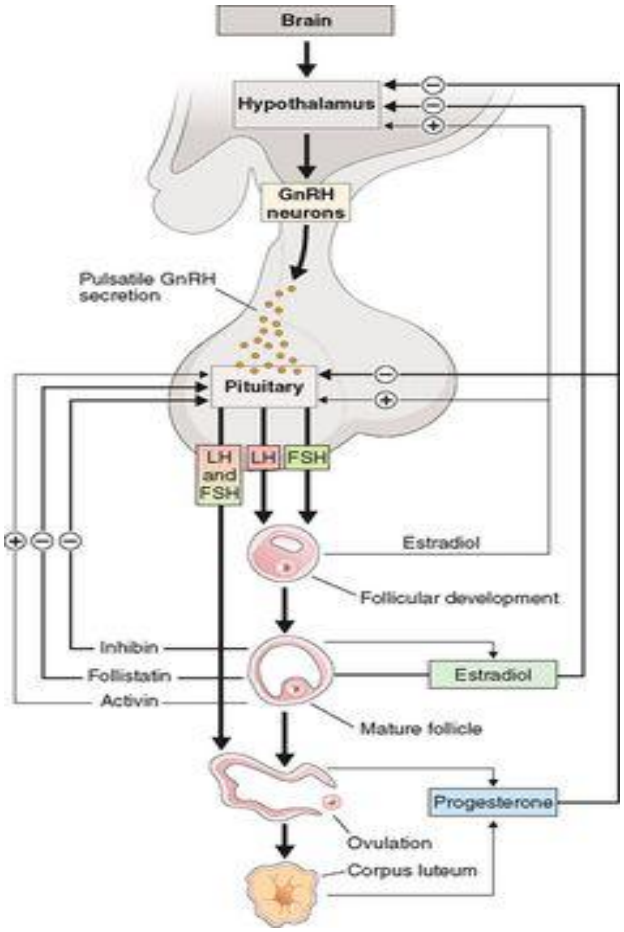

Figure 1: Endocrine interaction of the reproductive system in women. The most pronounced interactions of the hypothalamus, pituitary, ovaries.

The outstanding reproductive function of the hypothalamus is the pulsating secretion of gonadotropic hormones. Through the negative feedback with many hormones, including ovarian steroids, the hypothalamic secretion of gonadotropic hormones into the bloodstream is regulated.[14] The dopamine, norepinephrine, serotonin and opioids produced by the brain can mediate the regulation of the secretion of gonadotropic hormones by ovarian hormones. In response to the action of gonadotropic hormones, cells of the anterior pituitary gland secrete follicle-stimulating hormone and luteinizing hormone.[19,20] Steroidal (e.g. estradiol, progesterone) and peptides (e.g. inhibin) of ovarian origin or pituitary activin and follistatin change the secretion of FSH and LH. LH stimulates the production of androstenedione in ovarian theca cells; FSH regulates the secretion of estradiol and inhibin B in granulosa cells and follicular growth. The release of an egg from a mature follicle depends on a sudden increase in LH in the middle of the menstrual cycle. After ovulation, the follicle transforms into the corpus luteum, which secretes estradiol and progesterone under the control of FSH and LH. LH also stimulates the production of inhibin A in the granulosa-luteal cells of the corpus luteum. The endocrine effects of FSH, LH, estradiol, progesterone, inhibin A, and inhibin B depend on changes in their serum levels during the menstrual cycle.[17,18] Activin and follistatin are produced in the ovaries and pituitary gland. They probably act on FSH secretion through autocrine and paracrine mechanisms, but not endocrine ones. Activin stimulates the production of FSH, while follistatin suppresses the action of activin. Determination of the combination of inhibin B, AMH and FSH markers on the 3rd day of the cycle is by far the most reliable test for assessing ovarian reserve - a reflection of the exact number of functionally active follicles in a woman's ovaries. Inhibins reflect the ovarian reserve of the ovaries in prepubertate (measuring this marker in serum can confirm puberty and it is more reliable than more variable testosterone, LH and estradiol), during puberty, women of childbearing age, in perimenopause. The measuring of only pituitary FSH is in many cases limited: the values vary greatly from month to month, its high level is non-specific for young women (it can be found in women with normal fertility). This test is not sensitive enough for early signs of a decrease in ovarian reserve, in contrast to inhibin B and AMH, synthesized by directly developing preantral and antral follicles. Measurement of inhibin B allows direct more accurate assessment of ovarian function than FSH, since ovarian failure can be sporadic ("sprayed"), and normal levels of gonadotropins in this case do not exclude premature ovarian failure. The concentration of 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.[18] To identify pregnancy disorders and prevent various complications in patients, as well as to assess the state of the endocrine system, both routine tests and new markers that appear, such as inhibins A and B, activin and anti-mullerian hormone, are used.

Objective: To improve reproductive outcomes in women with prolactinomas by evaluating fertility predictors.

MATERIAL AND RESEARCH METHODS

A survey of 80 women with prolactinomas suffering from primary or secondary endocrine infertility (EI), the average age of which is 30.2 years (from 24 to 36 years). The duration of infertility ranged from 1 year to 12 years (an average of 5.8 years); More than half of the women observed 45 (56.2%) had primary infertility, 35 (43.7%) - secondary. In our work, we were guided by the continuity and stages of the examination of patients who sought gynecological help in connection with endocrine infertility. The examination included taking an anamnesis, examining the parity of pregnancy and childbirth, a standard general and gynecological examination, an ultrasound examination of the uterus and ovaries with folliculometry, a study of the health of the spouse, including spermatogenesis, MRI and CT of the hypothalamic-pituitary region (HPR), an ophthalmologist

(visual field and ocular bottom). Functional examinations and specialist consultations were conducted on the basis of the RSSPMC of Endocrinology named after Academician J.H. Turakulova, on the basis of the medical center "Diyor medical center", on the basis of RSSPMC of Obstetrics and Gynecology of Tashkent. Ultrasound of the uterus and ovaries with folliculometry was performed in a series of (2-3) menstrual cycles using a transvaginal probe with a frequency of 3.5 MHz (Aloka-630) without filling the bladder, with good bowel preparation. Ultrasonographic hysterosalpingoscopy (UGS) was performed on the 10-12th days of the menstrual cycle using transabdominal and transvaginal sensors with a frequency of 3.5 MHz (Aloka-630) without filling the bladder, with good bowel preparation (Ph.D. Kasymova A .V., Central Clinical Hospital of Uzbekistan Railways). The choice of UGS as a method for studying the patency of the fallopian tubes was made by us on the basis of published data on the good diagnostic reliability of the technique.[3,6] When carrying out this manipulation, the ovaries receive a disproportionately lower radiation dose than when performing x-ray contrast. This is especially important in women with reduced follicular reserve. The study of the state of the pituitary gland, thyroid gland and ovaries was carried out in the study of the content of follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), thyroid stimulating hormone (TSH), cortisol (C), dehydroepiandrosterone sulfate (DEAS-C), free thyroxine (FT4), estradiol (E2), progesterone (PG), testosterone (T); as well as inhibin A and B, activin and anti-mullerian hormone (AMH) in the serum of venous blood according to the standard method of enzyme-linked immunosorbent assay in the above centers.

RESULTS AND ITS DISCUSSION

Most of the patients who applied were residents of the city of Tashkent (50 people - 62.5%), 30 women (37.5%) lived in various regions of Uzbekistan. Material and living conditions in all patients were satisfactory. The average age of menarche in the observed patients with endocrine infertility with prolactinomas did not differ from the norm-appropriate indicator, amounting to 12.8 years. Next, we analyzed visualization methods: MRI of the hypothalamic-pituitary region and vaginal ultrasound of the ovaries and uterus with folliculometry. So, an MRI study in 80 cases (100%) revealed the presence of prolactinomas (including 55 microadenomas (68.7%) and 15 macroadenomas (18.7%)), 3 (3.7%) had an empty saddle syndrome (ESS), in 7 (8.7%) pituitary hyperplasia (Fig. 1)

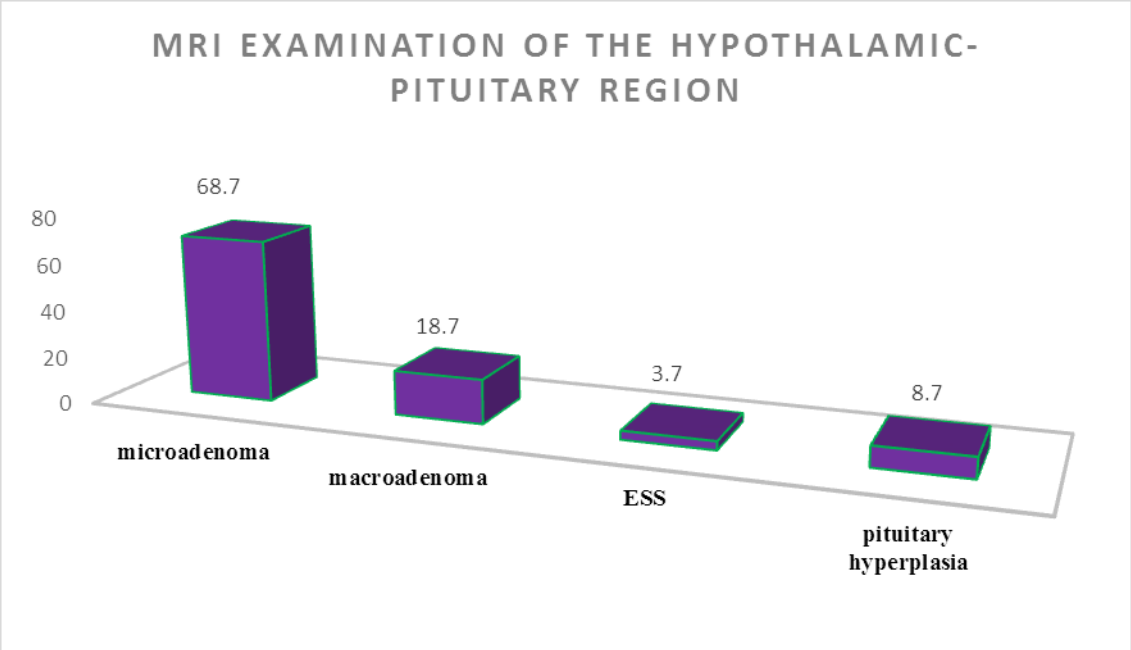

Figure 2: MRI examination of the hypothalamic-pituitary region in patients with EI.

Analysis of patients' complaints showed that women with prolactinomas have a high frequency of EI (100%), a decrease in libido of 68 (85%), galactorrhea of varying severity 70 (87%), swelling 45 (56.2%), headache 60 (75.8%) and weakness 64 (71%). dizziness 49 (61.3%), menstrual cycle disorders 47 (59.6%) hirsutism 18 (22.5%), and obesity in 10 (12.5%) patients were also relatively common (Fig. 3).

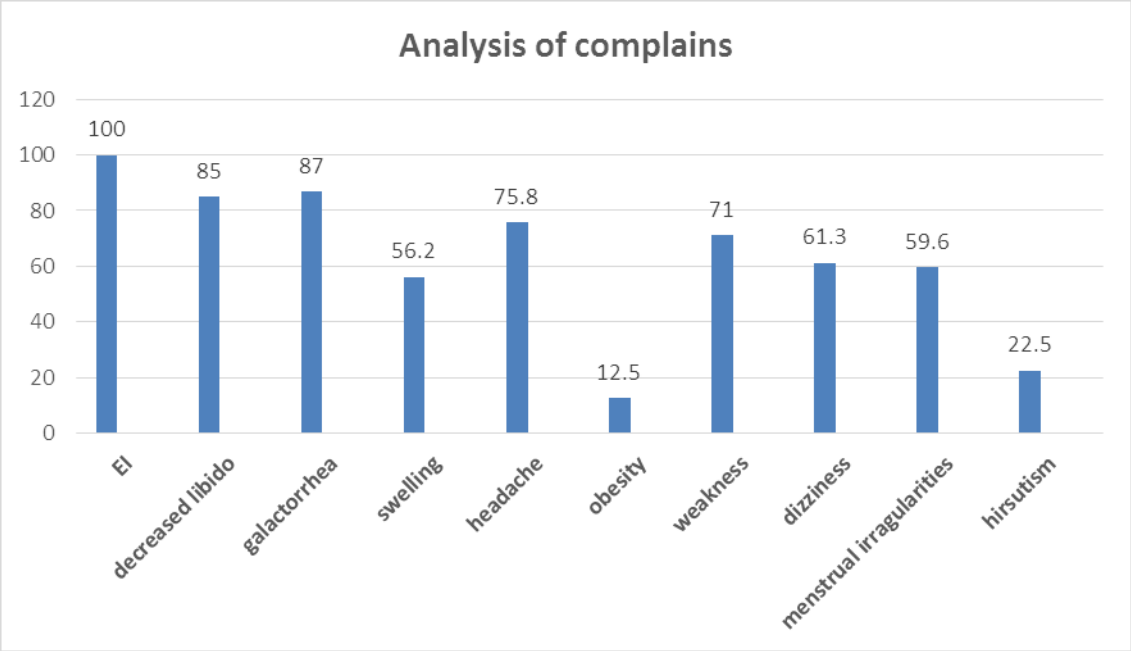

Figure 3: Analysis of complaints of patients with EI (endocrine infertility) with prolactinomas.

Two thirds of women who apply are 68 (85%); noted various disorders of the menstrual cycle. So, in 47 (59.6%) patients with dysregulation of the menstrual cycle, with endocrine infertility, amenorrhea in the anamnesis or at the time of treatment was observed in 15 (31.9%), hyperpolymenorrhea - in 5 (10.6%)), oligomenorrhea - in 8 (17%), dysmenorrhea - in 24 (51%) (Fig. 4)

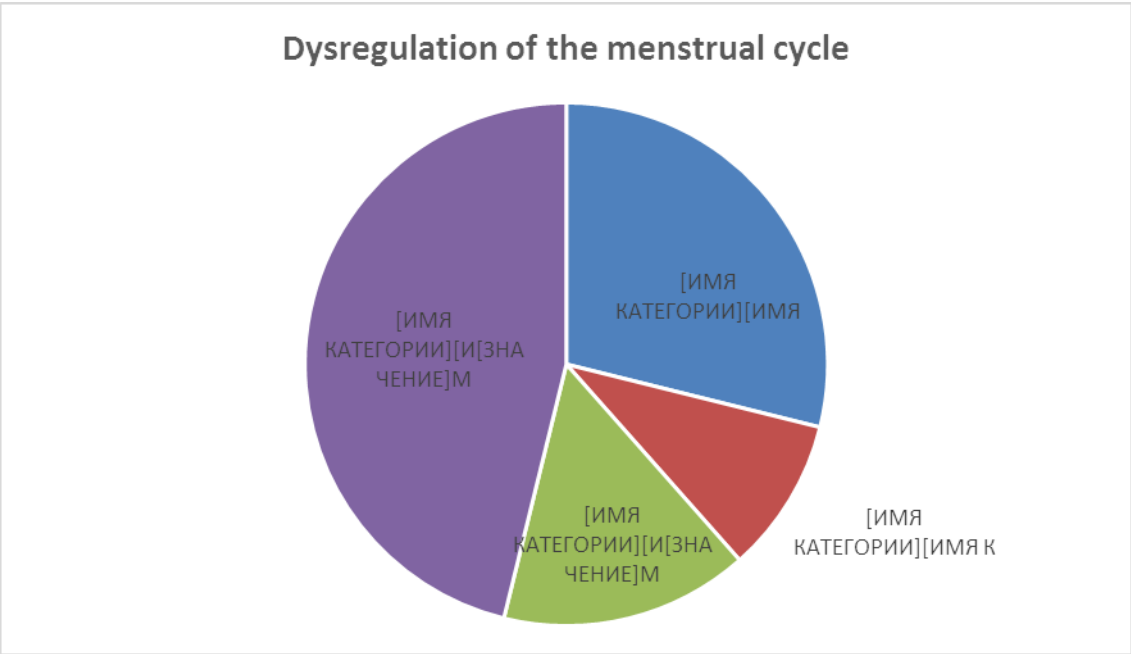

Figure 4: Dysregulation of the menstrual cycle in patients with endocrine infertility.

7 patients (8.7%) with an EI duration of more than 6 years had a history of laparoscopic surgery. So, restoration of patency of the fallopian tubes - in 12 (15%), wedge-shaped resection of the ovaries in connection with their scleropolycystic changes - in 2 (2.5%). In 15 cases (18.7%) anamnestic indications of gynecological pathology were not found. More than a third of the women examined 52 (65%) were recognized as somatically healthy. Reproductive health assessment, all patients underwent screening ultrasound examination of the pelvic organs on the 5-7th days of the menstrual cycle. The average size of the uterus and ovaries in the observed women corresponded to the average; the average thickness of the M-echo was equal to that at the beginning of the follicular phase with a biphasic menstrual cycle. When conducting a screening ultrasound examination, 7 women (8.7%) found signs of polycystic ovary syndrome (PCOS); uterine hypoplasia

of the 1st degree was diagnosed in 11 women (13.7%), 2 degrees in 9 (11.2%). A significant decrease in the follicular reserve in 20 (25%), a decrease in the ovulatory reserve in 15 (18.7%). When examining all cases of endocrine infertility, the male factor was excluded. On UGS on the 10-12th days of the menstrual cycle. All women did not find a violation of the patency of the fallopian tubes, and therefore the diagnosis of tubal-peritoneal infertility is excluded.

Recent studies have shown that hyperprolactinemia is one of the common causes of EI in women.[2,15] We have studied the levels of pituitary and ovarian hormones in the women. When studying the results of hormonal studies, the monotonicity of the rhythm of secretion of LH and FSH was revealed, which was reflected in the LH / FSH index (1.23). The level of prolactin was increased in all our patients and ranged from 37.9 to 186.3 ng / ml, on average, 77.4 + 11.4 ng / ml. Peripheral sex hormones corresponded to acceptable limits, but estradiol and progesterone were at the lower limit of normal. We can assume the presence of relative insufficiency of hormonal support of the follicular phase of the menstrual cycle, as well as a decrease in the function of the corpus luteum. Indicators of inhibin A and inhibin B were reduced in 7 (8.75%), in 73 (91.2%) within the normal range, activin level was within the normal range in all women studied, AMH in 12 (15%) were below normal, 68 (85%) within normal limits. The average thyroid and adrenal hormone levels were within normal limits. The average TSH values are approaching the upper limit of the norm. Subclinical hypothyroidism was diagnosed in 17 (21.2%), manifested by an increase in TSH with a normal rate of peripheral thyroid hormones. The study of folliculometry on days 9, 11, 15 of the preserved menstrual cycle in 68 patients (85%) had an anovulatory menstrual cycle in a series (2-3 months) of observations. Moreover, the lack of growth of the dominant follicle was detected in 46 women (57.5%), its reverse development (atresia) - in 8 (10%), the follicle persistence - in 14 (17.5%). In combination with the absence of ovulation, there was a failure of the corpus luteum: a shorter cycle of its existence (7 - 9 days) and its atresia (15 women - 18.7%). In 12 patients (15%), ovulatory menstrual cycles alternated with anovulatory. Thus, the state of the reproductive system of women with EI with prolactinomas revealed various dysfunctions of the pituitary-gonadal and thyroid-stimulating thyroid systems. A comprehensive examination allowed us to develop an individual approach to the treatment of this pathological condition in each of the patients. We began treatment of endocrine infertility in women with prolactinomas with the prescribing of dopamine agonists (cabergoline, the dose was established individually), to restore fertility and control the symptoms and size of the tumor, restore the menstrual cycle. For hormonal correction of infertility, we prescribed combined oral contraceptives (COCs) in standard mode, for 3-4 months, against the background of a maintenance dose of cabergoline, with their subsequent cancellation, counting on the opposite effect after short-term suppression of ovulation. Pregnancy was observed in 10 patients (12.5%) who had polycystic ovarian changes without thickening of the tunica albuginea. The next stage of infertility treatment, we used standard ovulation induction regimens: short, long protocols using pituitary estrogen receptor blockers, recombinant FSH, in standard doses, with a gradual increase in dose in subsequent cycles. When ovulation was stimulated, estrogens and progestogens were used, and the LH peak was simulated. During treatment, in 42 patients (52.5%), we received a pregnancy. On average, pregnancy required two cycles of ovulation induction. Moreover, out of 42 patients in 26 (61.9%) women, pregnancy occurred directly during the stimulation of ovulation, in 16 (38%) patients - 1 and 2 months after treatment. 34 (42.5%) women reported pregnancy before the term of delivery, miscarriage at the period of 8-11 weeks was observed in 5 (12%), non-developing pregnancy was observed in 3 (7.1%). 26 (76.4%) of 34 (42.5%) pregnant women had natural births in 26 (76.4%), Caesarean section was in 8 (23.5%). In the two patients we observed, ovulation induction led to ovarian hyperstimulation syndrome (mild to moderate). During pregnancy, many of our studied patients had threats of abortion, a chiasmal syndrome was observed. And these women were on dopamine agonist drugs. One of our patients had a child with Down syndrome. We referred patients to specialized centers assisted reproductive technologies after three unsuccessful attempts to stimulate ovulation; at the same time, we carried out conservative treatment of infertility for no more than two years, according to WHO recommendations. And 9 (11.2%) patients on the background of reduced inhibins and AMH were recommended IVF.

Thus, the complex organization of the reproductive system of the female body, a combination of disorders of the hypothalamic-pituitary-gonadal axis, causes difficulties in the treatment of endocrine infertility in prolactinomas. At the same time, staged nature examination of this category of women allows us to develop an individual treatment and observation program for each patient. This allows you to optimize conservative treatment and reduce its time in women with EI with prolactinomas, and timely resolve the issue of using assisted reproductive technologies. Particular attention should be paid to the study of reproduction markers in patients with endocrine infertility. Correction of the revealed violations will improve the results of conservative treatment of this condition, as well as the effectiveness of assisted reproductive technologies.

LIST OF REFERENCES

1. Sitiy V. P., Gonchar A. A., Sitiy Yu. V. Pituitary adenomas: history, prevalence, clinic, diagnosis, treatment / Journal of Health and Ecology Problems, 2010; 3: 41-50.
2. Rebekevsha V. G. Evaluation of proliferation markers in pituitary adenomas in women with

impaired reproductive function / Journal of Obstetrics and Female Diseases, 2010; 4-c: 111–117.
3. Radzinsky, V.E., Fuchs. A.M. Gynecology. - M.; "Geotar" - Media, 2014.-1000s. Erol. R. Norwich, John O. George. Visual obstetrics and gynecology. – M.; "GEOTAR" -Media, 2010; 160 s.
4. Nasybullina F.A., Vagapova G.R. Problematic issues of diagnosis and treatment with prolactin / Journal of the attending physician, 2013; 3: 23.
5. Petrov Yu. A. Modern approaches to the treatment of chronic endometritis in women with early reproductive losses // Vladikavkaz Medical and Biological Bulletin. 2011. –T.KhSh. No. 20-21. – P.42–46.
6. Petrov Yu. A. Results of the immuno-microbiological component in the genesis of chronic endometritis // Bulletin of the Volgograd State Medical University, 2011; 3: S.50–53.
7. Petrov Yu. A., Baykulova T. Yu. Clinical features of the course of pregnancy, childbirth and the postpartum period in primogenous re-pregnant women // International Journal of Applied and Basic Research, 2016; 8-5: S.719-723.
8. Romanenko V. A., Teplyakova M. A., Shabaeva V. I. Hormonal disorders in pituitary adenoma as a cause of infertility // Young Scientist, 2017; 14.2: S.36-39. - URL https://moluch.ru/archive/148/41929/ (accessed: December 4, 2019).
9. Fedorov, TA Infertility of unknown origin: some aspects of diagnosis and treatment / Fedorova T.A. // Gynecological, 2004; 5(3): 98100.
10. Guide to endocrine gynecology / Ed. EAT. Vikhlyaeva. - M., 2002; S. 9195.
11. Manukhin, I. B. Clinical lectures on gynecological endocrinology / Manukhin I.B., Tumilovich L.G., Gevorkyan M.A. - M., 2001; 247.
12. Dzeranova L. K., Barmina I. I. Features of the diagnosis and treatment of hyperprolactinemic syndrome. // Effective pharmacotherapy in endocrinology, 2009; 1: 10-17.
13. Nasyrova H.K., Halimova Z.Yu., Muhammedaminova D.T. The results of the analysis and synthesis of data on the diagnosis and treatment of prolactin. // Pediatrics. Scientific and practical journal, 2019; 3: 294-303.
14. Melmed, S, Casanueva, FF, Hoffman, AR, Kleinberg, DL, Montori, VM. "Diagnosis and treatment of hyperprolactinemia: An Endocrine Society clinical practice guideline". J Clin Endocrinol Metab., 2011; 96: 273-88.
15. Karaca, Z, Kelestimur, F. "Pregnancy and other pituitary disorders (including GH deficiency)". Best Pract Res Clin Endocrinol Metab., 2011; 25: 897-910.
16. Molitch, ME. "Endocrinology in pregnancy: Management of the pregnant patient with prolactinoma". Eur J Endocrinol, 2015; 172: R205-R213.
17. Benagiano G, d'Arcangues C, Harris Requejo J, Schafer A, Say L, Merialdi M. The special programme of research in human reproduction: forty years of activities to achieve reproductive health for all. Gynecol Obstet Investig, 2012; 74(3): 190–217. doi: 10.1159/000343067.
18. Penarrubia J, Fabregues F, Manau D. Basal and stimulation day 5 anti-Mullerian hormone serum concentrations as predictors of ovarian response and pregnancy in assisted reproductive technology cycles stimulated with gonadotropin-releasing hormone agonist: gonadotropin treatment. Hum Reprod, 2005; 20: 915–922. doi: 10.1093/humrep/deh718.
19. de Vet A, Laven JS, de Jong FH, Themmen AP, Fauser BC. Antimüllerian hormone serum levels: a putative marker for ovarian aging. Fertil Steril, 2002; 77(2): 357–362. doi: 10.1016/S0015-0282(01)02993-4.
20. Fanchin R, Maria Schonauer L, Righini C, Guibourdenche J, Frydman R, Taieb J. Serum AMH is more strongly related to ovarian follicular status than serum inhibin B, estradiol, FSH and LH on day 3. Hum Reprod, 2003; 18: 323–327. doi: 10.1093/humrep/deg042.
21. Colao A. Pituitary tumours: the prolactinoma // Best Pract Res Clin Endocrinol Metab, 2009; 23(5): 575-596.
22. De Camilli P., Macconi D., Spada A. Dopamine inhibits adenylate cyclase in human prolactinsecreting pituitary adenomas // Nature, 1979; 278: 252–254.