SECTION ONE

Counseling and preparation phase

1 Risk of cancer from ovarian stimulation

Nikos Kanakas, Miltiadis Pitsos and Themis Mantzavinos
Embryoland – Center for Assisted Reproduction, Athens, Greece

Case History: *A 36-year-old woman had controlled ovarian stimulation as part of IVF treatment, resulting in a term pregnancy 2 years previously. Following that, her mother developed breast cancer at the age of 61 years. Now the patient desires another pregnancy but she is concerned about the risk of cancer due to ovarian stimulation. How should this patient be counseled?*

Background

Women who undergo ovarian stimulation are often concerned about the safety of the drugs and the risk of cancer. One issue to note is that nulliparity itself is a risk factor for developing breast [1], ovarian [2] or endometrial [3] cancers. Furthermore, infertility by itself is associated with cancer risks. Ovarian stimulation drugs have been prescribed only for a few decades now, in different doses and duration, and their long-term effects are not yet well studied.

A population-based cohort study of women who gave birth in 1974–1976 showed that women who received any type of ovulation induction treatment had increased risk of developing cancer overall compared with women who did not receive therapy [4]. However, it is important to note that this study compared women with infertility with women who conceived naturally, and thus any difference observed could be because of the fertility drugs or infertility itself. This 'comparator problem' is common in epidemiologic studies of assisted reproduction techniques (ART) and cancer risk.

Management options

Breast cancer

Breast cancer is a hormone-related cancer; many studies have investigated the association between fertility drugs and breast cancer. One Danish cohort study included approximately 54,000 women with infertility from 1963 to 1998 [5]. In this study, the treatment with infertility drugs was not associated with breast cancer risk. Neither was there an association with the number of cycles, length of follow up or histologic type of malignancy. The only association was between gonadotropins and breast cancer in women who remained nulliparous [5]. However, in the Jerusalem Perinatal study, women who underwent ovulation induction had an increased risk for developing breast cancer though the risk disappeared after controlling for other factors, with the increased risk remaining only when ovulation induction was used for over 12 months [4]. Prolonged exposure to gonadotropins for six or more cycles was associated with increased risk of breast cancer compared with the general population in another study [6]. A cohort

Assisted reproduction techniques: Challenges and management options, First Edition. Edited by Khaldoun Sharif and Arri Coomarasamy.
 Published 2012 by Blackwell Publishing Ltd.

study which included 29,700 patients with a relatively short follow up of 7 years found a transient increase in the incidence of breast cancer the year following IVF but no overall increase in the incidence during the follow-up period [7]. Age at the first IVF cycle might be a factor related with increased risk of breast cancer, with age over 30 years having an increased risk [8], or age over 40 years as shown in another study [9]. In a study that consisted of a small number of patients, fertility medications did not alter the breast cancer risk in women with *BRCA1* or *BRCA2* mutations [10].

Ovarian cancer

Infertility itself may increase the risk of ovarian cancer in those patients who do not subsequently conceive [11]. There is evidence from an *in vitro* study that follicle-stimulating hormone (FSH) stimulates ovarian cancer cell growth [12]. A large retrospective study which included about 12,000 patients with a median follow up of 18 years showed that infertile patients had a higher risk for developing ovarian cancer than the general population; however, there was no difference between infertile patients who either used or never used infertility drugs [13]. A meta-analysis which included both case–control and cohort studies found that the incidence of exposure to infertility medications was significantly higher in ovarian cancer patients than the general population [14]. However, when the comparison was between fertility drug treated infertile patients and untreated infertile patients there was a trend towards lower ovarian cancer incidence in the treated group [14]. Thus, the increase in ovarian cancer risk appears attributable to infertility itself than ovarian stimulation drugs. This meta-analysis highlighted the importance of an appropriate comparator group (i.e. an untreated infertile group rather than the general population). A study of patients who were treated for infertility in the 1960s and 1970s in Sweden did not show any significant risk for ovarian cancer after follow up for almost 30 years [15]. A case–control study in the USA of more than 3000 women showed that women who used clomiphene citrate for over a year had a higher risk of developing ovarian malignancy than those infertile women who had never used the drug [16]. A pooled analysis of eight case–control studies showed that among subfertile nulliparous women, ovarian cancer was not associated with fertility drug use nor length of use [17]. There was no increase of ovarian cancer incidence in women treated with IVF compared with the general population in a cohort study with a short follow up of 7 years [7].

Endometrial cancer

Endometrial cancer is associated with anovulation and with the unopposed effect of estrogens on the endometrium [18]. A cohort study of 2496 infertile women with a mean follow up of 21.4 years showed an increased incidence of endometrial cancer when compared with the general population. However, this risk disappeared when treated infertile women were compared with untreated ones. The increased risk was attributed to the unopposed action of estrogens when researchers studied the hormonal status of women [19]. A recently published cohort study which included 54,362 infertile women reported that the use of gonadotropins increased the risk for uterine cancer after a 10-year follow up. The risk of uterine cancer was also increased with the number of cycles of clomiphene citrate use [20]. In the Jerusalem Perinatal Study, women who were treated with an ovulation induction medication had a higher risk of developing uterine cancer than women who conceived without treatment. The risk was even higher when the treatment was longer than 12 months [4]. As with breast cancer, in the same cohort of women who underwent IVF with a short follow up of 7 years, there was a transient increase in the incidence of uterine cancer the year following IVF without observing overall increase in the incidence of uterine cancer during the follow-up period [7].

Many of the current studies are based on epidemiologic data and follow up at the time when clomiphene citrate was the most common drug and the methods of IVF with superovulation were either not available or were of limited use. Prospective studies will answer the question whether ovarian stimulation increases the risk of cancer. At this time, we know that infertility and nulliparity are risk factors for gynecologic cancers and there is no proof that the medications used in the past decades have had a substantial impact on the cancer risk.

Key points

Challenge: Counseling women about the risks of cancer from ovarian stimulation.

Background:

- Nulliparity is a risk factor for breast, ovarian and endometrial cancers.
- Infertility itself may also be a risk factor for many gynecologic cancers.
- Polycystic ovary syndrome (PCOS), a condition associated with infertility, is linked to endometrial cancer.
- It is difficult to separate the cancer risks attributable to infertility from that of fertility drugs.
- Most epidemiologic studies that have examined the association between fertility drugs and cancer risks have employed the general population as the comparator. A more appropriate comparator is untreated infertile population as this would allow better assessment of the cancer risk attributable to fertility drugs.

Management options:

- Women should be counseled about the uncertainly in the available evidence.
- Women may be counseled that there is no clear evidence that short-term use of fertility drugs increases the risk of gynecologic cancers. Short term may be defined as:
  - less than 12 cycles for clomiphene, and
  - less than six cycles for gonadotropins

References

1. Key TJ, Verkasalo PK, Banks E. (2001) Epidemiology of breast cancer. *Lancet Oncol* 2(3), 133–40.
2. Modugno F, Ness RB, Wheeler JE. (2001) Reproductive risk factors for epithelial ovarian cancer according to histologic type and invasiveness. *Ann Epidemiol* 11(8), 568–74.
3. Brinton LA, Berman ML, Mortel R, Twiggs LB, Barrett RJ, Wilbanks GD, et al. (1992) Reproductive, menstrual, and medical risk factors for endometrial cancer: results from a case–control study. *Am J Obstet Gynecol* 167(5), 1317–25.
4. Calderon-Margalit R, Friedlander Y, Yanetz R, Kleinhaus K, Perrin MC, Manor O, et al. (2009) Cancer risk after exposure to treatments for ovulation induction. *Am J Epidemiol* 169(3), 365–75.
5. Jensen A, Sharif H, Svare EI, Frederiksen K, Kjaer SK. (2007) Risk of breast cancer after exposure to fertility drugs: results from a large Danish cohort study. *Cancer Epidemiol Biomarkers Prev* 16(7), 1400–7.
6. Burkman RT, Tang MT, Malone KE, Marchbanks PA, McDonald JA, Folger SG, et al. (2003) Infertility drugs and the risk of breast cancer: findings from the National Institute of Child Health and Human Development Women's Contraceptive and Reproductive Experiences Study. *Fertil Steril* 79(4), 844–51.
7. Venn A, Watson L, Bruinsma F, Giles G, Healy D. (1999) Risk of cancer after use of fertility drugs with in-vitro fertilisation. *Lancet* 354(9190), 1586–90.
8. Katz D, Paltiel O, Peretz T, Revel A, Sharon N, Maly B, et al. (2008) Beginning IVF treatments after age 30 increases the risk of breast cancer: results of a case–control study. *Breast J* 14(6), 517–22.
9. Pappo I, Lerner-Geva L, Halevy A, Olmer L, Friedler S, Raziel A, et al. (2008) The possible association between IVF and breast cancer incidence. *Ann Surg Oncol* 15(4), 1048–55.
10. Kotsopoulos J, Librach CL, Lubinski J, Gronwald J, Kim-Sing C, Ghadirian P, et al.; Hereditary Breast Cancer Clinical Study Group. (2008) Infertility, treatment of infertility, and the risk of breast cancer among women with BRCA1 and BRCA2 mutations: a case–control study. *Cancer Causes Control* 19(10), 1111–9.
11. Mosgaard BJ, Lidegaard O, Andersen AN. (1997) The impact of parity, infertility, and treatment with fertility drugs on the risk of ovarian cancer. *Acta Obstet Gynecol Scand* 76, 89–95.
12. Li Y, Ganta S, Cheng C, Craig R, Ganta RR, Freeman LC. (2007) FSH stimulates ovarian cancer cell growth by action on growth factor variant receptor. *Mol Cell Endocrinol* 267(1–2), 26–37.
13. Brinton LA, Lamb EJ, Moghissi KS, Scoccia B, Althuis MD, Mabie JE, et al. (2004) Ovarian cancer risk after the use of ovulation-stimulating drugs. *Obstet Gynecol* 103(6), 1194–203.
14. Kashyap S, Moher D, Fung MF, Rosenwaks Z. (2004) Assisted reproductive technology and the incidence of ovarian cancer: a meta-analysis. *Obstet Gynecol* 103(4), 785–94.
15. Sanner K, Conner P, Bergfeldt K, Dickman P, Sundfeldt K, Bergh T, et al. (2009) Ovarian epithelial neoplasia after hormonal infertility treatment: long-term follow-up of a historical cohort in Sweden. *Fertil Steril* 91(4), 1152–8.
16. Rossing MA, Daling JR, Weiss NS, Moore DE, Self SG. (1994) Ovarian tumors in a cohort of infertile women. *N Engl J Med* 331(12), 771–6.

17. Ness RB, Cramer DW, Goodman MT, Kjaer SK, Mallin K, Mosgaard BJ, et al. (2002) Infertility, fertility drugs, and ovarian cancer: a pooled analysis of case–control studies. *Am J Epidemiol* 155(3), 217–24.
18. Navaratnarajah R, Pillay OC, Hardiman P. (2008) Polycystic ovary syndrome and endometrial cancer. *Semin Reprod Med* 26(1), 62–71.
19. Modan B, Ron E, Lerner-Geva L, Blumstein T, Menczer J, Rabinovici J, et al. (1998) Cancer incidence in a cohort of infertile women. *Am J Epidemiol* 147(11), 1038–42.
20. Jensen A, Sharif H, Kjaer SK. (2009) Use of fertility drugs and risk of uterine cancer: results from a large Danish population-based cohort study. *Am J Epidemiol* 170(11), 1408–14.