Gynecology & Obstetrics
ISSN: 2161-0932

Serikawa et al., Gynecol Obstet 2013, 3:3
DOI: 10.4172/2161-0932.1000159

Mini Review Open Access

Management of Patients with Pregnancy-Associated Ovarian Clear Cell Carcinoma: A Mini-Review

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Abstract

A 39-years-old pregnant woman in the 9th week of gestation was referred to hospital for an ovarian mass of 5 cm in diameter. The size did not increase during the pregnancy and a female infant was delivered at term. Nine months after delivery, the solid part of the mass grew and clear cell borderline tumor was suspected by MRI. A laparotomy was performed, the pathological diagnosis was a Clear Cell Carcinoma (CCC), and FIGO stage was stage Ia. The patient remains free of disease at 6 months after the operation. The incidence of ovarian cancer diagnosed during pregnancy is very low and CCC is rare, so that there are very few reports of pregnancy-associated CCC. We reviewed the existing literature, using the key words "ovarian clear cell carcinoma" and "pregnancy". Besides our case, we were able to accumulate 8 cases. Their mean age is 34 years old. Eight of the 9 patients were asymptomatic at diagnosis. The size of cyst was larger than 6 cm, except for our case. All 9 patients underwent surgery and the tumors were all resectable. The FIGO stage was stage I or II. Fortunately, all patients and live-born infants were alive and well.

Keywords: Ovarian cancer; Clear cell carcinoma; Pregnancy

Introduction

The incidence of an ovarian mass complicating a pregnancy is somewhere 1 in 100 to 1 in 2000 pregnancies; the most common of such masses are cystic [1]. Ovarian cancer associated with pregnancy is quite rare, only 1-8% of the ovarian masses detected in pregnant women are malignant, with another 1% of low-malignant potential [2,3].

The proper management of ovarian cysts and ovarian cancer occurring in early pregnancy is provided in "Guidelines for Obstetrical Practice in Japan 2011". They recommend that tumor-like lesions, such as a theca-lutein cyst or chocolate cyst, especially and cysts of 5 cm or less should be simply observed, because most will undergo spontaneous resolution. However, any malignancy or borderline malignancy requires surgery, despite tumor size or gestational age [4].

We have recently experienced treating an ovarian clear cell carcinoma that was diagnosed only after birth. The patient had been diagnosed with a benign chocolate cyst by MRI before the pregnancy, and she was observed only, because there was no change in tumor size before or during pregnancy. She delivered a healthy female infant at the 40th week of gestation. We continued to observe the ovarian mass after the birth, at the gynecological outpatient ward, because a solid portion was detected in the ovarian mass. In spite of there being no ovarian enlargement, an MRI hinted at a borderline tumor. A laparotomy was performed and it revealed that the mass was a Clear Cell Carcinoma (CCC). We herein present the details of our own above noted case and we give a summary from the literature of the ovarian CCC associated with pregnancy collected as a review.

Case Report

A 39-years-old pregnant woman (gravida 4, para 1) in her 9th week of gestation was referred to the Obstetric Outpatient Clinic of Niigata University Medical and Dental Hospital for close examination of an ovarian mass of 5 cm in diameter revealed by ultrasound imaging. When she was 38 years old, she was previously diagnosed with a left chocolate cyst of 5 cm in diameter by Magnetic Resonance Imaging (MRI), showing high intensity on T1-weighted and low intensity on T2-weighted scoring. The cyst wall was not thickened, and the several mural nodules showing low intensity in T1- and T2-weighted MRI, which was suspected as hemosiderin, were not enhanced. At that time, the serum level of CA125 was 13 U/ml (normal level 0-32).

Serial ultrasonographic examinations were performed during the pregnancy and the size of the ovarian tumor did not increase. She was counseled about the potential for chromosomal anomaly due to her age, and genetic amniocentesis was performed at the 16th week of gestation. The results of a cytogenetic analysis of cultured amniotic cells revealed a normal karyotype of 46, XY. The patient was hospitalized with the onset of spontaneous labor pain in the 40th week of gestation, and a female infant weighing 3324 g was delivered, with Apgar scores of eight and nine at one and five minutes after delivery. Mild atonic bleeding occurred. Oxytocin and methylergometine maleate were promptly injected. She was discharged from our hospital on the 5th day postpartum.

Thereafter, she underwent repeated examinations by ultrasound to monitor the ovarian mass at 1, 2 and 5 months after birth. Nine months after delivery, the solid part of the mass grew to 4 cm in diameter by ultrasound. The serum level of CA125 was still 6. MRI of the pelvis with intravenous contrast enhancement was performed. It revealed a cystic tumor measuring 4.1×3.2 cm in size in the pelvis. The tumor was composed of multiple cystic parts. The mural nodules were gradually enhanced by a dynamic study. Computed Tomography (CT) scans of the chest, abdomen, and pelvis were performed. The scans revealed that the upper abdomen and chest were within the normal limits. Clear cell borderline tumor was highly suspected and a laparotomy was performed, after obtaining the patient's informed consent. Both pelvic and peritoneal washing specimens were obtained, but revealed no malignant cells. An intraoperative examination of frozen sections of the left ovary revealed a serous borderline tumor. Therefore, a total hysterectomy, bilateral salpingo-oophorectomy, partial omentectomy, and biopsies of the pelvic lymph nodes were performed. The final

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Received July 03, 2013; **Accepted** August 01, 2013; **Published** August 08, 2013

Citation: Serikawa T, Takakuwa K, Enomoto T (2013) Management of Patients with Pregnancy-Associated Ovarian Clear Cell Carcinoma: A Mini-Review. Gynecol Obstet 3: 159. doi:10.4172/2161-0932.1000159

pathological diagnosis was confirmed to be a clear cell carcinoma within the left ovary. All other specimens were benign, thus the final disease stage was classified as FIGO stage Ia: pT1apN0M0. The patient's postoperative course was satisfactory and she was discharged 9 days after the surgery. The patient received no further treatment and remains free of disease at 6 months after the operation.

Review

Overview and collection of data

The incidence of ovarian cancer diagnosed during pregnancy is very low, ranging from 3 to 8 in 100,000 pregnancies [5,6]. As Behtash et al. [7] reported that the distribution of histologic types of ovarian cancer during pregnancy was similar to that among nonpregnant women of a corresponding reproductive age, there seems to be no relation characteristic between pregnancy and ovarian cancer. Clear Cell Carcinoma (CCC) is relatively rare and constitutes only about 4% to 12% of all epithelial ovarian cancers in Western countries, whereas, for unknown reasons, it comprises more than 20% of such cancers in Japan [8]. In general, women with CCC are likely to be younger than for other epithelial ovarian cancers [9]; however, there are very few published reports of pregnancy-associated CCC.

To determine the characteristics of pregnancy-associated CCC, we reviewed the existing literature on this specific condition [10-17]. A search was conducted on PubMed and the Japana Centra Revuo Medicina database using "ovarian clear cell carcinoma" and "pregnancy" as key words. Hits were carefully examined. Besides our case, we were able to accumulate 8 cases of pregnancy-associated CCC that had been reported on from 1996 to 2012.

Clinical background and surgical treatment

The clinical features of the nine patients are shown in Table 1. Concerning the age of patients, their mean age is 33.9 ± 5.0 years old. Regarding the symptoms at diagnosis, 8 of the 9 patients (88.9%) were asymptomatic. The size of cyst was generally larger than 6 cm, except for our case, which was about 4 cm. This what made it so difficult to diagnosis the malignancy during the pregnancy.

All 9 patients underwent surgery and the tumors were all resectable. A salpingo-oophorectomy was performed, on at least the affected ovary, and the FIGO stage, of those ovarian cancers with a description of the disease, were classified as FIGO stage I or II.

Obstetrical management and prognosis

According to the "Guidelines for Obstetrical Practice in Japan 2011", the treatment for ovarian cancer or borderline malignancy in pregnant women is surgical intervention, in spite of the tumor size or gestational age [4], Therefore, it is preferable to start surgical intervention as early as possible for a pregnancy-associated ovarian cancer, in order to increase the possibility of a maternal cure of the ovarian cancer.

When the first laparotomy was performed, the 9 cases were divided into four groups: 3 cases (33%) detected during pregnancy, 3 cases (33%) at cesarean section, 2 cases (22%) after termination of the pregnancy by induced abortion, and our case (11%), detected after delivery at term, respectively. Fortunately, all patients were alive and well, and all babies (except the two terminated by induced abortion) were alive and well.

In our case, the 5 cm ovarian tumor had existed before the pregnancy, but MRI did not indicate a malignancy and a tumor marker for ovarian cancer was within normal range. The mass size did not change during the course of a normal pregnancy, so we had no reason to perform a laparotomy. We only operated when the solid portion of the ovarian mass began to grow after birth and MRI suspected a borderline or malignant tumor.

Discussion

Steroid receptors, such as estrogen, progesterone, and androgen, are present in many malignant ovarian tumors [18]. As pregnancy suppresses secretion of pituitary gonadotrophins, pregnancy is expected to reduce the risk of epithelial ovarian cancer [19].

Case	Age (years)	Presenting Symptom	Size of cyst	Clinical course	Type of surgery	Chemotherapy	FIGO Stage	Maternal and Fetal outcome		Author/year*
								Mother	Fetus	
1	31	Asymptomatic	14	Laparotomy at 10 weks, then normal vaginal delivery at 39 weeks	R-SO, L-WR and biopsy of PLN	None	Ia	A/W, 2 years	A/W	Kobayashi/1996 [9]
2	33	Asymptomatic	6.5	Laparotomy at 13 weeks,then POC	TAH, BL-SO, OMT, and LND	Cisplatin irinotecan	Ic	Unknown	Dead, 12 weeks	Sugiyama/1997 [10]
3	31	Abdominal pain		1st laparotomy at 33 weeks, POC, then 2nd laparotomy and POC	1: CS and R-WR 2: MRH, B-SO, OMT, LND	Cisplatin irinotecan	IIc (a)	A/W, 1 years	A/W	Nagano/1999 [11]
4	28	Asymptomatic	6.5	Laparotomy at 37 weeks	CS and R-SO	None	Ia	A/W, 3 years	A/W	Satoh/2000 [12]
5	37	Asymptomatic	6	1st laparotomy at 14 weeks, then 2nd laparotomy at 34 weeks	1: L-Cystectomy 2: CS, TAH, B-SO and OMT	None	Ic	A/W, 4 years	A/W	Markrydimas/2003 [13]
6	35	Asymptomatic	13.8	1st laparotomy at 36 weeks, then 2nd laparotomy at POC	1: CS 2: L-SO	Paclitaxel carboplatin	Ic	A/W, 6 years	A/W	Hwang/2003 [14]
7	41	Asymptomatic	10	Laparotomy, then D&C	R-SO and OMT	None	Ic (b)	A/W	Dead, 12 weeks	Matsui/2010 [15]
8	28	Asymptomatic	10	Laparotomy at 9 weeks, then vaginal delivery at term	R-SO, L-WR, OMT and biopsy of PLN	None	IIc	A/W, 5 years	A/W	Shin/2012 [16]
9	41	Asymptomatic	4.1	Laparotomy at 1 year after birth	B-SO, TAH, OMT, and and biopsy of PLN	None	Ia	A/W, 6 years	A/W	Present case

*Number in Parenthesis, reference number

Abbreviations: A/W: alive and well; BL: Bilateral; CS: Cesarean Section; D&C: Dilatation and Curettage; L: Left; LND: Lymph Node Dissection; mRH: modified Radical Hysterectomy; OMT: Omentectomy; PAN: Paraaortic lymph Node; POC: Postoperative Chemotherapy; R: Right; SO: Salpingo-oophorectomy; TAH: Total Abdominal Simple Hysterectomy; WR: Wedge Resection

Table 1: Eight cases of ovarian clear cell carcinoma associated pregnancy.

Endometrioid and clear cell carcinomas are suspected of developing from ovarian endometriotic cysts and malignant change occurred in 8 of 950 (0.8%) cases of ovarian endometriosis [20]. And Nishida et al. reported that malignant change occurred in 0.7% of ovarian endometriosis [21]. However the hormone receptor status of the ovarian tumor during pregnancy and pregnancy-related malignant change were not reported to the best of our knowledge. Furthermore the guideline for ovarian cancer complicated with pregnancy does not exist at present.

Therefore, it will be needed to explore the malignant change of endometriotic cysts related to the pregnancy. We fortunately diagnosed early stage of ovarian cancer because of close follow-up after birth, so that careful follow-up for patients with endometriotic cysts not only during pregnancy but also after giving birth is important for early detection of ovarian cancer.

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