Pregnant Women With Malignant Ovarian Tumors: A Case Series

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Abstract- Ovarian cancer management during pregnancy is a topic of limited research due to low occurrence rates of malignant adnexal tumors. To shed further light on this issue, we present a case series of 22 pregnant ovarian cancer patients referred to an academic hospital's gynecology oncology department over six years. Data on each patient's demographic and clinical background were collected using a registry software recording surgical tumor staging, disease-free survival (DFS), and overall survival (OS). According to the data analysis reports, subtype epithelial tumor and germ cell pathology were equally 45.4%. However, sex-cord tumors were observed in a smaller percentage of cases (9.1%). Serous adenocarcinoma was the most common subtype among those with epithelial tumors (60%). Meanwhile, 72.7% of these pregnant women had a palpable mass in physical examination. In addition, adnexal mass was detected in 95.4% of ultrasonography. Due to the young age of the patients, fertility-preserving surgery was performed on 63.6% of patients, and chemotherapy was prescripted on 59% of patients. Over a six-year follow-up period, there was a recurrence rate of 22.7%, while DFS and OS were reported as 56% and 82%, respectively. In conclusion, treatment of ovarian malignancies during pregnancy requires an experienced multidisciplinary approach. However, more extensive studies with larger samples are needed to gain more insight into the treatment of ovarian cancer during pregnancy.

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Introduction

Ovarian cancer is the fifth most common cancer in women and the second most common gynecologic cancer in pregnancy. Malignancy during pregnancy has become a significant cause of maternal death in the world. Considering the increase in maternal age and the rising incidence of ovarian cancer in younger women, we need to carefully identify clinical aspects of ovarian malignancy during pregnancy (1).

Adnexal masses are usually found incidentally during routine fetal screening ultrasounds in one in 19-88 pregnancies. Most of these masses are pregnancy-related and resolve spontaneously within the first 16 weeks of pregnancy (2). In general, 2.15-13.5% of adnexal masses in pregnancy are malignant. The most common symptoms are abdominal or lower back pain, discomfort, constipation, abdominal swelling, and urinary symptoms. Acute abdominal pain seldom occurs in these patients. However, these symptoms are often encountered in normal pregnancies and do not trigger a diagnostic evaluation. Complications of concern for ovarian tumors in pregnancy include torsion, rupture, or blockage of the delivery canal (3,4).

Proper management of ovarian cancer in pregnancy requires a multidisciplinary approach while keeping feto-maternal risks in mind. The second trimester is suggested as the best time for surgery to reduce the occurrence of miscarriage, torsion, or rupture (5). Chemotherapy in the first trimester is associated with a higher risk of

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congenital malformations and miscarriage; therefore, it is best administered during the second or third trimester (6). These results suggest that further studies are required to help gynecologists gain more confidence in managing their patients and offer treatments that would benefit both the fetus and the mother.

Despite the growing prevalence of ovarian cancers during pregnancy, comparative studies and high-quality clinical trials are lacking to provide insights into this field. Most of our current understanding and treatment decisions are based on case reports, case series, and expert opinions. This study aimed to describe a case series of patients diagnosed with and treated for ovarian cancer during pregnancy and to report their clinical characteristics and treatment outcomes.

Materials and Methods

The present case series describes 22 pregnant patients with ovarian cancer who, from January 2011 to December 2016, were referred to the gynecology-oncology department of an academic hospital affiliated with Mashhad University of Medical Sciences.

The following demographic and clinical data were retrospectively collected: age, symptoms, serum level of available tumor markers, surgical treatment, pathological findings, stage, and grade of the tumor. Moreover, the chemotherapy regimen, disease-free survival (DFS), and overall survival (OS) were determined.

All patients underwent surgical staging through open surgery of ovarian cancer by a group of experienced gynecologist oncologists. Most of the patients were operated on between the 14^{th} and 16^{th} week of gestation. An expert gynecologic pathologist assessed the histopathological findings of all samples. Based on the stage of the tumor and pathologic findings, the plan for preserving or terminating the pregnancy and the time of delivery were determined by the gynecologists.

Chemotherapy was performed under the supervision of a group of expert radiotherapist oncologists. The need for chemotherapy and the proper regimen was determined in each patient based on several parameters including pathological findings, staging, and grading of the tumor.

All data were analyzed using SPSS software (version 23 for Windows, IBM Statistics, Chicago, IL) and appropriate statistical tests. Univariate survival analysis using the Kaplan-Meier method was performed to calculate 5-year disease- free survival and overall survival. In all tests, $P<0.05$ were considered statistically significant.

Results

Of 464 cases of malignant ovarian tumors who were referred to our center during the 6-year study period, 22 patients (4.76%) were pregnant and were included in this case series. The mean age of these patients was 28.23±6.04 years. None of the patients had a history of infertility or any history of hereditary diseases in their family.

Pathologic findings of the tumors are summarized in table 1. The epithelial and germ cell subtypes had the same incidence (45.45%), while two patients (9.1%) had sex-cord tumors. The most common subtype of epithelial tumors was serous cyst adenocarcinoma with a prevalence of 27.27% (Table 1).

The mean level of CA-125 in patients with epithelial tumors was 295.00±362.22 units. Three of these patients had a CA-125 level of fewer than 35 units, while the minimum level of CA-125 was five units. Other tumor markers were not assessed because pregnancy can influence these markers.

The majority of patients (N=20, 90.9%) were diagnosed initially using abdominopelvic ultrasound. Two patients (9.1%), who had stage 3 and 4 epithelial carcinomas, were diagnosed during their Cesarean section delivery. They had only mild symptoms during pregnancy, which were imputed to the gestational changes.

Four other patients also underwent Cesarean section at 35 weeks of pregnancy, due to the impossibility of fertility-preserving surgery. In the remaining 16 cases, termination of pregnancy and mode of delivery was determined according to obstetrical indications. No obstetric complications (e.g. miscarriage, anomalies, etc.) were observed.

All patients underwent surgical staging surgery for ovarian cancer (100%). Optimal surgery was performed on the majority of patients (90.9%), while two (9.1%) had non-optimal surgery. One patient with a stage IVb epithelial tumor underwent non-optimal surgery in 28^{th} week and received one course of chemotherapy in 31^{st} week. After the Cesarean section in 35^{th} week, she received the remaining 4 courses of chemotherapy.

Fertility-preserving surgery was performed in 14 cases (63.6%) during the second or third trimester. Two patients with sex-cord tumors of stage Ia were operated on at the 14^{th} and 16^{th} weeks. Of four patients with borderline epithelial tumors, three were operated at the 16^{th} week and one on the 28^{th} week. Two patients with stage Ic and one with stage IIc epithelial tumors were operated on at 14^{th}-16^{th} weeks and received 5 courses of

chemotherapy during pregnancy. Three weeks after the Cesarean section at the 35th week, they received the remaining course of chemotherapy. Of six patients who had dysgerminoma, five with stage Ia tumors underwent fertility-preserving surgery at the 14th and 16th weeks and the one with stage IIIc tumor received 4 courses of chemotherapy followed by an optimal surgery simultaneous with Cesarean section at the 37th week. Four patients with immature teratoma (3 in stage Ia and one in stage IIb) received chemotherapy followed by fertility-preserving surgery at the 14th-20th weeks.

In most of the patients (N=12, 54.54%), the surgical staging surgery revealed stage Ia of ovarian cancer, followed by Ic and IIIc with 3 patients (13.63%) in each stage (Table 1). Disseminated metastases (stage IV) were only found in two cases (9.1%). The nuclear grading of the majority of patients showed grade 1 (56%) tumors, while grades 2 and 3 accounted for 11% and 33% of the cases, respectively.

Of the 22 patients, 12 (54.54%) received chemotherapy for their tumors (Table 1). Six of them received Carboplatin+Taxol (C+T), of whom 5 received six courses and 1 received five courses. The other six cases received a Bleomycin, Etoposide, and Cisplatin (BEP) regimen, of whom 3 had four courses and 3 received three courses. Of 12 women who underwent chemotherapy, 6 (50%) had epithelial tumors of high stages i.e. IVa, IVb, IIIc, IIc, and Ic (2 patients). The other six patients (50%) had germ cell tumors, of whom two had dysgerminoma of stage IIIc and four had high-grade immature teratoma of stage Ia or IIb.

None of our patients experienced complications due to surgery or chemotherapy and the full course of treatment was completed in all patients. All patients were discharged at a maximum of three days after their surgery. After patients' treatments were completed, they were followed up using tumor markers every three months. If a rise in tumor markers was observed, an abdominopelvic computed tomography was performed.

Six patients (27.27%) whose tumors were in stages Ic, IIIc, and IVb experienced recurrences. In 4 patients, the disease recurred 6 months after completing the treatment, while one had a relapse after 18 months and another with stage Ic cancer had two episodes of recurrence after 12 and 22 months. The mean interval between surgery and recurrence was 9.00±5.01 months in these patients.

Patients were followed for a minimum of 17 months and a maximum of 64 months (mean 37.45±16.21 months). Two patients were lost during the follow-up (mortality rate: 18%), one of them had stage IIIc mucinous carcinoma and the other had stage IVb clear cell tumor. The mean interval between their surgery and mortality was 16 months. Five-year DFS and OS were 56% and 82%, respectively.

Table 1. Clinical characteristics of patients

Parameter			Number (%)
Pathologic subtype	Epithelial	Serous	6 (27.27 %)
		Mucinous	3 (13.63 %)
		Clear cell	1 (4.54 %)
	Germ cell	Borderline (Serous)	4 (18.18 %)
		Immature teratoma	4 (18.18 %)
		Dysgerminoma	6 (27.27 %)
	Sex-cord granulosa		2 (9.09 %)
Signs and symptoms	Mass		16 (72.72 %)
	Pain		10 (45.45 %)
	Abdominal distention		1 (4.54 %)
	Other		5 (22.72%)
Ultrasound features	Mass		21 (95.45 %)
	Ascites		3 (13.63 %)
	Omental involvement		5 (22.72 %)
	Other involvements		2 (9.09 %)
Surgery	Optimal		20 (90.90 %)
	Non-optimal		2 (9.09 %)
Chemotherapy	No chemotherapy		10 (45.45 %)
	Carboplatin + Taxol		6 (27.27 %)
	Bleomycin + Etoposide + Cisplatin		6 (27.27 %)
Stage	Ia		12 (54.54 %)
	Ic		3 (13.63 %)
	IIb		1 (4.54 %)
	IIc		1 (4.54 %)
	IIIc		3 (13.63 %)
	IVa		1 (4.54 %)
	IVb		1 (4.54 %)

Discussion

Experts claim that with proper and careful management of ovarian cancer, obstetric outcomes will not be adversely affected (7). In a study by Tamauchi *et al*., the majority of patients with malignant ovarian germ cell tumors who received chemotherapy after fertility-preserving surgery were able to deliver healthy babies (8). However, another study states that almost half of the gynecologists would suggest termination of pregnancy in patients with ovarian cancer and around a third of physicians do not administer chemotherapy during pregnancy (9).

We evaluated 22 pregnant patients that initially presented with a mass in ultrasound or associated symptoms of ovarian masses and were finally diagnosed with ovarian cancer. Although ovarian masses during pregnancy are common, malignant ovarian tumors are rare. The most common malignant pathology is epithelial ovarian tumors. Our findings revealed a 45% prevalence of epithelial cancer among our patients, 40% of which were borderline tumors. This finding was in line with previous studies (10).

Most pregnant women with adnexal masses are reported to be asymptomatic (10,11). However, signs and symptoms in our patients were more prominent as 59% of our patients were symptomatic at the time of diagnosis and only two patients had no signs or symptoms. The most common sign in the physical examination was an adnexal mass, found in 72% of our patients, which is mainly because our series included only malignancies. Therefore, more signs and symptoms were expected compared to other studies (1).

Similar to other studies, most of our patients were at the International Federation of Gynecology and Obstetrics (FIGO) stage I (12). However, ovarian cancer is mostly diagnosed in the late stages in non-pregnant patients. The most probable explanation for this phenomenon is the fact that most lesions in pregnancy are found incidentally by routine ultrasound before the malignant cells have the chance to become disseminated.

Despite malignancy being very rare in pregnancy, its timely diagnosis and management are paramount. Facing malignancy in a pregnant patient, one must keep in mind three factors: the effect of treatment on the mother, fetus, and the malignancy. Because of the low prevalence of ovarian malignancy among pregnant patients, most of our knowledge about this topic comes from case reports and small-sized case series.

Sonographic findings such as septation, solid components, nodules, papillary projections, or mass greater than 5 cm in diameter suggest malignancy (11,13). A study reported that more than half of pregnant patients with malignant ovarian tumors were diagnosed during routine first-trimester ultrasonography. Moreover, the authors suggested that further evaluation using transvaginal ultrasound or magnetic resonance imaging (MRI) helps with the diagnosis of suspicious cases (14). In our study, except for two cases, all patients were initially diagnosed by a routine ultrasound during pregnancy. With only one exception, patients had ascites in imaging and a mass was seen in the ultrasound, which confirmed malignancy. This can underscore the importance of accurate ultrasound examination in the timely diagnosis of adnexal masses during pregnancy.

Experts state that diagnosis of ovarian malignancy in pregnant patients requires at least Doppler imaging alongside regular ultrasound to assess the vasculature of the mass. However, MRI is recommended whenever ultrasound findings are inconclusive. Gadolinium injections are feasible after the first trimester. Although pelvic computed tomography is contraindicated in pregnancy, a thoracic computed tomography scan should be obtained in case of an advanced-stage tumor to assess the spread of malignancy into the thoracic cavity (15). However, the initial diagnosis was made by ultrasound in nearly all of our patients.

Management of malignant ovarian cancer in pregnancy includes surgery and chemotherapy if indicated. The best time to carry out surgery during pregnancy is the second trimester (1). Therefore, most surgeries in this study were performed in the second trimester.

Laparotomy is a commonly used approach and is associated with lower side effects. However, laparoscopic surgery can only be administered by expert surgeons. It is critically important that the surgery, whether laparotomy or laparoscopy, be performed by a surgeon highly experienced in the field of gynecologic oncology.

A 2016 study by Saghafi *et al*., carried out at the same center, showed that patients undergoing mass excision during pregnancy had a higher rate of malignant tumors compared to those who underwent mass excision during Caesarian section. Perhaps the type of tumors which was removed during the Cesarian section tends to be less malignant (16). The authors emphasized the accurate diagnosis and proper management of ovarian tumors alongside consultation by an oncologist gynecologist.

Chemotherapy is usually a helpful option for the management of patients with ovarian cancer since these tumors are very chemosensitive. However, the use of chemotherapy is limited because of its teratogenicity.

Experts recommend that in the early stages of the disease, the best time for chemotherapy is the second trimester. Nevertheless, the use of neoadjuvant chemotherapy is permitted for pregnant patients with advanced-stage disease. The recommended regimen for epithelial ovarian cancer is T+C whereas in non-epithelial cancer a BEP regimen is more suitable (11).

Epithelial ovarian tumors are extremely chemosensitive, mainly to platinum and paclitaxel. Interestingly, it was shown that platinum derivatives are not associated with teratogenic effects if administered during the second or third trimester (17). Mendez *et al*., reported a patient with stage IIIc ovarian papillary serous cystadenocarcinoma who underwent six courses of C+T chemotherapy during pregnancy and delivered a healthy infant who remained so until the end of their 15-month follow-up (18). Furthermore, a systematic review reported that 76.7% of patients with breast cancer treated with paclitaxel during pregnancy had a completely uneventful neonatal outcome (19). Studies have also shown a good pregnancy outcome profile and reasonable efficacy for the BEP regimen in the treatment of non-epithelial ovarian cancer in pregnancy (20). For germ cell tumors, the European Society for Medical Oncology recommends the combination of cisplatin and weekly paclitaxel (21). In this study, none of the patients who received chemotherapy showed fetal problems.

In our series, the OS was calculated to be 82%, which is very close to the findings of a study by Machado *et al*., who indicated the 5-year OS to be around 80%. Other similar studies also reported OS ranging from 60% to 80% (10). The favorable prognosis of pregnant patients diagnosed with ovarian cancer is mainly due to the early detection of tumors in these patients, which can be possible through routine ultrasound monitoring during pregnancy. This in turn allows for the early management of cancers, which could otherwise reach higher stages and become difficult to manage.

Our study had some limitations. We only included patients with ovarian cancer; therefore, we could not assess the prevalence of ovarian cancer and ovarian tumors in pregnancy. Another limitation is that the level of tumor markers reported in our study might have been affected by the pregnancy conditions and thus cannot accurately reflect the serum level of tumor markers for the ovarian masses reported. Moreover, we did not use other diagnostic modalities such as MRI to confirm ultrasound findings.

Ovarian malignancy is a rare event during pregnancy and its management requires an experienced multidisciplinary team. Adnexal tumors are mostly diagnosed during routine gestational sonography and they might go unnoticed otherwise. Therefore, careful evaluation of adnexal masses during prenatal sonography, especially in the first trimester, is strongly recommended. Further studies with larger sample sizes and stronger designs are required to improve the management of ovarian cancer during pregnancy.

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