Treatment for infertility and risk of invasive epithelial ovarian cancer - a case report

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Summary

A 30-year-old women was admitted to the Institute of Gynecology and Obstetrics, Clinical Center of Serbia in April 2004 with the following diagnosis: *adnexal mass* soon after in vitro fertilization. Her history revealed salpingo-oophorectomy for mucinous cystadenofibroma of the left ovary eight years before and cystectomy of the right ovary three years before. At admission, the most remarkable findings were high temperature and elevated white blood cells with erythrocyte sedimentation rate. After the antibiotic treatment, laparatomy was performed and a multilocular right adnexal tumor was found. The right salpingo-oophorectomy was performed and pathological diagnosis was mucinous ovarian adenocarcinoma. Two weeks later, radical surgery was carried out and chemotherapy was applied. There is an urgent need for clear interpretation of the link between ovarian stimulation and ovarian cancer. An association between ovarian stimulation treatment and ovarian cancer has still not been completely proven.

Key words: Ovarian cancer; Ovarian stimulation.

Introduction

There is evidence that infertility in women and malignant tumors in female organs of reproduction can be seriously associated. An association between malignant ovarian tumors and infertility, as well as with early menarche and late menopause is also well known [1]. This is grounds for the hypothesis that changes that occur in the epithelium of the ovary during ovulation very likely cause spontaneous mutations which can bring about an oncogenic phenotype [2]. Likewise, reproduction hormones can lead to generation of malignant ovarian tumors [3]. Mucinous tumors account for 10-15% of all ovarian tumors. Out of that 75-80% are benign tumors, 10-15% are the so-called borderline tumors, and 5-10% are malignant tumors [4]. Mucinous adenocarcinoma is relatively rare and accounts for 5-10% of primary malignant ovarian tumors, and most often occurs between the age of 40 and 60 [4].

Case report

A 30-year-old woman was referred to the Institute of Gynecology and Obstetrics of the Clinical Center of Serbia in April 2004 due to pain in the abdomen, fever, and an adnexal tumor, generated after ovulation stimulation. The adnexal tumor had been punctured four days before admission. Her history revealed salpingo-oophorectomy for mucinous cystadenofibroma of the left ovary eight years before, and cystectomy due to cystadenoma of the right ovary three years before. During infertility treatment the previous year she had undergone triple ovarian stimulation according to the long protocol and with 35 ampoules of human menopausal gonadotropins (hMG).

Clinical findings were infection with signs of peritoneal inflammation. At admission the patient had a high temperature (up to 38,6 C), tachycardia with a pulse of 100 beats per minute, as well as slight peristalsis. Her white blood cell count was 18,000/ml and high granulocytosis was present. An immediate sonography was performed and a right adnexal tumor 140 x 100 ml in size was identified.

Due to the grave general condition of the patient and her wish to preserve fertility, it was decided that conservative treatment be applied. Ultrasound guided puncture of the right adnexal tumor was performed for the second time; 200 ml of mucinous fluid was removed and sent for bacteriological analysis. The result showed sterile tumor content.

Six days after admission, however, the patient developed a so-called acute abdomen with repeated high temperature, and therefore immediate laparotomy was performed. During the operation a multilocular right adnexal tumor 150 x 130 x 100 mm in size was identified. It was smooth, with a small quantity of fluid in the abdominal cavity, and was sent for cytological analysis. On removing the tumor from the adhesions on the adjoining tissues it ruptured, and a major quantity of mucinous content outflowed into the abdominal cavity. Bearing in mind the parity and age of the patient, no hysterectomy was performed, but a biopsy of the omentum majus was done, together with multiple peritoneal biopsies and appendectomy. Postoperational cure went on regularly.

When the histopathologic result arrived (ovarian mucinous adenocarcinoma GI NG I), it was decided that radical surgery should be undertaken. On performing another laparotomy, massive adhesions were observed both in the small intestine and the parietal peritoneum of the anterior abdominal wall. Thus adhesiolysis, total hysterectomy, total omentectomy and regional lymphadenectomy were performed. The postoperational course was unremarkable.

Of all histopathological samples that were examined, malignancy was found only in the right ovary sample, which had several points with benign cystadenoma. In view of the diagnosis of ovarian cancer at FIGO Stage Ic, cytostatics were prescribed.

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Discussion and Conclusion

The presented case is noteworthy for the fact that eight years before the appearance of the malignancy the patient was operated on due to a benign tumor on the other ovary of the same histological type. Moreover, in the ovary with the malignancy it was observed that both benign and malignant tissue of the same histological nature were present at the same time. This tumor was identical to the histological type of cancer on the ovary removed eight years before. Similar cases of patients with malignant tumors of the colon and breast, as well as benign and so-called borderline ovarian tumors, have been presented by other authors [5-7]. These findings raise the question of the carcinogenic potential of contemporary ovulation induction drugs, as well as the need for additional evaluation of patients that should undergo this kind of treatment.

Mucinous cystadenocarcinomas usually appear as large multiloculated cysic lesions containing echogenic material and papillary excrescences as was the case in our patient.

Transvaginal ultrasonography plays an important role in the assessment of adnexal masses [7]. Ultrasonic signs of malignant ovarian tumors include multilocular or multiple cysts, thick or irregular septa or walls, poorly defined borders, papillary projections, solid components and echogenic elements [7].

It is widely thought that there are common biological causes of infertility and ovarian cancer in women, and that therefore use of specific infertility medications does not increase the initial risk of ovarian cancer in these patients [8-10]. Such a conclusion is based on the analysis of eight different studies conducted from 1989 to 1999; the research did not show any association between unsuccessful treatment of infertility and increased risk of ovarian cancer, although a high incidence of borderline tumors was observed [8]. The research also showed that there is a specific association between endometriosis and endometrial and so-called clear cell tumors, with the hypothesis that endometriosis is a stage of development of these two histological types of ovarian cancer [8].

The study by Venn *et al.* [11] which covers 20,656 women undergoing ovulation stimulation in Australia does not show a long-term association between breast, ovarian and uterine cancer incidence and number of stimulation attempts. This study, however, reveals a high risk of breast and uterine cancer in the first year after in vitro fertilization. Of special importance is the hypothesis that ovulation stimulation in these patients may induce clinical manifestation of asymptomatic cancer. The patients were monitored for seven years, which does not mean that increased incidence could have been identified if the observation period had been longer.

In view of the fact that the role of gonadotropins in the stimulation of cell proliferation of ovarian epithelia, as well as presence of FSH receivers in these cells have been proven experimentally, the hypothesis that high levels of FSH may play a part in initiating carcinogenesis of the ovary is not groundless [12]. This hypothesis accounts for the highest incidence of epithelial ovarian cancer in perimenopausal and postmenapausal women, as well for the ever more frequent literature on the incidence of malignant epithelial ovarian tumors in patients undergoing ovulation stimulation. GhRH receivers have been found in the tissue of around 80% of epithelial ovarian tumors and in numerous cancer cell lines, such as EFO-21, EFO-27 and OV-1063/2 [12].

Epidemiology studies have shown an association between high incidence of ovarian cancer and exposure to high levels of gonadotropins during infertility treatment. Elevated gonadotropins are thought to influence growth of human ovarian cancer by inducing tumor angiogenesis [2]. Receivers of these hormones and factors of growth in epithelial ovarian cells are indicative of their role in malignant transformation and progression [2]. Association between fertility drugs and ovarian cancer is still unclear, which is why there is an urgent need for new studies that would interpret the controversial findings of the research that has been conducted so far in this area [12].

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