ADVANCED ENDODERMAL SINUS TUMOR WITH CONTRALATERAL DERMOID TUMOR DURING PREGNANCY: A CASE REPORT AND LITERATURE REVIEW

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SUMMARY

Objective: An endodermal sinus tumor (EST) of the ovary and a contralateral dermoid cyst occur rarely in pregnancy. Alternative treatment for reducing the long-term sequelae in both the mother and fetus should be considered during pregnancy.

Case Report: At 27 weeks of gestation, a patient was diagnosed with advanced EST, FIGO (International Federation of Gynecology and Obstetrics) stage IIIC, by magnetic resonance imaging and surgery. Following optimal debulking surgery, three cycles of multi-agent chemotherapy, consisting of 25 mg/m² cisplatin and 100 mg/m² etoposide on days 1 to 4, were instituted at 21-day intervals. Maternal serum α-fetoprotein and CA125 titers soon returned to normal pregnancy levels. A healthy male infant was delivered at 38 weeks of gestation by cesarean section, after which a second-look laparotomy was performed. The micropathologic findings were negative for malignancy, except that a dermoid tumor of the right ovary was confirmed. Consolidation treatment with two cycles of chemotherapy, consisting of 20 mg/m² cisplatin and 100 mg/m² etoposide on days 1 to 5 and a total of 30 mg/day of bleomycin on days 6 and 7, was administered at 28-day intervals. The patient had no evidence of disease for 16 months, and her infant son has shown adequate growth and normal development.

Conclusions: For pregnant women with an EST of the ovary, the optimal treatment modalities might be initial optimal debulking surgery followed by alternative chemotherapy, and further standard chemotherapy after delivery. [Taiwanese J Obstet Gynecol 2004;43(2):113–119]

Key Words: endodermal sinus tumor, pregnancy, chemotherapy

Introduction

Ovarian cancer occurs rarely during pregnancy, averaging about 1 in every 18,000 to 25,000 deliveries; it is usually confined to the ovaries (71% stage I) [1]. A review of the English literature from 1976 to the present revealed eight cases of pure endodermal sinus tumor (EST) in pregnancy, all of which were treated with chemotherapy (Table) [2–9]; advanced disease was rare (1/8). In about one of every 1,000 pregnancies, surgical exploration is necessary due to an adnexal mass, according to the American College of Obstetricians and Gynecologists [10]. This mass is malignant in only about 5% of cases, compared with 15% to 20% in non-pregnant women. An adnexal mass during pregnancy may become symptomatic in 10% to 15% of patients as a result of torsion, rupture, or hemorrhage of the tumor [11].

ESTs are rapidly growing tumors but are also very chemo-sensitive. Nevertheless, cancer treatment during
pregnancy must be individualized and may differ from normal in order to take into account the health and welfare of both the mother and fetus, which are at odds when it comes to the use of chemotherapy. Experience with combination chemotherapy has demonstrated the maximal tumor cell kill rate possible within the range of toxicity [12]. However, the use of more than one drug is likely to have a more negative impact on the developing fetus. Thus, we attempted to determine whether a new treatment would be able to reduce the long-term sequelae of chemotoxicity in the fetus (neurodevelopmental and cardiopulmonary complications, etc.). The side effects of bleomycin when used in adults include fever, interstitial pneumonitis, and pulmonary fibrosis. However, the long-term complications of bleomycin to an exposed fetus, in which the lungs are immature before 34 weeks of gestation, have not been adequately studied because of the rarity of its use, and, thus, this remains a concern [10–12].

Our patient experienced spontaneous rupture of an advanced EST with bloody ascites and carcinomatosis at 27 weeks of gestation. After initial debulking surgery (<1 cm), modified chemotherapy with cisplatin and etoposide during pregnancy followed by a second-look laparotomy, she achieved micropathologic remission. The mother and baby are well, and the infant has shown normal growth and neurodevelopment up to the time of writing. We considered it worthwhile to report this rare case, presenting our experience and a follow-up discussion.

### Case Report

A 31-year-old woman, gravida 5, para 2, at 27 weeks of gestation was referred to the emergency department of our hospital with left upper abdominal distension and tightness for 4 days. A huge left adnexal mass with complex content was found on ultrasound. The left adnexa had only been 4 cm in diameter 1 month previously. Magnetic resonance imaging (MRI) showed an $18 \times 12 \times 10$ cm complex mass with both solid and

<table>
<thead>
<tr>
<th>Study</th>
<th>Gestational age at diagnosis</th>
<th>Stage and surgery</th>
<th>Chemotherapy during pregnancy</th>
<th>Maternal status</th>
<th>Delivery at</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malone et al, 1986 [2]</td>
<td>25 wk</td>
<td>Stage Ia, RSO</td>
<td>VBP $\times$ 2 courses, then additional 3 courses after delivery</td>
<td>A+W 27 mo</td>
<td>32 wk</td>
</tr>
<tr>
<td>Kim &amp; Park, 1989 [3]</td>
<td>15 wk</td>
<td>Stage Ic</td>
<td>6 courses (non-cisplatin), then additional 2 courses after delivery</td>
<td>A+W 33 mo</td>
<td>37 wk</td>
</tr>
<tr>
<td>Metz et al, 1989 [4]</td>
<td>13 wk</td>
<td>Stage I</td>
<td>VAC $\times$ 5 courses, then additional 7 courses after delivery</td>
<td>A+W 12 mo</td>
<td>Term</td>
</tr>
<tr>
<td>Farahmand et al, 1991 [5]</td>
<td>17 wk</td>
<td>Stage I, BSO, omentectomy</td>
<td>VBP $\times$ 6 courses, but bleomycin stopped after 4 courses</td>
<td>A+W 27 mo</td>
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<tr>
<td>Van der Zee et al, 1991 [6]</td>
<td>17 wk</td>
<td>Stage I</td>
<td>No chemotherapy, but 4 courses of chemotherapy (PEB) after delivery</td>
<td>A+W 24 mo</td>
<td>33 wk</td>
</tr>
<tr>
<td>Elit et al, 1999 [7]</td>
<td>23 wk</td>
<td>Stage II, LSO</td>
<td>PEB $\times$ 1 course</td>
<td>A+W 16 mo</td>
<td>28 wk</td>
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<td>Rajendran et al, 1999 [8]</td>
<td>19 wk</td>
<td>Stage Ia, RSO</td>
<td>No chemotherapy, but recurrence at 32 wk</td>
<td>A+W 12 mo</td>
<td>32 wk</td>
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<tr>
<td>Shimizu et al, 2003 [9]</td>
<td>19 wk</td>
<td>Stage Ic, SO</td>
<td>No chemotherapy, then 3 courses of chemotherapy (PEB) after delivery</td>
<td>A+W 27 mo</td>
<td>36 wk</td>
</tr>
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RSO = right salpingo-oophorectomy; VBP = vinblastine + bleomycin + cisplatin; A+W = alive and well; VAC = vincristine + actinomycin + cyclophosphamide; BSO = bilateral salpingo-oophorectomy; LSO = left salpingo-oophorectomy; PEB = cisplatin + etoposide + bleomycin; SO = salpingo-oophorectomy.
cystic components. Ascites was also noted (Figure 1). No relevant personal or family history was noted. Ovarian malignancy was suspected.

Laboratory studies showed a lactate dehydrogenase of 159 U/L and a serum \( \beta \)-human chorionic gonadotropin of 27,765 mIU/mL. Maternal serum \( \alpha \)-fetoprotein (MSAFP) was markedly elevated at 4,314.77 mIU/mL (> 12 × the median for gestation) and CA125 was 214.2 U/mL. Ultrasound revealed that the status of the fetus was adequate for gestational age, and showed an 11 × 10 cm complex mass thought to be of ovarian origin.

Progressive abdominal distension and tightness, not related to uterine contractions, were noted. Emergency laparotomy was performed under the impression of either acute tumor torsion of the ovarian malignancy or spontaneous rupture with internal bleeding. Through a midline incision, bloody ascites (1,400 mL) was found. The tumor was 17 × 11.5 × 10 cm, with parts of multiple cysts and a hemorrhagic solid tumor and a disrupted capsule growing out towards the left upper abdomen (32 cm in diameter) (Figure 2A). Disseminating tumors on the omentum, bilateral paracolic gutters, and bladder serosa were found. Debulking surgery included a left salpingo-oophorectomy, a partial omentectomy, and radical resection of tumor seedings. The residual tumors were smaller than 1 cm. The mother and fetus were well after surgery.

Frozen-section pathology showed EST at stage IIIc. Micropathologically, sections showed an ovarian tumor with nests of neoplastic hyperchromic and pleomorphic cells that were arranged in reticular, cord-like, papillary, or tubular structures in mucin-like pools. Schiller-Duval bodies, hyaline bodies, and large areas of necrosis were present (Figure 2B).

The next day, laboratory results showed that the activated partial thromboplastin time (APTT) and plasma thromboplastin (PT) were, surprisingly, elevated (APTT/control > 120/29.2; PT/control 46.5/10.2). However, no signs or symptoms of a bleeding tendency were found. Based on our past experience with yolk sac tumors, prolongation of APTT and PT may be induced by tumors and surgical manipulation. The APTT and PT values had fallen sharply by the next day, to APTT/control of 62.5/28.2 and PT/control of 10.2/10.2. The APTT/control on the second postoperative day was 42.5/28.
We decided to proceed with alternative chemotherapy using only cisplatin (25 mg/m²/day) and etoposide (100 mg/m²/day) for adjuvant treatment, injected on days 1 to 4 for three 21-day cycles until delivery. MSAFP and CA125 values were closely monitored to evaluate the chemotherapeutic response (Figure 3). Regular sonographic monitoring using Doppler flow showed a normal systolic/diastolic ratio and a normal amniotic fluid index, but the fetus was the size of one of 3 weeks’ less gestational age.

At 38 weeks of gestation, cesarean section and second-look laparotomy were performed. A 2,180 g male infant (< 5th percentile) was delivered; 1 and 5 minute Apgar scores were 8 and 9, respectively. No gross fetal anomalies were identified. In the mother, many scattered tiny papillary nodularities were found, disseminated throughout the abdominopelvic cavity, especially on the intestinal surface. No additional ascites was found. Surgery included total hysterectomy, bilateral salpingo-oophorectomy, appendectomy, retroperitoneal lymph node sampling, and excision of all the tiny scattered nodularities and adhesive bands on the peritoneal surfaces of the intestines, pelvis, and abdomen. The final pathology report showed no residual EST tissue, but there was a 3.7 × 2.0 × 1.0 cm dermoid cyst on the right ovary. MSAFP concentration was 58.8 ng/mL and the CA125 concentration was 42.3 µ/mL 5 days postoperatively. Two-cycle adjuvant chemotherapy with the addition of bleomycin was given to consolidate the cancer treatment. Cisplatin 20 mg/m² and etoposide 100 mg/m² were given for 5 days, followed by 30 mg bleomycin on days 6 and 7. Side effects of bleomycin chemotherapy included maternal fever, leukocytosis, and chest distress on day 7 of each course. The newborn baby suffered from growth restriction, hypoglycemia, and physiologic hyperbilirubinemia that was treated using phototherapy, but he did not develop leukocytopenia or thrombocytopenia. He has demonstrated normal growth up to the time of writing. The mother has also been disease-free for 16 months.

**Discussion**

The incidence of ovarian cancer in pregnancy varies widely in the literature, from 1 in 8,000 to 1 in 12,000 deliveries. About 44% of ovarian tumors during pregnancy are diagnosed in the first trimester, 17% during the second, 17% during the third trimester or at the time of cesarean section, and 22% during puerperium. However, only 3% to 6% of adnexal masses are true malignant neoplasms, including germ-cell (30–33%) and epithelial-cell (35–40%) malignancies [12]. ESTs are the second most frequent type of ovarian germ-cell tumor, the most aggressive and rapid-growing neoplasm, and are rarely found at an advanced stage during pregnancy.

Standard treatment for an EST consists of cytoreductive surgery with either adjuvant or therapeutic chemotherapy. Cisplatin-containing combination chemotherapy, preferably BEP (bleomycin, etoposide, and cisplatin) or POMB-ACE (cisplatin, vincristine, methotrexate, bleomycin, actinomycin, cyclophosphamide, and etoposide), should be used as primary chemotherapy. The introduction of multi-agent chemotherapy has revolutionized the treatment of malignant ovarian germ-cell tumors and can cure most advanced disease in more than 80% of patients.

Based on a review of the literature, exposure during the second and third trimesters leads to a 1.3% incidence of fetal malformations and to non-teratogenic sequelae (e.g. intrauterine growth restriction, neurodevelopmental complications of the central nervous systems) [7,13]. However, the long-term delayed effects on the infant’s hematologic, cardiac, and pulmonary systems, and on fertility, have yet to be described. The side effects of bleomycin include interstitial pneumonitis, fever, and pulmonary fibrosis, all of which were experienced by the mother in this case. In 1991, Loehrer et al conducted a randomized study of three cycles of etoposide plus cisplatin with or without bleomycin in 166 patients with germ-cell tumors of the testes [14]. They found that the BEP regimen had a relapse-free survival rate of 84% compared with 69% for the cisplatin and etoposide regimen (p = 0.03). Therefore, we tried an alternative chemotherapeutic strategy in which bleomycin was not used during the pregnancy but was
added after delivery, leading to final successful pathologic remission of the EST. Thus, alternative cisplatin-based chemotherapy may be considered after optimal surgery and with strict follow-up of tumor markers to eliminate, as far as possible, the side effects of multiple chemotherapeutic agents on fetuses.

Elevated MSAFP can result from pregnancy-related sources, as noted by Horbelt et al [15]. Extremely high MSAFP levels (> 9 multiples of the median) in the absence of fetal abdominal wall defects and anencephaly should raise the possibility of germ-cell tumors of either gonadal or extragonadal origin [15,16]. Extragonadal origins include non-malignant (hepatitis and inflammatory bowel disease) and malignant conditions (hepatocellular carcinoma). MRI is now routinely used to evaluate focal and diffuse hepatic disease in both non-pregnant and pregnant women. In our case, MRI excluded a hepatic pathology. Non-pregnant women have very low to nondetectable serum α-fetoprotein levels (usually < 2 ng/mL), and all α-fetoprotein in excess of basal levels found during pregnancy is thought to originate from the fetus. Bergstrand and Czar demonstrated that MSAFP rises rapidly in the second trimester, reaching a maximum at about 32 weeks, and then declines until birth, when it is approximately 55 ng/mL. After birth, MSAFP rapidly disappears from the serum, and 3 weeks after full-term delivery, it can be detected only in very small amounts (0–15 ng/mL) [17]. In our case, the MSAFP and CA125 levels declined rapidly and reached a 75% response rate after the first chemotherapy course. This encouraged us to continue to administer this chemotherapeutic regimen. The tumor markers were close to normal and were compatible with the micropathologic findings from surgical exploration. Thus, we consider that, when there is an EST during pregnancy, MSAFP and CA125 are good follow-up markers to evaluate chemotherapeutic potency and response rate.

EST should be considered in the differential diagnosis of a complex abdominal mass in girls and young women. The cut surface of the tumor has cystic and solid areas, as well as extensive areas of hemorrhage and necrosis. On sonography and computed tomography (CT), EST presents as a large, complex abdominal mass, with the cystic components more visible on CT. ESTs are well-enhanced solid tumors on both CT and MRI. However, compared with CT findings, these tumors in MRI studies are associated with striking enhancement and numerous signal voids (because of their hypervascular nature), areas of hemorrhage that exhibit a high intensity on T1-weighted MRI, and heterogeneous high intensity (reflecting edematous stroma, cysts, and hemorrhage) on T2-weighted MRI, as in our case [18–20].

A coagulatory disorder may be strongly related to angiogenesis and tumor progression. Cancer patients may experience problems with hemostasis due to coagulation factor inhibitors or fibrinolytic activators produced by the neoplasm. Some tumors directly synthesize inhibitors, whereas others produce inhibitors via tumor necrosis. In either case, these inhibitors cause dysfunction of naturally occurring coagulation factors and coagulopathies ensue, leading to disseminated intravascular coagulation (DIC). DIC is noted most frequently in the latter phases of malignancy, when the host is debilitated and the neoplasm widespread. Chronic DIC, which occurs less frequently, may present with only laboratory abnormalities, such as APTT and PT, as evidence of the ongoing process. As with other cancer-related coagulopathies, successful treatment of DIC consists of eliminating the underlying neoplasm, as in our case [21].

In a normal pregnancy, the components of coagulation and blood volume are altered to facilitate hemostasis. Factors I (fibrinogen), VII, VIII, IX, and X are elevated, but changes in the platelet count are negligible. When stress such as hemorrhage occurs, plasminogen-plasmin conversion is stimulated, initiating coagulation and fibrinolysis. However, the incidence of DIC in obstetric patients is difficult to ascertain owing to the wide variation in precipitating events and the exceedingly complex range of clinical manifestations. The syndrome may occur in association with a wide variety of obstetric complications, including pregnancy-induced hypertension, abruptio placenta, amniotic fluid embolism, intra-amniotic injection of saline, hemorrhagic shock, and sepsis [22]. No obstetric problem related to coagulopathy occurred in this case. We postulated that the DIC syndrome, especially the postoperative laboratory abnormalities in this case, is attributable to cancer induction by the advanced stage of the EST [21,22]. However, larger studies need to be conducted to investigate this relationship further.

An etiologic classification of some known causes of small-for-gestational-age fetuses includes constitutionally small mothers, poor maternal weight gain, congenital fetal infections, congenital malformation, chromosome abnormalities, severe malnutrition, vascular disease, chronic renal disease, chronic hypoxia, maternal anemia, placental and cord abnormalities, teratogens, and drugs. Limited use of cisplatin in pregnancy has been reported, with no known complications that can be clearly attributed to cisplatin alone [23]. There have been no reports concerning fetal malformation related to the use of etoposide; however, intrauterine growth restriction and pancytopenia in neonates have been reported [24].
Benign cystic teratoma is associated with 5% to 10% of malignant germ-cell tumors. However, an ipsilateral or contralateral dermoid cyst is present in 14% of ESTs, as in our case [25]. The pathogenic theory, which suggests an origin from a primordial germ cell, is now the most widely accepted. These tumors arise from a single germ cell [26].

The occurrence of a malignancy during pregnancy and the decision-making process are difficult for the patient, her family, and the health care team. In the third trimester, the baby can often be delivered before beginning therapy, if the condition of the fetus is good based on a strict evaluation. The decision-making process, in our experience, should include the expectant mother and her family. The consultation should include information on fetal well-being and prematurity, the prognosis under hospital care, the toxicities of chemotherapeutic agents, and the relationship between cancer, pregnancy, and maternal outcome. Maternal outcome is strongly associated with optimal debulking surgery and the chemotherapeutic effect together with close follow-up of tumor markers (AFP and CA125) if pregnancy is to be continued. On the other hand, delays in initiating chemotherapy should be avoided because of the progressive nature and fatal characteristics of this disease. Fetal outcome is strongly related to an assessment of fetal well-being by ultrasound and a biophysical profile. If problems with fetal lung maturity or fetal distress are detected or suspected, immediate cessation of therapy is indicated.

In the rare event of ovarian cancer during pregnancy, we suggest trying an alternative multi-agent chemotherapy regimen during pregnancy, based on non-pregnancy experience for cancer treatment, then changing to standard treatment after delivery. The potential benefits of alternative chemotherapy with deletion of bleomycin include not only reduced long-term undesirable toxicities to the fetus and mother without significantly compromising anti-tumor activity, but also the reduced possibility of consequent multidrug resistance. Further evaluation is required to confirm the activity and therapeutic index, and to determine the optimal dose and schedule to be used in a pregnancy with ovarian cancer.

References


