BORDERLINE OVARIAN TUMORS IN PREGNANCY

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Borderline ovarian tumors (BOTs) are common in women in their reproductive years. In more than one-third of patients tumors are detected at the age of 15–29, the average age at initial diagnosis is 40. The study was aimed to improve methods for BOTs diagnosis in pregnancy and to determine the possibilities of organ preservation treatment. A group of 300 pregnant women with various tumor-like formations and ovarian tumors was examined. Of them, 25 patients had borderline epithelial tumors (22 patients had serous and 3 patients had mucinous tumors). Ultrasound examination together with blood serum CA-125, sFas, VEGF and IL6 level assessment were performed prior to surgery. The results obtained were compared with the results of morphological studies. Organ preservation and radical surgical treatment were carried out, and chemotherapy, if necessary. Perinatal outcomes were studied when performing the cross-comparison. It was discovered, that ultrasonography and logistic regression analysis made it possible to distinguish between benign ovarian tumors, BOTs and malignant ovarian tumors. The levels of VEGF above the 500 pg/ml, IL6 above the 8.1 pg/ml and CA-125 above the 300 U/ml indicated the high probability of malignant ovarian tumors in pregnant women. Only the morphological study of ovarian tissue, obtained regardless of surgical methods, ensured understanding of the ovarian tumor's true nature during pregnancy. At the same time, in three pregnant women with ovarian tumors, the morphological examination revealed some tissue areas common both for BOTs and malignant ovarian tumors. Thus, the predominance of the tumor early stages, relatively mild course and, favorable prognosis in patients with BOTs make it possible to use gentle surgical treatment making it possible to preserve menstrual function and fertility.

Keywords: ultrasound, morphological examination, ovarian tumors in pregnant women, CD31

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ПОГРАНИЧНЫЕ ОПУХОЛИ ЯИЧНИКОВ У БЕРЕМЕННЫХ

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Пограничные опухоли яичников характерны для женщин репродуктивного периода, более чем у трети больных опухоли выявляют в возрасте 15–29 лет, средний возраст при первичной постановке диагноза составляет 40 лет. Целью исследования было усовершенствовать методы диагностики пограничных опухолей яичников на фоне беременности и определить возможности выполнения органосохраняющего лечения. Обследовано 300 беременных с различными опухолевидными образованиями (ООЯ) и опухолями яичников (ОЯ), из которых 25 имели пограничные эпителиальные опухоли: 22 — серозные, три — муцинозные. До операции проводили УЗИ, определяли концентрацию в сыворотке крови CA-125, sFas, VEGF и IL6. Полученные результаты сопоставляли с морфологическими исследованиями. Проводили органосохраняющее и радикальное хирургическое лечение, при необходимости — химиотерапию. При перекрестном сравнении изучали перинатальные исходы. Обнаружено, что различить доброкачественные опухоли яичников от пограничных (ПОЯ) и злокачественных (ЗОЯ) возможно с помощью УЗИ и логрегрессионных моделей. Уровни VEGF выше 500 пг/мл, IL6 выше 8,1 пг/мл и CA-125 выше 300 ЕД/мл свидетельствуют о высокой вероятности ЗОЯ у беременных. И только морфологическое исследование тканей яичников, полученных независимо от хирургических способов, давало истинное представление о характере опухоли яичников у беременных. Вместе с тем у трех беременных с ОЯ при морфологическом исследовании выявлены участки ткани, характерные как для ПОЯ, так и для ЗОЯ. Таким образом, преобладание начальных форм опухолевого процесса, относительно благоприятное течение и прогноз при ПОЯ позволяют достаточно широко использовать хирургическое лечение щадящего характера с сохранением менструальной функции и фертильности.

Ключевые слова: ультразвуковое исследование, морфологическое исследование, опухоли яичников у беременных, CD31

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Borderline epithelial tumors (borderline ovarian tumors, BOTs) are ovarian neoplasms associated with cellular and nuclear atypia without destructive stromal invasion which have a favorable prognosis. BOTs account for 15–20% of all ovarian neoplasms [1–3]. However, the data of specialized oncological clinics analysis revealed a higher incidence (21–35%) due to specialized patients' selection [4–8]. In pregnant women, the incidence of malignant ovarian neoplasms, together with BOTs, does not exceed 9%. Due to no pathognomonic signs, reliable ultrasound signs and the results of marker glycoprotein CA-125 determination, BOTs are difficult to diagnose, often it is hard to distinguish between BOTs, benign and malignant ovarian neoplasms. Therefore, the borderline tumor can be diagnosed reliably only during the post-operative tumor morphology

examination [9–10]. In more than 70% of pregnant women, the tumors are detected during the ultrasound scan in the early stages of gestation (tumor early stages according to the FIGO system). Surgical treatment of malignant ovarian tumors and BOTs in pregnant women is normally performed in the first and second trimesters of pregnancy [5, 11–12], which leads to increased perinatal morbidity and early infant mortality.

The study was aimed to improve methods for BOTs diagnosis in pregnancy and to determine the possibilities of organ preservation treatment.

METHODS

In 2000–2017 a group of 300 pregnant women with various tumor-like formations and ovarian tumors was prospectively examined. Inclusion criteria: pregnant women with tumor-like formations/ovarian tumors diagnosed during I–III trimesters. Exclusion criteria: the woman's refuse to participate in the study; pregnant women with cancer diagnosed before the study; patients with threatened abortion, intrauterine infection, impairments in a fetus diagnosed before the study. The results of the study were evaluated by cross-analysis. The results' distribution in accordance with the morphological structure, tumor stage and the abnormality degree is presented in Fig. 1.

In 76 of 300 pregnant women with ovarian neoplasms, BOTs and malignant ovarian tumors were detected. Of 25 patients with BOTs, 22 patients had serous and 3 had mucinous forms. It should be noted that the study was carried out for a long time and the patients' recruitment was random, not population-based.

Ultrasonographic examination was performed with the Voluson 530 MT (Kretztechnik; Austria) and Voluson E8 (General Electric; USA) systems, and the RIC5-9-D (4–9 MHz), C1-5-D (2–5 MHz), RAB4-8-D (2–8 MHz) probes. An ultrasound scan was carried out in 2D and 3D mode, combined with color and energy Doppler mapping, as well as with three-dimensional angiography. The color Doppler mapping was used for assessment of the following features: vascularization pattern (tumor periphery, central parts of the tumor, septa, papillary features), the curve of the blood flow velocity analysis together with resistance index (RI) and peak systolic blood flow velocity (cm/s) determination. Of 30 ultrasound signs of tumor-like formations, benign ovarian tumors, BOTs and malignant ovarian tumors, 17 signs appeared to be informative. For ultrasound diagnostics the proposed model was used allowing one to distinguish between benign ovarian tumors, BOTs and malignant ovarian tumors [13]. Our previous studies [14] demonstrated that ovarian tumors in pregnant women had ultrasound signs allowing one to differentiate between benign and malignant ovarian tumors with high accuracy. During the study it was noted that the differences in the ultrasound features of various ovarian neoplasms were significant. When studying the ultrasound signs of malignant epithelial tumors of the ovaries (ovarian cancer), four types of structure, and, which in most important, unique hemodynamic parameters were identified. At the same time, the assessment scale based on the ultrasound signs analysis was created. To evaluate the accuracy of the model, in addition to the actual percentage of correct assignments, the sensitivity (Se) and specificity (Sp) parameters were taken into account.

Molecular biology techniques were applied as follows. Concentration of CA-125 was determined using the enzyme immunoassay test system (Siemens; Germany). Enzyme immunoassay method was used to determine the sFas concentration in the blood serum using monoclonal antibodies, and the VEGF concentration using the reagent kits (R@D; USA). The concentration of IL6 was evaluated by the Sandwich Enzyme-Linked ImmunoSorbent Assay (ELISA) using the reagent kits (R&D; USA).

Different pathologists examined the hematoxylin and eosin stains. The WHO Classification of Tumors of Female Reproductive Organs (2003) was used for morphological diagnosis, since that classification was adopted in the Russian Federation at the time of the study. For immunohistochemical studies, paraffin blocks of 15 pregnant women with BOTs and 10 pregnant women with malignant ovarian tumors were selected. Analysis of the angiogenesis was performed using antibodies to the vascular endothelial growth factor, VEGF, the major signal transducer for angiogenesis (VENTANA; USA), and antibodies to CD31 endothelial marker, the type 1 platelet endothelial

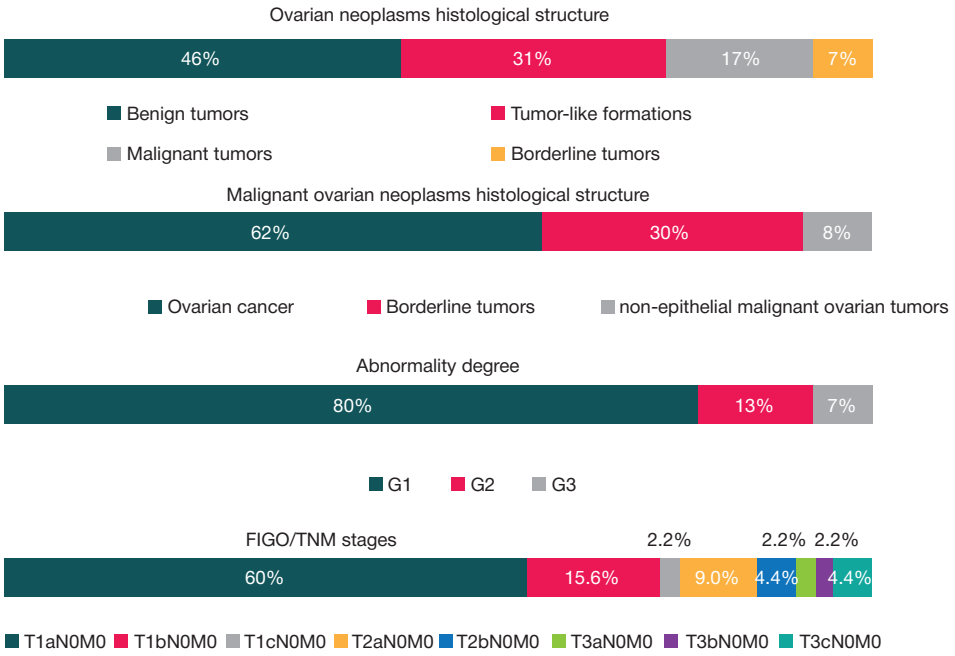

Fig. 1. Ovarian tumors/tumor-like formations distribution in accordance with the histological structure, stage (BOTs/ malignant ovarian tumors) and abnormality degree (ovarian cancer)

cell adhesion molecule (JC70 clone; VENTANA, USA). When evaluating the expression of CD31 under the microscope with small magnification, first, the areas with the largest number of microvessels were selected. Subsequently, in two separate fields of view with the increased microvasculature density, the number of all positive microvessels was calculated (200-fold magnification). The VEGF expression level was evaluated by semi-quantitative method (comparison of staining intensity and number of positive cells) in five fields of view (400-fold magnification). When measuring the staining intensity, unstained cells were assigned score 0, cells with pale yellow staining were assigned score 1, yellow-brown stained cells were assigned score 2, and brown stained cells were assigned score 3. The number of positively stained cells varied: score 0 corresponded to less than 10% of all cells, score 1 corresponded to 10–49% of stained cells, score 2 corresponded to 50–74% of stained cells, score 3 corresponded to over than 75% of stained cells. The results of both counts were added, the score over 2 was considered positive.

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

Statistical analysis was carried out using the SPSS 15.0 software package (IBM; USA). Data were analyzed by the frequency method using the crosstabs. The differences were considered significant when $p < 0.05$.

RESULTS

The study demonstrated that the examined pregnant women's clinical characteristics did not vary significantly between the groups. Thus, the age of 76 pregnant women with BOTs and malignant ovarian tumors varied in a wide range, from 18 to 45 years. More than 60% of patients were aged 30. Pain in the lower abdomen and impaired function of neighboring organs (9% of cases), increase in abdomen size (10.9% of cases) were registered, and the history of menstruation irregularities (10.9% of cases) and infertility (2.7% of cases) was revealed in pregnant women with BOTs/malignant ovarian tumors. The structure of concomitant extragenital, gynecological pathologies and previous gynecological operations before pregnancy in patients with tumor-like formations/ovarian tumors correlated mainly with age and did not depend on the tumors' morphology.

Among the BOTs histological types the serous types prevailed (22 (88%) patients). Mucinous tumors were detected in 3 (12%) pregnant women. The 28% of patients had bilateral ovarian lesions. In most pregnant patients stage I BOTs were diagnosed (19 (76%) patients). Stage II was revealed in 5 (20%) patients, and stage III was verified only in one patient.

Ultrasonic signs in pregnant women with BOTs matched several morphological types: in 32.6% of patients, mixed tumors with the predominant solid pattern were diagnosed. About 55% of patients had tumors with the predominant cystic component, over 10% of patients had solid tumors. Doppler sonography revealed central and peripheral hypervascularization with low RI values (less than or equal to 0.4) and high values of peak systolic blood flow velocity (over 15 cm/s) obtained during the curve of the blood flow velocity analysis, as well as the mosaic vessels indicating the presence of arteriovenous shunting in the tumor vasculature.

The use of the proposed model for the differential diagnosis of ovarian tumors in pregnant women made it possible to distinguish between tumor-like formations, benign ovarian tumors, BOTs and malignant ovarian tumors (sensitivity was 100%, specificity 92.3%, with an overall accuracy of the model 92.8%). Due to the similarity of images and hemodynamic indicators during the ultrasound scan, it was impossible to distinguish BOTs from malignant ovarian tumors. At the same time, in all patients with neoplasms of the described type, blood vessels were located in the center with a branched network in the septa, solid component, and papillary components. The low-resistance blood flow was revealed.

In pregnant women with BOTs, the CA-125 concentration varied in the range from 24.4 to 361 U/ml in the I trimester, and from 24.1 to 223 U/ml in the II trimester of pregnancy. The level of sFas was 40–200 ng/ml in the I trimester, and 46–180 in the

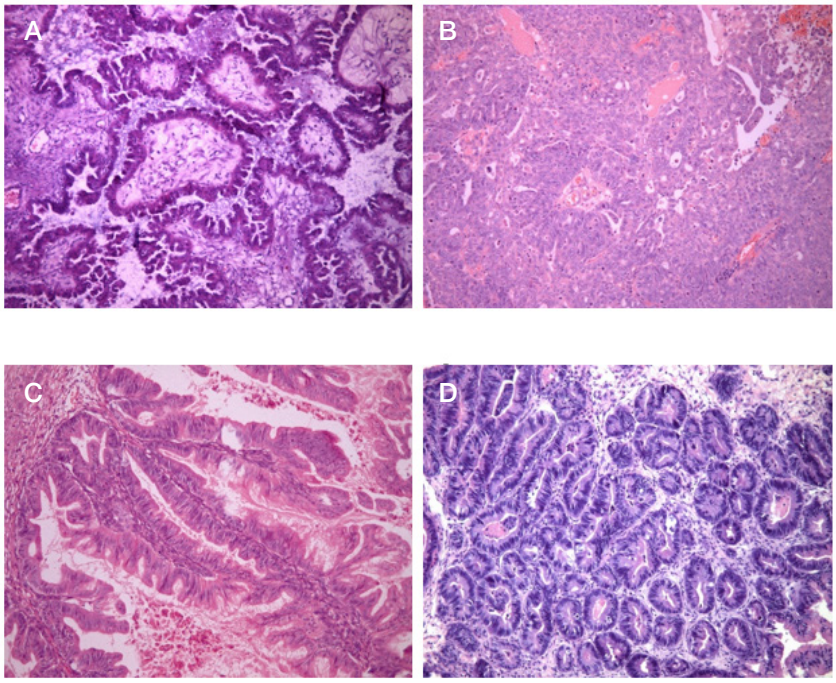

Fig. 2. Morphology of BOTs and malignant ovarian tumors in pregnant women. **A**. Borderline serous ovarian cystadenoma (×10, hematoxylin and eosin staining). **B**. Poorly differentiated serous ovarian carcinoma (×10, hematoxylin and eosin staining). **C**. Borderline mucinous ovarian cystadenoma (×10, hematoxylin and eosin staining). **D**. Mucinous ovarian carcinoma (×10, hematoxylin and eosin staining).

II trimester. The VEGF concentration varied in the range from 89 to 286 pg/ml in the I trimester, and from 92 to 480 pg/ml in the II trimester of pregnancy. IL6 reached 3.6–12 in the I trimester and 8–40.9 pg/ml in the II trimester.

In patients with malignant ovarian tumors (compared to patients with BOTs) the significant increase of CA-125 and other tumor markers (sFas, VEGF, IL6) levels in blood serum was observed at any time during pregnancy. In the blood of 3 patients with adenocarcinoma of the ovary the CA-125 level was 540–1224.6 U/ml, the sFas level was 180–312.6 ng/ml, the VEGF level was 510–1028 pg/ml, and the IL6 level was 9.8–40.9 pg/ml. The same concentration of molecular factors was observed in the blood of patients with dysgerminoma, mixed germ cell tumor and immature teratoma. In these patients, the CA-125 level exceeded 361 U/ml, the sFas level was above 240 ng/ml, the VEGF level above 490 pg/ml, and the IL6 level above 8.1 pg/ml.

When studying the BOTs morphology (Fig. 2), the features making it possible to distinguish BOTs from benign and malignant ovarian tumors were detected in 22 cases. In 3 cases, the inconsistencies were found in the final histological response of patients diagnosed with serous adenocarcinoma against the background serous borderline tumor. During the second preparations review no elements of the malignant tumor were found.

The borderline serous cystadenoma was a cystic tumor with discohesive wall and the pronounced papillary features which filled the entire inner surface and in 70% of cases were present on the outer surface. BOTs were characterized by the presence of epithelial features with the formation of cell bundles and separation of cells groups simultaneously with strictly ordered branching, in which small papilla came from large, centrally located papillae. Cells of the borderline serous tumors had some features of epithelial and mesothelial differentiation. Ciliated cells similar to cells of the fallopian tube were detected in one third of tumors. Cells with abundant eosinophilic cytoplasm and rounded nuclei resembled mesothelium, they were located on the tops of papilla. Cell nuclei were located basally, oval or round, with -slight atypia, delicate chromatin, and sometimes with pronounced nucleoli. Rare mitoses were detected (usually 4–10 in the fields of view). Psammoma (sand) bodies were revealed in a half of preparations.

Serous carcinomas reached large sizes (up to 20 cm in diameter), they consisted of cysts with serous or sanious contents, filled with soft loose papillary features. The outer surface was smooth with some papillary structures on it. The solid tumors usually had less pronounced pink gray papilla, they were soft or dense depending on the underlying stroma type. At the same time the foci of hemorrhage and necrosis were observed. Under the microscope the serous carcinomas had a papillary structure with solid foci, large round cells with polymorphic hyperchromatic nuclei, clumpy nuclear chromatin pattern and increased nuclear-cytoplasmic ratio, pseudostratified epithelium. Those were characterized by the loss of polarity, no cilia on the cell surface, increased mitotic activity.

The borderline mucinous cystadenoma of the ovary was usually multilocular with a diameter up to 30 cm, it contained the straw-colored liquid or mucus. Morphological examination of the described tumors' preparations revealed areas lined with the multi-layered mucinous epithelium of the intestinal type with the villous glandular and papillary features and- slight atypia of cell nuclei.

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

CD31 expression (Fig. 3–4) was detected in the tumor stroma in all patients. The average number of CD31-positive vessels in women with BOTs was 36 (12–48), and in women with malignant ovarian tumors it was 44 (19–56). The evaluated by the semi-quantitative method immunoreactivity for VEGF was scored 5 (4–6) in women with BOTs, and 6 (5–7) in women with malignant ovarian tumors. No significant differences in both markers' expression levels were revealed.

The medical history analysis of pregnant women with BOTs and malignant ovarian tumors showed that those of them who had disseminated tumors underwent the cytoreductive surgery with abortion. The other patients underwent the cytoreductive surgery twice: upon the detection of a tumor and after the cesarean section.

All patients demonstrating signs of ovarian tumor malignization got the midline laparotomy with the curve around the umbilicus on the left. In six patients, diagnostic laparoscopy was performed first, and after that laparotomy and primary lesion removal (due to the suspected ovarian cancer).

The volume of the surgical procedure was determined intraoperatively in accordance with the clinical picture, reproductive history, age, ultrasonography, serum tumor marker levels and express histopathological examination results. During the intervention, surgical tumor staging was performed, as well as the abdomen and pelvic organs revision, greater omentum resection/removal, multiple peritoneal biopsies, taking swabs or ascitic fluid from the abdominal cavity. In patients with mucinous tumors, an appendectomy was carried out. The patients not interested in pregnancy maintenance and fertility underwent the radical surgery (7 patients of 76). At the first stage during pregnancy, 20 patients with BOTs underwent the organ sparing intervention preserving uterus and the healthy ovary fragment. In two patients, the bilateral adnexectomy was performed. In one of them, the borderline tumor was found during the histopathological examination of the resected part of the visually unchanged contralateral ovary (stage IB).

It should be noted that during the histopathological examination of biopsy material or tumor preparations, errors and inaccuracies may occur. Thus, during our study, in three pregnant women with ovarian tumors, morphological examination revealed tissue features characteristic of both BOT and malignant ovarian tumors. The patients were diagnosed with well-differentiated adenocarcinoma of both ovaries against the background of the borderline serous cystadenoma. In one of those patients, bilateral ovarian tumors with signs of malignization and ascites were clinically defined during the weeks 11–12 of pregnancy. In the oncology hospital the

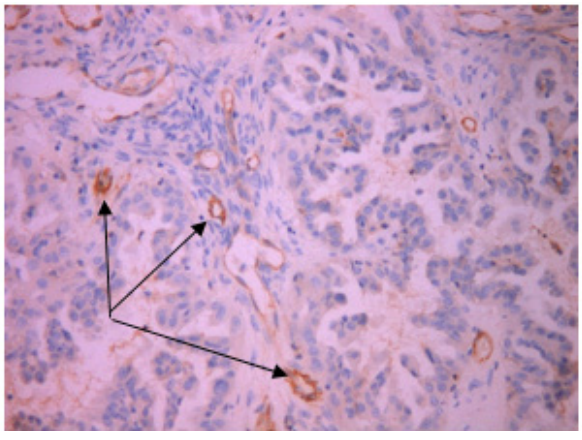

Fig. 3. CD31 expression in the malignant ovarian tumor (×20). Vessels are marked with arrows

diagnostic laparoscopy (right-sided adnexectomy with express histological examination) was performed, and the borderline cystadenoma was diagnosed. The laparoscopic entry was changed to laparotomy. A midline laparotomy was used for the left ovary biopsy, greater omentum resection and multiple peritoneal biopsies. The differentiated adenocarcinoma developed against the background of a serous borderline tumor with cancer emboli in the lumen of the greater omentum vessels was diagnosed by the morphological examination (ovarian cancer T3cN0M0). Artificial abortion and radical surgery were performed (hysterectomy with left adnexectomy and the subtotal greater omentum resection). The abdominal cavity swabs' cytological studies revealed the adenogenic cancer signs. Prior to the chemotherapy appointment, the interdisciplinary oncological consultation was held due to discrepancy in the cytological and histological studies results interpretation by different specialists. The initial diagnosis was not confirmed. The patient was diagnosed with the borderline tumor of the ovary with noninvasive implants in the greater omentum. It was decided not to use chemotherapy. The patient observed for four years demonstrates no signs of the disease progression.

The results of the patients with borderline tumors treatment were as follows: 3 pregnant women underwent abortion and surgery (panhysterectomy due to the presence of adenocarcinoma together with the serous BOT), 2 women had spontaneous abortion, 10 patients delivered on their own on time, 6 women delivered prematurely by cesarean section due to obstetric indications, in 4 patients the repeated surgery was carried out for restaging.

Later the tumor recurrence was observed in two pregnant women with BOTs. In one of them, diagnosed with serous histological type IA stage tumor in the resected ovarian tissue after the organ preservation surgery, the recurrence was detected in the 5th year of observation. The morphological examination revealed a well-differentiated adenocarcinoma, followed by a radical intervention supplemented with chemotherapy. In the 2nd patient, 2 years after the first surgery the recurrence was detected, and the tumor in its histological pattern was similar to the primary tumor (atypical proliferative serous tumor). After the recurrent neoplasm removal, the patient received combined therapy. Both patients remained alive for more than 3 years. Five patients dropped out of the observation. We tracked the long-term effect of treatment in 17 of 25 patients for 3–10 years. All patients were alive at the time of the study. The overall 5-year survival rate was 100%.

In patients with BOTs, 2–5 years after surgery 9 pregnancies occurred, the four of which ended in delivery with a favorable outcome. In three patients, pregnancy ended in spontaneous abortion.

DISCUSSION

Literature data indicate no specific clinical manifestations of BOTs during pregnancy. Doppler ultrasonography used in the model for differential diagnosis has high specificity.

Currently, no molecular factors have been identified that reliably characterize BOTs [2, 15]. The use of most tumor markers is limited due to the high variability of their values, including those depending on the gestational age. In our study, the significant increase of the carcinogenesis markers levels over the threshold (VEGF level exceeded 500 pg/ml, IL6 level was above 8.1 pg/ml) was detected in pregnant women with malignant neoplasms of the ovary. The test specificity was 91.5%, and the sensitivity was 75%. The CA-125 concentration in pregnant women with malignant ovarian tumors exceeded 300 U/ml. Our results were consistent with the other authors' data [16].

When evaluating the VEGF expression level in the paraffin blocks by the semi-quantitative method, the increased immunoreactivity for the marker (score 5–7) was detected in ovarian carcinomas. The VEGF expression association with ovarian cancer has been confirmed by many studies. An increase in VEGF immunoreactivity in ovarian carcinoma (compared to BOT) has been proven, while a high VEGF expression level indicates the disease progression [17]. Increased immunoreactivity of CD31 in the malignant ovarian tumors preparations compared to BOT preparations indicates increased blood flow in the tumor tissues due to neovascularization detected in malignant tumors [18].

The main method of the BOTs treatment is surgery (organ preservation or radical approach). Researchers of the world are actively discussing the possibility of ultra-conservative interventions as an organ preservation option leaving the affected with BOT ovarian tissue unchanged after the resection/cystectomy [2, 19]. Adnexectomy on the lesion side with a morphological study of peritoneal swabs and multiple biopsies is considered the optimal intervention volume. The final surgical staging should be performed during cesarean section or after delivery (in case of vaginal birth) [20, 21]. We did not use the ultraconservative interventions in our study, 80% of patients with BOTs underwent organ preservation surgery. The restaging surgery was performed in 16% of patients.

Approximately one-third of the patients with BOTs and well-differentiated adenocarcinoma need a final postoperative morphological study using paraffin blocks [2, 22–24]. According to some reports, the high overdiagnosis rate in patients with BOTs having the suspicious for ovarian cancer foci leads to an unreasonable overestimation of the surgical interventions volume, even when performing the final histopathological examination in the specialized institutions [3]. According to our results, the morphological response interpretation discrepancies in the differential diagnosis of BOTs and ovarian cancer have been detected in 12% of patients. The diverse BOTs structure and the need for a thorough study of multiple slices are the reason for the strict requirements for the morphologist's qualification and experience. The other researchers hold a similar opinion [3, 9, 22].

The overall recurrence rate in patients with BOTs varies from 3 to 10%, and the recurrence occurs in 25% of patients with common tumor stages. Our study has revealed recurrence in 8% of patients. According to the literature data, the 5-year survival rate of patients with I–II stage tumors is 98–99%, and

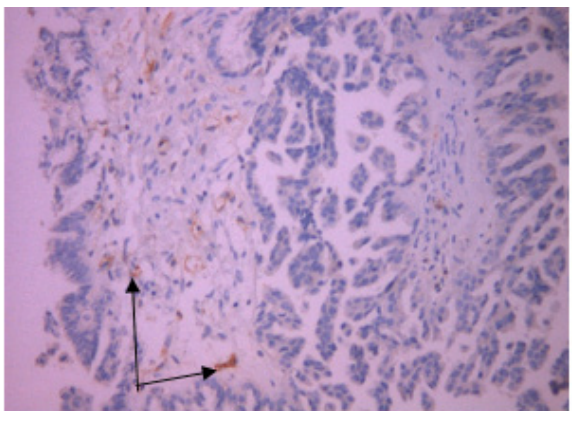

Fig. 4. CD31 expression in the borderline ovarian tumor (×20). Vessels are marked with arrows

in patients with III–IV tumors it is 82–90% [25, 26]. Possibly, the high the 5-year survival rate values are associated with the BOTs early stages detection and with the small sample size.

The papers on the study of fertility after the organ preservation treatment report that spontaneous pregnancies occur in 40–72% of patients. The effect of pregnancy on the course of the disease remains unknown [1, 2, 27, 28]. It is worth mentioning, that the reproductive results obtained during our study were pregnancies detected in more than 35% of patients with BOTs diagnosed in pregnancy after the organ preservation surgical interventions. The results obtained made it possible to highlight the following important signs complex in the diagnostic algorithm for pregnant women with suspected malignization of the ovarian tumors: mixed echographic structure with hypervascular supply pattern and low RI values, VEGF value exceeding 500 pg/ml and IL6 value over 8.1 pg/ml, CA-125 concentration exceeding 300 U/ml. However, the similarity of BOTs and malignant ovarian tumors ultrasonic signs did not allow us to distinguish between these types of neoplasms accurately. The diagnosis of BOT is confirmed during the final postoperative morphological examination. The results of the express ovarian tissue histological analysis in frozen sections not always provide true information on the ovarian tumors nature in pregnant women. High 5-year survival rate after the BOTs organ preservation surgical treatment carried out during pregnancy indicates the possibility to use the gentle approach in the treatment of the tumor's early stages.

CONCLUSION

Despite significant scientific and practical interest to BOTs, many problems related to improving the diagnosis and to the treatment of patients in pregnancy have not been resolved. The predominance of the tumor early stages, relatively mild course and favorable prognosis in patients with BOTs make it possible to use the gentle surgical treatment preserving menstrual function and fertility.

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