

Malignant Ovarian Tumors During Pregnancy: A Multicenter Retrospective Analysis

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Purpose: The aim of this study was to investigate the clinical characteristics and management of malignant ovarian tumors during pregnancy, as well as the feto-maternal outcomes and analyze the influential factors on the pregnancy outcomes.

Patients and Methods: Eighty-five patients with ovarian malignancies during pregnancy treated at 12 tertiary hospitals between 2009 and 2019 were analyzed in this study. The clinical features, histopathological characteristics, clinical management, and maternal and perinatal outcomes were retrospectively analyzed. The clinical features and managements were compared between abortion group and live birth group.

Results: The following diagnoses were made: 41 (48.24%) patients with borderline ovarian tumors, 18 (21.18%) patients with epithelial ovarian cancers, 17 (20.00%) patients with non-epithelial ovarian malignancies and 9 (10.59%) patients with metastatic ovarian tumors. Thirty-six (42.45%) patients underwent conservative surgical treatment. Thirty-four (40.00%) patients opted for fertility-sparing surgery, and fifteen (17.56%) patients received radical surgery. Chemotherapy was administered to 32.94% of the patients. The proportion of ovarian malignancies diagnosed in the first trimester in the abortion group was higher than that in the live birth group ($P < 0.05$). However, tumor diameter, reproductive history, stage and surgical indications showed no significant differences between groups. A total of 67 live babies were recorded in this study, including 19 premature babies and 1 full-term newborn who died of respiratory distress. All of the BOTs were diagnosed with stage I, among whom 38 (92.68%) patients exhibited disease-free survival. Twenty-eight ovarian cancers were in stage I–II and 26 of them had disease-free survival with the longest follow-up time of 10 years. Five of the sixteen patients in advanced stage (stage III–IV) died, four of whom had metastatic tumors.

Conclusion: Pregnant women with early-stage malignant ovarian tumors appear to have favorable outcomes. Conservative surgery is acceptable for early-stage borderline ovarian tumors during pregnancy. The gestational age of ovarian malignancy detection is key for pregnancy outcomes.

Keywords: malignant ovarian tumor, pregnancy, management, prognosis

Introduction

Malignant ovarian tumors are the second most frequent gynecological cancer diagnosed during pregnancy after cervical carcinoma. According to previous studies, the incidence of ovarian cancer is 0.02 to 0.38 per 10,000 pregnancies, and that of ovarian masses with low malignancy potential is 0.11 to 0.24 per 10,000 pregnancies.^{1,2} Although the incidence of gestational ovarian malignancy is low, it poses challenges in maternal and perinatal management.

When a malignant tumor is suspected, surgery treatment is indispensable and can be performed safely during pregnancy. According to the latest guidelines for

gynecologic cancers in pregnancy,³ surgery staging should be performed for early-stage malignant disease (low malignant potential, invasive or germ cell). The current recommendations state that if surgical procedures are restricted during pregnancy because of an enlarged uterus and the limited possibility for manipulation, restaging should be planned postpartum. However, the adverse effects of a second surgery, such as new anesthesia and operative complications, must be considered. In previous studies, fetomaternal outcomes have been highly contingent on tumor stage at diagnosis and histological type.^{4–6} Herein, we evaluated the effects of surgery without staging on recurrence in pregnant women with malignant ovarian tumors, and compared the factors associated with different pregnancy outcomes through a multicenter review study. Our aim was to improve the knowledge of ovarian malignancies during pregnancy.

Patients and Methods

Study Population and Data Collection

This was a multicenter retrospective review of patients with malignant ovarian tumors during pregnancy who were diagnosed and treated at 12 independent hospitals between 2009 and 2019. A total of 91 patients with malignant ovarian tumors were treated during the 10 years period. The study was approved by each of the universities or hospitals involved. To better evaluate the therapeutic effects, we excluded six pregnant women with fetomaternal prognosis who were lost to follow-up after the initial treatment from further analysis. The collected data for the remaining 85 patients included the following: clinical and histopathological characteristics, stage (FIGO/2013), timing of diagnosis and surgery, indication of surgery, chemotherapy applied and fetomaternal outcomes. The clinical features and managements were compared between abortion group and live birth group. Adnexal masses were detected in routine pre-pregnancy or prenatal examination by ultrasound scans or MRI (magnetic resonance imaging). All patients underwent surgical resection for ovarian tumors. The pathological diagnoses were made by specialists from the department of pathology at each hospital. Patient treatment and follow-up were performed at the department of obstetrics and gynecology in each hospital. According to a previous study,⁷ conservative surgery was defined as cystectomy or unilateral salpingo-oophorectomy with no complementary surgical treatment.

Fertility-sparing surgery was defined as at least one ovary being preserved with comprehensive staging (omentectomy, appendectomy, pelvic-peritoneal biopsies and/or lymphadenectomy). Radical surgery was defined as cytoreductive operation with hysterectomy.

Statistical Analysis

Quantitative data are shown as mean \pm SD, and qualitative data are expressed as numbers (percentages). Independent samples *t*-tests were used to compare the quantitative data. The chi-square test and Fisher's exact test were used to examine the differences in clinical features between the abortion group and live birth group. A *P* value <0.05 was considered statistically significant. SPSS software 17.0 (IBM Corporation, Armonk, NY, USA) was used for data analysis.

Results

Clinical Features

A total of 1,069,041 deliveries were recorded between 2009 and 2019, of which 91 were diagnosed with malignant tumors. The proportion of pregnant patients with malignant ovarian tumors in the 12 hospitals was 0.85 per 10,000 deliveries, ranging from 0.44 to 1.71 per 10,000 pregnancies. The clinical characteristics of the 85 patients are summarized in Table 1. The median age of the patients was 31.08 ± 5.25 years, with a range from 19 to 43 years, and there were 35 (41.18%) nulliparous patients. Four patients had a history of borderline ovarian tumors, one had a familial breast cancer history, and the remaining 80 (94.12%) had no previous history of cancer. Seventy-two (84.70%) tumors were unilateral, and 13 (15.29%) were bilateral. Patients mainly presented with tumors larger than 6 cm in diameter (82.35%; $N=70$). Tumors were diagnosed in the first, second, and third trimesters in 24, 21 and 35 patients, respectively. Adnexal masses were identified before pregnancy in five patients and were pathologically confirmed after surgery during pregnancy. Most patients were asymptomatic (88.24%; $N=75$), and ten patients had abdominal pain. Eighty-four patients underwent surgery during pregnancy: 13 (15.29%) during the first trimester, 29 (34.12%) underwent surgery during the second trimester, and 42 (49.41%) underwent surgery during the third trimester. One patient received surgical treatment in the postpartum period. Sixty (70.59%) women underwent cesarean section, 7 (8.24%) women delivered vaginally, and 18 (21.18%) women opted for elective abortion. A total of 67 (78.82%) live birth infants were

Table 1 Patient Characteristics and Obstetric Outcomes

Clinical Characteristics	No. of Patients (%)
Age (years)	
<35	65 (76.47)
≥35	20 (23.53)
Parity (n)	
0	35 (41.18)
≥1	50 (58.82)
Location	
UO	72 (84.70)
BO	13 (15.29)
Tumor diameter (cm)	
<6	15 (17.65)
≥6	70 (82.35)
GA of detection	
Pre-pregnancy	5 (5.88)
1st trimester	24 (28.24)
2nd trimester	21 (24.71)
3rd trimester	35 (41.18)
Symptoms	
Abdominal pain	10 (11.76)
Asymptomatic	75 (88.24)
GA of Surgery	
1st trimester	13 (15.29)
2nd trimester	29 (34.12)
3rd trimester	42 (49.41)
Postpartum	1 (1.18)
Delivery mode	
Elective abortion	18 (21.18)
Transvaginal	7 (8.24)
CS	60 (70.59)
Pregnancy outcome	
Miscarriage	18 (21.18)
Pre-term	19 (22.35)
Full-term	48 (56.47)

Abbreviations: UO, unilateral ovarian; BO, bilateral ovaries; CS, cesarean section.

delivered, including 48 (56.47%) full-term neonates (one newborn died of respiratory distress) and 19 (22.35%) premature (one with chromosome abnormality).

Tumor Histopathological Characteristics, Treatments and Feto-Maternal Outcomes

The distribution by histological type of borderline ovarian tumors and ovarian cancers are shown in [Table 2](#). A total of 59 patients (69.41%) had epithelial ovarian tumors, including 41 (48.24%) borderline ovarian tumors (BOTs) and 18 (21.17%)

Table 2 Histological Subtypes Analysis of Ovarian Malignant Tumors

Histological Subtype	No. of Patients (%)
BOT (n=41)	
Serous	23 (56.10)
Mucinous	14 (34.15)
Endometrioid	2 (4.88)
Seromucinous	1 (2.44)
Other ^a	1 (2.44)
EOC (n=18)	
Serous	6 (33.33)
Mucinous	7 (38.89)
Primary peritoneal cancer	2 (11.11)
Clear cell	2 (11.11)
Brenner	1 (5.56)
MOGCT (n=14)	
Immature teratoma	7 (50.00)
Dysgerminoma	6 (42.86)
Strumal carcinoid	1 (7.14)
MSCT (n=2)	
Sertoli-Leydig tumor	1 (50.00)
Granulosa cell tumor	1 (50.00)
SCLC (n=1)	
Small cell carcinoma (hypercalcaemic type)	1 (100.00)
Metastatic carcinoma (n=9)	
Krukenberg tumor	7 (77.78)
Cervix mixed adenocarcinoma	1 (11.11)
B-cell lymphoma	1 (11.11)

Note: ^aThe patient was diagnosed with bilateral ovarian tumors, including serous borderline ovarian tumor (SBOT) on one side and mucinous borderline ovarian tumor (MBOT) on the other side.

Abbreviations: BOT, borderline ovarian tumor; EOC, epithelial ovarian cancer; MOGCT, malignant ovarian germ cell tumors; MSCT, malignant sex cord-stromal tumors; SCLC, small cell carcinoma.

epithelial ovarian cancers (EOCs). Other histopathological types were germ cell tumors (16.47%; N=14), sex cord-stromal tumors (2.35%; N=2), metastatic ovarian tumors (10.59%; N=9) and small cell carcinoma (1.18%; N=1).

[Table 3](#) shows the patient distribution by stage, surgery, chemotherapy and feto-maternal outcomes. In this study, 67 cases (78.82%) were in stage I (FIGO 2013), including 41 BOTs and 26 ovarian cancers, 2 cases (2.35%) were in stage II (epithelial ovarian tumors), 7 cases (8.23%) were in stage III (6 epithelial ovarian cancer, 1 small cell carcinoma), and 9 metastatic ovarian tumors (10.59%) were in stage IV (7 Krukenberg tumors, 1 metastatic B-cell lymphoma tumor and 1 metastatic cervical tumor).

All patients underwent surgical treatment: 36 patients (42.35%) underwent conservative surgery without staging,

Table 3 Patients' Demography by Histological Type, Stage, Surgery, Chemotherapy, Maternal and Perinatal Outcome

	BOT (n=41)	EOC (n=18)	MOGCT (n=14)	MSCT (n=2)	SCLC (n=1)	Metastatic Carcinoma (n=9)	Total (%)
FIGO stage							
I	41	10	14	2	–	–	67 (78.82)
II	–	2	–	–	–	–	2 (2.35)
III	–	6	–	–	1	–	7 (8.23)
IV	–	–	–	–	–	9	9 (10.59)
Surgery							
Conservative surgery ^a	26	4	3	1	–	2	36 (42.35)
Fertility-sparing surgery	13	6	9	1	–	5	34 (40.00)
Radical surgery	2	8	2	–	1	2	15 (17.65)
Chemotherapy							
Yes	1	13	9	–	–	5	28 (32.94)
No	40	4	5	2	–	–	51 (60.00)
Missing	–	1	–	–	1	4	6 (7.06)
Pregnancy outcome							
Abortion	8	1	5	–	1	3	18 (21.18)
Live birth	33	17	9	2	–	6	67 (78.82)
Maternal outcome							
DFS	38	14	12	2	–	–	66 (77.65)
Recurrence	2	1	1	–	–	1	5 (5.88)
DOD	–	1	–	–	–	4	5 (5.88)
Missing	1	2	1	–	1	4	9 (10.59)

Note: ^acystectomy or unilateral salpingo-oophorectomy merely without staging.

Abbreviations: BOT, borderline ovarian tumor; EOC, epithelial ovarian cancer; MOGCT, malignant ovarian germ cell tumors; MSCT, malignant sex cord-stromal tumors; SCLC, small cell carcinoma; DOD, death of disease; DFS, disease-free survival.

including 26 patients with BOTs; 34 patients (40.00%) underwent fertility-sparing surgery with standard staging; and the other 15 patients (17.65%) were treated with radical surgery with complete staging. Most of the BOTs did not receive adjuvant chemotherapy, except for one case with pathological type as serous BOTs with invasive implants in stage Ic. Twenty-seven (61.36%; 27/44) patients with ovarian cancers received systematic chemotherapy after the initial surgery, three of whom received neoadjuvant chemotherapy during their pregnancies.

Eighteen (21.18%) pregnant women terminated their pregnancies to prioritize the treatment of the ovarian tumor, whereas 67 (78.82%) patients delivered live births. The birth weights ranged from 1295 g to 4180 g, and two neonates were classified as SGA. The median follow-up period was 28 months (ranging from 3 to 126 months). Information on maternal prognosis was available for 76 patients. At the time of review, five patients with stage III–IV cancer died (four metastatic ovarian tumors and one poorly differentiated adenocarcinoma in stage III). Tumor recurrence occurred in five patients (with 2 BOTs and 1 germ cell tumor, 1 adenocarcinoma in

stage IIIc and 1 metastatic ovarian tumor). Thirty-eight (92.68%, 38/41) BOTs had complete remission. Twenty-eight (63.64%, 28/44) ovarian cancers had disease-free survival (26 ovarian cancers with stage I–II) with the longest follow-up of 10 years. Nine patients with maternal outcomes were lost to follow-up. The global survival rate was 83.53% (71/85).

Comparison of Clinical Characteristics Among Pregnancy Outcomes

The patients were divided into abortion group (N=18) and live birth group (N=67) according to pregnancy outcomes. The clinical features between groups are compared in Table 4. Thirty-five patients with tumors diagnosed during the third trimester (≥ 28 weeks) of pregnancy delivered live births. In the abortion group, the proportion of ovarian malignancies diagnosed in pre-pregnancy, and in the first and the second trimesters were 0 (0/18), 72.22% (13/18) and 27.78% (5/18), respectively. In live birth group, the proportions of ovarian malignancies diagnosed at different gestational ages were 15.62% (5/32), 34.37% (11/32) and 50% (16/32), and the

Table 4 Comparison of Clinical Features Between Abortion Group and Live Birth Group

	Abortion	Live Birth	P value
Tumor diameter (cm), Mean \pm SD	13.92 \pm 6.87	12.52 \pm 7.39	>0.05
Reproductive history			>0.05
Unipara	7	34	
Multipara	11	33	
FIGO stage			>0.05
I	13	54	
> I	5	13	
Surgical indication			>0.05
Emergency	3	7	
Select	15	60	
GA of detection ^a			0.023*
Pre-pregnancy	0	5	
1st trimester	13	11	
2nd trimester	5	16	
GA of surgery			0.000*
1st trimester	12	1	
2nd trimester	6	24	
3rd trimester	0	41	
Postpartum	0	1	
Surgery			>0.05
Conservative surgery	5	31	
Fertility-sparing surgery	10	24	
Radical surgery	3	12	

Notes: ^a35 patients of tumor diagnosed during the third trimester (≥ 28 weeks) of pregnancy all delivered live births. * $P < 0.05$, refers to the comparison between abortion group and live birth group.

difference between the groups was statistically significant ($P < 0.05$). In live birth group, 65 patients underwent surgery during the second and the third trimester of pregnancy: 24 (35.82%) underwent surgery during the second trimester, and 41 (61.19%) underwent surgery during the third trimester. Whereas, in abortion group, more than half of the patients (66.67%, 12/18) underwent surgery during the first trimester. Moreover, tumor diameter, reproductive history, stage, surgical indication and operation type showed no significant differences (Table 4).

Discussion

The occurrence of adnexal masses in pregnancy is reported in 1 per 76 to 1 per 2328 deliveries, and most are benign.⁸ The recently reported incidence of ovarian cancer in pregnancy varies from 0.31 to 0.67 per 10,000 pregnancies.⁹

Diagnosis of malignant ovarian tumors during pregnancy is increasing, owing to the tendency to delay of child-bearing to later reproductive ages and the application of assisted reproductive technologies.¹⁰ We found that malignant ovarian tumors in pregnancy occurred in approximately 0.44 to 1.71 per 10,000 pregnancies, a rate is slightly higher than the incidence described previously. In the data presented here, in pregnant women, BOT was the most frequent ovarian malignancy (41 patients), followed by epithelial ovarian tumors (18 patients) and germ cell tumors (14 patients). This trend is consistent with those in other reports.^{4,8} Metastatic ovarian tumors are not commonly seen in pregnancy. Ten percent of ovarian cancers are estimated to be metastatic.¹¹ In our study, nine patients with metastatic tumors were reported, accounting for 10.59%. Most maternal ovarian malignancies are in stage I (79.12%; $N=72$) at diagnosis, as previously reported.^{2,5}

Management of ovarian masses during pregnancy is similar to that during non-pregnancy, with the consideration of maternal and fetal factors. Treatment should be individualized according to pathological type, stage, gestational age and maternal preference. Surgical treatment, a cornerstone of treatment of malignant ovarian tumors, is recommended in the second trimester of pregnancy to decrease the risks of miscarriage, torsion, rupture and delayed diagnosis of malignancy.¹² The principles of management include comprehensive surgical staging. If the pelvic peritoneum and the pouch of Douglas cannot be reliably examined during surgery, restaging surgery at cesarean section or post-delivery may be important to determine the treatment plan.^{3,13}

The most widely accepted surgical treatment of EOC in non-pregnant women is radical surgery, which includes bilateral adnexectomy and hysterectomy.¹⁴ For pregnant women with EOC who opt to preserve their pregnancies, the primary ovarian cancer treatment consists of appropriate surgical staging and debulking surgery followed by chemotherapy, timely delivery as well as neo-adjuvant chemotherapy with subsequent completing surgery.¹⁵ Previous reports have suggested that fertility-sparing surgery may be safe to stage IA/IC EOC.^{16,17} Most pregnant women with non-epithelial ovarian cancer (germ cell and sex cord-stromal tumors) are diagnosed with early-stage disease. Given the favorable prognosis of stage I tumors, fertility-sparing surgery with comprehensive staging is recommended. Another review has also stated that fertility-sparing surgery can be offered to patients with stage

I epithelial ovarian tumors, germ cell ovarian or sex-cord stromal ovarian tumors.⁶ In our study, 16 of 28 patients with ovarian cancers at stage I/II received fertility-sparing operations. Although eight patients with ovarian cancers (stage IA/IC) received conservative treatment, such treatment remains strictly limited because of frequent relapse rates.

BOTs have excellent prognosis and in most patients are treated surgically without chemotherapy. Fertility-sparing surgery is preferred in women of childbearing age with stage I cancers.⁷ A meta-analysis has suggested that restaging surgery does not significantly decrease recurrence in patients with BOTs, and it exposes the patients to new anesthetic and operative complications.¹⁸ Zapardiel et al have indicated that restaging surgery does not affect the management of BOTs, particularly those with mucinous subtype and apparent FIGO stages above I.¹⁹ However, this treatment should be offered to patients with serous subtype and micropapillary patterns. This histological subtype has a high rate of occult extraovarian disease with invasive implants.²⁰ A French multicenter study has indicated that pregnancy, compared with non-pregnancy, promotes borderline ovarian tumor progression, and complete staging surgeries are rarely performed initially. Up-front salpingo-oophorectomy should be considered, and restaging should be planned.²¹ In our study, 63.41% (26/41) of patients with BOTs underwent conservative surgery without staging; 2 of them relapsed, and 24 survived without tumors. Therefore, conservative surgery is acceptable for borderline ovarian tumors associated with pregnancy in early stage of tumor. Because of the lack of randomized controlled trials or prospective cohorts on this subject, our study has limitations, and the results should be interpreted with caution. Herein, we focused our analysis exclusively on the recurrence rates.

When necessary, adjuvant chemotherapy or neoadjuvant chemotherapy should be applied. Previous studies have indicated that chemotherapy is recommended at the 2nd or 3rd trimester of gestation and should be discontinued 3 to 4 weeks before delivery to prevent myelosuppression in the parturient and neonates.^{22,23} According to available data, chemotherapy during the first trimester poses a high risk of fetal malformation and may increase the risk of premature rupture of membranes, infants being small for their gestational ages, premature labor and NICU admission during the second or third trimesters.^{22,24–26} Moreover, the administration of chemotherapy increases maternal stress.²⁷

In a previous study, pregnant women with ovarian cancer have been found to be more likely to terminate the pregnancy, whereas those with borderline tumors or non-epithelial tumors are able to successfully deliver live newborns.⁴ In patients with advanced-stage epithelial ovarian cancer, termination of the pregnancy should be considered when the diagnosis is made in early pregnancy stages.⁶ We found that the abortion rates were significantly higher with ovarian malignancy detection in the first trimester than that in later trimesters. Further analysis showed no significant relationships among tumor size, reproductive history, stage, surgical indications and type. These data indicate that pregnancy outcomes are associated with gestational age at the time of tumor diagnosis. Patients with ovarian tumors detected in early stages of pregnancy often chose to prioritize treatment of diseases at the sacrifice of their babies, whereas those in the second trimester had higher expectations for the fetus. This result may be associated with doctors' guidance, and patients' awareness of tumors and fertility desires.

Evidence from the literature has indicated that pregnancy does not significantly affect the prognosis of ovarian tumors.^{28,29} The overall survival and recurrence-free survival rates of malignancy patients during pregnancy are similar to or better than those of non-pregnant patients.^{2,20} Mortality due to ovarian cancer has been reported to occur in 4.7% of patients with either ovarian cancer or borderline ovarian tumors, and the 5-year survival rate is 72% to 90%.² Tumor stage is the most important prognostic factor,^{5,28,30} because it may be associated with the early detection and treatment of ovarian tumors by regular antenatal examination, and most tumors are in early stages.

Our findings show overall good outcomes of pregnancies with complications of ovarian tumors. In the present cases, seven of nine metastatic tumors were Krukenberg tumors. More than half the pregnancies ended in live birth (6/9). The prognosis of Krukenberg tumors during pregnancies is overall very poor, and the reported median survival time is 6 months; however, prognosis may be improved if radical surgery is achievable.³¹ In this study, four patients with metastatic tumors died, one had recurrence, and five were not followed up, thus suggesting that the actual mortality rate might have been higher. Prematurity is a significant newborn risk factor in women with malignant ovarian tumors. Other associated risks are intrauterine growth restriction, preterm rupture of membranes and intrauterine death.^{1,15} In our study, there

were 19 (22.35%) premature and 2 low birth weight infants, in agreement with previous findings.

Conclusion

The diagnosis of ovarian malignancy is extremely low during pregnancy, and most patients are in stage I. The overall fetomaternal prognosis for early stages of tumor is favorable. Patients with ovarian tumors detected in early stages of pregnancy chose to prioritize cancer treatment and to sacrifice their babies, thus indicating that the gestational age at ovarian malignancy diagnosis is a high-risk factor for pregnancy outcomes. Conservative surgery is acceptable for early-stage borderline ovarian tumors during pregnancy with a low recurrence rate, whereas staging surgery is recommended for other ovarian cancers in any stages. Our data reveal several clinical features that might be beneficial in future studies on malignant ovarian tumors in pregnant women.

Ethical Statement

This study was approved by the Ethics Committee of International Peace Maternity and Child Health Hospital in Shanghai and conducted in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The ethical approval covered all the researches which were conducted in the 12 hospitals. Owing to the retrospective study design and analysis of clinical data, written informed consent was formally waived by the Ethics Committee of International Peace Maternity and Child Health Hospital. All clinical data were anonymously analyzed.

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the

version to be published; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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