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HYSTERECTOMY WITH OPPORTUNISTIC SALPINGECTOMY AND ITS INFLUENCE ON STRUCTURAL-FUNCTIONAL PARAMETERS OF OVARIAN TISSUE

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The study examined the development of posthysterectomy syndrome in patients after hysterectomy with preservation of ovarian tissue.

The aim of the study was to assess the functionality of ovarian tissue in patients with hysterectomy and opportunistic salpingectomy performed for uterine fibroids.

Materials and methods of the research. The study was performed in 160 women of reproductive age. The first group included 90 patients after vaginal hysterectomy with tubectomy and associated with laparoscopy, the second group - 70 patients after abdominal hysterectomy with tubectomy. The control group included 50 women of reproductive age 45.7±1.3 years with asymptomatic fibroids. The diagnostic algorithm included assessment of hormonal status and instrumental study of structural and functional parameters of ovarian tissue both at the stage of preoperative observation and for 12 months, 3 and 5 years after surgery.

Research results and their discussion. At the preoperative stage in both groups found a higher percentage of thyroid disease, hypertension and metabolic disorders, as well as combined proliferative processes of the uterus. Normal ultrasound picture of the ovaries was found in 67.8 % - in the first group and in 47.1 % - in the second group. Significant increase in blood flow in the ovarian artery, in the remote period showing atrophic changes with the development of ovarian depletion syndrome. Assessment of hormonal status in both groups shows marked changes in baseline levels of gonadotropic hormones (FSH and LH): increase in baseline FSH levels by 2.2 times, LH - 1.5 times against the control group ($p < 0.05$), dyshormonal disorders persist for up to 5 years after surgery in one third of cases, and up to 36 months - there is an increase in the proportion of cystic and trophic changes, most pronounced in patients with reduced ovarian reserve, dysmetabolic manifestations and combined proliferative processes of the uterus and appendages before surgery, and syndrome chronic pelvic pain and venous pelvic blood supply in the postoperative period.

Conclusions. The technique of performing a hysterectomy does not have a significant effect on the functional state of the ovaries in the long term. The main indicators of ovarian blood flow and steroid hormone production after hysterectomy with opportunistic salpingectomy for uterine fibroids are close to the reference values up to 36 months postoperatively

Keywords: hysterectomy with salpingectomy, ovarian blood supply disorders, structural and functional parameters of the ovaries, hormonal imbalance after hysterectomy

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1. Introduction

According to statistics, hysterectomy (HE) is one of the most common surgical interventions in late reproductive age, and every third woman in the world after 55–60 years does not have a uterus [1]. Literature sources show that in the USA about 600 thousand HE are performed annually, in Ukraine in the structure of gynecological operations this surgical intervention is about 38.0 %, in the structure of obstetrics - about 6.0 % [2, 3].

It should be emphasized that even with the preservation of ovarian tissue after HE, patients develop a characteristic symptom complex of emotional, neurovegetative, sexual, urogenital, and vascular manifestations, called posthysterectomy syndrome [1]. It is thought that HE with opportunistic salpingectomy itself has a certain effect on the morpho-functional parameters of

ovarian tissue and initiates the imbalance of hormonal homeostasis associated with hypoestrogenic state. And in the development of such disorders, first, a certain place belongs to microcirculatory changes and the development of acute ischemia of ovarian tissue, due to the reaction to interference in the blood supply system of the uterine artery [4, 5].

According to several scientific studies, three types of ovarian blood supply have been identified: uniform blood supply from the uterine and ovarian arteries (51 %), predominant blood supply due to uterine artery branches (38 %) and blood supply mainly due to ovarian artery branches (11 %) [6]. This confirms the opinion that ovarian function is directly dependent on the type of blood supply, and HE itself, as a radical procedure, could cause catastrophic changes in ovarian function, which is widely

discussed in the literature and is controversial and controversial [3]. Some authors point to ovarian depletion after HE, but do not show unambiguous data on the timing and frequency of hormonal deficiency [6], while other researchers have presented clear data on impaired hemomicrocirculation in the vessels of preserved ovarian tissue [4, 5]. In this case, complete ovarian ischemia (reduction of maximum and minimum blood pressure to zero, conversion of pulsed blood flow to continuous) occurs after subtotal hysterectomy provided blood supply exclusively or mainly due to the branches of the uterine artery, which are cut off as a result of ligation of own connection of an ovary and an ovarian branch of a uterine artery, which determines, as the most favourable option, a uniform type of blood supply due to both uterine and ovarian arteries [4, 5]. Impaired ovarian hemodynamics triggers a cascade of intracellular changes at the organ level, and ischemic disorders in ovarian tissue led to activation of prostaglandins, spasm of arterioles and secondary circulatory disorders, and changes in steroidogenesis, while increasing the synthesis of cytokines that promote luteolysis and further tissue damage. Also noteworthy is the theory that the uterus, as another secretory organ, affects the secretion of pituitary follicle-stimulating hormone (FSH), where, when this function is eliminated, the level of this parameter increases with accelerating follicular exhaustion and ovarian failure [7]. As a result of the simultaneous removal of the local estrogen depot, a breakdown of adaptive mechanisms and the development of hormonal imbalance is generated. Most studies demonstrate changes in women of early reproductive age as the most striking and influential on quality-of-life parameters and psychological status after surgery. The evaluation of the impact of various surgical techniques on the morphofunctional state of the ovaries and disorders of steroidogenesis, as well as the role of age, the combination of proliferative gynecological pathology and postoperative complications, remains ambiguous in scientific research.

The aim of the research – assessment of ovarian tissue functionality in patients with hysterectomy and opportunistic salpingectomy performed for uterine fibroids.

2. Materials and methods of the research

This research was performed in the gynecological department of the Kyiv Perinatal Center for the period 2015–2019, where was performed a set of clinical, laboratory and instrumental studies in 160 women of reproductive age, which were divided into two groups. The first group included 90 patients (mean age 45.9 ± 1.3 years) who underwent vaginal hysterectomy with tubectomy, both classical and associated with laparoscopy, the second group consisted of 70 patients with uterine leiomyoma (mean age 47.2 ± 1.6 years), where abdominal hysterectomy with tubectomy was performed. The control group included 50 women with asymptomatic fibroids, mean age 45.7 ± 1.3 years. The diagnostic algorithm included assessment of hormonal status by the level of gonadotropin and steroid hormones and instrumental study of structural and functional parameters of ovarian tissue both at the stage of preoperative observation and for 12 months, 3 and 5 years after surgery. Criteria for inclu-

sion in the study were: age of patients from 40 to 49 years, HE for uterine fibroids with opportunistic salpingectomy with preservation of ovarian tissue, the patient's consent to participate in the study. Exclusion criteria: severe somatic diseases that formed the patient's premorbid background before surgery, patients' refusal to participate in the study. Functional status of the hypothalamic-pituitary-ovarian system was assessed before and after surgery for serum levels of FSH, LH, estradiol, progesterone and prolactin, as well as anti-Müllerian hormone (AMH) by enzyme-linked immunosorbent assay using test system Core using AMHGenIIELISA kits (BeckmanCoulter). Ultrasound examination of the pelvic organs before and after surgery was performed using a series of cross-sectional and longitudinal sections of complex scanning devices "Voluson E8", using transvaginal and transabdominal sensors with a frequency of 3.5, 5, 6.5 and 7.5 MHz. Echogenicity, volume and size, and the condition of the follicular apparatus were determined during ovarian tissue examination. Doppler color mapping was performed with pulse Doppler in the right and left branches of the a.uterina, in the ovarian arteries, and in the stroma of both ovaries. Weak blood flow was assessed at the registration of 1–5 loci of blood flow, moderate – at 5–10 points of vascularization, and active – more than 10 loci of blood flow. Evaluation of pelvic ultrasound was performed in all groups before surgery and at different times in the postoperative period.

All questions regarding the possibility of conducting these studies were agreed with the Commission on Bioethical Expertise and Ethics of Scientific Research of the Bogomolets National Medical University protocol No. 140 dated 21.12.2020, the study was performed with the analysis of medical records before surgical recovery in retrospect, all patients gave their voluntary consent to the examination. The research is based on ethical standards in accordance with the Helsinki Declaration of the World Medical Association.

Statistical processing of the results was performed using statistical packages IBM SPSS Statistics (ver. 21) and statistical environment R (ver. 3.1). Assessment of variability of indicators was performed by methods of variation statistics. For comparative analysis, we used the methods of nonparametric statistics – the Chi-square criterion (χ^2) and used Fisher's exact criterion.

3. Research results

When comparing the frequency of extragenital diseases, it is necessary to indicate an increase in the percentage of thyroid disease, hypertension and metabolic disorders. In the analysis of anthropometric data, we noted in one third of patients overweight and obesity of I–II degree, which confirms the existing data in the literature on the increased risk of uterine leiomyoma in metabolic disorders [8]. The analysis of menstrual function should indicate a significant predominance of menstrual disorders by type of menorrhagia (61.9 %), no differences in the parity of pregnancies and births, but in the second group – an increase in the history of such features as abortion, miscarriage, traumatic childbirth etc. It is also necessary to point out the high proportion of combined proliferative processes, such as endometrial hyperplasia, endometriosis, functional ovarian cysts, i.e.,

hormone-dependent pathological conditions, which allows to classify uterine fibroids to the group of so-called monoclonal hormone-sensitive proliferates.

The results of ultrasound are traditionally used to diagnose the onset of secondary gonadal insufficiency, but the processes of imbalance in the hypothalamic-pituitary-ovarian system in patients after HE with opportunistic salpingectomy for uterine fibroids performed in reproductive age are insufficiently presented in the literature and are contradictory [9–11]. It should be noted that immediately after surgery, the first group showed an insignificant increase in the volume of the right ovary and stable indicators of the left, although in the second group the increase in the volume of both ovaries was observed almost twice. Characterizing the sonographic features of ovarian tissue 12 months after surgery, we obtained data on the reduction of ovarian tissue in both study groups, but more significant – only in the second group against the control data ($p < 0.05$). Up to 36 months of follow-up, there was a tendency to decrease the volume of the ovaries in both groups – ($3.28 \pm 0.02 \text{ cm}^3$) and ($3.18 \pm 0.03 \text{ cm}^3$), respectively – in the first group of patients ($2.94 \pm 1.01 \text{ cm}^3$) and ($3.02 \pm 0.03 \text{ cm}^3$), respectively – in the second group, compared with the ovarian volume in the control ($5.42 \pm 0.03 \text{ cm}^3$ and $5.88 \pm 0.04 \text{ cm}^3$). At the same time in 21 observations – 23.3 % of group I and 29 – 41.4 % of group II functional cysts or seroma were found. Normal ultrasound picture of structural parameters of the ovaries was found in 61 patients of the first group (67.8 %) and 33 patients of the second group (47.1 %).

Immediately after surgery, the main dopplerometric parameters, namely pulse rate of blood flow (PRBF) and resistance index (RI) changed downwards, except for

central blood supply, where in both study groups there was an insignificant increase in mean PRBF (by 0.9 and 0.5 cm/sec). Up to 12 months of monitoring, most indicators continue to show a decrease in mean blood flow values in both groups, but in the first group with less pronounced deviations. Up to 24 months of monitoring revealed restoration of gonadal hemodynamics in both groups.

Thus, in patients of the second group, an increase in ovarian volume was observed in 1.8 times, there was a decrease in echogenicity immediately after surgery, as well as a decrease in Doppler parameters of ovarian blood flow. Restoration of ovarian structure and function in two thirds of patients was observed after 12 months of follow-up, in one third found progressive deterioration of ovarian function with a decrease in their volume, number and size of follicles, deterioration of blood supply by Doppler, which should be associated not only with insufficiency collateral circulation and violation of the architecture of the vascular bed, but also with the removal of one of the links of the self-regulating system – the uterus itself. It should be noted that in 13 (18.6 %) blood flow in the ovarian artery was not determined, and it should be noted that these were patients with varicose veins of the pelvis, including the ovarian plexus.

As shown by the data of Fig. 1, the study of hemodynamics and structural parameters of ovarian tissue in women with verified connective tissue disease, pelvic varicose disease, as well as the manifestations of pelvic floor prolapse and symptoms of chronic pelvic pain in the postoperative period, had their own characteristics, and the most significant differences were found in patients with venous pelvic hemorrhage and chronic pelvic pain syndrome.

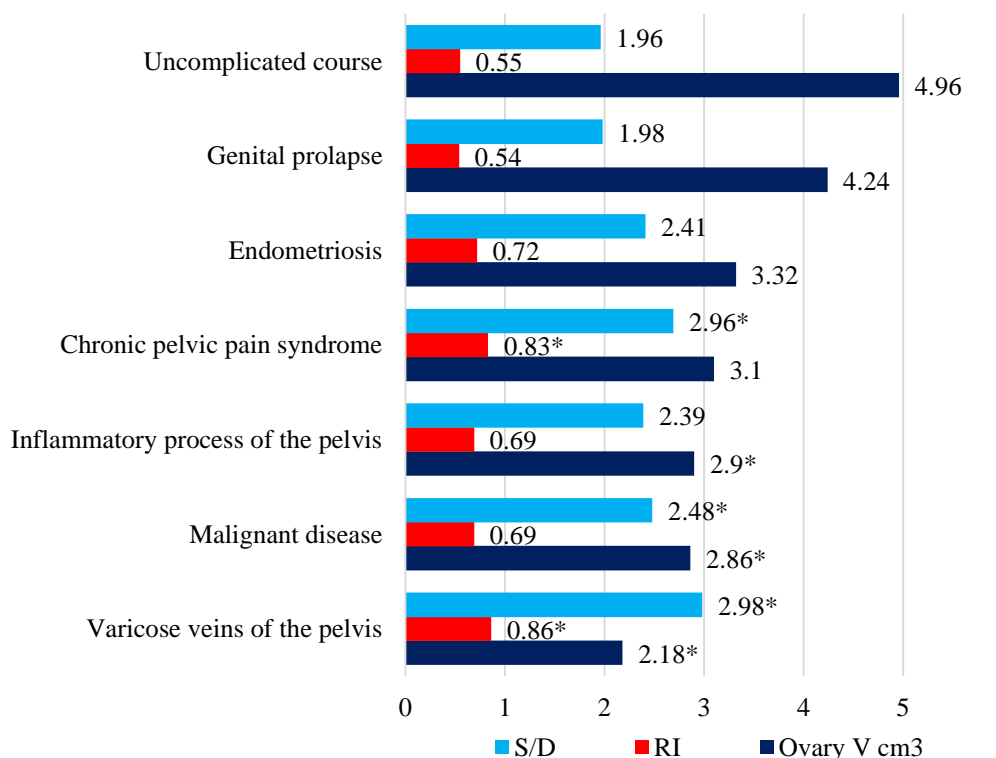


Fig. 1. Indicators of ovarian volume and blood flow in the ovarian artery in the case of comorbid genital pathology and postoperative complications, c.u.: * – the difference is significant relative to the indicators of the group with uncomplicated postoperative period, $p < 0.05$

Studies have shown that ovarian volume in women after HE is characterized by a progressive decrease with increasing duration of postoperative follow-up. In addition, an important factor determining the structural and functional parameters of ovarian tissue is the age of the woman who underwent radical surgery: in patients of late reproductive age immediately after surgery, the average ovarian volume was significantly higher than in the control and in patients under 45 years of age, in parallel, a significant increase in blood flow in the ovarian artery (RI and S/D), in the remote period showing atrophic changes with the development of ovarian de-

pletion syndrome. Progression and development of pelvic varicose disease and chronic pelvic pain syndrome in the postoperative period most significantly aggravated hemodynamic disorders and contributed to ovarian tissue atrophy.

Assessment of hormonal status is presented in Table 1 and shows in both groups pronounced changes in baseline levels of gonadotropic hormones (FSH and LH): increase in baseline FSH levels by 2.2 times, LH – 1.5 times against the control group ($p < 0.05$). Approximation to the reference limits was noted only in 41 patients (25.6 %) up to 12 months of follow-up.

Table 1

Indicators of the level of pituitary and ovarian hormones in women of the studied groups 12 months after hysterectomy without supplements, $M \pm m$

Indicators	Output data	Studied groups		
		Group I (n=90)	Group II (n=70)	Control group (n=50)
FSH, mIU/ml	16.26±4.12*	19.62±1.24*	20.18±1.42*	9.06±2.12
LH, mIU/ml	13.18±2.16*	10.68±3.24	11.28±2.32	7.16±1.14
FSH/LH	1.23±0.14	1.84±0.66*×	1.79±0.14*×	1.27±0.08
Estradiol, pg/ml	296.92±16.14*	106.64±4.14*×	98.44±4.22 *×	198.22±14.12
Progesterone, ng/ml	1.96±0.02	1.12±0.01*×	1.16±0.04*×	1.90±0.03

Note: * – the difference is significant relative to the indicators of the control group, $p < 0.05$; × – the difference is significant relative to the original data, $p < 0.05$

The average values of ovarian steroid hormones in the postoperative period indicated a decrease in these parameters in all patients of the second group and in more than half of the samples in the first group (47–52.2 %) ($p < 0.05$), and statistically significant – in 2.5 times against the initial data, during 6 months of observation of the restoration of ovarian blood supply due to collaterals contributed to a gradual approximation to the values characteristic of this reproductive age, but still maintained a tendency to decrease from the reference parameters. In 61 patients (67.7 %) of the first group the FSH level remained unchanged, in almost all women of the second group it increased 3.5 times and remained stable high up to 36 months of observation, and estradiol content decreased to postmenopausal values ($p < 0.05$). As a biochemical marker of ovarian reserve of the left ovarian tissue in practice the so-called “triple” test is used – determination of follicle-stimulating hormone, inhibin B, AMH in blood serum. According to the results of our studies, the most significant level of AMH deviated after 12 months of the postoperative period (2.9 times) ($p < 0.05$), the level of inhibin B showed a decrease of 2.1 times, and in 20 patients of the second group (31, 4 %) – 3.2 times ($p < 0.05$). It is necessary to note the dependence of the dynamics and degree of deviations of the ovarian panel with the parity of surgical interventions and their volume, especially on the ovaries.

Thus, in women of reproductive age with HE and opportunistic salpingectomy in a third of cases, dys hormonal disorders persist for up to 5 years after surgery, impaired blood flow in the remaining ovaries is accompanied by an increase to 12 months, and up to 36 months – an increase in the proportion of cystic and trophic changes, which is most pronounced in patients with reduced ovarian reserve, dysmetabolic manifestations and

combined proliferative processes of the uterus and appendages before surgery, as well as chronic pelvic pain and venous pelvic blood supply in the postoperative period. Performing HE with opportunistic salpingectomy exacerbates preoperative hormonal imbalance, which is manifested by increasing hypoestrogenemia, increased FSH and LH parameters, increased hemodynamic disorders and pelvic innervation [12]. These changes could be explained by the following mechanisms: due to the exclusion from the blood supply of uterine arteries there is a natural decrease in hemodynamics in the ovarian branches of uterine arteries, intra-ovarian blood flow, which undoubtedly affects steroidogenesis with reflex enhancement of gonadotropic products. Restoration of ovarian function to reference values occurs up to 5 years in 109 (68.1 %) patients of both groups.

It should be noted that in each case the problem of the appropriateness of the volume and timing of hormone therapy rehabilitation therapy should be addressed considering the patient's age, premorbid status and severity of hemodynamic disorders and estrogen deficiency.

4. Discussion of research results

According to some published literature reports, any surgical intervention on the pelvic organs leads to a violation of hormonal homeostasis at the level of both pituitary and steroid hormones, most pronounced in the first days after surgery, manifested by increased FSH, LH, decreased estradiol levels and progesterone, and due to acute circulatory disorders of ovarian microcirculation, edema and actual surgical trauma.

According to modern literature, there is an increased risk of secondary ovarian failure in women after HE from 6–12 months to 3.5 years [2, 5, 12]. Some reports emphasize that acquired ovarian failure occurs only

in women after unilateral ovariectomy and vaginal hysterectomy, whereas in the group of patients with abdominal hysterectomy such changes occur in only 2 % of women a year after surgery and 14 % – after 5 years [5]. Separate reports demonstrate changes in ovarian blood flow Doppler parameters and serum AMH levels with corresponding correlations [11]. However, most scientists agree that the cause of posthysterectomy syndrome is not only the operation itself and the resulting hemodynamic and microcirculatory disorders, but also the previous state of the hypothalamic-pituitary-ovarian system and metabolic imbalance, which increases the risk of early ovarian failure [7, 12, 13].

According to some literature sources, there is the ability of myomatous cells to produce estrogen due to the increased content of aromatase – an enzyme that converts androstenedione to estradiol. Local hyperhormonemia of uterine origin is confirmed by a higher content of steroids in the tubular-ovarian arterioles (2–8 times higher) than in the serum of the ulnar vein. The larger the volume of the uterus, the more functionally important is the system of uterine and ovarian vascular network in the ligament, i.e., the higher the saturation of arterial vessels with sex hormones [3, 12]. Of interest are several literature sources demonstrating the state of ovarian reserve in patients with HE and opportunistic salpingectomy for uterine fibroids [10, 14], indicating the role of previous gynecological pathology (uterine leiomyoma, endometrial hyperplasia). in comparison with the same parameters in women of this age category from the control group [15]. An important point is the feasibility and role of tubectomy in the development of ovarian failure syndrome [10, 14], according to which HE for uterine fibroids, performed with opportunistic salpingectomy, further exacerbates ovarian hemodynamics, which, according to some researchers, justifies organ storage. and preservation of fallopian tubes [10, 14], but these studies are also ambiguous and insufficiently covered. According to some data, estradiol levels in patients after salpingectomy are reduced by 2.9 times, while the preservation of matte tubes – only 1.2 times, and ultrasound dopplerometric examination reveals changes in ovarian echogenicity and sharp depletion of the follicular apparatus [1, 15]. Other retrospective studies have shown that hormonal and ultrasound parameters do not change significantly if a salpingectomy is performed while performing HE [15]. In this case, laparoscopic bilateral salpingectomy is safer when performing subtotal HE [16]. For the first time, Canadian and German scientists have suggested that the fimbrial division of the fallopian tubes is a source of serous ovarian cancer [14]. There is an opinion about the role of distal fallopian tubes in the seizure of serous ovarian cancer in women with mutations in the BRCA1 and BRCA2 genes. According to US statistics, epithelial ovarian cancer is diagnosed in 25,000 women annually [10, 14, 15]. The results of a study have been published, according to which serous tubular carcinoma in situ occurs in 60–100 % of women with this mutation, and in 30–60 % of patients in the absence of BRCA1 or BRCA2 mutation [9]. This allowed us to determine the feasibility of salpingectomy in patients with BRCA mutations to prevent ovarian cancer, as there are three hypotheses of carcinoma: origin from the epithelium of the

distal fallopian tubes, by invagination and inclusion of coelomic epithelium in the cortical layer during ovulation, ovulation retrograde menstrual blood flow. Therefore, most authors believe that opportunistic salpingectomy should become a new clinical standard, as there is ample evidence of serous cancer from the distal epithelium of the fallopian tubes, even in the absence of mutations in the BRCA1 and 2 genes, which reduces the risk by 34–40 % [14]. There are also published data that in patients after HE without supplements the risk of developing ovarian cancer within 15 years is already significant (up to 36 %). Analysis of the literature has shown that there are conflicting data on the structural and functional state of the ovaries after HE without appendages with opportunistic salpingectomy. A detailed study of pathological processes at the cellular-tissue level is promising, which will allow us to understand the mechanisms of ovarian failure after hysterectomy and its impact on steroidogenesis and the like.

Study limitations. The results of the analysis reflect the data only of the gynecological department of the “Kyiv Perinatal Center”. Because not all patients joined the study after hysterectomy, there may be shifts in the results of the study due to underrepresentation. However, the study has representative and comparable groups.

Prospects for further research. The obtained results allowed to outline the main measures to prevent the depletion of steroidogenesis with the restoration of blood flow in the gonadal vessels, and if necessary – hormonal correction.

5. Conclusions

A decrease in ovarian tissue volume was found in both study groups 12 months after surgery after a previous compensatory increase in volume in the early postoperative period.

There was a decrease in the production of ovarian steroid hormones in all patients of the second group and in more than half of the samples in the first group (47–52.2 %) ($p < 0.05$), and 2.5 times against the original data; reduction of AMH in 2.9 times compared with control after 12 months of the postoperative period ($p < 0.05$).

Restoration of gonadal hemodynamics according to sonographic data in both groups up to 24 months of the postoperative period, and up to 36 months of steroid hormone production is close to the reference values in two thirds of those examined in both groups.

The most pronounced changes in the hormonal profile were observed in patients under 45 years of age with combined proliferative diseases of the endometrium.

It was demonstrated that the operative approach to performing a hysterectomy with a tubectomy does not affect the functional state of the ovaries - the indicators for both groups did not differ statistically significantly.

Thus, the results confirm the existing literature, indicating the development of neurodystrophic changes and reduced functional reserve of ovarian tissue and impaired blood supply to the pelvis after hysterectomy with opportunistic salpingectomy.

Conflict of interests

The authors declare that they have no conflicts of interest.

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