

Border Ovarian Tumors in Pregnant Women

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Abstract

Borderline ovarian tumors are typical for women of the reproductive period, in more than a third of patients, tumors are detected at the age of 15-29 years, the average age at the initial diagnosis is 40 years. The aim of the study was to improve methods for diagnosing borderline ovarian tumors during pregnancy and to determine the possibility of performing organ-preserving treatment. The study involved 300 pregnant women with various tumor-like formations (OC) and ovarian tumors (OC), of which 25 had borderline epithelial tumors: 22 - serous, three - mucinous. Before the operation, ultrasound was performed, the concentration in serum of CA-125, sFas, VEGF and IL6 was determined. The results obtained were compared with morphological studies. Organ-preserving and radical surgical treatment was carried out, if necessary, chemotherapy. Perinatal outcomes were studied in a crossover comparison. It was found that it is possible to distinguish between benign ovarian tumors from borderline (OOT) and malignant (OO) tumors using ultrasound and log regression models. VEGF levels above 500 pg / ml, IL6 above 8.1 pg / ml and CA-125 above 300 U / ml indicate a high probability of OST in pregnant women. And only a morphological study of ovarian tissue obtained regardless of surgical methods gave a true idea of the nature of ovarian tumors in pregnant women. At the same time, in three pregnant women with OO, morphological examination revealed tissue areas characteristic of both OO and OO. Thus, the predominance of the initial forms of the tumor process, the relatively favorable course and prognosis in POT allow a fairly widespread use of surgical treatment of a sparing nature with the preservation of menstrual function and fertility.

KEY WORDS: ultrasound examination, morphological examination, ovarian tumors in pregnant women, CD31.

Introduction:

Borderline epithelial tumors (BOT) are ovarian neoplasms with cellular and nuclear atypia without destructive stromal invasion and have a favorable prognosis. Among all ovarian neoplasias, PON is 15–20% [Novikova *et al*, 2013]. However, the analysis of data from

specialized oncological clinics revealed a high frequency - 21–35% in connection with the profile selection of patients [Aggarwal and Kehoe, 2011]. In pregnant women, the frequency of ovarian malignancies (OOT) together with OOT does not exceed 9%. Due to the absence of pathognomonic symptoms, reliable signs of echography and the results of determining the marker glycoprotein CA-125, the clinical diagnosis of PON is difficult, and often difficulties arise in differentiating them from benign and malignant types of ovarian neoplasia. Therefore, the diagnosis of a limited tumor can be reliably established only based on the results of postoperative morphological examination [Davydova *et al*, 2019]. In more than 70% of pregnant women, tumors are detected during ultrasound examination (ultrasound) in early gestation and they correspond to the initial stages according to the FIGO classification. Surgical treatment of OST and PON in pregnant women is performed, as a rule, in the first and second trimesters of pregnancy [Yongsoon *et al*, 2010], which leads to an increase in perinatal morbidity and early infant mortality.

The aim of the study was to improve the methods for diagnosing POO during pregnancy and to determine the possibilities of performing organ-preserving treatment.

Pathogenesis

The pathogenesis of ovarian tumors is not well understood and causes a lot of controversy. It is believed that ovarian epithelial tumors develop from the integumentary epithelium as a result of the formation of inclusive cysts, possibly against the background of hypergonadotropinemia. Hormonal disorders, like immune disorders, are not considered primary from the standpoint of evidence-based medicine. Perhaps hyperhormonemia is associated with a low content of sex hormone binding globulin. It is known that the consumption of vegetable fiber with food leads to the release into the lumen of the small intestine and reabsorption into the bloodstream of compounds with weak estrogenic activity, which increase the synthesis of globulin, which binds sex hormones by the liver. This mechanism increases serum free steroid levels.

In the pathogenesis of ovarian tumors, the role of disturbances in the barrier functions of the small intestine and associated endotoxemia has been proven. Sexual cord tumors and stromal cell tumors develop from embryonic anlagen against the background of hypergonadotropinemia and unrealized reproductive function [Magnitskaya, 2012]

CLINICAL MANIFESTATIONS OF OVARIAN TUMORS AND TUMORS IN PREGNANCY

Benign ovarian tumors of various histological structures, excluding hormone-producing

ones, have a largely similar clinical picture. The early stages of the disease are usually asymptomatic. Even when the first signs of the disease appear, some patients do not operate for a long time. This is due to the fact that a woman either does not consult a doctor, or the doctor, observing her, does not recommend surgical treatment. With a retrospective survey, it can be established that certain symptoms of the disease were present for a long time. The preclinical phase can last for tens of years. Initially, the course of the disease is slow and benign, but over time, signs of malignant growth appear. Most patients undergo surgery for an ovarian tumor within the first year after its detection. However, 33.3% of patients observe the formation in the uterine appendages from 2 to 10 years, they are given (as a rule, to no avail) courses of conservative therapy in connection with the alleged inflammation of the uterine appendages. These data indicate the absence of oncological alertness among doctors. Symptoms of the disease depend on the size and location of the tumor. In most cases, patients present with nonspecific complaints. The most common of them is pain in the lower abdomen, less often in the lower back and groin areas. Most often, the pain is dull, aching. Acute pain occurs when the legs of the tumor are twisted and with hemorrhages (in case of rupture of the tumor capsule). Typically, pain is not associated with menstruation. It occurs due to irritation or inflammation of the serous integument and spasm of the smooth muscles of the hollow organs, as well as due to the tension of the tumor capsule and, as a result, irritation of the receptor apparatus and disruption of the blood supply to the tumor wall. Most often, it is the pain syndrome that makes a woman see a doctor. Almost 20% of patients report constipation and urinary disorders. With a significant tumor, women complain of a feeling of heaviness in the abdomen and an increase in its volume. Weakness and dyspnea disturb 14.7% of patients. In 7.8% of patients, the main complaint is infertility. It must be remembered that a significant number of patients have no symptoms of the disease. In 25% of women with mucinous and almost 20% with dermoid and celioepithelialcystomas, the tumor is found accidentally. During pregnancy, the uterus increases in volume, which changes the anatomotopographic relationships of the appendages [Solomatina,2006]. In this regard, the risk of complications associated with tumor or tumor formation in the ovaries increases.

These complications include:

- early termination of pregnancy (in 18% of cases);
- torsion of the legs of the ovarian tumor in serous tumors and dermoid cysts (in 12% of cases);
- compression of the tumor by the uterus at 12–13 weeks of gestation;
- oblique or transverse position of the fetus (with interconnective development of an

ovarian tumor);

- malignancy of a benign ovarian tumor (in 25% of cases);
- rupture of the tumor capsule at the end of the first stage of labor;
- violation of the advancement of the fetal head through the birth canal with large

sedentary ovarian tumors;

- torsion of the legs and necrosis of the capsule of the ovarian tumor with the onset of symptoms of "acute abdomen" in the third stage of labor and the postpartum period.

PATIENTS AND METHODS

During the period from 2000 to 2017, 300 pregnant women with various tumor-like formations (OO) and ovarian tumors (OO) were prospectively examined. Criteria for the inclusion of patients in the study: pregnant women with OO / OO in the I – III trimesters. Exclusion criteria: refusal of the pregnant woman to participate in the study; pregnant women with an oncological disease established before the start of the study; patients with the threat of termination of pregnancy, intrauterine infection, prenatal fetal injuries established before the study. The results of the study were evaluated by cross-sectional analysis. Their distribution depending on the morphological structure, stage of the tumor process and the degree of differentiation is shown in Fig. 1.

In 76 out of 300 pregnant women with ovarian neoplasms, borderline (BOT) and malignant (BOT) tumors were identified. Among 25 POTs, the serous form was recorded in 22 cases, mucinous in three. It should be noted that the study was carried out for a long time and the recruitment of patients was random, not population-based.

Ultrasound was performed on a Voluson 530 MT (Kretztechnik; Austria) and Voluson E8 (General Electric; USA) apparatus using sensors: RIC5-9-D (4-9 MHz), C1-5-D (2-5 MHz), RAB4 -8-D (2-8 MHz). Complex ultrasound was performed in 2D and 3D modes in combination with the use of Doppler techniques in the color and energy mapping mode (CDC and EDA), as well as three-dimensional angiography. A number of parameters were investigated in CDC: the nature of the vascular pattern (along the periphery, in the central part of the tumor, in the septa, in the papillary growths), analysis of the blood flow velocity (CVC) curve with the determination of the vascular resistance index - the resistance index (RI) and the maximum systolic blood flow velocity (MSS, cm/s). Out of 30 sonographic signs of OO, benign formations (DOY), OO and OOA, 17 turned out to be informative. For ultrasound diagnostics, we used the proposed model

separating OO from OO and OO [Gerasimova *et al*,2007].

In our previous studies [Gerasimova *et al*,2013], it was shown that ovarian tumors in pregnant women have ultrasound signs, with the help of which they can be differentiated with fairly high accuracy into DOT and OZ. In the course of the study, it was found that the ultrasound features of various OBs have statistically significant differences. When studying echographic signs of malignant epithelial tumors of the ovaries (ovarian cancer, or OC), four types of structure were identified, and most importantly, the originality of hemodynamic parameters. At the same time, an expert scale was created based on the analysis of ultrasound indicators. To assess the accuracy of the model, in addition to the actual percentage of correct assignments, the parameters of sensitivity (Se) and specificity (Sp) were taken into account.

Molecular biological studies were carried out according to the following scheme. The concentration of CA-125 was determined by enzyme immunoassay using a test system (Siemens; Germany).

In blood serum, the concentration of sFas was measured by the enzyme immunoassay using monoclonal antibodies, and the VEGF concentration was measured by the immunoassay method using reagent kits (R @ D; USA). Determination of IL6 concentration was performed by ELISA "sandwich" type using reagent kits (R&D; USA).

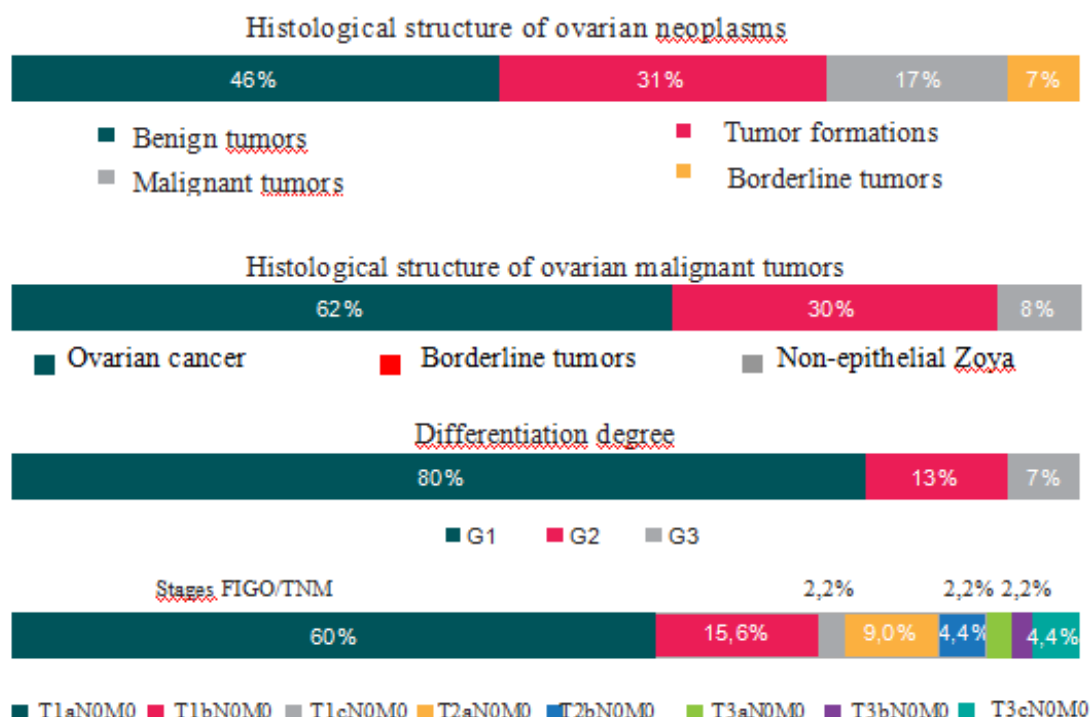


Figure: 1. Distribution of OC / OC depending on the histological structure, stages of the tumor

process (OC / OC) and the degree of differentiation (OC)

Histological preparations stained with hematoxylin-eosin were evaluated by various pathologists. When making a morphological diagnosis, the WHO 2003 classification of tumors of the female reproductive system was used, since it was it that was adopted on the territory of the Russian Federation during the study. For immunohistochemical study, paraffin blocks were selected in 15 pregnant women with OOC and in 10 women with OOC. Angiogenesis was analyzed using antibodies to vascular endothelial growth factor (VEGF), the main signaling protein of angiogenesis (VENTANA; USA) and endothelial marker CD31, a molecule of intercellular adhesion of platelets and endothelium type 1 (clone JC70). VENTANA, USA. When assessing the expression of CD31, the areas with the largest number of microvessels were first selected at low microscope magnification. Subsequently, the number of all positive microvessels was counted in two separate fields of view with an increased microvascular area at a 200x microscope magnification. The level of VEGF expression was assessed by a semi-quantitative method in five fields of view at 400x microscope magnification, including comparison of the staining intensity and the number of positive cells. When measuring the intensity of staining, unstained cells corresponded to 0 points, cells with slightly yellow staining - 1 point, cells with yellow-brown staining - 2 points, cells with brown staining - 3 points. The number of positively stained cells varied: 0 points - less than 10% of all cells, 1 point - 10–49% of stained cells, 2 points - 50–74% of stained cells, 3 points - more than 75% of stained cells. The results of both counts were added, the value of more than 2 points was considered positive.

In addition, medical records and outcomes of pregnancy and childbirth were studied in 300 patients with ovarian neoplasms after treatment.

The SPSS 15.0 software package (IBM; USA) was used for statistical data processing. The data were subjected to frequency analysis by constructing cross-tabulations. Differences were considered statistically significant at $p < 0.05$.

RESULTS OF THE STUDY

Studies have shown that the clinical characteristics of the examined pregnant women did not differ significantly between groups. For example, the age of 76 pregnant women with POS and POS varied in a wide range, from 18 to 45 years. In more than 60% of observations, it was 30 years. In pregnant women with PO / ZOJ, pain in the lower abdomen and dysfunctions of neighboring organs were noted - in 9% of cases, an increase in abdominal volume - in 10.9%, a history of menstrual irregularities in 10.9% and infertility - in 2.7%. The structure of concomitant

extragenital, gynecological pathologies and gynecological surgeries before this pregnancy in patients with OO / OO correlated to a greater extent with age and did not depend on the morphological structure of tumors.

Among the histological forms of POT, serous ones prevailed - in 22 (88%) patients, mucinous types were found in 3 (12%) pregnant women. Bilateral ovarian involvement was found in 28% of cases. The majority of PON against the background of pregnancy were diagnosed in stage I of the tumor process - in 19 (76%) patients, stage II was detected in 5 (20%) patients, and only in one observation stage III was verified.

Ultrasound signs in pregnant women with borderline ovarian tumors corresponded to several variants of the structure: in 32.6% of cases, a mixed type of tumor structure with a predominance of a solid component was stated, in about 55% of patients, a predominance of the cystic component was noted, more than 10% were attributed to solid tumors. Doppler

revealed central and peripheral hypervascularization with low RI values (less than or equal to 0.4) and high MCC values (more than 15 cm / s) when assessing CSC, with the presence of a mosaic type of blood flow, indicating the presence of arteriovenous shunting in the tumor vasculature.

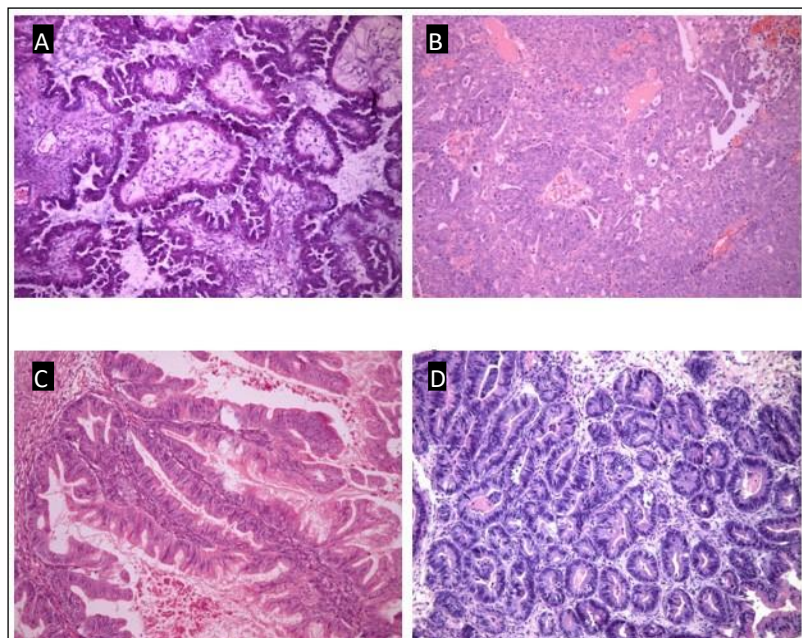


Figure: 2. Morphological picture of the ovarian ovary and ovary ovary in pregnant women.

A. Serous borderline ovarian cystadenoma ($\times 10$, stained with hematoxylin-eosin).

B. Serous low-grade ovarian carcinoma ($\times 10$, stained with hematoxylin-eosin)

C. Mucinous borderline ovarian cystadenoma ($\times 10$, staining with hematoxylin-eosin).

D. Mucinous carcinoma of the ovary ($\times 10$, hematoxylin-eosin staining)

The use of our proposed model for the differential diagnosis of OO in pregnant women made it possible to distinguish OO and DO from OO and OO (sensitivity was 100%, specificity 92.3% with a total model accuracy of 92.8%). Due to the pronounced similarity of the image and hemodynamic parameters during the complex echography, it was not possible to differentiate the PON and the OST. At the same time, with these neoplasms, in all observations, the central location of vessels with a branched network in the septa, solid component, papillary growths and low-resistance blood flow were revealed.

In PON, the concentration of CA-125 in the blood of pregnant women varied from 24.4 to 361 U / ml in the first trimester and from 24.1 to 223 U / ml in the second trimester of pregnancy. The sFas level was 40-200 ng / ml in the first trimester and 46-180 ng / ml in the second trimester of pregnancy. The VEGF concentration ranged from 89 to 286 pg / ml in the first trimester and from 92 to 480 pg / ml in the second trimester of pregnancy. IL6 reached 3.6-12 pg / ml in the first trimester and 8-40.9 pg / ml in the second trimester of pregnancy.

With OST, a significant increase was observed in the serum of both CA-125 and other markers of carcinogenesis - sFas, VEGF, IL6 in comparison with the OOT at any time of pregnancy. In the blood of three patients with ovarian adenocarcinoma CA-125 was 540-1224.6 U / ml, sFas - 180-312.6 ng / ml, VEGF - 510-1028 pg / ml, IL6 - 9.8-40.9 pg / ml. A similar concentration of molecular biological factors was observed in the blood of patients with dysgerminoma, mixed germ cell tumor and immature teratoma. In these observations, the level of CA-125 exceeded 361 U / ml, sFas - 240 ng / ml, VEGF - 490 pg / ml, IL6 - 8.1 pg / ml.

During the morphological study of the POT (Fig. 2), in 22 observations, signs were recorded that made it possible to differentiate them from both the DOT and the OST. In three cases, discrepancies were found in the interpretation of the final histological response in patients who were diagnosed with serous adenocarcinoma against the background of a serous borderline tumor. During the repeated revision of the preparations, no elements of the malignant tumor were found.

Borderline serous cystadenoma was a cystic tumor with a loose wall and pronounced papillary growths that occupied the entire inner surface and in 70% of cases were also detected on the outer surface. PONs were distinguished by epithelial growths with the formation of cell

bundles and budding of groups of cells simultaneously with strictly ordered branching, in which small papillae originate from large, centrally located papillae. The cells of borderline serous tumors had features of epithelial and mesothelial differentiation. The ciliated cells were similar to those of the fallopian tube and were found in a third of the tumors. Cells with abundant eosinophilic cytoplasm and rounded nuclei resembled mesothelium and were located at the tops of papillae. The cell nuclei were located basally, oval or rounded, with mild atypia, delicate chromatin, and sometimes pronounced nucleoli. Revealed rare mitoses (usually 4 in 10 fields of view). Psammary bodies were found in half of the observations.

Serous carcinomas reached large sizes (up to 20 cm in diameter), they were cysts with serous or sacral contents, filled with soft loose papillary growths. The outer surface was smooth, occasionally with papillary structures. Tumors of a solid structure usually had less pronounced papillae, pink-gray in color, were soft or dense, depending on the nature of the underlying stroma. Hemorrhages and necrosis were observed simultaneously. On microscopic examination, serous carcinomas had a papillary solid structure with foci, enlarged rounded cells with polymorphic, hyperchromic nuclei, lumpy nuclear chromatin and an increased nuclear-cytoplasmic ratio, pseudo-multiplicity of the epithelium, characterized by a loss of polarity, lack of cilia on the cell surface, increased mitotic activity.

Border mucinous ovarian cystadenoma was usually multi-chambered, up to 30 cm in diameter, and contained straw-colored liquid or mucus. Morphological study of the preparations of these tumors revealed areas lined with multi-row mucinous epithelium of the intestinal type with the formation of villous-glandular and papillary structures with a mild degree of atypia of cell nuclei.

Mucinous carcinoma differed from borderline mucinous cystadenoma by the presence of foci with a complex arrangement of glands lined with cells with moderate and severe atypia of the nuclei, mitoses, and the presence of foci of necrosis in the tumor.

Expression of CD31 (Fig. 3-4) was detected in the tumor stroma in all cases. The average number of CD31 positive vessels in women with OOC was 36 (from 12 to 48), in patients with OOC - 44 (from 19 to 56). Immunoreactivity against the VEGF marker, assessed by a semi-quantitative method, in women with POS corresponded to 5 points (from 4 to 6), in patients with OOS - 6 points (from 5 to 7). No significant differences were found in the study of the expression of both markers.

An analysis of the case histories of pregnant women with OOJ and OOJ showed that some of them underwent complete cytoreductive surgeries with abortion in case of a common tumor process. In other patients, cytoreductive operations were performed twice: upon detection of a tumor and after a caesarean section.

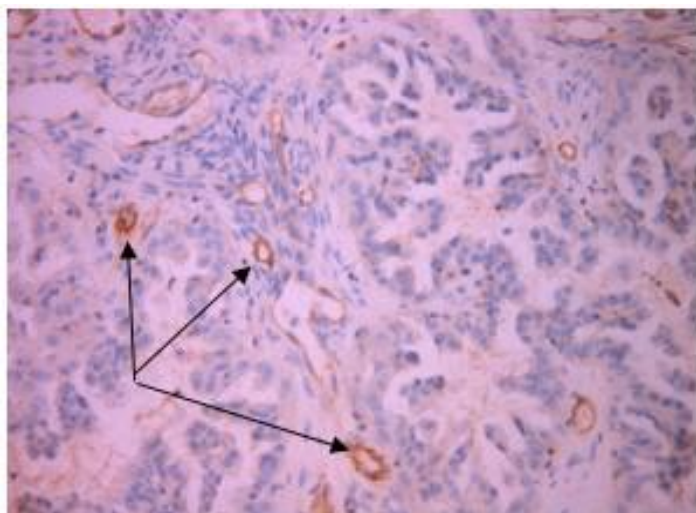


Figure: 3. Expression of CD31 in the OST ($\times 20$). Arrows indicate vessels

All patients with signs of malignancy of ovarian tumors underwent a midline laparotomy with a bypass of the navel on the left. In six cases, first diagnostic laparoscopy was performed, and then, in connection with suspected OC, laparotomy and removal of the primary focus.

The volume of surgical intervention was determined intraoperatively in accordance with the data of the clinical picture of the disease, the reproductive history and the patient's age, the results of ultrasound, the levels of tumor markers in the blood serum, and the results of urgent histological examination. During the operations, surgical staging of the tumor process, revision of the abdominal and pelvic organs, resection / removal of the greater omentum, multiple biopsies of the peritoneum, and the collection of washes or ascitic fluid from the abdominal cavity were performed. Appendectomy was performed for the mucinous type of tumor. Patients who were not interested in maintaining pregnancy and fertility underwent radical surgery - in seven out of 76 cases. At the first stage, during pregnancy, 20 patients with PON underwent organ-preserving surgery with the preservation of the uterus and part of the healthy ovary. In two cases, bilateral adnexectomy was performed. In one of them, a borderline tumor became a find after histological examination of the resected part of the visually unchanged contralateral ovary (stage IB).

It should be noted that during the histological examination of biopsy material or tumor preparations, errors and inaccuracies may occur. Thus, in our observations, in three patients with

OO against the background of pregnancy, during morphological examination, tissue areas characteristic of both OO and OO were recorded. The diagnosis was made of highly differentiated adenocarcinoma of both ovaries on the background of borderline serous cystadenoma. In one of them, at 11–12 weeks of pregnancy, bilateral ovarian tumors with signs of malignancy, ascites, were clinically determined. In the oncological hospital after carrying out diagnostic laparoscopy, right-sided adnexectomy with express histological examination, the conclusion was made: borderline cystadenoma. Conversion of laparoscopic access to laparotomy was performed. Biopsy of the left ovary, resection of the greater omentum, and multiple biopsies of the peritoneum were performed by means of a midline laparotomy. Morphologically, the diagnosis was made of a highly differentiated adenocarcinoma that developed against the background of a serous borderline tumor with cancerous emboli in the lumen of the greater omentum vessels (ovarian cancer T3cN0M0). An artificial termination of pregnancy and a radical operation were performed: extirpation of the uterus with left appendages, subtotal resection of the greater omentum. Cytological examination of abdominal washings revealed elements of adenogenic cancer. Before the appointment of chemotherapy, an interdisciplinary oncological consultation was held due to the discrepancy in the interpretation of the results of cytological and histological studies by different specialists. The primary diagnosis was not confirmed. Diagnosis: borderline ovarian tumor with non-invasive implants in the greater omentum. It was decided to refuse chemotherapy. The patient has been observed for four years without signs of disease progression.

The results of treatment of patients with borderline tumors were as follows: three pregnant women underwent abortion with surgical treatment in the amount of panhysterectomy due to the presence of adenocarcinoma against the background of serous PON, two pregnant women had miscarriages, 10 patients gave birth on their own on time, six pregnant women delivered early by caesarean section when obstetric indications appeared, in four cases, repeated operations were performed with the aim of restoring. Pregnant women with POO subsequently developed tumor relapses in two cases. In one with serous histotype stage IA tumor in the tissue of the resected ovary after breast-conserving surgery, a relapse was detected in the fifth year of follow-up. A morphological examination revealed a highly differentiated adenocarcinoma, after which a radical operation was performed, supplemented by chemotherapy. In the second observation, 2 years after the first operation, a relapse occurred that was identical in histological structure to the primary tumor (atypically proliferating serous tumor). After removal of the recurrent neoplasm, combined treatment was performed. Both patients have been alive for over 3 years. 5 patients dropped out from observation. Long-term results of treatment were followed in 17 of 25 patients for 3–10

years. All subjects were alive at the time of the study. The overall five-year survival rate was 100%.

In patients with PON, 9 pregnancies occurred 2–5 years after the surgery, 4 of which ended in childbirth with a favorable outcome. In 3 cases, pregnancies ended in spontaneous abortion.

THE DISCUSSION OF THE RESULTS

Literature data indicate the absence of specific clinical manifestations of POO during pregnancy. Comprehensive sonography using Doppler techniques included in the differential diagnostic models is highly specific.

At present, no molecular biological factors have been identified that reliably characterize the PON [Tinelliet *al*,2006]. The use of most tumor markers is limited due to the high variability of their indicators,

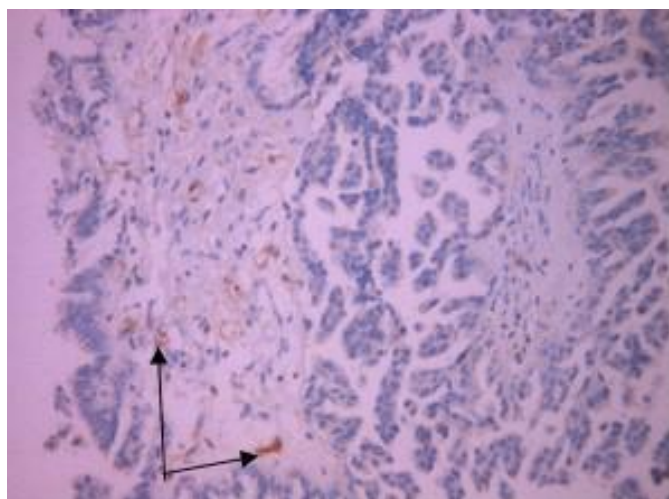


Figure: 4. Expression of CD31 in POT (× 20). Arrows indicate vessels

including depending on the gestational age. In the study, a significant increase in the levels of carcinogenesis markers above the threshold (VEGF - above 500 pg / ml, IL6 - 8.1 pg / ml) was detected in the presence of malignant ovarian neoplasms in pregnant women. The specificity of the test was 91.5%, the sensitivity was 75%. The concentration of CA-125 during OST in pregnant women exceeded 300 U / ml. These results agree with the data of other authors [Manuhinet *al*,2007].

When assessing the level of VEGF expression in paraffin blocks by a semiquantitative method, increased immunoreactivity against this marker, corresponding to 5–7 points, was

registered in ovarian carcinomas. The association between VEGF expression and ovarian cancer has been confirmed by many studies. An increase in the immunoreactivity of VEGF in ovarian carcinoma has been shown as compared to OOT, while a high level of VEGF expression indicates the progression of the disease [Moghaddam *et al*,2012]. The increased CD31 immunoreactivity in the OST preparations compared to the OOT samples indicates an increased blood flow in the tumor tissue due to neovascularization recorded in malignant tumors [Viallard and Larrivee,2017].

The main method of treating PON with an organ-preserving or radical approach remains the surgical method. The world literature is actively discussing the issue of the possibility of ultraconservative interventions as an organ-preserving option with the preservation of unchanged ovarian tissue affected by the PON by performing resection / cystectomy [Novikova and Shevchuk,2014]. The optimal volume of the operation is adnexectomy on the side of the lesion with morphological examination of flushes from the peritoneum and its multiple biopsies; definitive surgical staging should be performed at the time of caesarean section or postpartum if delivery was via vaginal delivery [Zagouri *et al*,2016]. In our study, ultra-conservative interventions were not performed; in 80% of cases, organ-preserving surgical treatment was used in patients with POS. For the purpose of restoring, reoperations were performed in 16% of patients.

Approximately 1/3 of patients require a final postoperative morphological study on paraffin blocks in POC and highly differentiated adenocarcinoma [Brunet *et al*,2008]. According to some reports, the high frequency of overdiagnosis in the presence of foci suspicious of ovarian cancer in OOC, even when conducting a final histological examination in specialized institutions, leads to an unreasonable overestimation of the volume of surgical interventions [Davydova,2018]. According to our results, discrepancies in the interpretation of the morphological response in the differential diagnosis of POT and OC were found in 12% of cases. The varied structure of the PON, the need for a thorough study of multiple slices cause increased requirements for the qualifications and experience of the morphologist, a similar opinion is shared by other researchers [Shloma *et al*,2012].

The overall frequency of relapses in OOC varies from 3 to 10%, with common stages, relapses develop in 25% of patients. In our study, relapses were detected in 8% of cases. According to the results of publications, the five-year survival rate at stages I – II is about 98–99%, at stages III – IV - 82–90% [Trope *et al*,2009]. It is possible that such high rates of five-year

survival in the study performed are associated with the detection of PON in the initial stages of the process and a small number of studied groups.

In studies of fertility after organ-preserving treatment, it is reported that spontaneous pregnancies occur in 40–72% of cases. The influence of pregnancy on the course of the disease has not been established [Fauvet *et al*, 2005]. It should be noted that the reproductive results obtained in our work were recorded pregnancies in more than 35% of patients after breast-conserving surgical interventions when PON was detected during pregnancy. Our results allowed us to identify in the diagnostic algorithm for examining pregnant women with suspected malignant OO a set of such signs as a mixed echographic structure with a hypervascular type of blood flow and low indices of vascular resistance, VEGF values exceeding 500 pg / ml, and IL6 more than 8.1 pg. / ml, the concentration of CA-125 is higher than 300 U / ml, as the most important. However, the similarity of ultrasound signs of OOT and OOJ did not allow unambiguous differentiation of these types of neoplasias. The diagnosis of POO is the prerogative of the final postoperative morphological examination. The results of an urgent histological analysis of ovarian tissue on frozen sections, not in all cases, allow one to get a true idea of the nature of OO in pregnant women. High rates of overall five-year survival after surgical treatment of PON in organ-preserving volume against the background of pregnancy in this study demonstrate the possibility of implementing such sparing approaches in the initial stages.

CONCLUSIONS

Despite the significant scientific and practical interest in POT, many problems related to the improvement of diagnostics and methods of treatment of patients during pregnancy are far from being solved. The predominance of the initial forms of the tumor process, the relatively favorable course and prognosis in PON allow a fairly wide use of the sparing nature of surgical treatment while maintaining menstrual function and fertility.

Reference

1. Aggarwal P, Kehoe S. Ovarian tumors in pregnancy a literature review. *Eur J ObstetGynecolReprod Biol*. 2011; 155 (2): 119–24.
2. Brun JL, Cortez A, Rouzier R. Factors influencing the use and accuracy of frozen section diagnosis of epithelial ovarian tumors. *Am J Obstet Gynecol*. 2008; 199 (3): 241–7.
3. Davydova IYu. Serous borderline ovarian tumors (clinical and morphological features, treatment, prognosis) [dissertation]. M., 2018. Russian.
4. Davydova IYu, Kuznetsov VV, Karseladze AI, Meshcheryakova LA. Borderline ovarian tumors. *Obstetrics and gynecology: news, opinions, training*. 2019; 7 (1): 92–104.
5. Fauvet R, Brzakowski M, Morice P, Resch B, Marret H, Graesslin O, et al. Borderline

- ovarian tumors diagnosed during pregnancy exhibit a high incidence of aggressive features: results of a French multicenter study. *Ann Oncol.* 2012; 23 (6): 1481–7.
6. Fauvet R, Poncelet C, Boccara J. Fertility after conservative treatment for borderline ovarian tumors a French multicenter study. *FertilSteril.* 2005; 83: 284.
7. Gerasimova AA, Gus AI, Klimenko PA, inventor; KlimenkoPetrAfanasevich, assignee. A method for the differential diagnosis of tumorous formations and tumors of the ovaries in pregnant women. Russian Federation patent RF 2325118. 2007 Jun 1. Russan.
8. Gerasimova AA, Shvyrev S, Solomatina AA, Gus AI, Klimenko PA. Procedure for detecting the pattern of ovarian masses. *Oncology.* 2013; 1: 34–40.
9. Moghaddam SM, Amini A, Morris D, Pourgholami H. Significance of vascular endothelial growth factor in growth and peritoneal dissemination of ovarian cancer. *Cancer Metastasis Rev.* 2012; 31 (1–2): 143–62. DOI: 10.1007/s10555-011-9337-5.
10. Manuhin IB, Vysockij MM, Kushlinskij NE. Molekuljarno- biologicheskiefactory v patogeneze i hirurgicheskomecheniioPUholejjaichnikov. M.: Izd-vo «Dinastija», 2007; 208 s. Russian.
11. Magnitskaya N.A. Diagnostics and treatment of ovarian formations in pregnant women: dis. . Cand. honey. sciences. M., 2012.189 p.
12. Novikova EG, AndreevaYuYu, Shevchuk AS. Fertility sparing treatment for patients with bilateral borderline ovarian tumors. *Oncology.* 2013; (1): 84–91.
13. Novikova EG, Shevchuk AS. Organ-preserving treatment of patients with borderline ovarian tumors. *Oncology issues.* 2014; 60 (3): 267–73.
14. Shloma EN, Fridman MV, Shelkovich SE, DemidchikYuE. Borderline epithelial tumors of the ovaries: clinical course and problems of morphological diagnosis. Minsk: Publishing house "Bel MAPO", 2012; 80 s.
15. Shevchuk AS. Repeated laparoscopic operations in patients with malignant ovarian tumors [dissertation]. M., 2005.
16. Solomatina A.A. Ovarian formations. New technologies in diagnostics and treatment: dissertation of Dr. med. sciences. M., 2006.312 p.
17. Tinelli R, Tinelli A, Tinelli F, Cicenelli E, Malvasi A. Conservative surgery for borderline ovarian tumors: a review. *GynecolOncol.* 2006; 100 (1): 185–91.
18. Trope C, Davidson B, Paulsen T, Abeler VM, Kaern J. Diagnosis and treatment of borderline ovarian neoplasms «the state of the art». *Eur J GynecolOncol.* 2009; 30 (5): 471–82.
19. Viallard C, Larrivé B. Tumor angiogenesis and vascular normalization: alternative therapeutic targets. *Angiogenesis.* 2017; 20 (4): 409–26. DOI: 10.1007/s10456-017-9562-9.
20. Yong-Soon K, Jung-Eun M, Kyung-Taek L, In-Ho L, Tae-Jin K, Ki-Heon L, et al. Ovarian cancer during pregnancy clinical and pregnancy outcome. *Korean Med Sci.* 2010; 25 (2): 230–4.
21. Zagouri F, Dimitrakakis C, Marinopoulos S, Tsigginou A, Dimopoulos MA. Cancer in pregnancy: disentangling treatment modalities. *ESMO.* 2016; 1 (3). Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5070264/>