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Borderline Malignancy of the Ovary and Controlled Hyperstimulation, A Report of 2 Cases

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We report 2 patients who developed a borderline malignancy of the ovary after treatment with follicular stimulants in the context of an *in vitro* fertilisation (IVF) programme. In both cases, conservative surgery for the borderline malignancy was sufficient treatment. Ultimately, both patients became pregnant, 1 after IVF treatment and 1 without treatment, and both delivered healthy babies. In addition to the presentation of both cases, the literature concerning the possible risks of treating patients with high dosage, exogenously administered hormones is reviewed and the possible association between exogenous hormones and the risk of developing ovarian cancer is discussed.

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INTRODUCTION

FOLLICULAR STIMULANTS such as human menopausal gonadotrophins (hMG) and human chorion gonadotrophins (hCG) have now been used widely in *in vitro* fertilisation (IVF) programmes in eumenorrhoeic women. Induction of superovulation with hMG results in supraphysiological oestrogen serum levels and multiple ovulations. The hyperstimulation syndrome occurs in up to 3% of all cases during gonadotrophin therapy [1], while mild ovarian hyperstimulation with ovarian enlargement requiring observation is quite common.

There has never been any mitogenic potential of gonadotrophins described in the female. Nevertheless, 5 cases of ovarian carcinoma diagnosed in patients following treatment with follicular stimulants have been published up to now [2–5]. This report presents two more patients, stimulated with hMG, luteinizing hormone releasing hormone analogues (LHRH-a) and hCG, who were subsequently diagnosed as having borderline ovarian carcinomas. A possible association between the two conditions is discussed.

Case reports

Case 1. A 38-year-old woman with primary infertility of 4 years duration; her medical history reveals a severe adnexitis in 1984. In December 1988, a laparoscopy had demonstrated occluded fallopian tubes. Subsequently, she received treatment in an IVF program in which she was administered LHRH-a (intranasally) and hMG, three ampoules [75 U follicle stimulating hormone (FSH) and 75 U luteinizing hormone (LH) per ampoule] intramuscularly at day 1, and two ampoules per day from day 2 to day 7. On day 8, 10,000 U of hCG was administered intramuscularly. No pregnancy occurred in the first cycle.

For the second attempt, in April 1989, she was referred to our hospital. Ovulation was induced with hMG, three ampoules per day intramuscularly, from day 3 to day 9 in combination with LHRH-a (intranasally), total dosage 900 μg/day. On day 10, 10000 U hCG was given intramuscularly and 2 days later, six oocytes were aspirated from the right ovary and fertilised. Five pre-embryos were transferred on day 14. Again, she did not become pregnant.

During oocyte-aspiration, fluid from a transonic space (diameter 4 cm) of the left ovary was also aspirated. This fluid did not contain oocytes, but lymphocytes, granulocytes and (keratin-positive) papillary epithelial atypical cell groups (Figs 1, 2). Very unexpectedly, the cytological examination revealed strong evidence for adenocarcinoma. For this reason, a laparotomy was performed 4 weeks after the fluid aspiration. The left ovary was found to be enlarged (5 × 4 × 5 cm). Throughout the pelvis many small wart-like tumours (1–3 mm in diameter) were seen on the pelvic peritoneum. After peritoneal washing, oophorectomy of the left ovary was performed and biopsies were taken from the small tumours described above. Histological examination revealed small cyst-like structures consisting of atypical papillomatous epithelial cell proliferation, highly suspicious for carcinoma of the left ovary (Fig. 3), to be present within the ovary and in all pelvic biopsies. The peritoneal washing contained these atypical proliferating cells as found earlier in the cyst fluid (Figs 1, 2). Two weeks later the patient

Fig. 1. Fluid of the transonic space containing, in addition to lymphocytes and granulocytes, psammoma-bodies and atypical cells suspicious for adenocarcinoma.

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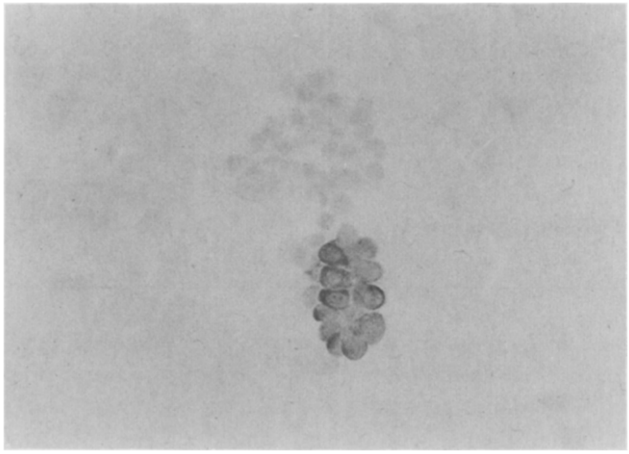

Fig. 2. Immunocytochemical examination revealed a positivity for EMA, making the atypical cells more suspicious for adenocarcinoma cells.

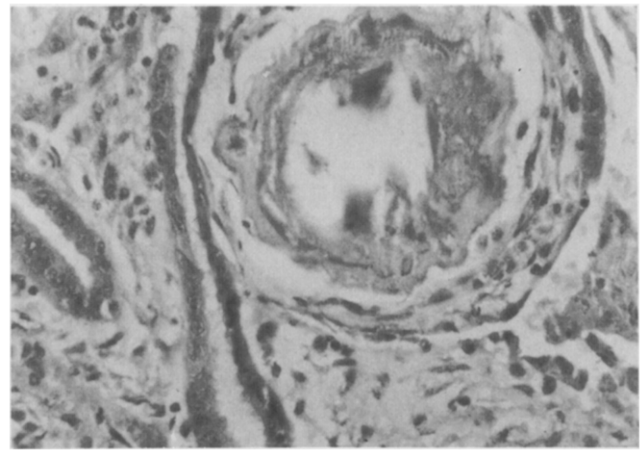

Fig. 4. Psammoma-bodies and one microscopic non-invasive lesion staining mild and moderate but not marked atypia. Note the low epithelial percentage and absence of mitotic activity (morphometric favourable).

underwent a conservative staging laparotomy. The uterus and half of the right ovary were left *in situ*. Para-aortic lymph node sampling and infracolic omentectomy were performed and multiple biopsy specimens were taken from the peritoneal cavity. Histological examination of the omentum revealed reactive mesothelial cells and one single lesion less than 1 mm in size which was diagnosed as borderline malignancy (Fig. 4). In four out of 10 para-aortic lymph nodes endosalpingiosis was found. Morphometric characteristics, such as mitotic activity index and volume percentage epithelium demonstrated low values, which is associated with a prognostically favourable type of borderline malignancy [6, 7]. After revision of all slides (J.B.) the patient was classified as having a serous borderline malignancy of the ovary stage IIIa (FIGO, 1987). Also on the basis of the morphometric analysis it was decided that no further treatment was necessary and that IVF treatment could be continued. The patient was monitored every 3 months by means of ultrasound and physical examination.

In January 1990, a cystic structure was diagnosed by transvaginal sonography located near the right ovary. Laparoscopy revealed a pseudocyst (diameter 7 cm) around the right ovary ($3 \times 4 \times 3$ cm) which was punctured. The pseudocyst fluid did not contain malignant cells. A biopsy specimen of a small lesion located near the fundus of the uterus was taken and diagnosed as borderline malignancy of the ovary. In the fourth IVF course, a viable pregnancy was diagnosed 30 days after follicle aspiration by transvaginal sonography (August 1990). Finally, the patient delivered a healthy daughter.

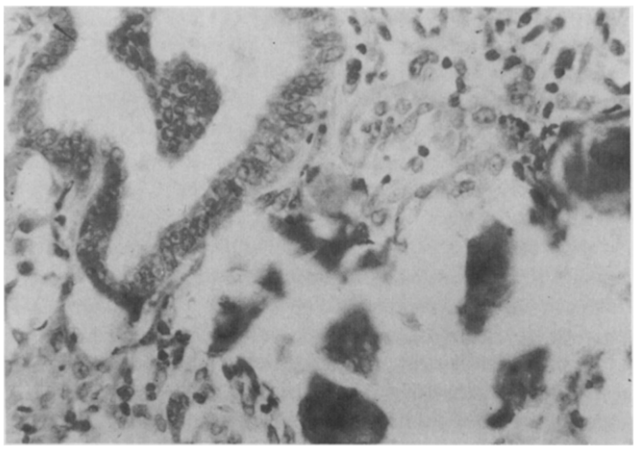

Fig. 3. Papillary atypical cell proliferations lining the cystic ovarian structures.

Case 2. In February 1990, a 36-year-old woman with secondary infertility of 7 years duration was referred to our hospital. Her medical history revealed a left-sided ovarian cystectomy and a conservative treatment for an extra-uterine pregnancy. A laparoscopy in 1987 had shown occluded fallopian tubes without further abnormalities. Ovulation had been induced four times as part of an IVF procedure in the period between October 1988 and January 1990. In every course hMG and LHRH-a were used, in the same dosage as in the first course of patient 1. In each treatment cycle, four pre-embryos were transferred. The third treatment ended in an early abortion.

In February 1990, after the fourth course, she started complaining of abdominal pain, starting a few days before the normal menstruation. At this time she was admitted to our hospital. Body temperature at the time of hospitalisation was 38.9°C. At physical examination, a right-sided cystic mass in the true pelvis was palpated. Laboratory tests were compatible with an infection (white blood cell count 31.6×10^9/l, erythrocyte sedimentation rate 110 mm/h). Abdominal ultrasonography showed a cyst (size: $10 \times 7 \times 6$ cm) on the right side of the uterus. Initial treatment with antibiotics proved to be unsuccessful. Two days after this treatment was started, the decision was made to perform a laparotomy. A right-sided tubal-ovarian abscess was found; the abscess was incised to evacuate the pus. Because of adhesions accurate inspection of uterus and adnexa was not possible. Recovery from this operation was uneventful. Postoperatively, a small right sided mass was found ultrasonographically. Five months after the first operation, a second laparotomy "à froid" was performed to remove this mass which was considered to be a remnant of the abscess. Inspection of the pelvis showed a normal left ovary but on the right side, ovary and tube were not distinguishable from the cystic mass (diameter 5 cm). A right-sided salpingo-oophorectomy was performed. Histopathological examination of the right adnex revealed that the cystic mass was a serous borderline malignancy of the ovary, stage IIa (FIGO, 1987). Morphometric analysis [6] showed a prognostically favourable type of borderline malignancy and because of

this, it was decided that further surgical staging was not necessary. One year later the patient became pregnant without treatment delivering a healthy son.

DISCUSSION

Including the two cases described in this report, a total number of 7 patients have developed ovarian cancer at the time of or following ovulation induction with exogenous hormones. Similar case reports have been described previously [2–5] concerning young women treated with clomiphene-citrate or gonadotrophins for ovulation induction. Shortly after ovulation induction, these 5 patients developed a malignancy of the ovary. 1 patient also had an endometrial carcinoma. Our patients were stimulated with the exogenous hormones, hMG, LHRH-a and hCG for IVF treatment in dosages much higher than the cases reported thus far [2–5]. The question of whether there is a possible causal relationship between ovulation induction and the development of ovarian cancer is an intriguing one. The 2 patients described here both had a borderline malignancy of the ovary, with favourable morphometric prognostic characteristics. The literature data available suggest that controlled hyperstimulation induces highly differentiated indolent tumours. A similar condition exists for the endometrium in which the use of hormone replacement therapy without progesterones is associated with superficially growing highly differentiated "favourable" cancers.

Reviewing the literature reveals some evidence for an association between (exogenous) hormones and the development of an ovarian neoplasm. In 1944, Biskind and Biskind, in an animal study, found a correlation between high levels of gonadotrophins and development of ovarian neoplasm [8]. Others demonstrated the formation of malignant ovarian tumours in animals after chronic administration of oestrogens, progestins or androgens [9–11]. Most of these tumours, however, did not arise from the epithelium but from stromal cells. Oestrogens increase granulosa cell proliferation and hence the frequency of mitotic activity, which may lead to malignant phenotypes [12, 13]. Stadel [14] and Cramer [15] pointed out that elevated gonadotrophins, directly or through steroid hormones, might be implicated in the development of ovarian cancer in women. Epidemiological studies provide circumstantial evidence to support the theory of elevated gonadotrophins as a causal factor. After the menopause, when gonadotrophin levels are high, the incidence of ovarian cancer increases significantly. In contrast, when LH and FSH levels have become suppressed, for example during pregnancy, lactation and use of oral contraceptives, a fall in the incidence of ovarian carcinoma is observed.

On the other hand, the association observed could be explained differently. In the "incessant ovulation theory" of Fathalla [16] it is assumed that the repeated replication of the epithelial cells, after each ovulation, to cover the exposed surface of the ovary, might play a role in the aetiology of ovarian cancer. Casagrande [17] introduced the term "ovulatory age", referring to the idea that the more ovulations, the greater the risk of developing ovarian cancer will be. Whittemore *et al.* [18] speculated that it is not the number of years of uninterrupted ovulation which increases the risk of developing ovarian cancer, but the inability to conceive, due to endocrine disorders which exposed these women to a doubled risk of developing ovarian cancer compared with women who were fertile.

The two theories described above, together with Fishel's assumption [19] that the number of ovulating follicles arising in a single stimulated cycle during IVF treatment may be equivalent to about 2 years of normal ovulation during the natural menstrual cycle, explain why these women are prone to the development of ovarian cancer.

Thus, the data available suggest that the use of gonadotrophins for ovulation induction and the multiple ovulations may add to the already increased risk of infertile women developing an ovarian malignancy. From a clinical management point, the data available lead us to the conclusion that when there is a persistent enlarged ovary in a patient who is stimulated with exogenous hormones, further evaluation is warranted. In both cases described here, the diagnosis, a prognostically favourable type of a borderline malignancy of the ovary, led to conservative treatment. Follow-up accords well with this decision. Both women became pregnant, one without treatment and one after IVF treatment and both pregnancies ended in the birth of healthy babies. These patients will need long-term monitoring by means of ultrasound and physical examination.

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