Clear cell ovarian carcinoma in a pregnant woman with a history of infertility, endometriosis and unsuccessful IVF treatment

G. Makrydimas[1], A. Sotiriadis[1], E. Paraskevaidis[1], N. Pavlidis[2], N. Agnantis[3], D. Lolis[1]

[1]Department of Obstetrics and Gynecology, [2]Department of Medical Oncology, [3]Department of Pathology, University Hospital of Ioannina, Ioannina (Greece)

Summary

Ovarian cancer in pregnancy is a very rare event. We present here the case of a 37-year-old woman in whom a clear cell ovarian carcinoma was diagnosed in the first trimester of pregnancy.

This patient had a history of infertility, endometriosis and two previous unsuccessful attempts of in vitro fertilization. Transvaginal sonography at six gestational weeks revealed a 6 x 4 cm ovarian cyst with an internal papillary excrescence. The cyst persisted throughout the first trimester, whereas the initial CA 125 value of 226 U/ml dropped to 61 U/ml at 12 gestational weeks. Exploratory laparotomy and cystectomy was performed at 14 weeks and the disease was classified as Stage Ic, arising in endometriosis. The couple decided to continue with pregnancy and the woman was followed by serial sonographic, MRI and CA 125 examinations. A cesarean section, hysterectomy, bilateral salpingo-oophorectomy and omentectomy was performed at 34 weeks. Histology and cytology were negative for recurrence. Four months later the woman and baby are doing well. We review cases of ovarian clear cell carcinoma diagnosed during pregnancy and discuss the association of endometriosis, infertility, infertility drugs and ovarian cancer.

Key words: CA 125; Clear cell cancer; Endometriosis; Ovarian cancer; Pregnancy.

Introduction

The coexistence of ovarian cancer and pregnancy is a very rare event with an estimated incidence between 1 in 10,000 and 1 in 100,000 deliveries [1]. This happens mainly because pregnant women are usually young, while ovarian cancer presents later in life. However, maternal age has been increasing in most Western countries during the last decades, and the incidence of cancer in pregnancy is expected to be higher.

It is also possible that the true incidence of this condition is underestimated, since diagnosis of ovarian neoplasms may be difficult during pregnancy as a result of their extrapelvic displacement by the growing uterus. In general, ovarian tumors are asymptomatic or accompanied with only mild, non-specific symptoms and can be incidentally discovered at the time of cesarean section [2]. Alternatively, acute abdominal pain in case of ovarian torsion can lead to surgical operation and the diagnosis is set intraoperatively. However, the increasing use of transvaginal sonography early in pregnancy is now allowing accurate diagnosis of ovarian tumors and suspicious cases can be further investigated.

We present a case of a 37-year-old woman in whom ovarian clear cell carcinoma was diagnosed during pregnancy. This patient had a history of endometriosis and infertility, with two unsuccessful attempts of in vitro fertilization (IVF), conditions that have been associated with ovarian cancer.

Revised manuscript accepted for publication March 20, 2003

Case report

A 37-year-old, para-0 gravida-0, woman presented with amenorrhea of six weeks' duration and a positive pregnancy test. The patient had a 15-year history of primary infertility, with two unsuccessful attempts of in vitro fertilization, 18 and 12 months before. Diagnostic laparoscopy, which had been performed in the context of an infertility survey, revealed Stage III endometriosis, and an endometrioid cyst was removed from the left ovary, followed by treatment with GnRH agonist for six months. Her medical history was not remarkable, except for a well-regulated hypothyroidism. Her family history was negative for colon, ovarian and breast cancer.

Transvaginal ultrasound at admission revealed a normal intrauterine pregnancy. In the left ovary, a cystic formation (6.1 x 3.8 cm) was found, with thick but regular walls, containing a papillary excrescence (Figure 1). Repeat transvaginal sonography after two weeks demonstrated persistence of the cyst. Despite the young age of the patient and her negative family history, the morphologic features of the cyst raised the suspicion of malignancy. Initial serum CA 125 levels were 226 U/ml. The parents were counseled about the possibility of malignancy. Because of their desire to continue with the pregnancy, they chose to have serial CA 125 measurements (Figure 2) and sonographic examinations, and to have exploratory laparotomy performed after the first trimester when the operation is considered to be safer. Follow-up ultrasound scan at 12 weeks revealed a live fetus with normal growth and apparently normal anatomy, nuchal translucency thickness of 1.3 mm and presence of the nasal bone. The latter sonographic features practically decreased the risk of carrying a fetus with Down's syndrome to the levels of a 20-22 year old woman.

Laparotomy at 14^{+4} weeks revealed a large (approximately 4 x 6 cm) cyst in the left ovary, with a smooth external surface and features of an endometrioid cyst. On palpation a firm internal bulk was felt to be present. The cyst was removed with preservation of the ovary (cystectomy). During removal of the cyst, its

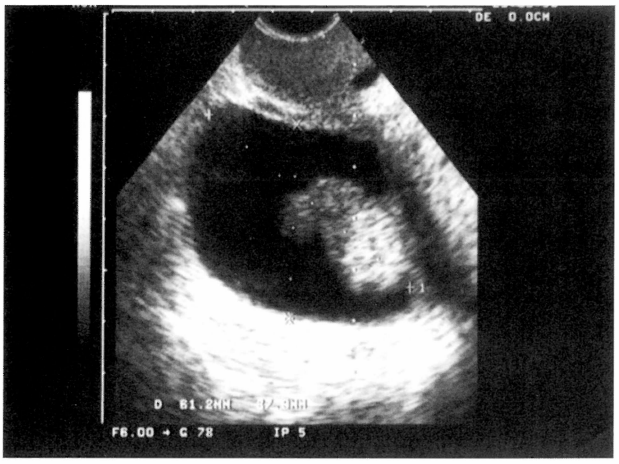

Figure 1. — Transvaginal sonographic examination during the sixth gestational week: Left ovarian cystic mass.

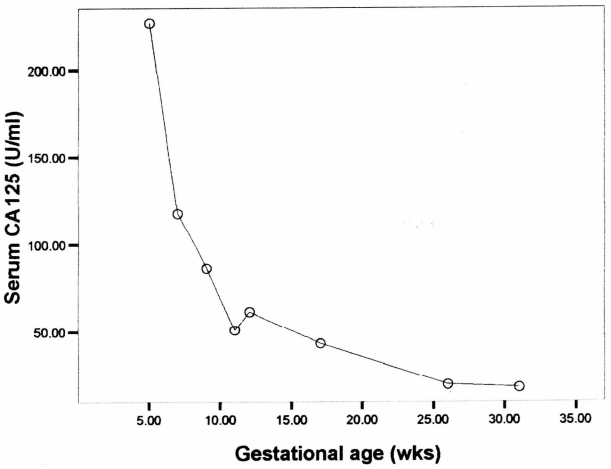

Figure 2. — Maternal serum CA125 levels during pregnancy.

wall spontaneously ruptured and thick, brownish fluid was aspirated. Peritoneal and omental samples were obtained for pathologic examination. Peritoneal lavage was done before and after cystectomy and the fluid was sent for cytologic examination.

Pathologic examination of the cystic wall demonstrated decidual transformation of the epithelium and development of clear cell carcinoma (Figure 3). The internal excrescence was also composed of neoplastic tissue, with cells that formed either compact foci divided by thin diaphragms, or papillary, tubular or microcystic formations. The neoplastic tissue did not invade into the cystic wall. Adjacent to the cystic wall there were multiple foci of ovarian endometriosis presenting decidual transformation. No signs of malignancy were found in the omental and peritoneal samples and no malignant cells were identified in the peritoneal fluid.

The parents were informed in detail about the diagnosis and the therapeutic options. They chose to continue the pregnancy and to postpone definitive treatment until delivery. The patient was followed as before, with serial biochemical, sonographic and magnetic resonance imaging (MRI) examinations. There was a continuous significant decline in CA 125 levels, from the initial value of 226 U/ml to 22 U/ml at the 31st gestational week. Detailed ultrasound demonstrated normal fetal anatomy, and ultrasound at 31 gestational weeks demonstrated normal fetal development. MRI at 18 and 28 gestational weeks showed no evidence of recurrence of the disease.

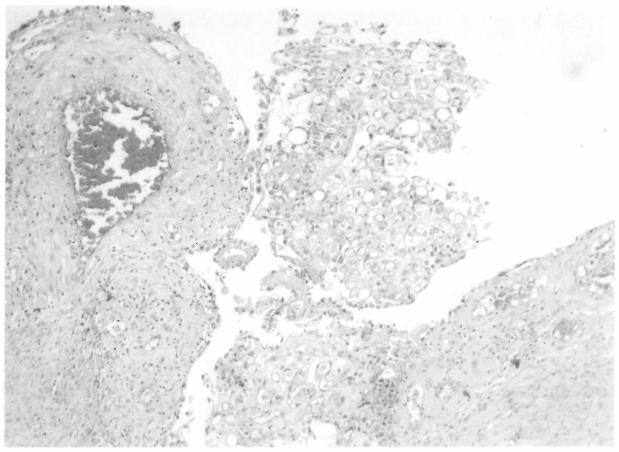

Figure 3. — Cystic wall with decidual transformation of the epithelium and development of clear cell carcinoma.

At 34 weeks and three days, when prematurity-related complications were practically eliminated, a scheduled cesarean section was performed, followed by total hysterectomy and bilateral salpingo-oophorectomy. A live female baby was born, with normal birthweight (2800 g) and an Apgar score of 10. The uterus and adnexae were removed uneventfully, and no macroscopic evidence of recurrence was found. Omentectomy was performed and peritoneal samples were obtained for histologic examination. Peritoneal lavage was performed before cesarean section and at the end of the operation and the fluid was sent for cytologic examination. No intra- or perioperative complications were noted.

Pathological examination of the uterus, adnexae, omentum, placenta, umbilical cord and peritoneal specimens was negative for malignancy. No malignant cells were identified in cytologic examination of the peritoneal fluid.

Four months postpartum, the patient is doing well, the infant is developing normally and no further treatment has been recommended.

In order to identify other cases of clear cell carcinoma during pregnancy, a MEDLINE and EMBASE search of the literature was carried out. References of retrieved articles were also scanned.

Discussion

Our case illustrates the coexistence of ovarian clear cell carcinoma arising in endometriosis with pregnancy, in a woman with a history of infertility and two unsuccessful attempts of IVF.

During the last decade, both infertility and infertility drugs have been linked with increased risk for subsequent development of cancer, especially breast and endometrial; however, results regarding ovarian cancer are more conflicting. A number of studies have shown a possible relationship between infertility, superovulation drugs and ovarian cancer [3-6]; however, these findings have not been confirmed by larger, more recent studies. Indeed, the overall risk for ovarian cancer was not found to increase in a large series of infertile women, nor was intake, duration and kind of IVF drugs found to increase this risk [7-10]. Most types of infertility were not associated with increased risk; however, one study found that women with unexplained infertility had ovarian cancer significantly more often than expected (OR 2.64) [7], whereas a pooled analysis of case–control studies [10] found that infertile women

with a history of endometriosis presented an increased risk for ovarian cancer (OR 1.73).

The relationship between endometriosis and ovarian cancer has been noted since 1925. Sampson estimated a malignant transformation rate of about 1% [11], whereas more recently a transformation rate of 0.7% was found [12]. Although no firm causative link has been established, it has been speculated that inflammation plays a role in ovarian carcinogenesis, and endometriosis may act via its marked local inflammation [13, 14].

According to a nested case-control study including 290 patients, endometriosis-associated ovarian cancer is characterized by lower stage disease, significant over-representation of endometrioid and clear cell carcinomas, predominantly lower grade lesions and significantly better overall survival [15]. Clear cell and endometrioid cancer were the most common histological types (23% each) in a series of 115 patients who had synchronous endometriosis and intraperitoneal cancer, and such women tended to be premenopausal and to have a lower stage disease [16]. Conversely, the prevalence of endometriosis in cases of clear cell and endometrioid ovarian carcinomas has been estimated to be 39.2% and 21.2%, respectively, compared to only 3% in cases of serous and mucinous tumors [17].

However, there are only two previous cases reporting coexistence of clear cell ovarian carcinoma and pregnancy [18, 19], and this is the third such case. Features of these cases are summarized in Table 1. Similar to Kobayashi *et al.* and Sugiyama *et al.*, an endometriotic lesion was found adjacent to neoplastic tissue. Two out of the three cases had a history of infertility/infertility treatment.

Irrespectively of the histological type, ovarian cancer is a rare event during pregnancy, although there are several case reports and small series, including even pregnant women as young as 15 years old [20].

In our case, the suspicion of malignancy was set at six gestational weeks, as a non-homogeneous, large cystic ovarian formation was identified during the first sonographic assessment of pregnancy. Recent advances in transvaginal ultrasonography, in combination with the policy of early ultrasound examination of pregnancy, allow identification of most pelvic masses. Sonographic features that raise a suspicion of malignancy include a complex or solid appearance, size greater than 5 cm and persistence of the mass over time [21].

In such cases, the timing of surgical intervention has to be scheduled. While early ovarian surgery may result in abortion, surgical treatment at around 14 weeks of gestation allows sufficient time for resolution of functional cysts and is safer for the pregnancy [2].

Staging and treatment are both performed during laparotomy; management of each case is individualized depending on maternal and gestational age, desire for childbearing, macroscopic appearance of the tumor and histological findings. Conservative surgery comprising unilateral oophorectomy and allowing the pregnancy to continue is acceptable in low grade tumors, restricted growth and certain histological types, provided that the contralateral ovary is normal [22]. Indeed, for Stage I patients (including Ic), the risk of bilateral tumor appears to be as low as 3.6% when the contralateral ovary is normal macroscopically, and survival does not differ between patients who undergo fertility-sparing surgery and those who undergo more radical surgery [23].

In our case, the patient and her husband decided initially that they wanted the most conservative treatment. After counseling, they opted not to take frozen sections, as they had decided to continue with the pregnancy regardless of tumor histology, provided that macroscopic findings would not be prohibitive.

Although not adequately sensitive nor specific, CA 125 is considered the best marker available for follow-up of ovarian cancer. Unfortunately, its specificity further decreases during pregnancy, as CA 125 values appear normally elevated (> 65 U/ml) in many pregnant women during the first trimester [24, 25]. Moreover, the levels of CA 125 can be significantly increased in women with endometriosis, depending on the extent of the disease [26, 27]. In the case of our patient, the suspicion of malignancy was already set by the morphologic appearance of the cyst (size, solid component), and serial measurements of CA 125 were used as an adjunct to follow-up. The initially high values of CA 125 were most likely due to endometriosis and the subsequently observed drop may be attributed to improvement of this condition with advancing gestation. Check and Hornstein [28] reported the case of a patient with an endometriotic cyst in which CA 125 increased rapidly early in the first trimester, reaching levels as high as 1000 U/ml and then spontaneously dropped to substantially lower levels during the second trimester. Given the drawbacks of CA 125 evaluation in pregnancy, we chose to use imaging methods (ultrasound and MRI) to check for recurrence of the disease. The experience on MRI use during pregnancy is

Table 1. — *Cases of clear cell ovarian carcinoma during pregnancy.*

Author	Maternal age	Endometriosis	Infertility Hx/Drugs	Gestational age	Management	Outcome
Kobayashi 1996	31	Yes	Yes/yes	5 wks	Right salpingo-oophorectomy at 10 wks	Delivery of a 3010 g male baby at 39 wks. Healthy 2 yrs after operation.
Sugiyama 1997	33	Yes	Not mentioned	8 wks	Surgery at 12 wks. Termination of pregnancy. Simple hysterectomy, oophorectomy, omentectomy, chemotherapy.	
Makrydimas 2003 (present case)	37	Yes	Yes/yes	6 wks	Left oophorectomy at 14 wks	CS, female baby 2800 g. Hysterectomy, ophorectomy, omentectomy. Healthy 4 mos after operation.

limited; however, it appears safe so far, has quite high sensitivity and may help in the differential diagnosis in cases of inconclusive sonographic findings [29, 30]; thus we utilized the two methods in a complementary way.

Concerning the safety of chemotherapy during pregnancy, vinca alkaloids and antibiotics seem to have no effect on the fetus; however cisplatin is implicated in growth restriction and hearing loss, while etoposide is implicated in pancytopenia [31]. There are several cases reporting administration of chemotherapy, including paclitaxel [32], for ovarian neoplasms during pregnancy, and in one case development of fetal ventriculomegaly was reported after administration of a bleomycin/cisplatin/etoposide regimen [33].

Coexistence of pregnancy, ovarian cancer, endometriosis and infertility is extremely rare. However, in all three cases of clear cell ovarian carcinoma during pregnancy reported so far, endometriosis was present. The number of cases is too small to clarify whether endometriosis per se, endometriosis-related infertility, IVF drugs or the combination of these factors could trigger carcinogenesis. However, it seems that there may be a potential of malignancy where cystic ovarian lesions are identified in these women, especially when they are large (> 4-5 cm) or rapidly growing. Early identification may improve treatment options, thus first trimester ultrasound assessment should not be confined to the gravid uterus but include the small pelvis as well.

Acknowledgement

The authors thank Dr. E. Zioga for kindly providing the slides of histological examination.

References

[1] Jolles C.J.: "Gynecologic cancer associated with pregnancy". *Semin. Oncol.,* 1989, *16* (5), 417.

[2] Grendys E.C. Jr., Barnes W.A.: "Ovarian cancer in pregnancy". *Surg. Clin. North Am.,* 1995, *75* (1), 1.

[3] Ron E., Lunenfeld B., Menczer J., Blumstein T., Katz L., Oelsner G. *et al.*: "Cancer incidence in a cohort of infertile women". *Am. J. Epidemiol.,* 1987, *125* (5), 780.

[4] Rossing M.A., Daling J.R., Weiss N.S., Moore D.E., Self S.G.: "Ovarian tumors in a cohort of infertile women". *N. Engl. J. Med.,* 1994, *331* (12), 771.

[5] Brinton L.A., Melton L.J. 3rd, Malkasian G.D. Jr., Bond A., Hoover R.: "Cancer risk after evaluation for infertility". *Am. J. Epidemiol.*, 1989, *129* (4), 712.

[6] Venn A., Watson L., Lumley J., Giles G., King C., Healy D.: "Breast and ovarian cancer incidence after infertility and in vitro fertilisation". *Lancet,* 1995, *346* (8981), 995.

[7] Venn A., Watson L., Bruinsma F., Giles G., Healy D.: "Risk of cancer after use of fertility drugs with in-vitro fertilisation". *Lancet,* 1999, *354* (9190), 1586.

[8] Parazzini F., Pelucchi C., Negri E., Franceschi S., Talamini R., Montella M., La Vecchia C.: "Use of fertility drugs and risk of ovarian cancer". *Hum. Reprod.,* 2001, *16* (7), 1372.

[9] Dor J., Lerner-Geva L., Rabinovici J., Chetrit A., Levran D., Lunenfeld B. *et al.*: "Cancer incidence in a cohort of infertile women who underwent in vitro fertilization". *Fertil. Steril.,* 2002 *77* (2), 324.

[10] Ness R.B., Cramer D.W., Goodman M.T., Kjaer S.K., Mallin K., Mosgaard B.J. *et al.*: "Infertility, fertility drugs, and ovarian cancer: a pooled analysis of case-control studies". *Am. J. Epidemiol.*, 2002, *155* (3), 217.

[11] Sampson J.A.: "Endometrioid carcinoma of the ovary, arising in endometrial tissue in that organ". *Arch. Surg.,* 1925, *10,* 1.

[12] Nishida M., Watanabe K., Sato N., Ichikawa Y.: "Malignant transformation of ovarian endometriosis". Gynecol. Obstet. Invest., 2000, *50* (suppl.) 1, 18.

[13] Ness R.B., Cottreau C.: "Possible role of ovarian epithelial inflammation in ovarian cancer". *J. Natl. Cancer Inst.,* 1999, *91* (17), 1459.

[14] Ness R.B., Grisso J.A., Cottreau C., Klapper J., Vergona R., Wheeler J.E. *et al.*: "Factors related to inflammation of the ovarian epithelium and risk of ovarian cancer". *Epidemiology,* 2000, *11* (2), 111.

[15] Erzen M., Rakar S., Klancnik B., Syrjanen K., Klancar B.: "Endometriosis-associated ovarian carcinoma (EAOC): an entity distinct from other ovarian carcinomas as suggested by a nested case-control study". *Gynecol. Oncol.,* 2001, *83* (1), 100.

[16] Modesitt S.C., Tortolero-Luna G., Robinson J.B., Gershenson D.M., Wolf J.K.: "Ovarian and extraovarian endometriosis-associated cancer". *Obstet. Gynecol.,* 2002, *100* (4), 788.

[17] Yoshikawa H., Jimbo H., Okada S., Matsumoto K., Onda T., Yasugi T. *et al.*: "Prevalence of endometriosis in ovarian cancer". *Gynecol. Obstet. Invest.,* 2000, *50* (suppl.) 1, 11.

[18] Sugiyama T., Nishida T., Kataoka A., Okura N., Iwanaga S., Yakushiji M.: "A pregnant woman with clear cell adenocarcinoma of the ovary arising from endometriosis and with benign and borderline adenofibroma of the clear cell and endometrioid types". *Eur. J. Obstet. Gynecol. Reprod. Biol.,* 1997, *72* (1), 47.

[19] Kobayashi F., Monma C., Nanbu K., Konishi I., Sagawa N., Mori T.: "Rapid growth of an ovarian clear cell carcinoma expressing LH/hCG receptor arising from endometriosis during early pregnancy". *Gynecol. Oncol.,* 1996, *62* (2), 309.

[20] Petrucha R.A., Ruffolo E., Messina A.M., Bouis P.J., Praphat H.: "Endodermal sinus tumor: report of a case associated with pregnancy". *Obstet. Gynecol.,* 1980, *55* (suppl.), 90S.

[21] Lerner J.P., Timor-Tritsch I.E., Federman A., Abramovich G.: "Transvaginal ultrasonographic characterization of ovarian masses with an improved, weighted scoring system". *Am. J. Obstet. Gynecol.*, 1994, 170 (1 Pt 1), 81.

[22] Makar A.P., Trope C.: "Fertility preservation in gynecologic cancer". *Acta Obstet. Gynecol. Scand.*, 2001, *80* (9), 794.

[23] Zanetta G., Chiari S., Rota S., Bratina G., Maneo A., Torri V. et al.: "Conservative surgery for stage I ovarian carcinoma in women of childbearing age". *Br. J. Obstet. Gynaecol.,* 1997, *104* (9), 1030.

[24] Niloff J.M., Knapp R.C., Schaetzl E., Reynolds C., Bast R.C. Jr.: "CA 125 antigen levels in obstetric and gynecologic patients". *Obstet. Gynecol.,* 1984, *64* (5), 703.

[25] Kobayashi F., Sagawa N., Nakamura K., Nonogaki M., Ban C., Fujii S. *et al.*: "Mechanism and clinical significance of elevated CA 125 levels in the sera of pregnant women". Am. J. Obstet. Gynecol., 1989, *160* (3), 563.

[26] Barbieri R.L., Niloff J.M., Bast R.C. Jr., Scaetzl E., Kistner R.W., Knapp R.C.: "Elevated serum concentrations of CA-125 in patients with advanced endometriosis". *Fertil. Steril.*, 1986, *45* (5), 630.

[27] Cheng Y.M., Wang S.T., Chou C.Y.: "Serum CA-125 in preoperative patients at high risk for endometriosis". *Obstet. Gynecol.,* 2002, *99* (3), 375.

[28] Check J.H., Hornstein M.D.: "Endometriosis causing very high early first trimester serum CA 125 levels". *Int. J. Gynaecol. Obstet.,* 1995, *48* (2), 217.

[29] Weinreb J.C., Brown C.E., Lowe T.W., Cohen J.M., Erdman W.A.: "Pelvic masses in pregnant patients: MR and US imaging". *Radiology,* 1986, *159* (3), 717.

[30] Kier R., McCarthy S.M., Scoutt L.M., Viscarello R.R., Schwartz P.E.: "Pelvic masses in pregnancy: MR imaging". *Radiology,* 1990, *176* (3), 709.

[31] Pavlidis N.A.: "Coexistence of pregnancy and malignancy". *Oncologist.,* 2002, *7* (4), 279.

[32] Sood A.K., Shahin M.S., Sorosky J.I.: "Paclitaxel and platinum chemotherapy for ovarian carcinoma during pregnancy". *Gynecol. Oncol.,* 2001, *83* (3), 599.

[33] Elit L., Bocking A., Kenyon C., Natale R.: "An endodermal sinus tumor diagnosed in pregnancy: case report and review of the literature". *Gynecol. Oncol.,* 1999, *72* (1), 123.

Address reprint requests to:
G. MAKRYDIMAS, M.D.
Department of Obstetrics and Gynecology
University Hospital of Ioannina
45500 Ioannina (Greece)