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CASE REPORT

Ovarian Carcinoma and Fertility Drugs : a New Dilemma ?

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ABSTRACT

In September 1994 a thirty-nine year old woman was admitted for right lower abdominal pain. During 1993-1994 there were 7 ovulation induction with HMG/HCG followed by either artificial insemination or IVF-ET procedure, the last one in April. Complaints dated from that time. Right lower abdominal pain persisted and even worsened after treatment with antibiotics. After preoperative evaluation adnexectomy was performed. Multilocular highly differentiated serous papillary cystadenocarcinoma was found, displaying moderate nuclear atypia and small areas of clear-cell differentiation, with foci of necrosis and stromal microinvasion. Elevated serum CA-125 levels at the time of operation slightly decreased four weeks after (from 145 IU/ml to 124 IU/ml). Serum concentrations of CA-125 were within normal range between 6th to 8th postoperative week. Nine weeks after operation, at the end of December, severe metrorrhagia occurred and curettage was performed. Histological evaluation of the obtained material showed papillary cystadenocarcinoma endometrioid endometrium. Serum CA-125 were extremely elevated to the values of 1,360 IU/ml. In January 1995, hysterectomy, adnexectomy and omentectomy was performed. There were no apparent

metastatic features during the operative procedure. CA-125 levels decreased to 110 IU/ml six weeks thereafter. From that time up to now this tumour marker was regularly determined every twelfth week and stayed within normal range. Ultrasonographic and CT examination confirmed her well-being. This study demonstrates on the direct chronological relation between hormonal stimulation of previously unremarkable ovaries and development of ovarian carcinoma.

Key words : fertility drugs, ovarian carcinoma, CA-125

For an infertile woman trying to get pregnant, the desire for a baby often overwhelms everything else. At the same time, number one fear for many people is cancer. Therefore, after confirmation that fertility drugs may dramatically increase the risk of ovarian cancer, thousands of women were thrown into conflict. Which emotion should they heed ? Is creating a new life worth jeopardizing the other ?

CA-125 is a glycoprotein produced in substantial amounts by coelomic epithelium during embryonic development. Its physiological role has not been elucidated until now. Low concentrations of CA-125 were found in serum of healthy adult women, while slightly higher levels were reported in endometriosis.[1,2] Extremely elevated levels of this antigen were found in serum of women suffering from ovarian cancer.[2] Jager et al[3] reported the unexpected finding of rapidly increasing serum levels of CA-125 in patients developing ovarian hyperstimulation syndrome (OHSS) as a consequence of treatment with human menopausal gonadotropins and human chorionic gonadotropin administered during preparation for in vitro fertilization.

Ovulatory stimulants were introduced for the management of ovulatory dysfunction in the early 1960s. The major classes of these fertility enhancing drugs available to the clinician are : the triphenylethylenes (CC-clomiphene citrate, chlorotrianisene, tamoxifen), the gonadotropins (FSH, LH, HMG, HCG), gonadotropin-releasing hormone (GnRH), GnRH analogues, and bromocriptine. However, treatment with these drugs may result in their side-effects, such as ovarian hyperstimulation syndrome, multiple, ectopic and molar pregnancy, and carcinoma.[4] It is well known that the risk of ovarian carcinoma decreases with the number of pregnancies and the duration of the use of oral contraceptives. One explanation for this phenomenon is that frequent ovulations rupturing the coelomic epithelium may lead to the development of ovarian cancer. Another explanation is that the formation and proliferation of ovarian carcinoma might be dependent on a direct action of LH and FSH. Thus, the decrease of LH-and FSH-secretion associated with pregnancies and the use of oral contraceptives might be the mechanism conferring some protection against ovarian cancer.[5-7]

Case Report

A 39 year-old woman was admitted for right lower abdominal pain. During 1993, there were 4 ovulation inductions with HMG/HCG followed by artificial insemination. Three ovulation induction (HMG/HCG) with IVF-ET were performed in 1994, the last at the end of April. During the last procedure, eleven follicles were punctured and 11 embryos were available for the ET. Three of them were transferred transcervically, while eight were frozen. Soon afterwards she had presented with

lower right abdominal pain that irradiated both to the back and to the right hip with symptoms of irritation of right cutaneus femoris lateralis nerve, and leukocytosis which was believed to be due to an ovarian abscess following ovarian punctures. From May to September, she was treated by antibiotics (third and fourth generation cephalosporins, aminoglycosides, sulphonamides, chinolones) parenterally and orally. Right lower abdominal pain persisted and even worsened, while elevated white blood count analysis showed shift to the left. Ultrasound scan showed that the left ovary was normal. The right one was 80 x 60 x 40 mm, with hyper-and hypoechogenic areas interpreted as pyoovary. After preoperative evaluation, the right adnexectomy was performed. Postoperative course was uneventful, and she left the department on the eight postoperative day.

On macroscopic examination the fallopian tube was unchanged. The ovary weighed 40 g, and measured 60 x 40 x 35 mm in diameter, grayish-brown in colour, with slightly nodular, tense capsule. On the cut surface, few small follicular cysts were found, as well as a large cyst measuring 40 x 25 x 25 mm in diameter, partly filled with grayish shaggy material and grayish-red fragments of tissue of papillary appearance.

Microscopically, multilocular highly differentiated serous papillary cystadenocarcinoma was found, showing a moderate degree of nuclear atypia and small areas of clear-cell differentiation, with foci of necrosis and stromal microinvasion. No psammoma bodies and vascular/lymphatic invasion were observed.

Elevated serum CA-125 levels at the time of operation slightly decreased four weeks after (from 145 IU/ml to 124 IU/ml). Serum concentrations of CA-125 were within normal range between 6th to 8th postoperative week. Nine weeks after operation, at the end of December, severe metrorrhagia occurred and curettage was performed. Histological evaluation of the obtained material showed papillary cystadenocarcinoma endometrioid endometrium. Serum CA-125 were extremely elevated to the values of 1360 IU/ml (Figure 1). In January 1995, hysterectomy, adnexectomy and omentectomy was performed. There were no apparent metastatic features during the operative procedure. CA-125 levels decreased to 110 IU/ml six weeks thereafter. From that time up to now this tumour marker was regularly determined every twelfth week and stayed within normal range. Ultrasonographic and CT examination confirmed her well-being. In this study, we present a direct chronological relation between hormonal stimulation of previously unremarkable ovaries and development of ovarian carcinoma.

Discussion

Serum concentrations of CA-125 were found to be low in healthy adults and only slightly elevated in those with endometriosis. Grossly elevated levels of this antigen could be detected in a substantial number of patients suffering from ovarian cancer. Since a close correlation between pattern of CA-125 serum concentrations and progression or remission of that disease has been demonstrated; and since CA-125 levels in benign gynaecologic disorders usually do not exceed 65 IU/ml, CA-125 serum concentrations above that range are regarded as a rather reliable sign for the presence of malignant ovarian tissue. In adult women, dramatic but transient increase of CA-125 is not restricted to neoplastic tissue, but can also occur during supraphysiologic stimulation of normal ovaries in otherwise healthy subjects, as a consequence of massive proliferation of ovarian tissue.[3] But mechanisms directing these processes and the components of ovarian tissue

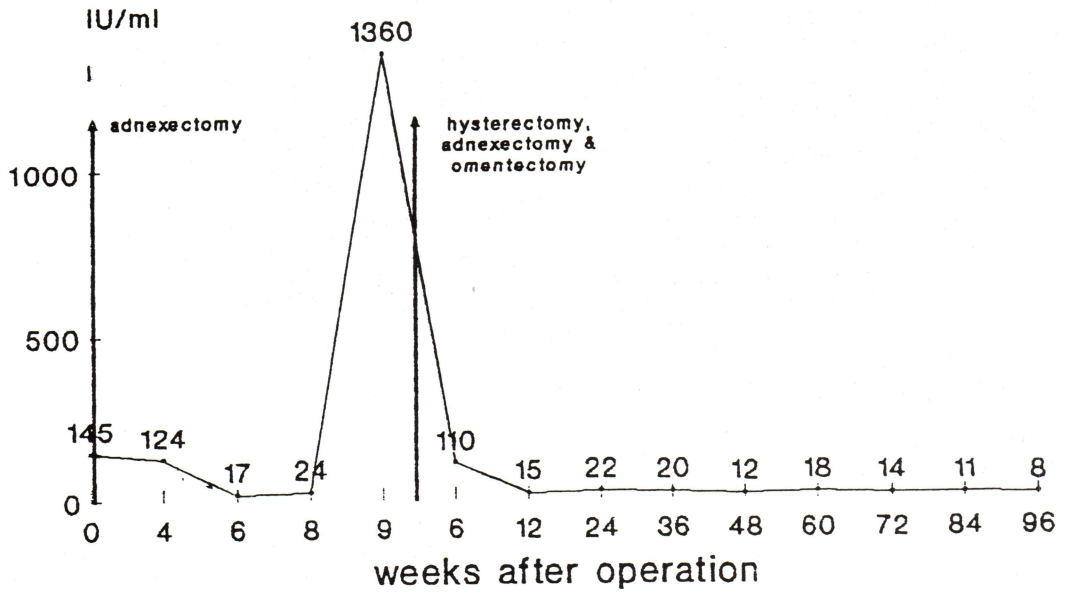


Fig. 1. Serum CA-125 concentrations in postoperative period.

responsible for CA-125 increase remains unknown.

There are a lot of studies that confirm the link between ovulation induction and the risk of various gynaecologic and other hormonally sensitive tumours appearance. An increased risk for endometrial, breast cancer and melanoma were found among women with hormonal infertility.[8,9] Ovarian cancer is of particular concern because it represents the most frequent cause of death from gynaecologic malignancies in the United States and Northwestern Europe.[10]

Epidemiologic evidence to date suggests that the risk of ovarian cancer is greater in women who have difficulties with conception.[11] The possibility of ovulation induction being associated with ovarian cancer concurs with Fathala's theory[12] of incessant ovulation, which states that epithelial ovarian cancer may result from repeated ovulations, causing minor trauma to the ovarian epithelium, and exposure of this surface to estrogen-rich follicular fluid. Defective cellular repair after ovulation leads to malignant transformation.[13,14]

High gonadotropin levels have also been linked with increased risk of ovarian cancer, either directly, or in conjunction with elevated concentrations of estrogens.[15,16] Many patients undergoing ovulation stimulation have exceedingly high levels of plasma estrogen. Only one published study to date has provided an estimate the risk of invasive epithelial ovarian cancer following the use of fertility drugs.[9,17] This study reported that nulligravid women with physician-diagnosed infertility who had used fertility drugs were 27 times more likely to develop ovarian cancer than women with no history of infertility. But no information was provided concerning types of the drugs used, doses, or temporal relation to ovarian cancer diagnosis.

Although there are many difficulties in assessing the risk of carcinoma following ovulation induction, particularly the inability of retrospective studies to separate the effects of infertility itself from the drugs used for the treatment, the literature is so limited that these methodological issues are almost moot. Case reports of cancer following treatment with fertility-enhancing drugs,

although provocative, provide insufficient data to the risk. Even though such individual reports do not prove a direct connection between stimulation and the induction of ovarian neoplasms, it is nevertheless possible that an existent tumour is substantially stimulated by this hormonal therapy. In this study, we present a direct chronological relation between hormonal stimulation of previously unremarkable ovaries and the development of ovarian carcinoma. It is upon further investigations to examine which fertility drugs are most hazardous and who is most at risk.

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