HORMONAL CARCINOGENESIS AND RATIONALE FOR THE USE OF HORMONE THERAPY IN THE TREATMENT OF PATIENTS WITH OVARIAN CANCER
(Review)

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Summary. The morbidity and mortality of patients with ovarian cancer in the CIS, Europe, the U.S. over the past 10 years are increasing, despite improvements in surgical-logical methods of treatment and the use of modern chemotherapy. The question on the application of hormonal therapy to date is still open. These foreign and domestic studies confirm the presence of hormone-dependent cancer of the ovary in a tumor cell receptor for all sex steroid hormones, but the data on the prognostic factors of the disease with the hormone receptor status and distribution of steroid hormone rOVARIES CANCER AND HORMONAL CANCEROGENESIS (Translated) 7eceptors in the tumor tissue, depending on its biological properties are contradictory. Purpose – to show on the basis of published data of interest to scientists studying the hormonal carcinogenesis, etiology and pathogenesis of ovarian cancer, the relevance of this issue and the need for further research in this direction.

Key words: ovarian cancer, hormonal carcinogenesis, hormonal status, estrogen, progesterone and testosterone, the degree of tumor differentiation, hormone therapy.

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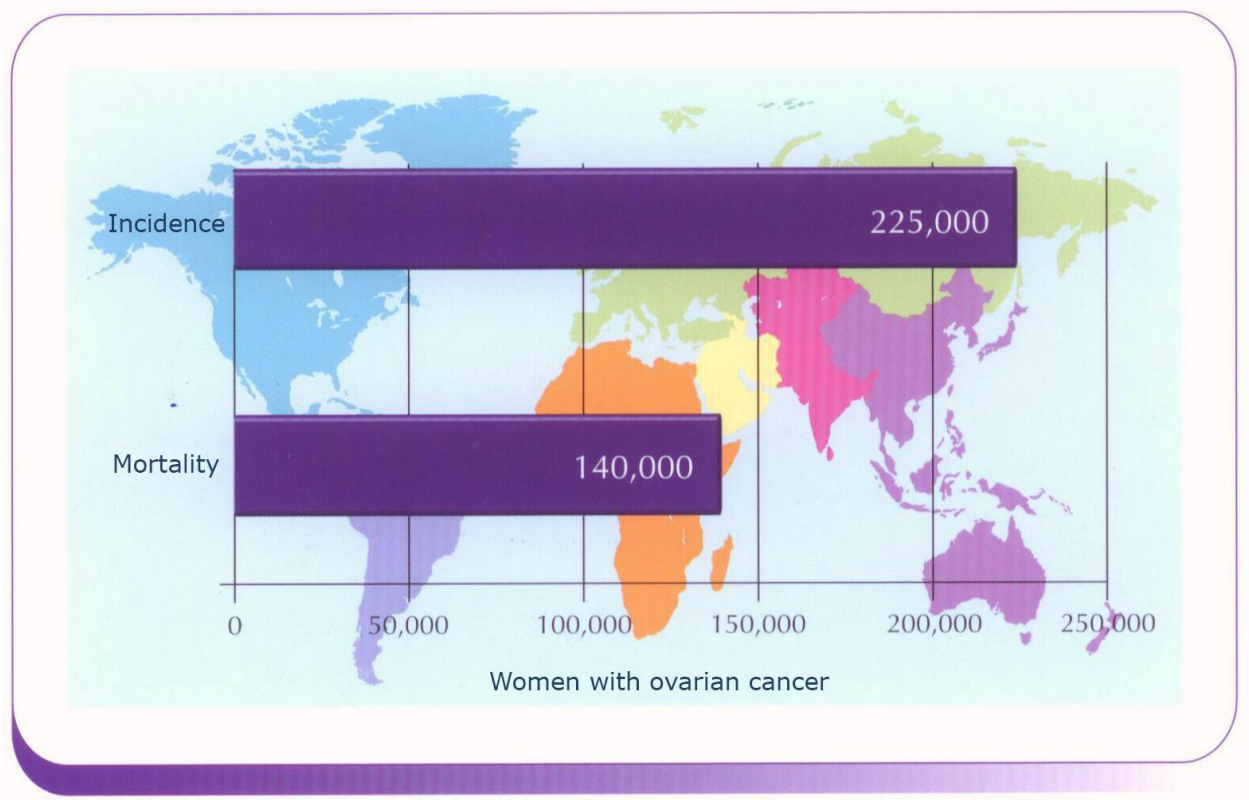
Introduction Ovarian cancer (OC) is one of the most complex problems of oncogynecology, taking the 7th place in a structure of morbidity and the 4th place – among the other mortality causes due to malignant tumors in women, and in a structure of female reproductive system tumors it takes the 4th place (after breast cancer, corpus uteri and uterus cervix) and the 1st place accordingly [10, 13, 31, 39, 63]. According to the data of International Agency on Cancer Research over 225 thousand new cases of malignant ovarian tumors (MOT) are registered annually worldwide and 140 thousand women experience mortality due to this disease. (Fig. 1) [70]. Over the past 10 years 8,5% increase in OC morbidity is being registered in the CIS countries. The highest morbidity rates are observed in the developed countries of Europe (Northern countries, Great Britain) and the USA (Fig. 2, 3) [56].



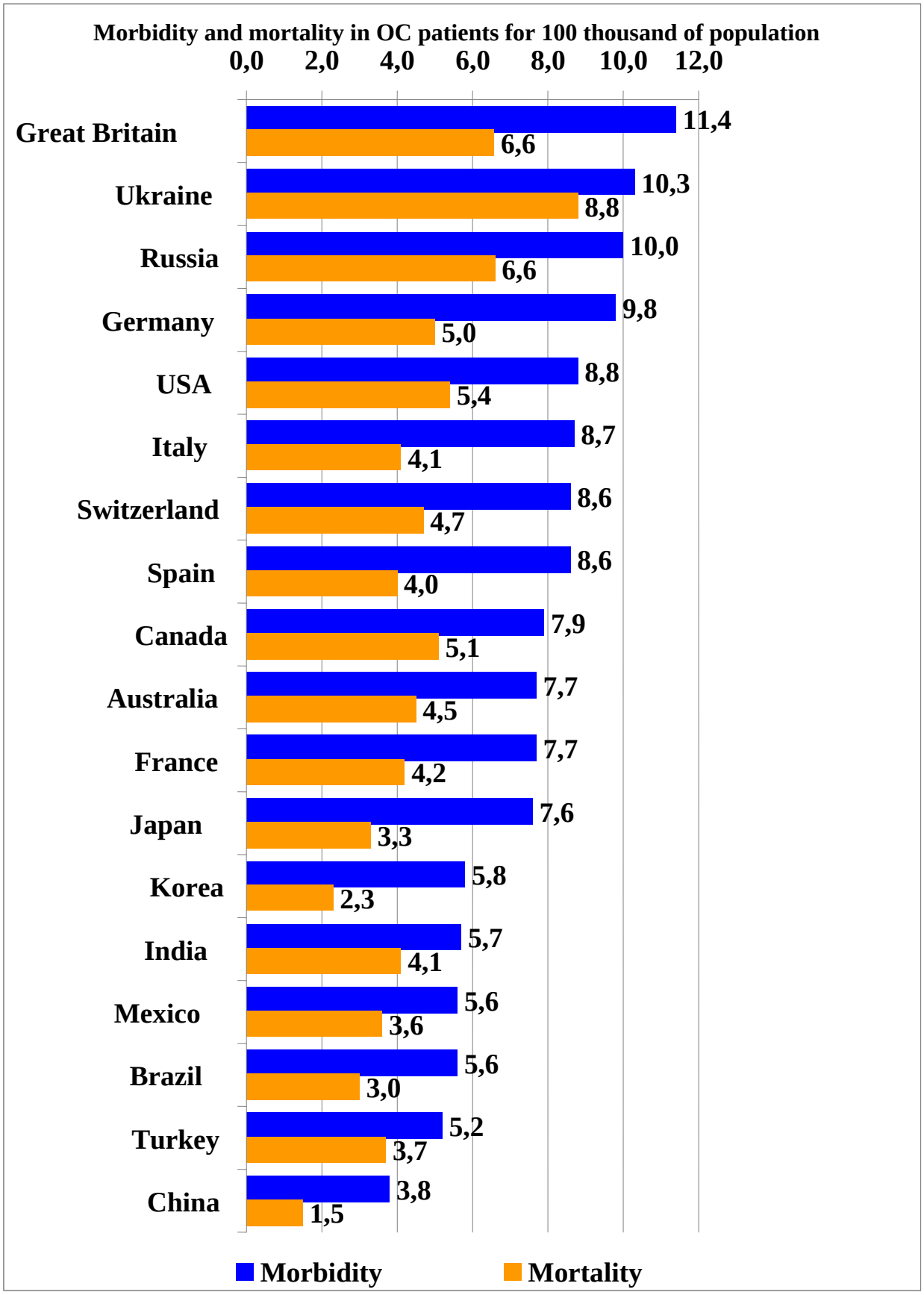
Source: GLOBOCAN, 2008 [70]

Fig. 1

OC Morbidity and Mortality among female population worldwide according to the data of International Agency on Cancer Research

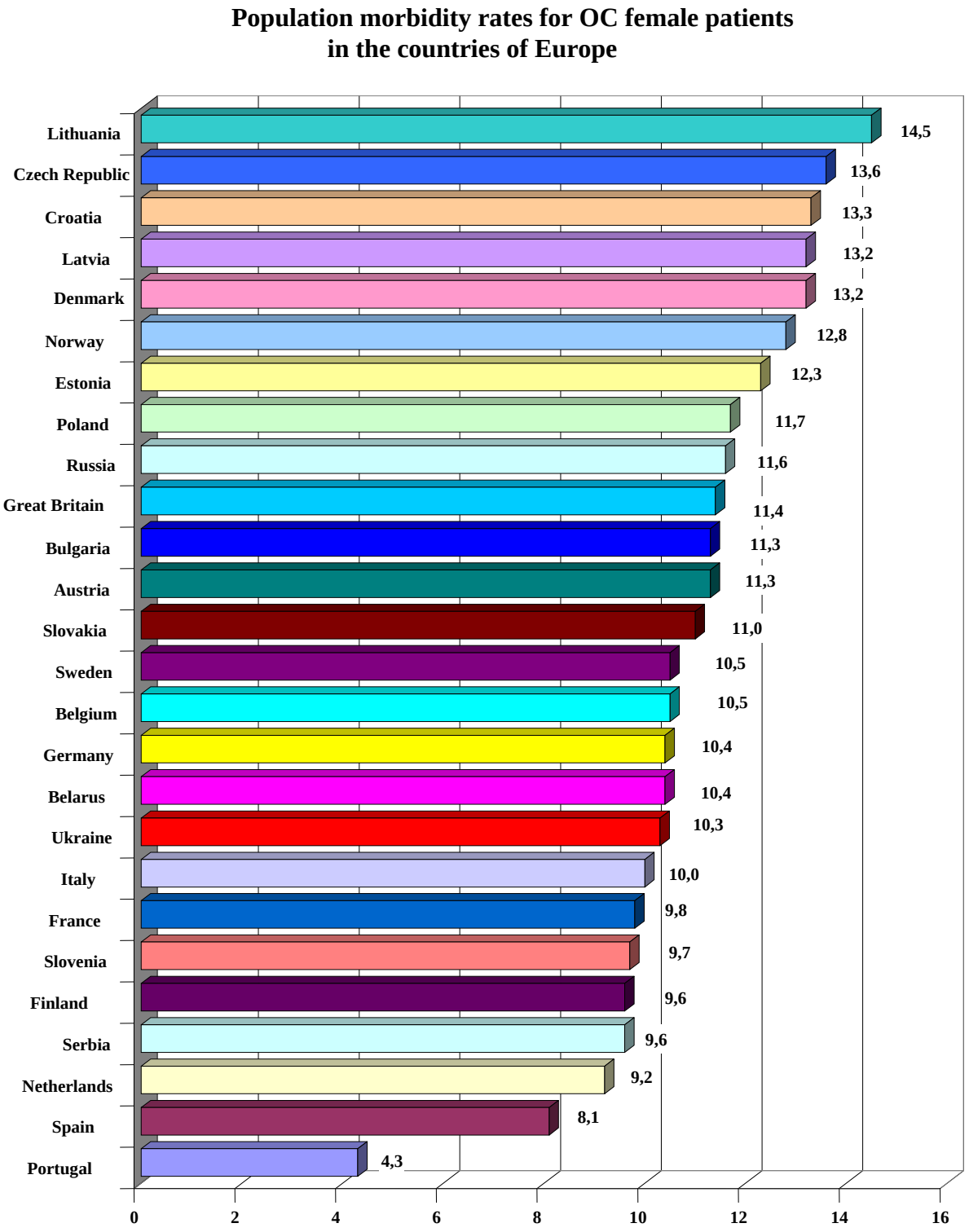
According to National Cancer Register data prevalence rate of OC for 2010 yr. in Ukraine made up – 17,0, and mortality rate – 8,7 cases per 100 thousand of female population, but for 2011 yr. it composed – 16,6 and 9,6 respectively [32].

Mortality due to OC in different countries worldwide, including Ukraine, tends to increase over the past 10 years (Fig. 4) [32, 56, 70]. In accordance with data of population cancer-registers in the countries of Europe 1-year survival rate of OC patients constitutes 63%; 3-year – 41%; 5-year – 35% [56].



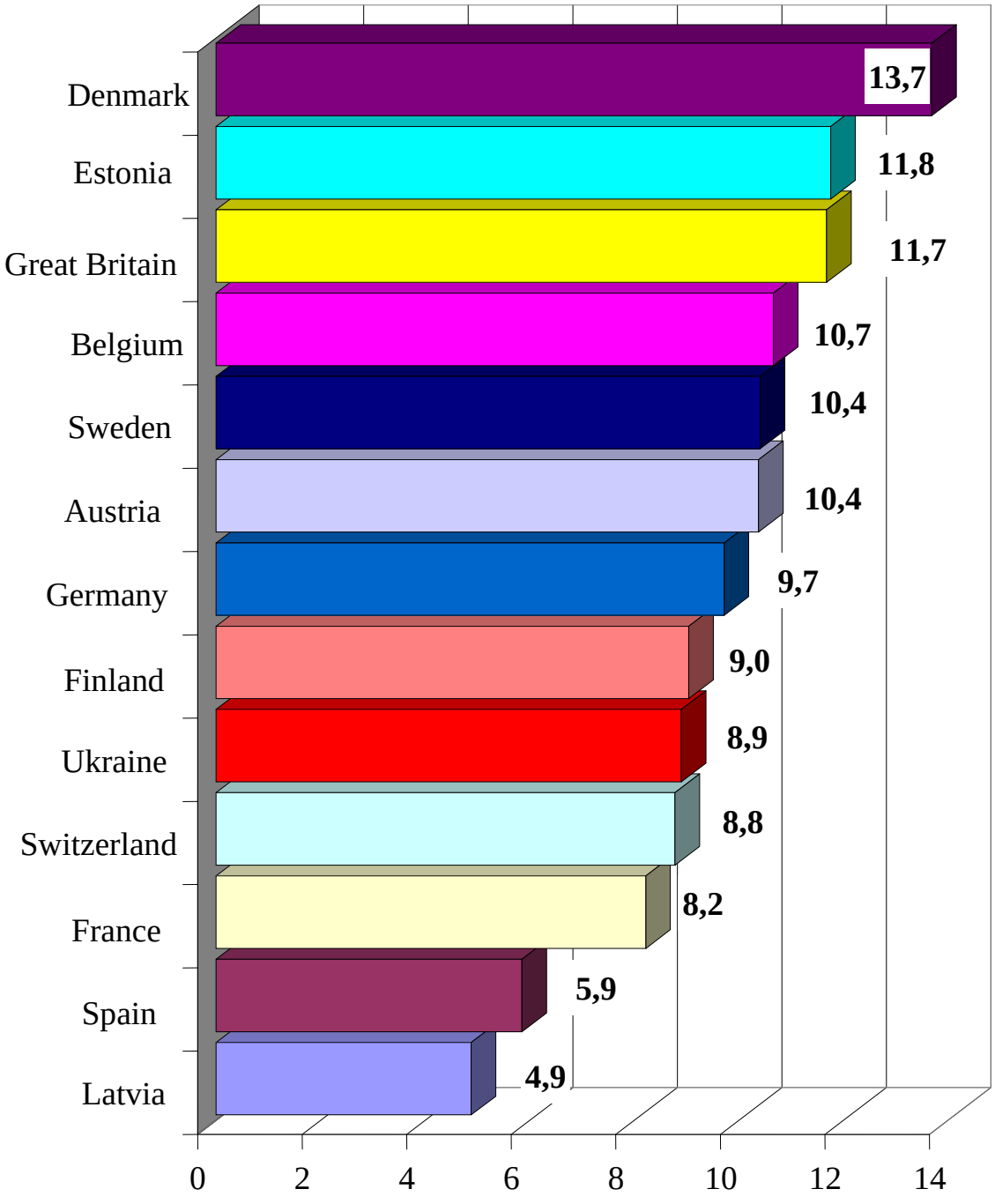
Source: GLOBOCAN, 2008 [70]

Fig. 2 OC Morbidity and mortality rates for 100.000 of female population in different countries worldwide



Source: Cancer Incidence in Five Continents, Vol. IX, 2007 [56]

Fig. 3



Source: Cancer Incidence in Five Continents, Vol. IX, 2007 [56]

Fig. 4

Population morbidity rates for OC patients in the countries of Europe

The following is referred to the principal causes of low survival in OC patients: asymptomatic disease course on early stages, absence of pathognomic symptoms, broard age-specific range of the diseased women, owing to this 75% of OC patients are diagnosed on the III – IV stage [13, 35, 42, 75].

Treatment strategy for OC patients contains surgery component and chemotherapy (ovarian tumors (OT) resistance to cytostatics makes up about 75%) [8, 10, 12, 13, 31, 63]. In some OT (dysgerminomas, androblastomas) radiation therapy is administered [12, 13]. Prossibility to use various treatment methods makes a background for continuous patients' treatment and allows considering this disease as a chronic process which requires constant step-by-step use of various treatment methods [7, 10, 31, 39, 63].

Despite of improved methods of surgery and modern chemotherapy schemes application [28, 41, 50, 52, 64], remote outcomes of patients' therapy with disseminated ovarian cancer remain unsatisfactory. According to National Cancer Register data 5-year survival rate on the II stage composes 55 – 67%, on the III stage – 11 – 15% and the IV stage – 0 – 5% [32, 36].

The problem of OC hormone-dependence remains disputable in modern oncogynecology. Its decision will contribute to not only specifying a pathogenesis of OC, its prognosis, but also substantiating the indications for hormonal therapy as a complex treatment.

Several hypotheses exist to explain malignant transformation in the ovaries epithelium (table) [58], where no genetic predisposition to OC appearance is determined owing to $BRCA_1$ and $BRCA_2$ genes mutation [57, 66, 68].

Hypothesis of ovarian hyperstimulation was suggested by M. F. Fathalla (1971) [65], that is based on OC risk increasing among the women with great number of ovulations. It is assumed that during the ovulations submergence and damage of superficial epithelial cells of ovarium occurs, and subsequent reparative processes in such cells increase a risk of developing mutations with further malignization. In conformity with this hypothesis OC risk is lower in women with multiple delivery [61, 92, 93, 104], those with long-time breastfeeding [72] and women administering oral contraceptives [85, 94, 104]. There is an experimental evidence of hypothesis of ovarian hyper stimulation obtained in experiments on the primates and other animals [67, 79]. However, evidence against such a hypothesis is that progestagens do not suppress ovulation and simultaneously they are not less effective in OC prevention than contraceptives which suppress this ovulation [93]. Furthermore, risk of OC increases in polycystic ovary syndrome though the number of ovulation cycles is low in these women [98]. Although, the latter statement is disputable for it has been recently defined that OC commonly develops in fallopian tubes infertility when ovulation remains whereas in women with endocrine infertility with anovulation cycle and also these hormonal disturbances combined with metabolic changes OC practically does not develop (S. M. Kartashov, V. F. Chekhun, 2003) [43].

Gonadotropic hypothesis, according to which stimulation of ovarian superficial epithelium by follicle-stimulating (FSH) and luteinizing (LH) hormones can increase the risk of its malignization. A.S. Whittemore et al. (1992) [104] conducted a "case-control" type of study where they demonstrated that infertile women administering medicines for ovulation stimulating and the risk of ovarian cancer was 2,8 times increased, and for marginal tumors it was 4 times higher compared with infertile women who did not receive preparations to increase fertility. However, subsequent studies ("case-control" and cohort types) did not reveal inconstancy of relation between gonadotropins administering and OC [53]. Receptors to FSH and LH are detected in 100% normal superficial epithelial cells of ovaries and in 60% of malignant cells [106]. Data of studies demonstrated that FSH, LH and human chorionic gonadotropin can stimulate proliferation of OC cells and mitogen-activating protein kinase [60]. Induced hyper expression of a receptor to FSH results in raising of expression of the receptor to epidermal growth factor (EGFR) and type 2 receptor to human epidermal growth

factor (HER2) [60]. β-katenin, Meis-1, cyclin G2, insulin-like growth factor 1 (IGF) and integrin β-1 are referred to the other likely oncogenes where expression is increased under the effect of FSH and LH *in vitro* [77, 101]. No one study has proved that gonadotropins action may induce malignant transformation in the superficial epithelium of ovaries yet. Although, gonadotroipic medicines tend to intensify tumor growth and angiogenesis in the studies with tumors transplsplantation to the animals, [96], they increase expression of endothelium growth factor (VEGF) [103] and cells adhesion [97]. These data testify that gonadotroipic hormones stimulate OC progression, but do not confirm their etiology significance.

Hormonal stimulation hypothesis. The data of epidemiological studies give evidence that progesterone, its derivatives and combined oral contraceptives decrease the risk of OC [93, 95]. States associated with increased androgens level (polycystic ovary syndrome PCOS), enhance the risk of OC [98]. The highest androgens concentration is created inside of growing follicles which make cells proliferation more intense via the receptor apparatus of superficial epithelium of ovaries [58].

Hypothesis of inflammation. The etiological significance of inflammation in ovarian carcinogenesis which accompanies each ovulation, resulting in the release of cytokines, and as a consequence – leads to tissue changes, which predisposes the superficial epithelium cells to genetic damage and malignant transformation was studied by the authors R. B., Ness, C. Cottreau (1999) [86]. Hypothesis is supported by a lower risk of ovarian cancer in women who regularly take non-steroidal anti-inflammatory drugs, aspirin and paracetamol specifically. [48] The ultimate targets of the signal system triggered by non-steroidal anti-inflammatory drugs are the NO-synthase, cyclooxygenase-2, VEGF and NF-kW which are involved in the mechanisms of carcinogenesis [48].

Table

Likely mechanisms of predisposition to OC development		
Hypothesis	Supposed mechanism	Evidences
Constant oculation	OSE is damaged during ovulation, and restoration processes raise susceptibility to mutations	OC risk decreases with reduction in number of ovulation cycles (in pregnancy, breastfeeding, oral contraceptive pills (OCP) administration)
Stimulation by gonadotropins	FSH and LH stimulate tumor growth, cells division and mutagenesis	Elevation of OC risk in case of infertility, PCOS; decreasing of risk in progestagens administration; FSH increases the expression of many oncogens and stimulates tumor growth (experimental data)
Hormonal Stimulation	High concentrations of androgens in a tumor microenvironment stimulate carcinogenesis while progestagens decrease the risk of OC	Conditions associated with a high level of circulating androgens (PCOS) increase the risk of OC; androgens – hormones which prevail in the inclusion cysts; use of progestagens decreases the OC risk.
Inflammation	OSE destruction during ovulation induces inflammation which stimulates tissue rearrangement and increases susceptibility to mutations	Likelihood of decreased risk of OC in NSAIDs administerion; high content of inflammatory mediators in a tumor tissue

Abbreviations: OSE – ovary superficial epithelium; OC – ovarian cancer; OCP – oral contraceptive pills; PCOS – polycystic ovary syndrome; NSAIDs – non-steriodal anti-inflammatory drugs

Hormonal carcinogenesis theory

Hormone-dependent cancer – a definite paradox in the theory of oncogenesis, since it suggests the transformation mechanism due to genotoxic effects of carcinogens but hormones are non-genotoxic and perform normal regulatory functions in the organism [42].

Hormonal carcinogenesis mechanism conventionally can be divided into two structures: the first - neurohormonal regulation at the organism level, violation of which results in excessive chronic proliferation in hormone-dependent tissue that is not investigated nowadays [17]. Problem of hormone-dependent cancer was not disclosed in oncogene theory and is associated with the second structure, which follows the change of proliferative regimen in tissue and explains oncology sense for hormonal stimulation of proliferation [44]. Maintenance of a constant internal environment in the body is conducted via a negative feedback mechanism [14]. Integration of hormones action occurs in the pituitary gland that controls activity of all endocrine glands. [15] However, pituitary gland receives hormonal nature signals mainly. All information coming through the autonomic nervous system is sustained by the hypothalamus – the coordinator of the autonomic and endocrine activity. Negative feedback mechanism appears in regulation of the integrated neuroendocrine system.

Hypothalamic-pituitary complex controls the central nervous system effects on the organism. Impaired function of hormone-dependent organ changes the hormonal balance in many systems [17, 42]. As a rule, stimulation and activation of compensation reserves follow which are directed at the restoration of imbalance. Compensatory and chronic proliferative processes in the endocrine-dependent organ [15, 16].

Hormone-dependent cancer develops as follows: impaired hormone synthesis or inactivation of peripheral endocrine glands leads to the cessation of inhibitory effect on the pituitary gland, which is a hypothalamus-mediated; synthesis of pituitary hormones is activated and peripheral gland hyperstimulation occurs [42]. Thus, blood hormones level increases resulting in stimulation of proliferation process in the tissue which undergoes tumor transformation [44].

In analyzing the role of the hormones proliferative effect I. P. Tereshchenko and A. P. Kashulin (1983) [22] conclude that all proliferative-active hormones under certain conditions and with sufficient persistence of the experimenter can become a cause of violation of the regulatory mechanisms of cells division and differentiation, which results in tissue malignazation.

I. A. Alov (1964) [2], O. I. Epifanova (1965) [19], S. S. Laguchev (1970) [26], studying the mechanism of regulation of cell proliferation with use of autoradiography method concluded that the hormones are mitotic regulators.

Y. M. Samundzhan (1973) [34] has been studying the role of cell proliferation as a factor in carcinogenesis for a couple of years and revealed the following correlations:

- dyshormonal tumors appearance is only caused by those hormones stimulating the proliferative processes in normal tissues;
- correlation exists between the breast cancer development, endometrial cancer and prolonged hyperestrogenization, between the ovarian and testicular tumor appearance and increased levels of pituitary gonadotropins, between the adrenal and thyroid gland tumors formation, and high levels of thyroid-stimulating and adrenocorticotropic pituitary hormones;
- adrenal glands increased hormonal activity, especially estrogen secretion, results in intense proliferation to the breast tissues in the castrated mice, which contributes to breast cancer developing.

V. S. Shapot (1975) [45] demonstrated the results of studies where the ovaries of the other animal were transplanted under the spleen capsule in a castrated female rat. The organ was successfully engrafted and produced the estrogens, but they got into portal vein and were destroyed by the liver immediately without reaching the pituitary gland. As a result, functions coordination via the feedback mechanism in both glands was disrupted leading to pituitary gonadotropins overproduction, which in turn – results in constantly stimulating proliferation of ovarian follicular epithelium. After only 157 days neoplastic cells in the corpus luteum appeared in the graft which were being transformed into luteoma as long as 300 days. The author concluded that the effect of hormones on the processes of cell division both depends on duration of action, and their dosage.

According to the standpoint of the famous French oncologist J. Mate (1983) [27], over-stimulation of cell proliferation by hormones is the cause of carcinogenesis as a condition along with the mutation or virus, that is, plays a role of the promoter. Though initially tumor-formation is reversible and depends on hormonal stimulation of the level of cells proliferation. Describing the role of hormones and other carcinogens, he specifies that DNA of the cell must be in a state of duplication, which could facilitate the viral DNA introduction into it. This explains not only the role of carcinogen factors (hormones particularly), the effect of which is based on the stimulation of cell proliferation by the tissue sensitized to them, but also the role of some effects which destroy cells (e.g. radiation), since depletion they cause, is accompanied by a compensatory reproduction. The scientist combines mitogenic and carcinogenic effects causing cell apoptosis, as the tissue is responsible for these effects by means of the same type of reaction – a compensatory proliferation.

In the process of tumor progression increase in the degree of tumor autonomy is observed, which is associated with the gradual loss of neoplastic tissue sensitivity to the hormones due to loss of their receptors in the cell cytoplasm. This phenomenon was confirmed in 1975 in Bethesda (USA) at the international workshop on breast cancer [42]. As shown by numerous studies, there is a correlation between the estrogen receptors (ER) concentration in breast tumors and response to hormonal therapy; also, there is a direct interrelation between the presence of receptors and the degree of differentiation [4].

S. V. Kuzmina, Y. B. Bakhtin et al. (1987) [5, 25] also indicated in their works a distinct correlation between the degree of tumors malignancy and two types of receptors available: as the cell anaplasia increases, the number of tumor ER “+” PR “+” (PR – receptors to progesterone) is reduced, whereas the number of tumor ER “–” PR “–” increases, that is, a tissue embryonization process leads to loss of the cell cytoplasm receptors. The structure of the tissue homeostasis and control of proliferation function normally provided constant reproduction takes place, therefore, progressing embryonization over time, by means of correlation change between the differentiated and clonogenic cells destroys the negative feedback which controls the stem clonogenic cells proliferation [20]. Feedback violation results in uncontrollable tumor growth of low-differentiated clonogenic cells.

Hormonal carcinogenesis mechanism can be outlined as follows [42]:

- hormonal disturbances, imbalances, increased mitogenic effect;
- accelerated proliferation;
- reversible blocking of differentiation;
- progressive tissue embryonization, loss of a number of receptors in cell cytoplasm;
- violation of tissue homeostasis structure and function, impaired control of cell proliferation;
- uncontrollable tumor growth of low-differentiated clonogenic cells with activated oncogenes, invasion, metastasizing.

Thus, the theory of hormone-dependent cancer takes into consideration not only the qualitative aspect of the carcinogenic factor, but also quantitative – intensity and mode of

action, the combination of which should cause a level of embryonization that exceeds the tissue homeostasis restorative capacity.

Endocrinology characteristics of a postmenopausal period in terms of carcinogenesis

According to the theory suggested by V. M. Dilman, each organism has 3 endocrinous homeostases – reproductive, adaptation and energy [14]. Ontogenetic changes in these systems create a predisposition to the development of hormone-dependent cancers and a combined disturbance at the "center-periphery" level is on the base of this [15]. On the side of "center" – there is an age decrease in hypothalamus sensitivity to the inhibitory effects of the peripheral hormonal regulators such as inhibin [11, 29, 82], causing compensatory production of gonadotropins by a feedback mechanism, which leads to a compensatory increase of ovarian function over definite time – on the side of the "periphery". And the more pronounced compensation is the more expressed adverse changes caused by the excessive action of sex hormones on the reproductive organs will be [15, 16].

Peripheral synthesis of non-classical menopausal estrogens (phenol steroids) with less pronounced inhibitory effect on the hypothalamic-pituitary system [16, 17] than the classical estrogens is being enhanced; and increased production of gonadotropins results in hyperplasia of the ovarian theca tissue [33]. After menopause stroma of the ovary is the main hormone-production place, and mainly it is androgenic [11, 29]. This is confirmed by the immunohistochemical study data with detecting 3-b- steroiddehydrogenase steroidogenesis ferment [33]. Non-classical phenol steroids and estrone are the main hormones in postmenopausal women, formed by androstenedione aromatization (secretion of which in menopause is realized by the adrenals to a considerable degree and less – by the ovaries). Phenol steroids are potent agonists of estradiol, the activity of these metabolites exceeds the activity of the latter several times (in particular, 16-α – OHEI is 8 times higher), they form stable connections to specific receptors of different tissues [15].

Conversion of androstenedione to estrone is proved to correlate in percentage with the women body mass. Increased production of postmenopausal estrogens with growth of body weight is associated with adipose tissue involvement into the process of androgens aromatization [6]. Estrogens supply through aromatization of androgens is not limited to the adipose tissue. Almost all tissues possess this property [6]. ER (α and β) are found in the brain, blood vessels, heart, bones, breasts, ovary, uterus [11]. Only ER-β was found in the lungs, kidneys, bladder and intestines. ER-α dominates in the uterus and breasts. Extra-gonadal estrogen-formation provides supplementary estrogen stimulation [6]. Assessment of the blood hormones level in the postmenopausal women, as studies revealed, does not give sufficient data about the likely variants for pathological processes development, as sufficient level of cytoplasmic receptors in tissues is required to realize the hormonal effect [11, 29].

Compensatory hyperinsulinemia develops among the age endocrine-metabolic changes in women presented by obesity and insulin resistance [15]. Insulin indirectly, through IGF I receptors, increases the enzymatic activity of androgen biosynthesis in the ovaries, similarly to LH, leading to a certain increase in their function [29].

Thus, in postmenopausal period, along with ovulatory ovarian function shutdown, there is a powerful trigger for the number of compensatory mechanisms to ensure sufficient level and diverse range of biologically active metabolites.

According to the theory by V. V. Frolkis (1975) [40], ageing – is a result of random mutations accumulation in chromosomes due to the worn mechanisms of DNA repair, which leads to a weakening of immunological response in the organism.

As V. M. Dilman considers (1989) [16, 17], hormones are not carcinogenic, but act as promoters, they do not induce irreversible stable changes in the genetic apparatus, which is necessary for the malignant transformation in the cells. The scientist separated 2 types of

hormonal carcinogenesis: promoter (physiological) and genetic. This concept is supported by the research of many foreign scientists (J. G. Liehr, 1997; S. Mas, N. Laso, 2003; S. Tang et al., 2004). The first type is associated with the "enhanced hormonal stimulation" (hormone acts as a factor creating the conditions for increasing the tumor cells number). For the second – growing production of free radicals in the metabolism of hormones is characteristic, which leads to oxidative damage to cellular membranes and DNA repair becomes weakened.

Research was made [1, 78, 80, 81, 91] where the levels of ER in the breasts, vulva, endometrium were studied at various terms of post-menopausal period. Based on the data obtained, the authors concluded that, with the onset of menopause fairly intensive decrease in ER concentration takes place in the cells of the target tissues, however, in some patients the presence of high ER concentrations regardless of the menopause duration is retained. The investigators identified 2 types of receptor status in target tissues among the menopausal patients:

- For the first – fairly intensive decrease in ER concentration during 5 – 10 years post-menopause occurs;
- For the second, regardless of the menopause duration, ER high concentration remains in the target tissues.

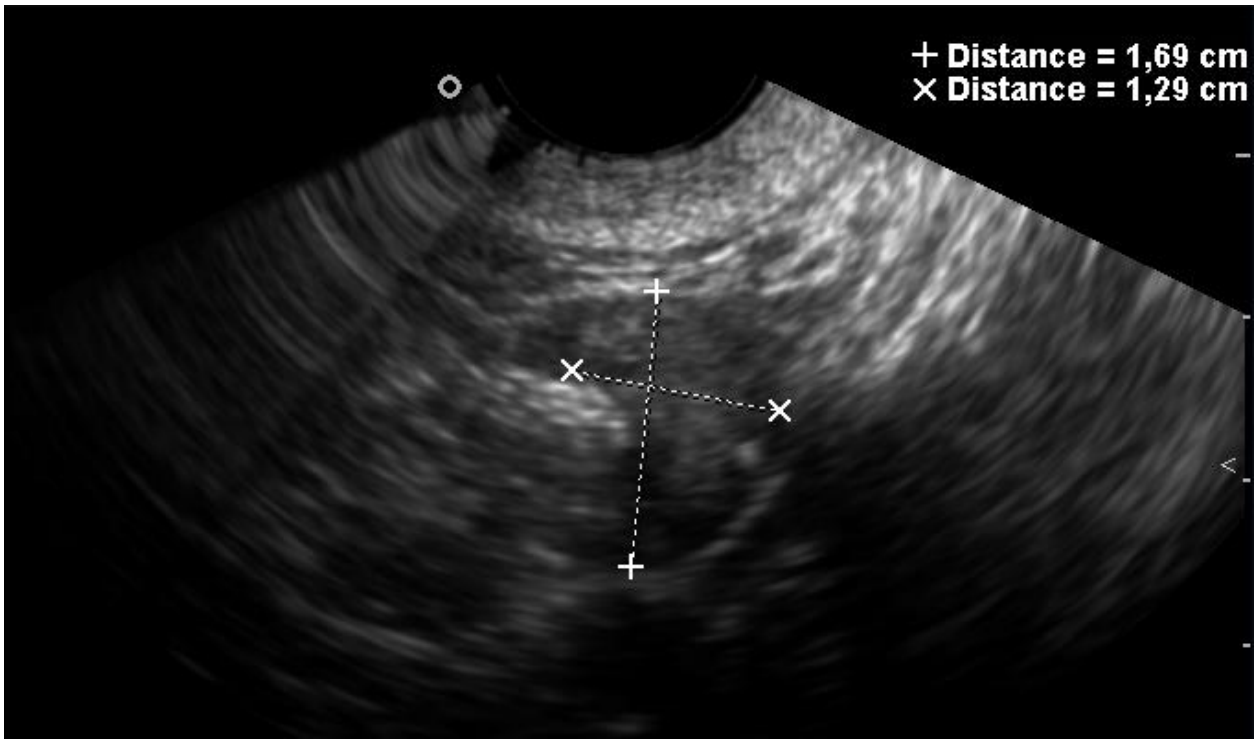
Thus, based on the above data, it can be concluded that, despite of the low levels of circulating steroid hormones in postmenopausal women, with certain factors, all necessary conditions for the estrogen excessive production and target organs stimulation by them are available.

Postmenopausal ovarian changes in the sonography investigation

There are 2 morphological types of ovaries in postmenopausal women: atrophic and hyperplastic (stromal hyperplasia) [11], which explain the individual variations of steroid hormones level in a woman's life during this period. In atrophic morphology type ovary is greatly reduced in size and volume, sound conductivity decreased, hyperechoic areas exist, that corresponds to prevalence of the connective tissue component (Fig. 5 a). In Doppler mapping investigation blood flow color echoes are not demonstrable; infrequently ovary clear visualization is absent (Fig. 5 b) [33].

In hyperplastic morphology type ovarian size decrease is slow, ovarian tissue average conduction is typical, small fluid inclusions are likely detected. In a small duration of menopause likely inclusions are due to the follicular apparatus maintenance, 5 years after menopause, only the isolated follicles are histologically determined in the ovaries that correspond to the inclusion cysts. In hyperplastic type of ovary single blood flow color echoes are likely to be visualized, mainly in its central part (Fig. 6 b) [33].

Particular feature for the postmenopausal ovarian disease is their infrequent combination with endometrial pathology – each 3rd female patient is diagnosed one or another intrauterine pathology. Glandular fibrous polyps against the endometrial atrophy (49%) is commonly combined with OT, and seldom – glandular endometrial hyperplasia (7.7%), and endometrial cancer (1.5%) [33]. High endometrial pathology frequency in OT assumes the existence of so-called "OT with functioning stroma" when hyperplasia in the theca cells likely to produce hormones exists in the tumor stroma [29]. From this perspective, endometrium changes, on the one hand, are the secondary process, on the other hand – common risk factors exist in the ovarian and endometrium pathology, which confirms the hormone-dependent OT character and the overall disease pathogenesis.



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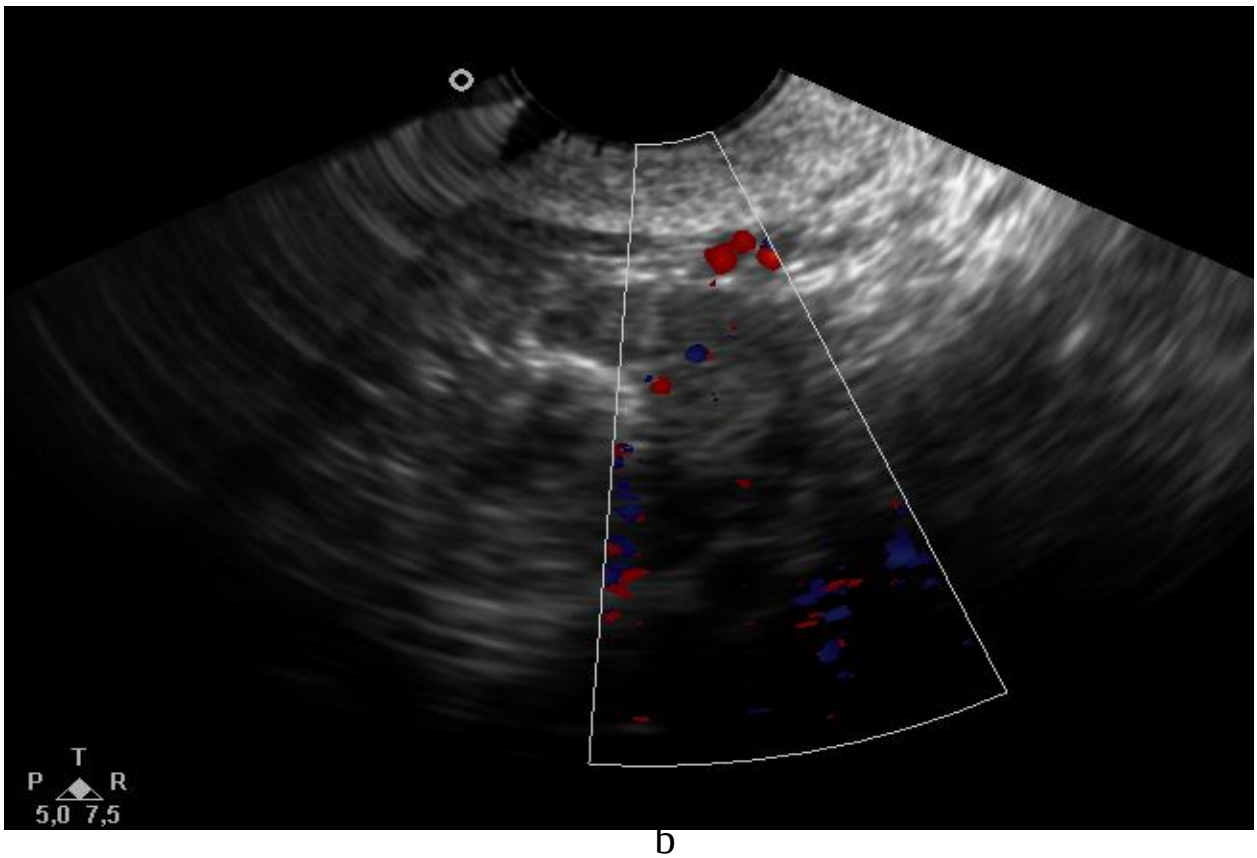
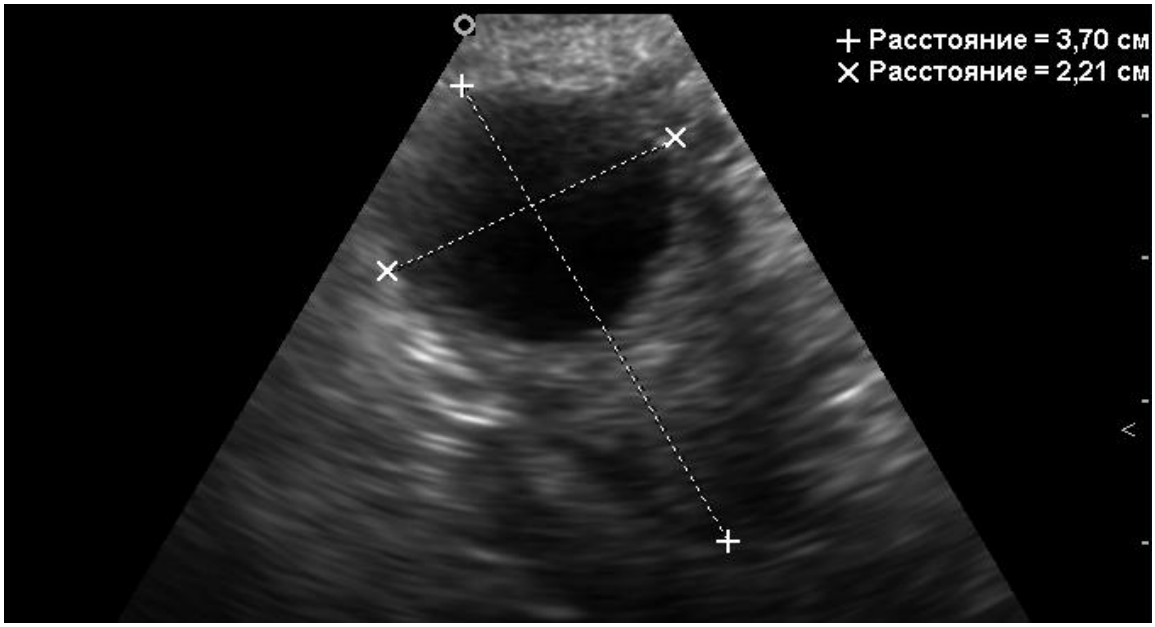


b

Fig. 7 Atrophic ovary (female patient aged 65):

a – echographic investigation;
b – doppler mapping.



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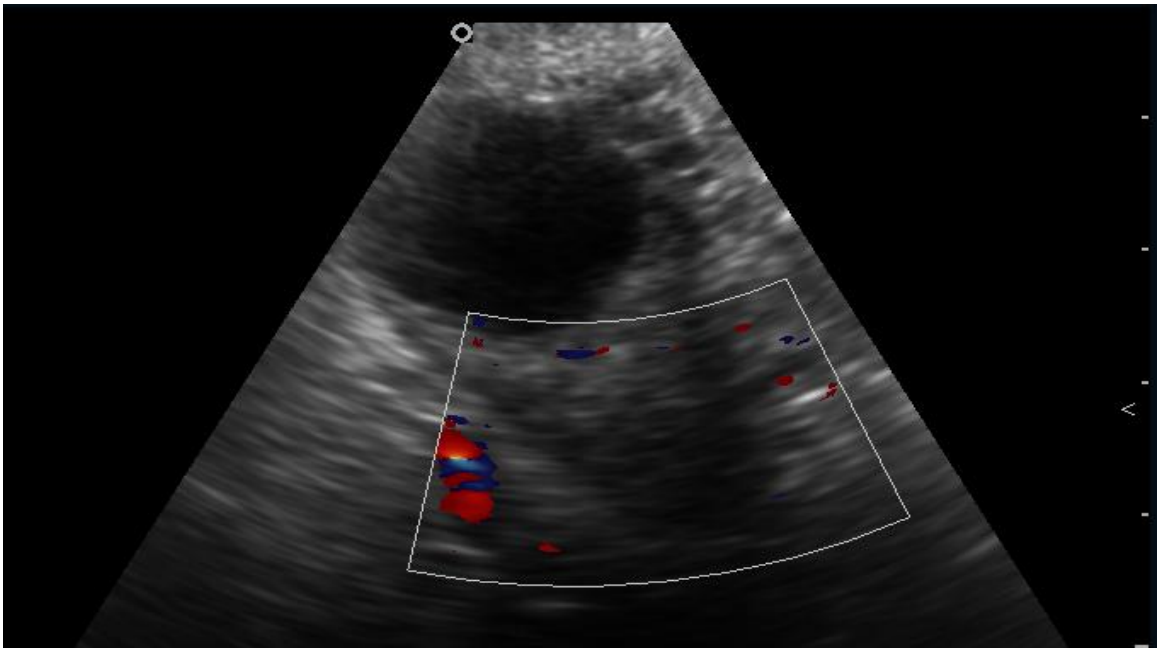

b

Fig. 8 Cystic ovary (female patient aged 62):

a – echographic investigation;
b – doppler mapping.

Studying the hormonal receptor status in ovarian neoplastic tissue and hormonal therapy use in ovarian cancer

Results of various studies provide an evidence of OC hormone-dependence which concluded that ovaries not only produce sex steroid hormones, but also serve as the target tissue for them [62].

N. Ahmad, R. Kumar (2011) studying the presence of receptors of steroid hormones (RSH) in rats ovarian tumors demonstrated that OC experimental models are hormone-depentent [46].

Studies of many domestic and foreign scientists are devoted to the research of hormone receptor status in the ovarian tissue. As early as surveys by Kauppila, Bergqvist et al. (1979), A. Vierikko (1981) demonstrated the normal ovarian tissue samples from benign and malignant tumor contained all RSH [4]. Simultaneously the percentage of ER "+" of the MOT was higher than in the benign one and corresponded to the level of ER in the normal ovarian tissue, and inverse correlation for PR and TR was observed [4]. These data contrast to the findings made by M. Galli et al. (1981) [4] and V. K. Kondratiuk (2008) [24], where it was estimated that ER, PR and TR are simultaneously present in 44% of MOT and not identified in any of benign tumor tissue samples. L. S. Bassalyk (1987) [4], according to the study results available indicated that ER and PR were found with equal frequency in both malignant and benign OT, whereas the receptors to androgenes in benign tumors were 15 times more often than in malignant tumors. M. Quinn et al. (1982) [4], A. S. Dudnichenko (2001) [18], G. V. Bondar (2009) [7], García-Velasco A., Mendiola C., Sánchez-Muñoz A. et al. (2008) [69] defined in their works that serous epithelial OT possess the highest levels of RSH.

According to Shuk-Mei Ho (2003), neoplastic ovarian tissue in 86% of cases was positively stained to ER, in 50% – to PR, in 45% – was positive to both receptors. ER-α were detected in 97% of cases with ovarian serous carcinomas, in 100% – endometrial, in 70% – mucinous carcinomas [99]. At the same time ER-α were found in any of the samples of normal ovarian tissue. Hovever, ER-β were identified in 39% of cases with normal ovarian tissue, in 41% – serous adenocarcinoma, in 30% – mucinous, in 75% – endometrial adenocarcinoma. In contrast, PR were detected similarly both in normal and in malignant ovarian tissue. The scientist suggested evidences about better prognosis in OC patients those administering the combined therapy with progesterone as the first line of treatment [99].

RSH content in epithelial OC, according to P. Schwarts et al. (1982) and H. Cafflez (1983), is not dependent on the stage of the disease, patients' age and radical tumor surgery [4]. These data confirm the study results by V. V. Barinov and N. Y. Kushlinsky (2006) [3], V. P. Kozachenko and Y. Y. Makhova (2007) [23], Nourieh Sharifi, Zohreh Yousefi (2009) [87]: distribution and the levels of ER, PR, AR in the OT are not significantly different in the reproductive age patients and those who are menopausal.

S. M. Kartashov (2000) [21] in his observations indicated that the percentage of ER "+" PR "+" of MOT among the menopausal period women made up 52,2%, whereas in benign OT – 28,6%. For ER "–" PR "+" of tumor tissues inverse correlation was recorded – 29,2% and 37,5%, respectively. The analogue correlation was registered among the reproductive age women – the percentage of ER "+" PR "+" in MOT composed 27,5%, and benign OT – 25,0%. The author, analyzing the receptor status of OT in the different age patients, concluded that receptor-positive (ER "+" PR "+") both benign and malignant tumors are more characteristic in menopause [21].

The research data of A. S. Dudnichenko, T. P. Yakimova (2001) [18] concluded that the ER "+" and PR "+" of OT tend to be more sensitive to chemotherapy. Y. Y. Makhova (2007) [23], Y. V. Novichkov and A. A. Votintsev (2006) [30], studying the hormone receptor status of the neoplastic ovarian tissue observed the higher effectiveness of chemotherapy in patients with OC whose tumors had high level of PR and TR.

Correlation between the ER and PR contents and the degree of OT differentiation was studied by A. Vierikko, G. Teufel et al. (1983) [4], Abdelmajid Khabira, Saloua Maknia, Mounir Frikhak (2010) [51], but they found no significant relation between the histological tumor type, the degree of its differentiation and the level of hormone receptors.

Studies by A. S. Dudnichenko and S. M. Kartashova (2001) [18], L. G. Buchinskaya, N. P. Yurchenko (2009) [54] however, demonstrate a relationship between the level of RSH and the degree of cancerous ovarian tissue differentiation: highly-differentiated tumors have high levels of ER and PR, which allows this OC type to be potentially considered as the most sensitive to hormone therapy [7]. Low-differentiated OT are characterized by low levels of ER and PR. However, the incidence of receptor-positive cases in OT patients of this group may not be significantly different from the group of patients with a high degree of OT differentiation. The authors conclude that, if in the process of carcinogenesis malignant cells tend to decrease their differentiation, this happens not due to tumor cells transforming from the receptor-positive into receptor-negative but as a result of reduction in the RSH expression and, accordingly, hormone-dependence is reduced. Based on these findings, the researchers suggest that low-differentiated OT may have some sensitivity to hormonal effect too. This is consistent with the study results where these hormone-dependent tumors such as breast cancer response positively to the hormone therapy at the minimal levels of ER and PR in the cancerous cells in certain conditions [18].

The domestic scientists determined that OT hormone receptor status changes in chemotherapy exposure: it is decreased in the high-differentiated tumors and, in contrary, in the moderate to low-grade differentiated tumors it tends to increase (T. P. Yakimova, A. S. Dudnichenko, 2001) [18].

However, some investigators [30, 47, 59, 69, 87] argue that the pronounced expression of ER in MOT is a high risk factor for recurrence of the disease, and the PR and TR identification should be evaluated as the factor for favorable prognosis in women with OC. The authors reveal that progression of OC (up to 6 months), is characteristic for patients with hyperestrogenemia, while development of recurrences episodes at more advanced stages of the disease – occur against the suppression of hormonal activity.

Based on the prognostic data received on the OC receptor status, L. Ayadia, S. Chaabounia, A. Khabira et al. (2010) [51], suggest 2 hypotheses about disease prognosis correlation with the hormonal receptor status in the neoplastic tissue:

- estrogen-sensitive tumor cells effectively restore the DNA and avoid apoptosis inducing the clonal division and resistance to drug therapy;
- progesterone causes cellular differentiation and apoptosis; inhibits DNA synthesis and cells division.

Absolutely different study results are recorded by A. Burges, A. Brüning, C. Dannenmann et al. (2010) [55]: better prognosis was observed in the patients with ER “+” serous epithelial OC, and with ER level diminishing in neoplatic tissue the patients survival decreased. These data are confirmed by the investigators A. Halon and et al. (2011) [73], where low survival and short period without recurrences in the patients with the low receptor status tumour with ER-α but favourable prognosis – with PR “+” of OT were recorded.

Interesting results were obtained in the study of OC hormone receptor status by Naifu Liu, Xingwu Wang, Xiugui Sheng (2012) [84]. The authors identified the type of epithelial OT where ER, PR and HER 2-neu were missing, – “triple negative type of OC” and revealed that epithelial OC has an aggressive disease course with unfavorable prognosis, it is similar to the “triple negative” breast cancer, which poorly responds to medication.

According to the result of H. Arias-Pulido and et al. (2009) 5-year survival of patients with OC depending on the hormonal receptor status in the neoplastic tissue composed: 83% – ER “–”/PR “+”, 79% – ER “+”/PR “–”, 61% – ER “+”/PR “+”, 48% – ER “–”/PR “–” accordingly [49].

Results of studies carried out in the National Cancer Institute [37] demonstrated that the patients with OC before treatment and 24 months after revealed a relative and absolute hyperestrogenemia and hyperandrogenemia on the background of pronounced absolute hypoprogesteronemia. In cases of early disease recurrences estrogen and testosterone levels in blood serum were elevated against the decreasing in FSH and increasing of LH levels. The investigator suggeted that these changes are caused not only by the ovaries tumor appearence (since removal of the latter does not eliminate them) but rather bring a pathogenetic role in the development of the disease and its recurrences.

Y. S. Sidorenko and et al. (2008) [35] studying the sex hormones contents in neoplastic tissue and blood of the patients with I-II stages of OC and concluded the following: reproductive age women with MOT demonstrated the imbalance in progesterone and estrogen levels correlation upto the relative hyperestrogenemia, despite the malignant process in the ovaries developed both on the background of increased secretion of sex steroid hormones and against the decreased secretion. And in case of disseminated OC blood estradiol level appeared increased in comparison with that among the healthy women, which the researchers associate with not only estrogen gonadal synthesis, but also with extragonadal one.

The problem of hormone therapy treatment in this group of patients over the years and at present remains disputable.

In Ukraine, Russia and other coutries plenty of non-randomized trials were held, in the course of which the patients with progressing and chemoresistant OC; and also the debilitated patients with disseminated neoplastic process were empirically treated with hormone therapy (tamoxifen, gozeriline, aromasine). Average period duration until disease progression made up 4 – 6 months [7, 74, 83, 90, 105].

J. F. Smyth (2007) in his non-randomized trial demonstrated a positive therapeutic effect of letrozole, which was assigned for the patients with recurrent OC with ER “+” tumor. The period before disease progression made up > 8 months, in some patients general survival rate exceeded the period of 3 years [100].

A. F. Urmancheyeva (2008) [39] recommends using tamoxifen for the patients with OC after the standard treatment administered, who subsequently experienced an increased level of CA-125 as the single disease sign.

Hormonal therapy administration (depo-provera and tamoxifen) in the complex treatment of patients with endometrial OC enabled increasing of 2-year survival rates for I stage by 12%, for II stage – 10,5%, and III – IV stages. – 33,3% accordingly [38].

Domestic scientists [9] experimentally proved the expressed anti-tumor effect of antagonists of gonadotropin-releasing hormones (aGn-RH) in induced OT treatment in rats, but in combined administration with cytostatic agents their anti-tumor effect significantly increased.

Amarican and British scientists (2006, 2008, 2010) in their studies reveled presence of antiproliferative and apoptotic effect of aGn-RH drugs in SKOV-3 and CaOV-3 cell lines of OC [71, 76, 102]. The investigators detected 2 types of receptors to gonadotropin-releasing hormone GnRH-I and GnRH-II in the cell lines of OC. Hence, they concluded that binding of aGn-RH with GnRH-II has stronger antiprolifgerative and apoptotic effect [102].

National standards of the U.S., which were revised in February 2011, recommend using hormonal therapy by aGn-RH and aromatase inhibitors both in patients with chemo-resistant and recurrent OC forms in the absence of data on tumor hormone receptor status, and in the debilitated patients with disseminated neoplastic process [89].

Conclusions. Thus, analyzing the data of numerous studies, it has been established that OC is a hormone-dependent tumor. All the GSH (ER, PR, TR) were detected in MOC and this enables a likely hormonal drugs effect on the tumor cells. OC is a chronic disease that requires ongoing medical therapy. Toxicity is not characteristic for the hormonal therapy and unlike chemotherapy it can be administered as a long-term and continuous treatment. However,

at present the indications and criteria for hormonal therapy application in OC patient's treatment have not been established. And the problem of significant factors for the prognostic disease course with consideration of OC hormone receptor status remains open, despite the fact that correlation between tumor differentiation degree and levels of RSH is supposedly defined in it. Everything above is an evidence of the urgent need for further studies in this direction.

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