

Ultrasound features and clinical outcome of patients with malignant ovarian masses diagnosed during pregnancy: experience of a gynecological oncology ultrasound center

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Highlights

- Morphological features of malignant tumors detected during pregnancy are similar to those described in non-pregnant patients.
- Primary malignant ovarian tumors presented no neonatal complications.
- Metastases to the ovaries may lead to neonatal complications.

ABSTRACT

Objective The number of women diagnosed with ovarian masses during pregnancy has increased in recent years and the management of these women can be controversial. We aim to describe ultrasound characteristics and clinical outcomes of patients with malignant ovarian masses diagnosed during pregnancy.

Methods Patients with a histological diagnosis of malignant ovarian mass detected during pregnancy who underwent pre-operative ultrasound by experienced ultrasound examiners between December 2000 and November 2017 were included in this retrospective observational study. Ultrasound characteristics of the masses were described using International Ovarian Tumor Analysis terminology. Patients with ovarian masses but without histopathological reports were excluded. Results are presented as absolute frequency (percentage) for nominal variables and as median (range) for continuous variables.

Results A total of 22 patients were included in the analysis. The median age was 32.5 (range 23–42) years and median gestational age at diagnosis was 13.5 (range 4–30) weeks. Eight (36.4%) patients had a serous/endocervical-type borderline tumor, seven (31.8%) patients had a primary epithelial ovarian carcinoma, five (22.8%) patients had a metastatic tumor to the ovary, and two (9%) patients had a mucinous borderline tumor. At ultrasound, mucinous borderline tumors were multilocular (1/2, 50%) or multilocular-solid (1/2, 50%) lesions. Serous/endocervical-type borderline tumors were unilocular-solid (3/8, 37.5%) or multilocular-solid (5/8, 62.5%) masses and all had papillary projections. Most invasive epithelial ovarian cancers were multilocular-solid masses (5/7, 71.4%). All metastatic tumors appeared as solid masses. No patients with borderline tumors had a cesarean section due to disease, whereas most patients with epithelial ovarian carcinomas (4/7, 57.2%) and with ovarian metastases (3/5, 60%) had a cesarean section due to disease. No neonatal complication was reported for patients with borderline tumors or epithelial ovarian

carcinomas, whereas two of three newborns of patients with metastatic tumor died of the disease.

Conclusion At ultrasound, morphological features of malignant ovarian masses detected during pregnancy are similar to those described in non-pregnant patients. The likelihood of undergoing cesarean section increases with malignant disease in the ovary.

INTRODUCTION

The number of women diagnosed with ovarian masses during pregnancy has increased in recent years mainly due to the widespread use of ultrasound in the first trimester. It has been reported that adnexal cysts can be seen on ultrasound scan in 4.1–24.9% of pregnant women,^{1,2} but most are benign and often regress spontaneously.^{3,4} The management of women with a persistent ovarian mass detected incidentally during pregnancy can be controversial, with a general recommendation to avoid surgery unless there is a clear indication to operate, such as torsion or high suspicion of malignancy. If malignancy is suspected, the treatment approach depends on tumor size, histological subtype, extent of disease (presence of extra-ovarian disease), age of gestation, and the patient's wishes.⁵

In early-stage disease, ovarian cancer surgery may be planned preferably before 16–18 weeks of gestation and chemotherapy can be administered from the second trimester, if indicated, as in non-pregnant patients.⁶ In advanced-stage disease, when optimal cytoreduction is not achievable, neoadjuvant chemotherapy may be administered even in pregnancy. In case of ovarian metastasis from another organ, the treatment is planned on the basis of the tumor origin.

Currently, ultrasound examination is considered the first line imaging method to diagnose an ovarian



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mass with high accuracy in discriminating between benign and malignant disease.⁷ Ultrasound examination is also an effective tool in distinguishing a primary ovarian cancer from metastasis.^{8,9} However, adnexal masses may be difficult to classify during pregnancy as hormonal changes associated with the pregnancy may cause alterations in the sonographic appearances of ovarian masses and, for instance, papillary projections can represent a challenge in discriminating between malignant masses (borderline and invasive) and benign ones (decidualized endometriomas and cystadenofibromas).¹⁰

Although some reports on ultrasound features of malignant ovarian masses diagnosed during pregnancy have been reported in the literature,^{11,12} no large case series has focused on the ultrasound features of ovarian malignancies detected during pregnancy. Moreover, no study reported if the ultrasound features of ovarian malignant masses in pregnant women are similar to those reported in non-pregnant women or if the hormonal changes associated with pregnancy modify the sonographic appearances of ovarian malignant masses.

The aim of this study was to describe the ultrasound features of malignant ovarian masses detected during pregnancy. In addition, we evaluated the management of the tumors during pregnancy, perinatal outcomes, and follow-up of the patients.

METHODS

We included patients with a histological diagnosis of malignant ovarian mass detected during pregnancy who underwent pre-operative ultrasound examination by an experienced ultrasonographer between December 2000 and November 2017. Patients included both in the International Ovarian Tumor Analysis (IOTA) protocol and outside the IOTA protocol were included in the study, as our ultrasound center is a member of the IOTA Group. The IOTA Group published a consensus statement in 2000 to develop standardized terms, definitions, and measurements of the ovarian masses. Since then, several protocols using IOTA terminology have been developed to pre-operatively discriminate between benign and malignant masses.

All patients had been examined pre-operatively with transvaginal ultrasound (supplemented with a transabdominal scan if necessary) using a standardized examination technique.¹³ All the ultrasonographers had more than 10 years of experience in gynecological ultrasound, and the examinations were carried out using high quality ultrasound equipment (Esaote Technos MP, Genova, Italy; Esaote MyLab 70 XVG, Genova, Italy; GE Voluson E8 Medical Systems, Zipf, Austria; GE Voluson E10 Medical Systems, Zipf, Austria; Samsung Medison Accuvix A30, Samsung Healthcare, Seoul, Korea; Samsung Elite WS80A, Samsung Healthcare, Seoul, Korea).

For women included in the IOTA studies, clinical and ultrasound information was obtained from IOTA prospectively collected data. For women who had been examined outside the IOTA study protocol, information was retrospectively retrieved from the patient medical and ultrasound records and entered into an Excel file by the principal investigator (FM). In patients with more than one ultrasound examination performed during pregnancy, the data of the pre-operative ultrasound examination were analyzed.

Nine of the 22 masses included had already been described in previous reports (five borderline tumors,¹⁰ one primary epithelial ovarian carcinoma,¹⁰ and three metastatic tumors).^{12,14,15} Gestational age at diagnosis, time of surgery, histology, International Federation of Gynecology and Obstetrics (FIGO) stage, management, and follow-up were recorded. Moreover, gestational age at delivery, type of delivery, indication of cesarean section, obstetrics, and perinatal outcomes were also noted. In case of bilateral adnexal masses, the mass with the most complex ultrasound morphology was used in our analysis. If both masses had similar ultrasound morphology, the largest mass or the one most easily accessible with ultrasound was included. The masses were described using the terms and definitions published by the IOTA Group.¹³ Papillary projections were defined as projections of solid tissue into the cystic cavity with a height ≥ 3 mm. The largest solid component other than a papillary projection was also measured, and if a papillary projection was the largest solid component of a mass, the papillary projection was recorded and measured both as a papillary projection and as the largest solid component.¹³ Presence of ascites and fluid in the pouch of Douglas was noted. The vascularization of the tumors on color Doppler was described using the IOTA color score: no detectable blood flow (color score=1), minimal blood flow (color score=2), moderate blood flow (color score=3) or abundant blood flow (color score=4). The specific diagnosis suggested by the original ultrasound examiner in the original ultrasound report was recorded. The gold standard was the histological diagnosis of the adnexal mass. The study was approved by the Institutional Review Board.

All clinical and ultrasound data were entered into a dedicated Excel file (Microsoft Office Excel 2007, Redmond, Washington, USA). Results are presented as absolute frequency (percentage) for nominal variables and as median (range) for continuous variables.

RESULTS

We identified 22 patients with a histological diagnosis of malignant ovarian mass detected during pregnancy: eight (36.4%) patients were included in the IOTA studies, whereas 14 (63.6%) patients were examined outside the IOTA studies. Eight (36.4%) patients had a serous/endocervical-type borderline tumor, seven (31.8%) patients a primary epithelial ovarian carcinoma, five (22.8%) patients had a metastatic tumor to the ovary, and two (9%) patients had a mucinous borderline tumor. The primary tumors metastatic to the ovary were: lung cancer, endometrial carcinoma, stomach cancer, Burkitt's lymphoma, or melanoma.

The median age at diagnosis was 32.5 (range 23–42) years and the median gestational age at diagnosis was 13.5 (range 4–30) weeks. The median gestational age at surgery was 20 (range 8–39) weeks. The median gestational age at delivery was 38 (range 28–40) weeks: 39 (range 38–40) weeks for patients with borderline tumors, 37 (range 31–39) weeks for patients with epithelial ovarian cancer, and 29 (range 28–36) weeks for those with metastatic tumor. The majority of patients had a cesarean delivery (13/22, 59.1%) and most patients had surgery during pregnancy (15/22, 68.2%) (Table 1).

The median CA125 level was 20 U/mL (range 10–707) for serous/mucinous endocervical borderline tumors, 10 U/mL (range 10–10)

Table 1 Clinical characteristics and histological diagnosis of patients with malignant ovarian masses detected during pregnancy

Characteristic	All (n=22)	Serous and mucinous endocervical-type borderline tumor (n=8)	Mucinous intestinal-type borderline tumor (n=2)	Invasive epithelial ovarian cancer (n=7)	Metastatic cancer (n=5)
Age at diagnosis (years)	32.5 (23–42)	32.5 (23–42)	33 (28–38)	38 (28–42)	30 (24–38)
Nulliparous	13 (59.1)	4 (50.0)	1 (50.0)	4 (57.1)	4 (80.0)
Gestational age at diagnosis (weeks)	13.5 (4–30)	11 (5–20)	5.5 (4–7)	14 (7–26)	23 (6–30)
Gestational age at surgery (weeks)*	20 (8–39)	19 (16–39)	8 (8–8)	21 (15–37)	23 (10–36)
Gestational age at delivery (weeks)†	38 (28–40)	39 (38–40)	39 (39–39)	37 (31–39)	29 (28–36)
Delivery					
Caesarean section	13 (59.1)	5 (62.5)	0 (0)	6 (85.7)	2 (40.0)
Spontaneous delivery	5 (22.7)	2 (25.0)	1 (50.0)	1 (14.3)	1 (20.0)
Spontaneous abortion	2 (9.1)	0 (0)	1 (50.0)	0 (0)	1 (20.0)
Voluntary abortion	2 (9.1)	1 (12.5)	0 (0)	0 (0)	1 (20.0)
Time of surgery					
During cesarean section	5 (22.7)	2 (25.0)	0 (0)	2 (28.6)	1 (20.0)
Antepartum	15 (68.2)	6 (75.0)	1 (50.0)	5 (71.4)	3 (60.0)
Post abortion	2 (9.1)	0 (0)	1 (50.0)	0 (0)	1 (20.0)
Type of surgery					
Ovarian biopsy	1 (4.5)	0 (0)	0 (0)	0 (0)	1 (20.0)
LPS	7 (31.8)	4 (50)	1 (50.0)	1 (14.3)	1 (20.0)
LPT	11 (50.0)	3 (37.5)	1 (50.0)	4 (57.1)	3 (60.0)
LPS and LPT	3 (13.6)	1 (12.5)	0 (0)	2 (28.6)	0 (0)
CA 125 (U/mL) at diagnosis‡	27.6 (10–1240)	20 (10–707)	10 (10–10)	105 (10–1240)	84 (10–103)
Histological diagnosis					
Borderline tumors	10 (45.5)	8 (100)	2 (100)	0 (0)	0 (0)
Mucinous borderline intestinal type	2 (9.1)	0 (0)	2 (100)	0 (0)	0 (0)
Serous borderline	7 (31.8)	7 (87.5)	0 (0)	0 (0)	0 (0)
Mucinous endocervical type	1 (4.5)	1 (12.5)	0 (0)	0 (0)	0 (0)
Primary invasive ovarian tumor	7 (31.8)	0 (0)	0 (0)	7 (100)	0 (0)
High grade serous carcinoma	3 (13.6)	0 (0)	0 (0)	3 (42.9)	0 (0)
Low grade serous carcinoma	1 (4.5)	0 (0)	0 (0)	1 (14.3)	0 (0)
Clear cells carcinoma	1 (4.5)	0 (0)	0 (0)	1 (14.3)	0 (0)
Endometrioid adenocarcinoma	2 (9.1)	0 (0)	0 (0)	2 (28.6)	0 (0)
Metastatic carcinoma	5 (22.7)	0 (0)	0 (0)	0 (0)	5 (100)
Small cell lung carcinoma	1 (4.5)	0 (0)	0 (0)	0 (0)	1 (20.0)
Burkitt lymphoma	1 (4.5)	0 (0)	0 (0)	0 (0)	1 (20.0)
Krukenberg	1 (4.5)	0 (0)	0 (0)	0 (0)	1 (20.0)
Melanoma	1 (4.5)	0 (0)	0 (0)	0 (0)	1 (20.0)
Endometrial carcinoma	1 (4.5)	0 (0)	0 (0)	0 (0)	1 (20.0)
FIGO stage					

Continued

Table 1 Continued

Characteristic	All (n=22)	Serous and mucinous endocervical-type borderline tumor (n=8)	Mucinous intestinal-type borderline tumor (n=2)	Invasive epithelial ovarian cancer (n=7)	Metastatic cancer (n=5)
IA	11 (50.0)	6 (75.0)	2 (100)	3 (42.9)	0 (0)
IB	1 (4.5)	1 (12.5)	0 (0)	0 (0)	0 (0)
IC	2 (9.1)	1 (12.5)	0 (0)	1 (14.3)	0 (0)
IIB	1 (4.5)	0 (0)	0 (0)	1 (14.3)	0 (0)
IIIA	1 (4.5)	0 (0)	0 (0)	1 (14.3)	0 (0)
IIIC	1 (4.5)	0 (0)	0 (0)	1 (14.3)	0 (0)
Not applicable	5 (22.7)	0 (0)	0 (0)	0 (0)	5 (100)
Patients included in IOTA studies (phase 1,2,3)	8 (36.4)	3 (37.5)	1 (50.0)	2 (28.6)	2 (40.0)

*Calculated on 20 patients as two patients underwent surgery after abortion.

†Calculated on 18 patients as four patients had abortion.

‡Information available for 18 patients.

FIGO, International Federation of Gynecology and Obstetrics; IOTA, International Ovarian Tumor Analysis; LPS, laparoscopic surgery; LPT, laparotomy surgery.

for mucinous borderline tumors, 105 U/mL (range 10–1240) for primary invasive ovarian cancers, and 84 U/mL (range 10–103) for metastatic tumors. The ultrasound characteristics of the masses are shown in Table 2. The median maximum diameter of the masses was 53 mm (range 40–100) for serous/mucinous endocervical borderline tumors, 100 mm (range 92–108) for mucinous intestinal borderline tumors, 114 mm (range 78–182) for invasive epithelial ovarian cancers, and 153 mm (range 70–165) for metastatic cancers. Serous/mucinous endocervical borderline lesions were described as unilocular-solid (3/8; 37.5%) or as multilocular-solid (5/8; 62.5%) cysts, containing papillary projections in all (100%) cases (Figure 1A). The median height of the largest papillary projection was 11.5 mm (range 5–31). The two mucinous intestinal-type borderline lesions were described as multilocular and multilocular-solid with ≤ 10 locules.

Most (5/7; 71.4%) invasive epithelial carcinomas were multilocular-solid cysts (Figure 1B). Papillary projections were observed in three (42.9%) of seven patients. The median height of the largest papillary projection was 20 mm (range 10–22). All metastatic ovarian carcinomas were described as solid masses. At color Doppler examination, both mucinous borderline tumors had minimal vascularization whereas serous/endocervical borderline tumors (4/8; 50%) and most epithelial ovarian carcinomas (4/7; 57.1%) had moderate vascularization. A majority (4/5; 80%) of metastatic tumors presented a rich vascularization. The vast majority (18/22, 81.8%) of patients underwent only one pre-operative ultrasound examination, as the surgery was planned in a limited time from the scan. The remaining four patients (19.2%) (three with a borderline ovarian tumor and one with an epithelial ovarian carcinoma) had additional ultrasound follow-ups after the first examination, as the surgery was planned at least after 2 months from the first scan. In particular, two patients with borderline tumors and one with an epithelial ovarian carcinoma had two follow-up scans and one with borderline tumor had four follow-up scans. No ultrasound

features appeared as modified during the follow-up scans in terms of morphology and dimension of the ovarian mass.

Surgical information, patient management during pregnancy, and follow-up after surgery are summarized in Table 3. Seven of 10 patients with borderline tumors underwent surgery during pregnancy, whereas one patient underwent surgery after spontaneous abortion and two patients during cesarean section. None of the patients received chemotherapy. Ultimately, one of these patients showed findings suspicious for recurrence on ultrasound examination 19 months after surgery. Among patients with invasive epithelial ovarian cancers, five of seven patients underwent surgery during pregnancy and the other two patients during cesarean section. Four patients (57.1%) received chemotherapy during pregnancy and three (42.9%) patients after delivery. Two patients (28.5%) had a recurrence during follow-up; however, at the last follow-up all patients were alive with no evidence of disease. Three of the five patients with a diagnosis of metastatic tumor underwent surgery during pregnancy, one after voluntary abortion and one during cesarean section. Three patients died within 4 months after delivery and the other two women died within 2 years (after 22 and 27 months, respectively).

Among 10 patients with borderline tumors, one patient (10%) had miscarriage and one (10%) had a termination due to a diagnosis of Down's syndrome, whereas eight patients (80%) had a delivery at term. Four (50%) of these had a cesarean section for reasons not related to the disease. Two (25%) patients had a diagnosis of intrauterine growth restriction. One newborn (12%) was admitted to the neonatal intensive care unit, but none had an Apgar score < 7 at 5 min and none died (Table 4). Among patients with epithelial ovarian carcinomas, three patients (42.9%) had a pre-term delivery and one had a twin pregnancy with an intrauterine death for bowel necrosis in one of the fetuses. Five (71.4%) patients had a cesarean section and all but one had a cesarean section for maternal disease. Two newborns (28%) were admitted to the neonatal intensive care

Table 2 Ultrasound characteristics of malignant ovarian masses detected during pregnancy

Characteristic	All (n=22)	Serous and mucinous endocervical-type borderline tumor (n=8)	Mucinous intestinal-type borderline tumor (n=2)	Invasive epithelial ovarian cancer (n=7)	Metastatic cancer (n=5)
Bilateral masses	6 (27.3)	0 (0)	0 (0)	3 (42.9)	3 (60)
Maximum diameter of the lesion (mm)	91.5 (40–182)	53 (40–100)	100 (92–108)	114 (78–182)	153 (70–165)
Type of tumor					
Unilocular-solid	4 (18.2)	3 (37.5)	0 (0)	1 (14.3)	0 (0)
Multilocular	1 (4.5)	0 (0)	1 (50.0)	0 (0)	0 (0)
Multilocular-solid	11 (50.0)	5 (62.5)	1 (50.0)	5 (71.4)	0 (0)
Solid	6 (27.3)	0 (0)	0 (0)	1 (14.3)	5 (100)
Number of locules for multilocular or multilocular-solid masses					
≤10	12 (100)	5 (100)	2 (100)	5 (100)	–
>10	0 (0)	0 (0)	0 (0)	0 (0)	–
Echogenicity of cyst fluid in tumors not classified as solid					
Anechoic	2 (12.5)	1 (12.5)	0 (0)	1 (16.7)	–
Low level	9 (56.3)	6 (75.0)	0 (0)	3 (50.0)	–
Ground glass	5 (31.3)	1 (12.5)	2 (100)	2 (33.3)	–
Hemorrhagic	0 (0)	0 (0)	0 (0)	0 (0)	–
Mixed	0 (0)	0 (0)	0 (0)	0 (0)	–
Color score					
1	1 (4.5)	1 (12.5)	0 (0)	0 (0)	0 (0)
2	8 (36.4)	3 (37.5)	2 (100)	2 (28.6)	1 (20)
3	8 (36.4)	4 (50.0)	0 (0)	4 (57.1)	0 (0)
4	5 (22.7)	0 (0)	0 (0)	1 (14.3)	4 (80)
Largest solid component (mm)	30 (8–165)	13 (8–31)	56 (56–56)	30 (20–98)	153 (70–165)
Presence of papillary projections	12 (54.5)	8 (100)	1 (50.0)	3 (42.9)	0 (0)
Number of papillary projections if papillary projections were present*					
1	2/11 (18.2)	2/7 (28.6)	0/1 (0)	0/3 (0)	–
2	0/11 (0)	0/7 (0)	0/1 (0)	0/3 (0)	–
3	1/11 (9.1)	1/7 (14.3)	0/1 (0)	0/3 (0)	–
>3	8/11 (72.7)	4/7 (57.1)	1/1 (100)	3/3 (100)	–
Height of the largest papillary projection (mm)	15.5 (5–31)	11.5 (5–31)	16 (16–16)	20 (10–22)	–
Papillation flow if papillary projections were present	11 (91.7)	7 (87.5)	1 (100)	3 (100)	–
Ascites	1 (4.5)	0 (0)	0 (0)	0 (0)	1 (20.0)

Continued

Table 2 Continued

Characteristic	All (n=22)	Serous and mucinous endocervical-type borderline tumor (n=8)	Mucinous intestinal-type borderline tumor (n=2)	Invasive epithelial ovarian cancer (n=7)	Metastatic cancer (n=5)
Free fluid in the pouch of Douglas	20 (90.9)	7 (87.5)	2 (100)	7 (100)	4 (80.0)
Diagnosis on the basis of subjective assessment					
Benign	2 (9.1)	2 (25.0)	0 (0)	0 (0)	0 (0)
Borderline	8 (36.4)	3 (37.5)	2 (100)	3 (42.9)	0 (0)
Malignant	9 (40.9)	2 (25.0)	0 (0)	4 (57.1)	3 (60.0)
Not available	3 (13.6)	1 (12.5)	0 (0)	0 (0)	2 (40.0)
Specific diagnosis suggested by the original examiner†					
Endometrioma	1/21 (4.8)	1/8 (12.5)	0/2 (0)	0/7 (0)	0/4 (0)
Mucinous cystoadenoma	1/21 (4.8)	1/8 (12.5)	0/2 (0)	0/7 (0)	0/4 (0)
Borderline tumor	8/21 (38.1)	3/8 (37.5)	1/2 (50.0)	4/7 (57.1)	0/4 (0)
Primary ovarian cancer	5/21 (23.8)	2/8 (25.0)	0/2 (0)	3/7 (42.9)	0/4 (0)
Metastatic ovarian cancer	3/21 (14.3)	0/8 (0)	0/2 (0)	0/7 (0)	3/4 (75.0)
Not possible	3/21 (14.3)	1/8 (12.5)	1/2 (50.0)	0/7 (0)	1/4 (25.0)

*Information available for 11/12 patients with papillary projections.

†Information available for 21 patients.

unit, but none had an Apgar score <7 at 5 min and none died. Among five patients with ovarian metastases, one (20%) patient had a termination due to the diagnosis of cancer, one (20%) had an intrauterine fetal death, whereas three (60%) patients had a pre-term delivery with a cesarean section due to maternal and fetal disease. All three newborns were admitted to the neonatal intensive care unit; two had an Apgar score <7 at 5 min and died within 3 months after delivery of cerebral metastases.

DISCUSSION

Our study found that the morphological features of malignant tumors detected by ultrasound during pregnancy are similar to those described in non-pregnant patients: serous/endocervical borderline tumors appeared as cysts with papillary projections and mucinous borderline tumors as multilocular or multilocular-solid cysts. Epithelial ovarian carcinomas were multilocular-solid masses and metastatic tumors as solid masses with rich vascularization.

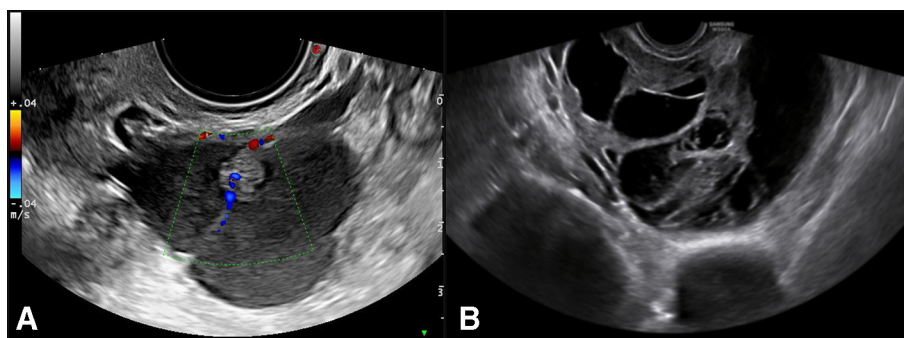


Figure 1 Ultrasound images of a multilocular-solid cyst with a vascularized papillary projection detected in a woman at 11 weeks of gestation (A) and a multilocular-solid tumor detected in a patient at 21 weeks of gestation (B). The histology was borderline endocervical-type ovarian tumor (A) and high grade serous ovarian carcinoma (B), respectively.

Table 3 Surgical information, management, and follow-up of the patients

Patients	Age (years)	Histology	FIGO stage	Gestational age at surgery (weeks)	Type of surgery	Chemotherapy	Follow-up	Duration of follow-up	Status at the last follow-up
1	28	Mucinous intestinal-type borderline tumors	IA	8	Laparoscopy, monolateral cystectomy during pregnancy and laparoscopy, monolateral salpingo-oophorectomy, appendicectomy, multiple biopsies in the post-partum	No	Negative	12	No evidence of disease
2	38	Mucinous intestinal-type borderline tumors	IA	After abortion	Laparotomy, monolateral salpingo-oophorectomy	No	Negative	78	No evidence of disease
3	36	Serous borderline IA tumors	IA	19	Laparoscopy, monolateral salpingo-oophorectomy during pregnancy	No	Negative	27	No evidence of disease
4	38	Serous borderline IA tumors	IA	16	Laparoscopy, monolateral cystectomy during pregnancy	No	Suspicious of recurrence after 19 months (planned for surgery)	19	Evidence of disease
5	42	Serous borderline IA tumors	IA	17	Laparoscopy, monolateral cystectomy during pregnancy	No	Negative	11	No evidence of disease
6	26	Serous borderline IC tumors	IC	39 (during cesarean section)	Laparoscopy, monolateral cystectomy (spillage) during cesarean section and laparoscopy, monolateral salpingo-oophorectomy, omentectomy in the post-partum	No	Negative	8	No evidence of disease
7	33	Serous borderline IA tumors	IA	20	Laparotomy, monolateral cystectomy during pregnancy	No	Negative	112	No evidence of disease
8	23	Serous borderline IA tumors	IA	20	Laparotomy, monolateral cystectomy during pregnancy	No	Negative	70	No evidence of disease
9	32	Serous borderline IA tumors	IA	16	Laparoscopy, monolateral cystectomy during pregnancy	No	Negative	97	No evidence of disease
10	27	Mucinous endocervical-type B borderline tumors	IB	39 (during cesarean section)	Laparotomy, bilateral cystectomy during cesarean section	No	Negative	10	No evidence of disease

Continued

Table 3 Continued

Patients	Age (years)	Histology	FIGO stage	Gestational age at surgery (weeks)	Type of surgery	Chemotherapy	Follow-up	Duration of follow-up	Status at the last follow-up
11	39	Low grade serous ovarian cancer	IIIC	31 (during cesarean section)	Laparotomy, monolateral cystectomy and total omentectomy, multiple biopsies during cesarean section	Post-delivery	Negative	169	No evidence of disease
12	29	High grade serous ovarian cancer	IC	16	Laparoscopy, bilateral cystectomy during pregnancy	During pregnancy	Negative	14	No evidence of disease
13	40	High grade serous ovarian cancer	IIIC	15	Laparotomy, bilateral salpingo-oophorectomy during pregnancy	During pregnancy	Two recurrences (both of them were treated with surgery and chemotherapy)	204	No evidence of disease
14	34	High grade serous ovarian cancer	IIIA	21	Laparoscopy, laparotomy, monolateral cystectomy and monolateral salpingo-oophorectomy during pregnancy and laparoscopy, hysterectomy, monolateral salpingo-oophorectomy, appendicectomy, multiple biopsies in the post-partum	During pregnancy	Negative	24	No evidence of disease
15	42	Endometrioid ovarian carcinoma	IIB	15	Laparoscopy, monolateral oophorectomy during pregnancy and laparoscopy hysterectomy, monolateral oophorectomy, omentectomy, pelvic lymphoadenectomy during cesarean section	During pregnancy	Negative	28	No evidence of disease
16	38	Endometrioid ovarian carcinoma	IA	31 (during cesarean section)	Laparotomy, bilateral cystectomy, omentectomy, multiple biopsies during cesarean section and laparoscopy, hysterectomy and bilateral salpingo-oophorectomy in the post-partum	After delivery	Recurrence after 12 months (treated with surgery and chemotherapy)	120	No evidence of disease

Continued

Table 3 Continued

Patients	Age (years)	Histology	FIGO stage	Gestational age at surgery (weeks)	Type of surgery	Chemotherapy	Follow-up	Duration of follow-up	Status at the last follow-up
17	28	Clear cell ovarian carcinoma	IA	22	Laparotomy, monolateral cystectomy during pregnancy and laparoscopy, hysterectomy, bilateral salpingo-oophorectomy, omentectomy, appendicectomy, multiple biopsies in the post-partum	After delivery	Negative	115	No evidence of disease
18	24	Small cell lung carcinoma	Ovarian metastases	After abortion	Laparotomy, monolateral oophorectomy, monolateral cystectomy, total omentectomy after abortion	After pregnancy	Recurrence after 11 months	22	Dead
19	31	Melanoma	Ovarian metastases	23 (emergency surgery for hemoperitoneum)	Laparoscopy, monolateral oophorectomy during pregnancy	No	Maternal death after 3 months from surgery	4	Dead
20	38	Krukenberg	Ovarian metastases	23	Laparotomy, monolateral oophorectomy and monolateral cystectomy during pregnancy	After delivery	Maternal death after 3 months from surgery	4	Dead
21	30	Burkitt's lymphoma	Ovarian metastases	22	Ovarian biopsy during pregnancy	During pregnancy	Maternal death after 27 months from biopsy	27	Dead
22	30	Endometrial carcinoma	Ovarian metastases	36 (during caesarian section)	Laparotomy, optimal cytoreduction during caesarian section	No	Maternal death after 1 month from surgery	1	Dead

Table 4 Perinatal outcomes

Patients	Histology	Gestation age at delivery	Singleton/twin pregnancy	Obstetric outcomes	Type of delivery	Indication for cesarean section	APGAR score	Fetal weight at delivery	Neonatal intensive care	
									unit admission	Neonatal outcomes
1	Mucinous intestinal-type borderline tumors	39	Singleton	No complications	Vaginal delivery	-	9/10	3030	No	No complications
2	Mucinous intestinal-type borderline tumors	-	-	Miscarriage	-	-	-	-	-	-
3	Serous borderline tumors	39	Singleton	No complications	Cesarean section	Previous cesarean section	9/10	3800	No	No complications
4	Serous borderline tumors	40	Singleton	No complications	Vaginal delivery	-	8/9	2940	No	No complications
5	Serous borderline tumors	-	-	Termination of pregnancy (Down Syndrome)	-	-	-	-	-	-
6	Serous borderline tumors	39	Singleton	No complications	Cesarean section	Maternal request	9/10	2905	No	No complications
7	Serous borderline tumors	38	Singleton	No complications	Cesarean section	Breech presentation	9/10	3150	No	No complications
8	Serous borderline tumors	39	Singleton	No complications	Vaginal delivery	-	9/10	2700	No	No complications
9	Serous borderline tumors	38	Singleton	Intrauterine growth restriction	Cesarean section	Abnormal CTG	9/9	2200	Yes	No complications
10	Mucinous endocervical-type borderline tumors	39	Singleton	Intrauterine growth restriction	Cesarean section	Abnormal CTG	8/9	2160	No	No complications
11	Low grade serous ovarian cancer	31	Singleton	Pre-term delivery	Cesarean section	Maternal cancer	8/8	1650	Yes	No complications
12	High grade serous ovarian cancer	38	Singleton	No complications	Cesarean section	Maternal cancer	9/9	3650	No	No complications
13	High grade serous ovarian cancer	39	Singleton	No complications	Vaginal delivery	-	9/10	2980	No	No complications
14	High grade serous ovarian cancer	36	Singleton	Late pre-term	Vaginal delivery	-	9/10	2760	No	No complications
15	Endometrioid OC	37	Singleton	No complications	Cesarean section	Maternal cancer	7/8	2200	No	No complications

Continued

Table 4 Continued

Patients	Histology	Gestation age at delivery	Singleton/twin pregnancy	Obstetric outcomes	Type of delivery	Indication for cesarean section	APGAR score	Fetal weight at delivery	Neonatal intensive care unit admission	Neonatal outcomes
16	Endometrioid ovarian cancer	31	Twin	Intrauterine death of one fetus at 28 weeks for bowel necrosis. Pre-term delivery of the other fetus.	Cesarean section	Placenta abruption	Not available	1350	Yes	No complications
17	Clear cell ovarian carcinoma	37	Singleton	No complications	Cesarean section	Maternal cancer	9/9	2790	No	No complications
18	Small cell lung carcinoma	-	-	Termination of pregnancy	-	-	-	-	-	-
19	Melanoma	28	Singleton	Fetal cerebral metastases	Cesarean section	Maternal cancer	5/7	830	Yes	Neonatal death from cerebral metastases
20	Krukenberg	29	Singleton	Pre-term delivery	Cesarean section	Maternal cancer	8/8	1245	Yes	No complications
21	Burkitt's lymphoma	-	-	Intrauterine fetal death	-	-	-	-	-	-
22	Endometrial carcinoma	36	Singleton	Placental and fetal cerebral metastases	Cesarean section	Maternal cancer	5/6	Not available	Yes	Death 3 months after birth from cerebral metastases

CTG, cardiotocography.

CA125 was elevated in epithelial ovarian tumors and in ovarian metastases. No patients with borderline tumors had a cesarean section because of disease and no patient had neonatal complications, and most patients with invasive epithelial carcinomas had a cesarean section because of maternal disease but no neonatal complications. On the other hand, all three patients with metastatic tumor who delivered had cesarean section because of disease, and two had infant deaths within 3 months of the delivery.

Our results confirm epidemiological data regarding the rarity of ovarian malignancy detected during pregnancy.^{16,17} Most are reported to be borderline tumors or primary invasive at an early stage, with favorable maternal and neonatal outcomes.¹⁷ In our series we observed that most borderline tumors were operated on during pregnancy without need for second surgery after pregnancy, and recurrence occurred during follow-up in only one patient. Indeed, there is no strict clinical indication to perform surgery during pregnancy in patients with borderline tumors as the slow growth rate¹⁸ and the good prognosis of this pathology¹⁹ could allow a delay in management after pregnancy. Outside of the setting of pregnancy, the normal size of the uterus could allow an optimal and easier laparoscopic exploration of the peritoneal cavity. On the other hand, during pregnancy laparoscopic evaluation of the abdomen could be difficult and, in this context, ultrasound could play an important role in tailoring the appropriate management and personalizing the treatment for the patient.

Our experience also demonstrated that patients with epithelial ovarian carcinomas may undergo surgery during pregnancy with neoadjuvant or adjuvant chemotherapy without neonatal complications. On the other hand, we found that patients with a metastatic tumor may have a higher risk of neonatal complications. Our data defined the typical ultrasound features which are indicative of malignancy, helping the clinician to discriminate invasive from borderline tumors: unilocular-solid or multilocular-solid cysts with small papillary projections are representative of borderline tumors, whereas multilocular-solid tumors with large solid components are typical of epithelial invasive tumor and solid masses with rich vascularization support a diagnosis of metastatic tumors. The possibility to recognize an ovarian malignant mass during pregnancy can help the clinician to understand the best management for the patient. For example, our data suggest that a primary ovarian cancer should be suspected in case of a multilocular-solid cyst with a large solid component at ultrasound examination and surgery should be performed in a referral center as soon as possible. In case of bilateral solid adnexal masses with rich vascularization at color Doppler, metastatic tumors should be suspected and other clinical examinations should be considered to rule out the possibility of a primary tumor elsewhere.

The strength of our study is the large series of malignant ovarian masses detected during pregnancy and described in a standardized manner. Indeed, considering the low incidence of malignant ovarian masses in pregnancy, we found a conspicuous number of malignant tumors allowing us to determine the ultrasound features and management of these masses. However, our study has some limitations. The retrospective nature of the analysis is the main limitation of the study. Another bias of the study is that some information was missing. This means that some parameters (one clinical and two ultrasound parameters) were not available for all cases and their analysis has been calculated for a smaller number of cases; it could

have over- or under-estimated the data of some parameters. Third, ultrasound images or video clips were not available for all cases, and this may have limited our possibility to revise the images and eventually detect typical ultrasound features.

CONCLUSION

The current study shows that malignant ovarian masses in pregnancy represent a rare pathological condition, given that we found only 22 malignant masses during a 17-year period. Further large prospective studies are needed to confirm our data and to delineate a clinical management of pregnant patients with ovarian masses.

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REFERENCES

- Hill LM, Connors-Beatty DJ, Nowak A, *et al.* The role of ultrasonography in the detection and management of adnexal masses during the second and third trimesters of pregnancy. *Am J Obstet Gynecol* 1998;179:703–7.
- Yazbek J, Salim R, Woelfer B, *et al.* The value of ultrasound visualization of the ovaries during the routine 11–14 weeks nuchal translucency scan. *Eur J Obstet Gynecol Reprod Biol* 2007;132:154–8.
- Hoover K, Jenkins TR. Evaluation and management of adnexal mass in pregnancy. *Am J Obstet Gynecol* 2011;205:97–102.
- Leiserowitz GS. Managing ovarian masses during pregnancy. *Obstet Gynecol Surv* 2006;61:463–70.
- Morice P, Uzan C, Gouy S, *et al.* Gynaecological cancers in pregnancy. *Lancet* 2012;379:558–69.
- Fruscio R, de Haan J, Van Calsteren K, *et al.* Ovarian cancer in pregnancy. *Best Pract Res Clin Obstet Gynaecol* 2017;41:108–17.
- Timmerman D, Testa AC, Bourne T, *et al.* Logistic regression model to distinguish between the benign and malignant adnexal mass before surgery: a multicenter study by the International Ovarian Tumor Analysis Group. *J Clin Oncol* 2005;23:8794–801.
- Van Calster B, Van Hoorde K, Valentin L, *et al.* Evaluating the risk of ovarian cancer before surgery using the ADNEX model to differentiate between benign, borderline, early and advanced stage invasive, and secondary metastatic tumours: prospective multicentre diagnostic study. *BMJ* 2014;349:g5920.
- Testa AC, Ferrandina G, Timmerman D, *et al.* Imaging in gynecological disease (1): ultrasound features of metastases in the ovaries differ depending on the origin of the primary tumor. *Ultrasound Obstet Gynecol* 2007;29:505–11.
- Mascilini F, Savelli L, Scifo MC, *et al.* Ovarian masses with papillary projections diagnosed and removed during pregnancy: ultrasound features and histological diagnosis. *Ultrasound Obstet Gynecol* 2017;50:116–23.
- Husz V, Bus D, Vajda G. Extremely large epithelial ovarian cancer associated with pregnancy: a case report. *Mol Clin Oncol* 2018;8:103–6.
- Testa AC, De Blasis I, Di Legge A, *et al.* Burkitt's lymphoma of the breast metastatic to the ovary diagnosed during pregnancy. *Ultrasound Obstet Gynecol* 2013;42:364–6.
- Timmerman D, Valentin L, Bourne TH, *et al.* Terms, definitions and measurements to describe the sonographic features of adnexal

- tumors: a consensus opinion from the International Ovarian Tumor Analysis (IOTA) Group. *Ultrasound Obstet Gynecol* 2000;16:500–5.
14. Moro F, Mascilini F, Casella E, *et al.* Small cell lung cancer metastatic to the ovary diagnosed during pregnancy. *Ultrasound Obstet Gynecol* 2017;50:802–3.
 15. Testa AC, Licameli A, Di Legge A, *et al.* Color Doppler sonographic features of a Krukenberg tumor in pregnancy. *J Ultrasound Med* 2009;28:695–8.
 16. Whitecar MP, Turner S, Higby MK. Adnexal masses in pregnancy: a review of 130 cases undergoing surgical management. *Am J Obstet Gynecol* 1999;181:19–24.
 17. Leiserowitz GS, Xing G, Cress R, *et al.* Adnexal masses in pregnancy: how often are they malignant? *Gynecol Oncol* 2006;101:315–21.
 18. Franchi D, Boveri S, Radice D, *et al.* Ultrasonographic diagnosis and longitudinal follow-up of recurrences after conservative surgery for borderline ovarian tumors. *Am J Obstet Gynecol* 2016;215:756:e1–756.
 19. Hannibal CG, Vang R, Junge J, *et al.* A nationwide study of serous "borderline" ovarian tumors in Denmark 1978-2002: centralized pathology review and overall survival compared with the general population. *Gynecol Oncol* 2014;134:267–73.