A case of endodermal sinus tumor associated with the first pregnancy and successful management of the second pregnancy: a case report and review of the literature

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Summary

Background: Pregnancy complicated by endodermal sinus tumor (EST) of the ovary has rarely been reported.

Case: A huge ovarian EST causing bowel obstruction was found in a 22-year-old patient at 34 weeks of gestation. Abnormally high alpha-fetoprotein (AFP) levels suggested a malignant germ cell tumor of the ovary. The patient was submitted to cesarean section and fertility sparing surgery, and then received four courses of combination chemotherapy. There was no evidence of recurrence 19 months after initial treatment but transvaginal ultrasound (US) evaluation showed an intrauterine pregnancy of six weeks. We delivered a 3,200 g healthy male baby with Apgar scores of 8 and 9 by elective cesarean section at 39 weeks of gestation.

Conclusions: Successful outcome of a second pregnancy is possible after treatment with fertility sparing surgery and combination chemotherapy for an endodermal sinus tumor associated with a first pregnancy. Moreover checking of weekly AFP levels and performing monthly abdominal US could be effective for surveillance of these pregnancies. However management of EST during pregnancy should be based on consideration of the patient's presenting condition, preferences, and gestational age.

Key words: Pregnancy; Endodemal sinus tumor.

Introduction

Endodermal sinus tumor (EST) comprises about one fifth of ovarian germ cell tumors and is the second most common malignant tumor of germ cell origin [1, 2].

Pregnancy complicated by an EST of the ovary is extremely rare. A search of MEDLINE showed that only 23 cases have been reported thus far (Table 1) [3-23]. In such situation, management of the pregnancy and the disease, chemotherapy usage during pregnancy, screening methods of first and following pregnancies and definitive therapy after completion of the family are subjects that should be considered.

A case of ovarian EST complicating a previous pregnancy and management of the second pregnancy and disease is presented.

Case Report

A 22-year-old, gravida 1, para 0, woman presented at our emergency gynecology clinic with the complaint of abdominal pain and a history of 5 kg weight loss during the previous month. She had had nausea and vomiting for three days at 34 weeks of gestation. There was no significant familial or past history. She was on no medication and had no allergies. On physical examination all findings were normal except for an abdominal mass on the left of the uterus extending from the pelvis to the xiphoid. Ultrasound (US) showed that the fetus had biometric measurements of 33 weeks and three days of gestation which corresponded with the date of her last menstrual period. No fetal anomalies were evident. A huge multilocular tumor (28 cm x 21 cm) reaching the xiphoid with some solid and cystic areas located left of the uterus, likely arising from the left ovary, was observed in US examination of the mass. Examination of serum tumor markers showed that alpha-fetoprotein (AFP) was > 1,210 ng/ml (normal value at 38 weeks of gestation < 102 ng/ml), CA125 was 266 U/ml, CA 19-9 was 5.6 U/ml (normal value < 34 U/ml), CEA was 1.4 ng/ml, β human chorionic gonadotropin (βhCG) was 7170 IU/l, and lactate dehydrogenase LDH was 589 U/ml. The abnormally high AFP level suggested a malignant germ cell tumor of the ovary.

Termination of the pregnancy was decided after stabilization of the patient's general condition and recognition of complete bowel obstruction. The patient delivered by cesarean section, through a midline incision, a 1,900 g female baby with Apgar scores of 7 and 9. A mass originating from the left ovary and measuring 28 x 18 x 14 cm was detected. It was densely adherent to the abdominal sidewalls and sigmoid flexure of the transverse colon, and ruptured during left salpingo-oophorectomy. After diagnosis of an EST on frozen section, fertility sparing surgery was carried out with omentectomy and multiple biopsies from where the tumor was attached to the peritoneal surfaces. Postoperatively the mother and fetus did well.

Final pathological evaluation reported an EST of the left ovary. Cytologic washings were negative. There were no evidence of metastatic involvement of the omentum, placenta or multiple biopsies. However, because of the intraoperative rupture of ovary, the tumor was classified as FIGO Stage Ic.

Postoperatively four courses of treatment with bleomycin (30 mg IV on days 1, 8, 15), etoposide (100 mg m^2 IV on days 1-5) and cisplatin (20 mg m^2 IV on days 1-5) (BEP) were given as adjuvant chemotherapy. The courses were repeated at 21-day intervals. No significant nephrotoxicity, neurotoxicity, pulmonary toxicity or myelotoxicity were observed. The patient was followed up by AFP levels, US evaluations carried out at 3-

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Table 1. — *Review of endodermal sinus tumor of the ovary associated with pregnancy.*

Reference	Presenting symptom	Gestational weeks at diagnosis	Stage	Therapy during pregnancy	Gestational week at delivery	Therapy after delivery	Outcome mother	Outcome of fetus
[1] Huntington R.W. *et al.*, 1970	–	–	–	–	–	–	–	–
[2] Novak E.R. *et al.*, 1975	–	–	–	–	–	–	Died of the disease at 6 months	
[3] Kurman R.J. *et al.*, 1976 (3 cases)	Abdominal pain	–	II	Surgery and chemotherapy	–	–	Died, cause no status	
[4] Azoury R.S. *et al.*, 1979	Abdominal distension	27		Surgery	–	–	Died of the disease at 2 months	–
[5] Weed J.C. *et al.*, 1979	Rapid abdominal enlargement	8	III in first pregnancy, second pregnancy	LSO, D&C 5 days after the operation	– 33	VAC 12 courses VAC 2 courses	Recurred 12 months after initial treatment at the 33 weeks of the second pregnancy. Died of the disease 8 days postpartum	–
[6] Petrucha R.A. *et al.*, 1980	Lower abdominal and back pain, abdominal distension	18	IIc	Termination	TAH, BSO	TAH+BSO VAC 12 courses	Died of the disease at 24 months	stillborn
[7] Schwartz R.P. *et al.*, 1983	Abdominal pain, shortness of breath	20	I	Termination	Hysterotomy	LSO, Omentectomy	Died of the disease at 6 months	stillborn
[8] Ito *et al.*,1984	Adnexal mass associated with pregnancy	9	I	Termination	D&C	TAH+LSO MMC 6 courses	20 months NED	–
[9] Malone *et al.*, 1986	Abdominal distension, pain, pedal edema	25	Ic	RSO, VBP 2 courses	32/CS	MSLL VBP 3 courses	12 months NED	Healthy
[10] Kim D.S., Park M.I., 1989	Low abdominal pain, rapid abdominal enlargement	15	Ic	LSO, VAC 6 courses	37/SD	VBP 2 couses TAH and RSO	33 months NED	Healthy
[11] Metz *et al.*, 1989	Acute abdominal pain	13	I	LSO VAC 5 courses Vincristine 2^{nd}, 3^{rd}, 4^{th} week of first course	37/SD	VAC 7 courses Actinomycin D replaced with Adriamycin for the last 3 courses	12 months NED	Healthy
[12] Farahmad *et al.*, 1991	Bilateral flank pain	17	I	Termination	TAH+BSO	TAH, BSO, PLN, omentectomy, VBP 6 courses	27 months NED	–
[13] Elit *et al.*, 1999	Abdominal pain	23	II	LSO BEP 3 courses	28/CS	BEP 4 courses	16 months NED	Ventri-culomegaly
[14] Van der Zee *et al.*, 1991	Increase in size of adnexal mass during follow-up of pregnancy	18	I	LSO, left pelvic lymphadenectomy, omentectomy	33/CS	BEP 4 courses, second-look laparotomy	24 months NED 12 months NED	Healthy
[15] Rajendran *et al.*, 1999	Abdominal pain	19	Ia	RSO	32/CS	TAH+LSO, colostomy BEP 4 courses		Healthy
[16] Arima *et al.*, 2000	Abdominal fullness virilization	28	I	–	32/CS	LSO, omentectomy, apendectomy	3 months NED	Healthy
[17] Malthora *et al.*, 2000	Acute abdominal pain	15	Ic	LSO, BEP 2 courses	31/CS	Suboptimal debulking	Died after surgery	Healthy
[18] Cyganek *et al.*, 2002	–	32	–	–	32/CS	–	Died of the disease at 6 months	–
[19] Shimizu *et al.*, 2003	Increase in size of adnexal mass during follow-up of pregnancy	19	Ic	RSO	36/CS	SLL, BEP 3 courses	27 months NED	Healthy
[20] Han *et al.*, 2005	Lower abdominal pain	20	Ic	RSO, omentectomy BEP 5 courses	35/VD	BEP 1 course	6 years NED	Healthy
[21] Aoki *et al.*, 2005	Increase in size of adnexal mass during follow-up of pregnancy	22	Ic	RSO	35/VD	PEPep 7 courses	39 months NED	Healthy
[22] Present report	Acute abdominal pain, complete bowel obstruction	34	Ic	–	34/CS	RSO, Omentectomy	30 months NED, successfully completed 2^{ns} pregnancy	Healthy

SLL: second-look laparotomy; MSLL: modified second-look laparotomy; CS: cesarean section; SD: Spontaneous delivery; RSO: right salpingooopherectomy; TAH: total abdominal hysterectomy; LSO: left salpingo-oophorectomy; TAH+BSO: total abdominal hysterectomy plus bilateral salpingo-oophorectomy; VAC: vincristine, actinomycin D, cyclophosphamide; MMC: mitomycin C, cis-platinium, cyclophosphamide; VBP: vincristin, bleomycin, cis-platinium; PEPep: cis-platinium, etoposide, peplomycin.

month intervals and computerized tomography (CT) performed at 6-month intervals. AFP levels returned to normal levels after the second chemotherapy course. The first menstruation occurred six weeks after completion of the chemotherapy courses. No evidence of recurrence was detected at 19 months after the initial treatment but transvaginal US evaluation showed an intrauterine pregnancy of six weeks. The β hCG level was over 6000 IU/ml. We informed the patient and her family. They decided to continue the pregnancy. Surveillance of the pregnancy and disease was performed by means of AFP levels at one-week intervals plus abdominal US at one-month intervals.

AFP levels determined at one-week intervals during the pregnancy were never over the values that are normal for the corresponding gestational age (1.47-173.54 ng/ml). Also the first trimester screening test applied for trisomies was negative (1/19000). Her AFP level was 68.07 ng/ml (1.47 MoM) and detailed US showed no anatomical abnormalities in terms of neural tube defects at 16 weeks of gestation. We delivered a 3,200 g male baby with Apgar scores of 8 and 9 by elective cesarean section at 39 weeks of gestation. No evidence of the disease was observed on the peritoneum or lymph nodes and washing was also negative. Postoperatively the mother and fetus did well.

Discussion

Endodermal sinus tumors are rare ovarian germ cell tumors which occur more frequently in adolescents and young adults, allowing the possibility to be detected during pregnancy [22]. The incidence of diagnosis of an adnexal mass during pregnancy is between one in 800 and one in 1,400. Moreover the incidence of malignancy in ovarian tumors complicating pregnancy is between 2% and 5%. Germ cell tumors and epithelial ovarian cancers are the most common ovarian malignancies diagnosed in pregnancy [24]. However EST is very rarely reported.

Endodermal sinus tumors associated with pregnancy grow rapidly; some cases develop serious symptoms within 24 hours to one week. As a result of this rapid growth, they may present with acute abdomen, torsion or bleeding into the tumor [5, 9, 25]. Additionally Arima *et al.* reported a pregnant woman with an EST who presented with virilization and elevated serum testosterone. Microscopic evaluation of this tumor showed Leydig cells [18].

Our patient was also 22 years old, at 33 weeks and three days of gestation, and presented to our emergency gynecology clinic with acute abdominal pain.

Complications of ovarian cysts in pregnancy include obstructed labor, torsion, hemorrhage, rupture, infection and malignant changes. However pregnancy does not alter the prognosis for ovarian malignancy where definitive treatment is given [26]. Bowel obstruction in patients with ovarian cancer may occur through several different mechanisms. Extrinsic occlusion may result from compression by the tumor, radiation, or postoperative adhesions [27]. In our case, bowel obstruction was diagnosed at presentation. This has not been reported in the other published 23 cases. An enlarged uterus due to gestation and an ovarian mass were thought to be the cause of the extrinsic compression resulting in bowel obstruction. All symptoms related to bowel obstruction vanished after the operation.

The measurement of tumor markers such as CA125, LDH, AFP, and βhCG in pregnancy poses a dilemma because these values are elevated in normal pregnancy and their clinical utility in pregnancy is therefore debatable [24]. Alpha-fetoprotein levels are elevated during pregnancy and are the predominant serum protein; it is therefore difficult to use AFP to diagnose and follow-up an EST in pregnancy [7, 24, 28]. However, detection of an adnexal mass and elevated AFP levels above the values matching with the gestational age led us to suspect the possibility of an EST preoperatively.

The treatment of ESTs consist of surgical exploration, unilateral salpingo-oophorectomy, and a frozen section for diagnosis. The addition of hysterectomy and contralateral salpingo-oophorectomy does not alter the outcome [29]. Also fertility sparing surgery has been advocated by some recent studies [28, 30].

Treatment of EST with surgery alone yields a poor prognosis with a five-year survival rate of only 13%. Fortunately this tumor is very sensitive to chemotherapy which can offer up to 80% long-term survival in early-stage disease. The BEP regime is the most widely used chemotherapy [31].

Our knowledge about the management of EST complicating pregnancy is limited with case reports in the literature because of its rarity. Although different approaches and chemotherapy combinations have been reported, the patient's presenting condition, age, preferences, and gestational age at diagnosis have been the main factors affecting the management frame.

The reported age of 23 cases at diagnosis varies between eight and 32 weeks of gestation. Management options that have been used to treat EST complicating pregnancies so far are termination of pregnancy plus surgery and chemotherapy [7, 8, 10, 14], termination of pregnancy plus surgery [9], surgery plus chemotherapy during pregnancy and chemotherapy after pregnancy [11, 13, 15, 22], surgery plus chemotherapy during pregnancy and surgery plus chemotherapy after pregnancy [12], surgery plus observation during pregnancy and surgery and chemotherapy after pregnancy [16, 17], and surgery during pregnancy and chemotherapy after pregnancy [21, 23] (Table 1).

The combination chemotherapy regimes that have been used so far are vincristine-actinomycinD-cyclophosphamide (VAC) [7, 8, 12, 13], vincristine-bleomycin-cisplatinum (VBP) [11, 12, 14], mitomycinC-cisplatinum-cyclophosphamide (MMC) [10], bleomycin-etoposide-cisplatinum BEP [15-17, 21, 22], and cisplatinum-etoposide-peplomycin (PEPep) [23].

There are several reports of pregnant women with ESTs treated with combination chemotherapy who delivered normal infants [7, 11-13, 19, 22, 32]. However Elit *et al.* reported a pregnant woman who was treated with postoperative chemotherapy with BEP at 25 weeks' gestation who delivered an infant with ventriculomegaly and cerebral atrophy [15]. Also Shimuzu *et al.* reported a

patient with a Stage Ic EST who underwent surgical resection at 19 weeks of gestation but did not receive postoperative therapy. She delivered a normal infant at 36 weeks by cesarean section combined with second-look laparotomy. Subsequently, three courses of combination chemotherapy with BEP were administered after delivery because the patient was worried about the safety of chemotherapy before delivery [21]. Rajendran *et al.* reported an early recurrence in a patient with a Stage Ic EST who underwent surgical resection at 19 weeks of gestation and had her chemotherapy delayed until after delivery because of its potentially adverse effects on the fetus [17].

Thus we preferred to perform cesarean section, left salpingo-oophorectomy, omentectomy and multiple peritoneal biopsies because the patient was at 34 weeks of gestation with acute abdominal pain at presentation and wanted to preserve her fertility. Consequently we put her on four courses of the BEP regimen.

Although Weed *et al.* reported a patient who during the first pregnancy was treated for an EST, which recurred during the second pregnancy at 12 months after the initial treatment [7], there are several studies reporting successful outcomes after fertility sparing surgery plus chemotherapy treatment for malign ovarian germ cell tumors [33, 34]. Starting a new pregnancy within two years of completing the treatment for an EST is not advised [31].

In our case, the patient started a new pregnancy 18 months after completion of the treatment for EST complicating her first pregnancy. During the pregnancy her AFP levels were within normal range. The fetus was also found to be anatomically normal by ultrasound.

Moreover Aoki *et al.* suggested monitoring maternal serum alpha-fetoprotein isoforms (AFP-L2), depending on the affinity for *Lens Culinaris* agglutinin (LCA), as an indicator for a maternal source of AFP. This may help in earlier recognition of tumor recurrence during pregnancy [23]. However we could not use this method because of technical reasons. We used serial AFP levels and ultrasonography for the same purpose.

In conclusion, a successful outcome of a second pregnancy is possible after treatment with fertility sparing surgery and combination chemotherapy of an endodermal sinus tumor associated with a first pregnancy. Weekly checking of AFP levels and performing monthly abdominal US can be a method for the surveillance of these pregnancies. Nonetheless management of EST during pregnancy should be based on consideration of the patient's presenting condition, preferences, and gestational age.

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