Case Reports

Synchronous endometrioid carcinoma of the ovary and endometrium associated with ovulation induction

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ABSTRACT

Over the last 2 decades great concern about the possible association between ovarian cancer and ovulation induction has been raised. Between the first reported case in 1982 and the end of year 2000, there have been 44 cases of ovarian carcinoma reported to occur in women previously treated with ovulation induction drugs. Most of these tumors were of the serous type with low malignant potential. In the present case, the patient had secondary anovulatory infertility and previous left cystoophorectomy for ovarian endometrioma. She was treated with human menopausal gonadotrophin alone or in combination with clomiphene citrate for 13 cycles prior to presentation. Screening ultrasound revealed multicystic right ovarian mass (15 x 9 x 6 cm). Hysterectomy and right salpingo-oophorectomy were carried out. Intraoperative and histological examinations showed stage 1A endometrioid ovarian cancer and well-differentiated endometrial adenoacanthoma with minimal myometrial invasion. A brief but critical review of published literature regarding the association of ovulation induction and increased risk of ovarian cancer is presented.

Keywords: Ovulation induction, endometrial cancer, endometrioid ovarian cancer.

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The etiology of ovarian cancer is still largely unknown; understanding the pathogenesis of ovarian cancer is necessary in order to plan strategies for better detection, prevention, and treatment. Several recent epidemiological studies suggest that environmental, genetic, and endocrinological factors play an important role in the etiology of ovarian cancer.[1-3] Data available in the literature regarding the endocrinological factor reveals that parity and ovulation suppression are the most important known protective factors affecting the risk of epithelial ovarian cancer.[2,4] On the other hand, women exposed to ovulation-inducing drugs are possibly at an increased risk of ovarian cancer.[3-5] Increasing numbers of ovarian cancer are being reported in association with human menopausal gonadotrophin (HMG) or in combination with clomiphene citrate (CC),[1,2] but the present case appears to be the first report in the literature in which concomitant endometrioid carcinoma of the ovary and endometrium were diagnosed within 6 months of long exposure to ovulation- inducing drugs.

Case Report. A 39-year-old woman, para 0+1, presented in 1999 with secondary infertility of 3 years duration. She had left cystoophorectomy in 1990 for large ovarian endometrioma. The patient conceived after she had had laparoscopic pelvic adhesolysis in 1996, but aborted spontaneously at 10 weeks gestation. She underwent 13 cycles of ovulation induction with HMG alone or in combination with CC over a 2-year period; the last cycle of ovulation induction was 6 months prior to

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presentation. Her past medical history was unremarkable, and there was no family history of breast or ovarian cancer in any of her first-degree relatives. Apart from distended lower quadrant abdomen, her physical examination was normal, transabdominal and transvaginal ultrasound showed a right adnexial multicystic mass with a few solid areas, measuring 15 x 10 cm. Computerized tomography (CT) confirmed the sonographic findings and showed no evidence of intraabdominal metastasis, enlarged lymph nodes or ascitis.

At laparatomy, a 15 cm smooth encapsulated and nodular right ovarian tumor was removed, the tumor was partly cystic and partly solid, abdominal organs including the uterus were explored and found to be normal, frozen sections revealed endometrioid carcinoma. Hysterectomy, infracolic omentectomy, pelvic lymphadenectomy, peritoneal wash and multiple peritoneal samples were performed. Cross-pathological examination showed a nodular right ovarian mass measuring 15 x 9 x 6 cm (Figure 1), with a loculated cut surface. The solid components showed a mucoid cut surface and the cystic components contained greenish and viscid fluid. The uterus measured 8 x 8 x 4 cm, and there was a friable mass inside the uterine cavity and superficially invading the myometrium. Microscopic examination of the uterus revealed well-differentiated adenocarcinoma with extensive metaplasia (also known as adenoacanthoma) (Figure 2). The tumor invaded less than one 3rd of the myometrium, and the endocervix and parametrial blood vessels were free from malignant cells (FIGO Stage 1B). Microscopic examination of the ovarian tumor revealed well-differentiated endometrioid carcinoma with extensive metaplasia (adenoacanthoma) and the histological appearance was uniform throughout (Figure 3). The cytology of peritoneal fluid was negative for malignant cells. The omentum, peritoneal biopsies and the pelvic lymph nodes showed no evidence of malignant cells, therefore the clinicopathological staging was FIGO Stage 1A. The postoperative period was uneventful, management was discussed with the patient, and the decision was made against chemotherapy. Over the past 2 years, she has been followed-up at 3-month intervals, her repeated physical examinations and pelvic ultrasound have showed no evidence of recurrence. Three months after surgery, serum CA-125 was 27 μ/ml (normal less than 35 μ/ml) and follow-up results were always less than 35 μ/ml.

Discussion. A synchronous primary endometrium carcinoma is found in 15%-50% of cases of endometrioid carcinoma of the ovary.[6] The clinical implications of correctly diagnosing these tumors as primaries versus ovarian cancer metastatic to the uterus are significant. Scully has suggested that if the endometrial carcinoma is less than 2 cm in

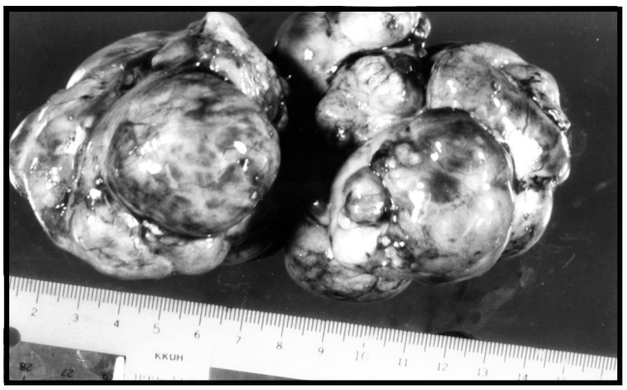

Figure 1 - Cross appearance of the cystic and nodular right ovarian mass.

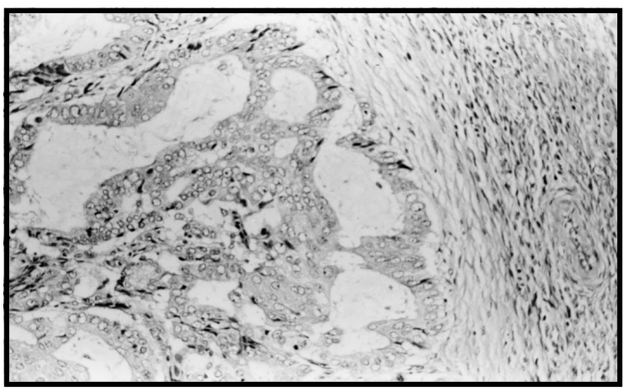

Figure 2 - Photomicrograph showing well-differentiated endometrium adenocarcinoma with superficial myometrium invasion (right side). (Hematoxylin and eosin, original magnification x 200).

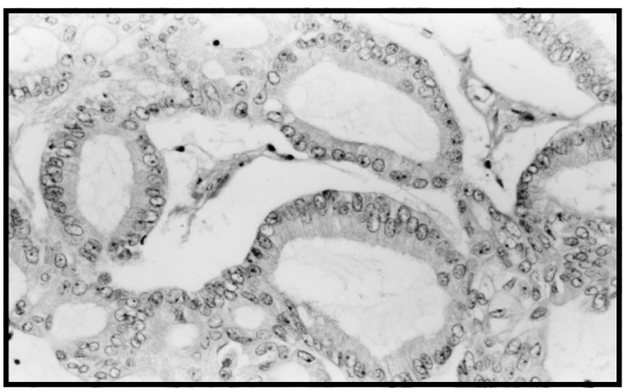

Figure 3 - High power view of ovarian tumor showing long slendor papillae lined by tall columnar pseudostratified cells characteristic of endometrioid adenocarcinoma and reminiscent to Figure 2. (Hematoxylim and eosin, original magnification x 400).

diameter, is well differentiated and only minimally invades the myometrium, the assumption of synchronous primary tumors in the ovary and endometrium can safely be made.[6] The presented patient appears to fulfill these criterias, and the prognosis of surgical treatment alone is considered to be good.[6] Six months prior to her presentation, the patient had been treated for a long period with HMG or in combination with CC, therefore the question of possible association between follicular stimulation and ovarian cancer was raised. At present, over 44 cases of ovarian cancer have been reported in association with CC or HMG,[1-4] however, these case reports entail clinical observation, and the reported association between ovarian cancer and ovulation induction drugs is not supported by any scientific data, they tend also to create false impressions, and may lead to unnecessary anxiety for patients and doctors alike.[7] Reviewing these case reports revealed that they do not prove a causal link between ovarian stimulation and ovarian cancer for several reasons; infertility alone is an independent factor for development of ovarian cancer,[8] type and duration of treatment are different, the time lag between treatment and diagnosis of tumor are variable, and most of the reported cases had inactive ovaries and ovulation was not induced in all treated cycles.

Case reports have highlighted concerns about the possible link between ovarian cancer and ovarian stimulation, however, the methodology used to investigate this association was mainly limited to retrospective case-control studies because ovarian cancer is a relatively rare disease. Epidemiological studies between 1992-2000 were identified using Medline database, 7 relevant papers are selected and briefly discussed. One of the first and most cited studies is the collaborative analysis of 12 United States of America (USA) case-control studies published in 1992.[9] The authors of the study concluded that the risk of invasive ovarian cancer was increased among women who had used fertility drugs and, in particular, nulliparous women. Two years later Rossing et al, showed that the relative risk of developing any ovarian tumor was 2.5 times higher in a cohort of infertile women who were using ovulation induction drugs, compared with the general population.[10] These 2 studies have aroused serious concern because of inadequate confounders control for cause of infertility, parity, and type and dose of drug used. However, the remaining 5 studies could not demonstrate any significant association between fertility drugs and invasive ovarian cancer.[4,5,8,11,12] According to a recent large Australian cohort study, women who take ovulation inducing drugs in conjunction with in-vitro fertilization are not at an increased risk of developing breast, ovarian or uterine cancer, however, women with unexplained infertility have elevated rates of uterine and ovarian cancer.[11] This study has the advantage of being based on a large cohort, but has several important limitations including the short period of median follow-up and 71% of the women had had no more than 3 treatment cycles of fertility drugs, nonetheless, it provides some reassurance for similarly treated women. Four studies show a statistically significant odds ratio when the association of ovulation induction and border line ovarian tumors are separately analyzed,[5,9,10,12] but another recent case control study found no statistical significant increase in the risk of borderline ovarian cancer among nulliparous women who were treated with fertility drugs compared with nulliparous untreated infertile women.[8]

In conclusion, current available data in the literature suggests that infertile women, particularly nulliparous women, are at risk of development of ovarian cancer irrespective of fertility treatment. While ovulation inducing drugs seem unlikely to cause invasive ovarian cancer, the data regarding the possible association of these drugs and borderline malignant ovarian tumors are inconclusive, therefore there is a great need for careful clinical evaluation of infertile patients during and after ovulation induction.

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