

## Another two cases of ovarian tumours in women who had undergone multiple ovulation induction cycles

B.Salle<sup>1,3</sup>, P.de Saint Hilaire<sup>1</sup>, M.Devouassoux<sup>2</sup>, P.Gaucherand<sup>1</sup> and C.Rudigoz<sup>1</sup>

<sup>1</sup>Department of Obstetrics, Gynecology, Ultrasound and Infertility and <sup>2</sup>Pathology Laboratory, Hôpital de la Croix Rousse, 94 grande rue de la Croix Rousse, 69004 Lyon, France

<sup>3</sup>To whom correspondence should be addressed

**Many questions have been raised recently about the possible association between ovulation induction and ovarian cancer. In order to contribute to the limited literature on this important issue, two cases of ovarian cancer in women who had multiple ovulation induction are presented here. In the first case the patient had ovarian induction by clomiphene citrate while she already had an ovarian cyst. The cyst enlarged under induction. During laparoscopy, the cyst was removed. Histological examination showed a borderline and invasive sero-papillary cystadenoma. In the second case, the patient underwent ovulation induction and intrauterine insemination. During the first ultrasound in the beginning of the cycle, an ovarian cyst was discovered. Laparoscopy was performed and the cyst removed. Histological examination showed a borderline and invasive mucinous cystadenoma.**

*Key words:* ovarian stimulation/ovarian tumours/ovulatory cycles

### Introduction

Ovarian stimulation is a unique aid for patients treated for anovulation and an important tool in various assisted reproduction treatments such as intrauterine insemination and in-vitro fertilization (IVF). However, it is very important to understand the risks and side-effects of those treatments.

The most common complication is ovarian hyperstimulation. Since 1992 and the publication by Whitemore *et al.* (1992a,b,c), the possibility that ovulation induction treatment may be carcinogenic, and particularly the possibility of a relationship between ovulation-inducing treatment and appearance of ovarian cancer, have been discussed. Those publications have raised more questions than answers (Societies I. F. O. F. 1993; Shushan *et al.*, 1996).

Prospective multicentric epidemiological studies are necessary to settle this matter once and for all. Nevertheless, it is useful to report clinical observations of patients who developed ovarian cancers after infertility treatment. The collation and analysis of similar observations would enable construction of a database dedicated to the relationship between ovarian cancer and ovarian stimulation.

To contribute to data about the relationship between ovarian cancer and the induction of ovulation, two new cases of patients who had developed ovarian cancer after treatment are presented here. Analysis of these cases is supported by their medical histories.

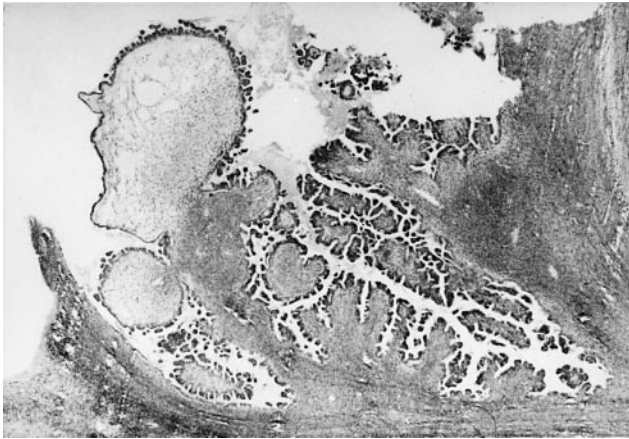
### Case 1

This patient had her first pregnancy in 1992 after a 2 year period of infertility. She had no family history of cancer. The pregnancy was obtained during the first cycle of ovulation induction for anovulation using clomiphene citrate. This pregnancy was uneventful. A Caesarean section was performed because of a breech presentation.

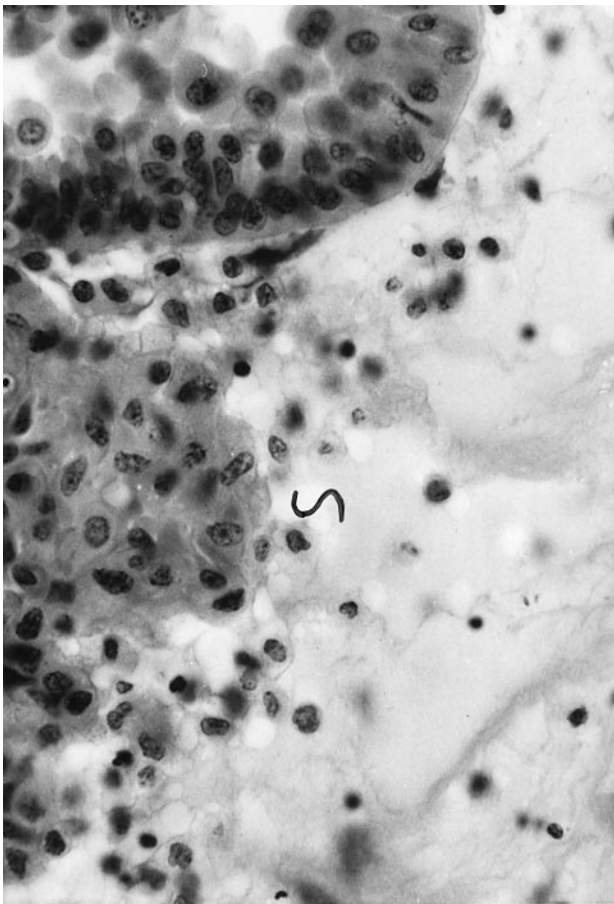
During normal follow-up, bilateral ovarian cysts were discovered in 1993, measuring 29 and 33 mm. These hypo-echogenic cysts were first treated with progestagens (Lutenyl<sup>®</sup>; Theramen, Monaco, France) and then oestro-progestagens (Adepal<sup>®</sup>; Wyeth, Paris, France) and finally by transvaginal puncture. In 1994, a laparoscopy was performed and the cyst removed. Histological examination revealed a benign tumour of the right ovary. Six months later, the right cyst re-appeared and it was decided to start treatment with luteinizing hormone releasing hormone (LHRH) analogues and progestagens. Despite persistence of the ovarian cyst, ovulation was induced by clomiphene citrate administered over 6 months from January 1st to July 1st, 1996.

As the cyst continued to grow, the patient was referred to our unit. The ovarian cyst measured 6 cm and was septate. A second laparoscopy was performed in December 1996. It revealed that the tumour had reached 16 cm in diameter.

A laparotomy was then decided upon, and a right ovariectomy was carried out with peritoneal cytology. Gross examination revealed a multilocular cyst of 15 cm covered by numerous coarse exophytic papillae. The cyst was filled with a watery fluid and its inner surface was lined by papillae. Microscopically, complex and branching papillae were seen on the ovarian surface and on the inner wall of the cyst. The papillary fronds were lined by stratified layers of epithelial cells forming tufts from the piling up of cells (Figure 1). Detachment of papillary buds was seen. Cuboidal cells with abundant eosinophilic cytoplasm invaded the stroma focally within the papillary stalks, without desmoplastic stromal reaction (Figure 2). This tumour corresponded to a serous borderline ovarian tumour with stromal invasion. The peritoneal cytology was positive. A total hysterectomy was carried out during a second laparotomy with a left adnexectomy associated with an omentectomy. The CA 125 concentration was 71 IU. It was a stage 1C



**Figure 1.** Serous ovarian tumour of low malignant potential in case 1, showing multiple branching papillary projections covered by stratified epithelial cells (haematoxylin eosin safran, 1:25). Original magnification  $\times 10$ .

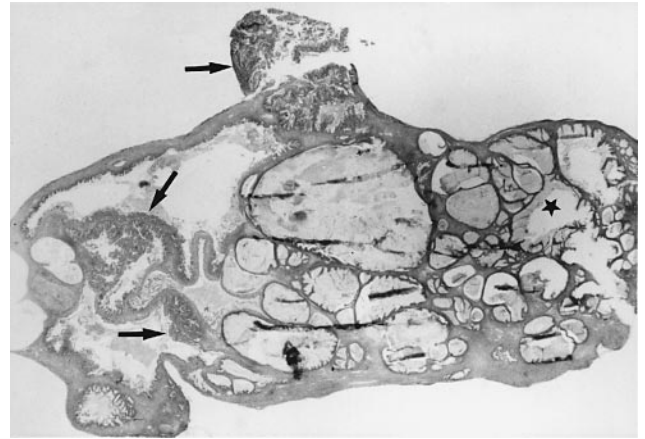


**Figure 2.** Early stromal invasion in case 1. Cells invading the stroma of papillary stalks (~) were characterized by abundant pink cytoplasm (haematoxylin eosin safran 1:400). Original magnification  $\times 40$ .

disease (Langley and Fox, 1987). This ovarian tumour was further treated by chemotherapy.

### Case 2

A 29 year old patient was referred to our infertility centre for primary infertility of 3 years duration. She had already had



**Figure 3.** Mucinous ovarian borderline tumour (★) with small carcinomatous foci (arrows) in case 2 (haematoxylin eosin safran 1:15). Original magnification  $\times 10$ .

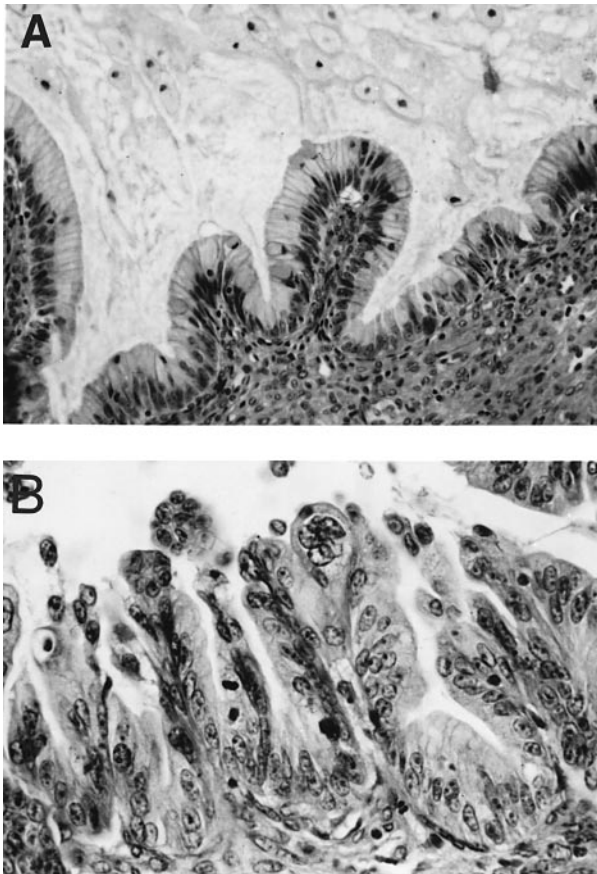
six cycles of stimulation by clomiphene citrate. The patient had normal ovulatory cycles. Hysterosalpingography revealed a total septate uterus. The septum was removed in October 1994 by hysteroscopy under laparoscopic control. Abdominal exploration was absolutely negative. Both ovaries were normal.

The spermogram revealed oligo-asthenoteratozoospermia according to the World Health Organization (WHO, 1992). The post-coital test was negative. Ovulation induction was then instigated, together with intrauterine insemination. At the beginning of the first cycle, ultrasonographic examination revealed a septate ovarian cyst 9 cm in diameter. The patient was treated with oestro-progestagens (Stediril<sup>®</sup>; Wyeth, Paris, France) for 1 month. A second laparoscopy was performed on April 10, 1995. During the laparoscopy, the cyst was removed. On gross examination, a multicystic tumour of 7 cm with endophytic papillae was noted. Microscopic examination revealed an intestinal-type mucinous borderline tumour with small carcinomatous foci (Figure 3). The cysts contained papillae covered by columnar, mucin-containing cells, frequently stratified into two or three layers (Figure 4a). In carcinomatous foci, neoplastic cells were extensively stratified with highly atypical nuclei (Figure 4b). Stromal invasion with desmoplastic stromal response was noted. To maintain fertility, a laparotomy was performed 1 month later. The right ovary and the omentum major were removed and contralateral ovarian biopsies and peritoneal biopsies were carried out. Histological examination led to the conclusion that there was no residual tumour tissue. It was a stage 1 disease. No additional treatment was judged to be necessary. Twelve natural cycles of intrauterine insemination were performed without any success.

### Discussion

Ovarian cancer is estimated to affect 7.3–13 women per 100 000 (Weiss *et al.*, 1977). Anovulation was not the reason for infertility in either of these two patients. However, infertility does seem to increase the risk of ovarian cancer. Transformation into a cancer is multi-factorial (Barber, 1982).

Many factors (Cramer *et al.*, 1983; Heintz *et al.*, 1985) in cancerous transformation have been identified. They can be



**Figure 4.** Case 2 (A) Papillae covered by two layers of mucinous cells, displaying features of mucinous borderline tumour (haematoxylin eosin safran 1:400); (B) cysts in carcinomatous areas were lined by atypical cells with pleomorphic nuclei and mitotic figures (haematoxylin eosin safran 1:400). Original magnification  $\times 40$ .

classified as genetic (Fatthala, 1971; Lynch *et al.*, 1978), environmental (Arlow *et al.*, 1988) and hormonal (Graham and Graham, 1967). Infertility could also increase the risk of ovarian cancer. Whittemore *et al.* (1992a,b,c) demonstrated a relationship between infertility treatment and the risk of inducing ovarian cancer. According to Whittemore *et al.* (1992a,b,c), the risk is multiplied by 2.8 in women undergoing treatment and by 27 in women undergoing treatment without success. However, the main limitation of the Whittemore study concerned the drugs (Mouzon *et al.*, 1993). The type, the dosage and duration of treatment are not known. In a case control study, Rossing *et al.* (1994) showed a link between treatment with clomiphene citrate for over 12 months and an increased risk of ovarian cancer.

The latency phase in both cases (i.e. the period of time between the first stimulation by clomiphene and the diagnosis of ovarian cancer) is too short to establish any relationship between induction of ovulation and cancer. Both observations show that great care must be taken if an ovarian cyst is discovered before or during ovulation induction (Lopes *et al.*, 1992; Jamet *et al.*, 1996).

In the first case, a persistent cyst had to be removed before treatment despite histological examination. It is possible that repeated ovarian stimulation expedited the development and

the clinical appearance of a pre-existing tumour. It is easy to imagine that ovulation inducers caused a quiescent stage I tumour to develop into a stage 1C disease. In this hypothesis, inducing ovulation would not increase the risk of ovarian cancer but would make it appear more rapidly. Epidemiological studies are needed to confirm or reject this hypothesis. Another point of discussion relevant to case 1 is the surgical procedure. Is laparoscopy reliable for establishing the suspicion of malignancy for an ovarian tumour? Several teams have demonstrated on the basis of large studies that laparoscopy is a reliable technique for the diagnosis of malignancy in ovarian lesions. The risk of a false negative diagnosis is not specific to endoscopic investigation, but has also been reported with laparotomy (Chapron *et al.*, 1996). However, the rate of discovery of an ovarian cancer in patients treated for infertility is extremely low. Laparoscopy is the gold standard method to explore ovarian lesions in such patients (Chapron *et al.*, 1996).

Our second case did not permit the deduction of a relationship between ovarian induction and cancer. The presence of a persistent ovarian cyst would seem to indicate that exploration is essential before treatment. This is particularly obvious in the case of suspicious ultrasonographic findings. This case shows that ultrasonography is useful before all ovulation induction treatments, particularly when sequencing ovulation induction cycles. Goldberg and Runowicz (1992) believe that the discovery of a benign mucinous cystadenoma or a borderline tumour enables early surgical exploration and stops the natural progression towards disseminated cancer. One of our observations is quite similar to that reported by Grimbizis *et al.* (1995), where an ovarian cyst was discovered at ultrasound screening during preparation of a second IVF attempt. Histological examination revealed an epithelial serous papillary cystadenoma of borderline malignancy. Our case 1 observation is quite different. It shows that every time an ovarian cyst is discovered before ovulation induction treatment, it has to be considered as suspicious. It needs histological examination before starting any treatment. These two observations are very different from those presented by Grimbizis *et al.* (1995) because our two cases are real ovarian cancer and not only borderline tumours. Tarlatzis *et al.* (1995) recently reported a meta-analysis of all the ovarian tumours related to infertility history in the literature: 30 epithelial tumours were collected, and 50% of these were tumours of borderline malignancy. The mean age at diagnosis of borderline tumours ranged from 39 to 45 years,  $\sim 10$  years earlier than the mean range at diagnosis of malignant epithelial tumours. Arlow *et al.* (1988) had reported that infertility but not nulliparity is associated with an increased incidence of borderline tumours. Harris *et al.* (1992) also reported that the risk of borderline tumours is higher than for invasive ones in women with a history of infertility. Thus, as Tarlatzis *et al.* (1995) observed, it seems that ovarian epithelial borderline tumours in their early preclinical stage may interfere with fertility. This is further supported by the achievement of pregnancy spontaneously or with medical assistance in some patients after removal of their tumour (Burger *et al.*, 1993; Grimbizis *et al.*, 1995). This point of view cannot be reliable for invasive tumours as in our two cases.

Clinical data about these two cases probably does not support evidence of a relationship between ovulation induction treatment and ovarian cancer. If a relationship exists, it would be facilitating rather than inducing. However, the discovery of an ovarian tumour must be thoroughly investigated before any treatment. One question remains unanswered: should patient no. 2 be treated by ovulation induction to enable IVF?

## References

- Arlow, B.L., Weiss, N.S., Roth, G.J. *et al.* (1988) Case control study of border line ovarian tumors: reproductive history and exposure to exogenous female hormone. *Cancer*, **48**, 5849–5852.
- Barber, R.K. (1982) Modern concepts of gynecology oncology. *Fertil. Steril.*, **23**, 23–40.
- Burger, C.W., Nijman, H.W., Baak, J.P.A. *et al.* (1993) Borderline tumor of the ovary and controlled hyperstimulation. A report of 2 cases. *Hum. Reprod.*, **8**, 144.
- Chapron, C., Dubuisson, J.B., Fritel, X. and Rambaud, D. (1996) Diagnosis and management of organic ovarian cysts; indications and procedure for laparoscopy. *Hum. Reprod. Update*, **2**, 435–446.
- Cramer, D.W., Hutchison, G.B., Welch, W.R. *et al.* (1983) Determinance of ovarian cancer risk. Reproductive experience and family history. *J. Natl Cancer Inst.*, **71**, 711–716.
- Fathala, M.F. (1971) Incessant ovulation – a factor in ovarian neoplasia. *Lancet*, **ii**, 163.
- Goldberg, G.L., and Runowicz C.D. (1992) Ovarian carcinoma of low malignant potential, infertility, and induction of ovulation – is there a link? *Am. J. Obstet. Gynecol.*, **166**, 853–854.
- Graham, J. and Graham, R. (1967) Ovarian cancer and asbestos. *Environ. Res.*, **1**, 115–128.
- Grimbizis, G., Tarlatzis, B.C., Bontis, J. *et al.* (1995) Two cases of ovarian tumours in women who had undergone multiple ovarian stimulation attempts. *Hum. Reprod.*, **10**, 520–523.
- Harris, R., Whittemore, A.S., Itnyre, J. and the Collaborative Ovarian Cancer Group (1992) Characteristic relating to ovarian cancer risk: collaborative analysis of 12 US case control studies. III Epithelial tumor of low malignant potential in white women. *Am. J. Epidemiol.*, **136**, 1204–1211.
- Heintz, A.P., Hacker, N.F. and Lagasse, L.D. (1985) Epidemiology and etiology of ovarian cancer. *Obstet. Gynecol.*, **66**, 127–135.
- Jamet, F., Mlamali, H., Bouard, V. *et al.* (1996) Tumeur borderline de l'ovaire et stimulation ovarienne. *JOBGYN*, **4**, 43–46.
- Langley, F.A. and Fox, H. (1987) Ovarian tumors: classification, histogenesis and aetiology. In Fox, H. (ed.), *Obstetrical and Gynecological Pathology*. Churchill Livingstone, London, pp. 542–555.
- Lopes, P., Mansier, A., Momballais, M.F. *et al.* (1992) Cancer de l'ovaire et endosalpingiose chez une patiente stérile en programmation de fécondation *in vitro*. *J. Gynecol. Obstet. Biol. Reprod.*, **43**, 87–91.
- Lynch, H.T., Harris, R.E., Guirgis, H.A. *et al.* (1978) Family association of breast/ovarian cancer. *Cancer*, **41**, 1543–1548.
- Mouzon, J., Cohen, J. and Spira, A. (1993) Cancer de l'ovaire et traitement de l'infécondité. A propos de l'article de Whittemore. *Contracept. Fertil. Sex.*, **21**, 566–570.
- Rosling, M.A., Dalling, J.R., Weiss, N.S. *et al.* (1994) Ovarian tumors in a cohort of infertile women. *N. Engl. J. Med.*, **331**, 335–339.
- Shushan, A., Paltiel, O., Iscovich, J. and Elchalal, U. (1996) Human menopausal gonadotrophin and the risk of epithelial ovarian cancer. *Fertil. Steril.*, **65**, 13–18.
- Societies, I. F. O. F. (1993) Fertility drugs and ovarian cancer. *Fertil. Steril.*, **60**, 406–412.
- Tarlatzis, B.C., Grimbizis, G., Bontis, J. and Mantalenakis, S. (1995) Ovarian stimulation and ovarian tumours: a critical reappraisal. *Hum. Reprod. Update*, **1**, 284–301.
- Weiss, N.S., Homonchuk, T. and Young, J.L. (1977) Incidence of the histologic types of ovarian cancer. *Gynecol. Oncol.*, **5**, 161–167.
- Whittemore, A.S., Harris, R., Itnyre, J. and Halpern, J. (1992a) Characteristics relating to ovarian cancer risk: collaborative analysis of 12 US case control studies. I. Methods. *Am. J. Epidemiol.*, **136**, 1175–1183.
- Whittemore, A. S., Harris, R., Itnyre, J. and Halpern, J. (1992b) Characteristics relating to ovarian cancer risk: collaborative analysis of 12 US case control

studies. II. Invasive epithelial ovarian cancer in white women. *Am. J. Epidemiol.*, **136**, 1184–1203.

Whittemore, A. S., Harris, R., Itnyre, J. and Halpern, J. (1992c) Characteristics relating to ovarian cancer risk: collaborative analysis of 12 US case control studies. IV. The pathogenesis of epithelial ovarian cancer. *Am. J. Epidemiol.*, **136**, 1212–1220.

World Health Organization (1992) *Laboratory Manual for the Examination of Human Semen and Sperm–Cervical Mucus Interaction*, 3rd edn. Cambridge University Press, Cambridge.

Received on February 14, 1997; accepted on May 14, 1997