1

Risk of cancer from ovarian stimulation

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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 she be counseled?*

Background

Women suffering from subfertility are often concerned about the safety of the drugs and the risk of cancer. A belief that using hormones could increase the risk of cancer is one of the most significant fears. In recent years, there have been many debates about the relationship between infertility, fertility drugs and cancer. Early studies raised substantial concern with ovulation-stimulating drugs being linked with large increases in ovarian cancer [1,2]. However, it is difficult to separate cancer risk after fertility treatment from the underlying condition of infertility. Comorbidities such as obesity, excessive smoking, anovulation, endometriosis and nulliparity are frequently related to subfertility, but they are also independently related to an increased risk of cancer [3]. The delay or the inability to achieve a pregnancy is an important risk factor for breast, endometrial and ovarian cancer. However, the relationship between infertility treatment and cancer incidence remains an open question [2,4].

Management options

Breast cancer

Breast cancer is the most common malignancy in women, affecting one in eight women. Breast cancer is a multifactorial disease; however, most breast cancers are hormone-dependent [5]. Compared with a normal menstrual cycle, estradiol concentration increases up to tenfold in ovulation stimulation cycle [6]. Therefore, the effect of subfertility and its treatment on breast cancer is widely investigated in the literature. The association between polycystic ovary syndrome (PCOS) and breast cancer has been examined in several studies. Meta-analysis showed that PCOS does not increase the risk of breast cancer [7, 8].

As for fertility drugs and breast cancer risk, some studies showed no association while

Assisted Reproduction Techniques: Challenges and Management Options, Second Edition.
Edited by Khaldoun Sharif and Arri Coomarasamy.

others demonstrated a possible increase in risk [9–12]. An Australian study (n = 21,025) showed commencing IVF treatment at a young age (less than 24 years of age) is associated with an increased rate of breast cancer [13]. It is expected that, if ovulation induction per se causes breast cancer, such tumors may have distinct characteristics such as strong estrogen receptor expression, but a study showed that breast cancer diagnosed within the first 2 years following infertility treatment is similar in tumor characteristics such as tumor size and histological types, estrogen receptor, progesterone receptor and Her2/Neu expression status compared to those occurring in patients without prior infertility treatment [14].

Women with BRCA1 or BRCA2 mutation have an increased risk of breast cancer. A study of 1,550 BRCA1 and 964 BRCA2 mutation carriers did not show any evidence that ovarian stimulation for IVF increases the breast cancer risk in BRCA1/2 mutation carriers [15]. A large UK-based data linkage cohort study of 255,786 women did not find an increase in the overall risk of breast cancer but a small increase in the risk of in situ breast cancer was reported [16]. A meta-analysis of eight cohort studies showed IVF treatment does not increase the breast cancer risk [17]. A total of seven systematic reviews or meta-analyses evaluated the relationship between fertility drugs and breast cancer [17-23]. They have either shown no increase in the risk of breast cancer or a decrease in risk following infertility treatment. Therefore, as per the American Society of Reproductive Medicine guideline, women could be reassured that fertility drugs are not associated with an increased risk of breast cancer [24].

Ovarian cancer

Ovulation is considered to be a potential biologic promoter of ovarian cancer, which is called the "incessant ovulation" hypothesis. A second hypothesis is that gonadotropin stimulation increases the risk of malignant changes directly, or by acting in combination with a raised concentration of estrogen. Yet another hypothesis frequently suggested by epidemiological data is that undiagnosed early ovarian cancer causes, in some manner, infertility [25]. Data from 12 case-control studies conducted in the period 1956–1986 showed pregnancy, breastfeeding and oral contraceptive use induce biological changes that protect against ovarian malignancy. A small fraction of the excess ovarian cancer risk among nulliparous women was due to infertility [26]. Only 3 of the 12 studies examined the association between the use of fertility drugs and invasive ovarian cancer. One study showed an increased risk of ovarian cancer in infertile women who had used fertility drugs. This study had several limitations. Subsequently, a large cohort study [27] suggested an increased risk of invasive and borderline ovarian tumors, a finding that was supported by other studies [28,29]. A pooled analysis of case-control studies showed fertility drug use in nulligravid women was associated with borderline serous tumors but not with any invasive histologic subtypes [30]. Several other epidemiological studies showed no convincing association between the use of fertility drugs and risk of ovarian cancer [18,31–34].

An important group of women who are at increased risk of developing ovarian cancer are those with BRCA1 and BRCA2 gene mutations. Recent studies suggested that BRCA mutation carriers may have decreased ovarian reserve compared with women without BRCA mutations [35,36]. The studies suggested that treatment for infertility does not significantly increase the risk of ovarian cancer among women with a BRCA mutation [37,38]. A meta-analysis of nine cohort studies showed that IVF is not associated with ovarian cancer when the confounding effect of infertility was adjusted for in such studies [39]. A recent Cochrane review consisting of 24 cohort studies and 13 case-control studies concluded that there is no convincing evidence of an increase in the risk of invasive ovarian tumors with fertility drug treatment, and even women with a BRCA genetic mutation are not at increased risk due

to fertility treatment [25]. Risk of borderline ovarian tumors may be increased in infertile women treated with *in vitro* fertilization, but the evidence is classed as low grade [25].

To summarize, current evidence is sufficient to reassure women that there is no clear increase in the risk of invasive ovarian cancer following the use of fertility drugs. A few studies have shown a small increase in the absolute risk of borderline ovarian tumors after fertility treatments, but this risk is small, and the evidence is insufficient to recommend against the use of fertility medications to avoid borderline ovarian tumors [24].

Endometrial cancer

Endometrial cancer is the most common malignancy of the lower female genital tract in developed countries [40]. It is a hormone-dependent malignancy in the majority of cases. PCOS and unexplained infertility have also been linked directly to endometrial cancer [9,41]. The suggested mechanism is that fertility drugs result in prolonged exposure of the endometrium to high levels of estrogen, which raises the risk of endometrial cancer by increasing mitotic activity and DNA replication errors [42]. However, fertility drugs induce ovulatory cycles and pregnancies, which results in progesterone production, exerting potentially protective effects and a reduction in endometrial cancer risk. A meta-analysis of nine cohort studies concluded that IVF does not seem to be associated with increased risk of cervical cancer or endometrial cancer when the confounding effect of infertility was neutralized [39]. A 2017 Cochrane review of 19 studies (1,937,880 participants) concluded that women who need treatment with clomiphene citrate should be aware that they are at increased risk of endometrial cancer. The risk is largely due to underlying conditions causing subfertility, and it is not possible to assess the additional effect of clomiphene citrate, based on available data [43]. The review found the quality of evidence was very low.

Overall, there is no evidence to support that fertility drugs are associated with an increased risk of endometrial cancer.

Cervical cancer

The literature investigating the risk of cervical cancer following fertility medication use has consistently shown no increased risk compared to both the general population and infertile patients as controls [44]. On the other hand, a few studies showed a reduced incidence of cervical cancer in women undergoing IVF which could be related to better access to healthcare and ensuring cervical cytology screening are up to date [18,45].

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 and associated comorbidities may act as a risk factor for many gynecological cancers.
- PCOS, a condition associated with infertility, is linked to endometrial cancer but not with breast 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 used the general population as the comparator. A more appropriate comparator is the untreated infertile population as this would allow better assessment of the cancer risk attributable to fertility drugs.
- Some studies have shown a small increase in the risk of borderline ovarian tumors following the use of fertility drugs, but the evidence is insufficient to recommend against their use.

Management options:

- Women should be counseled about the uncertainty in the available evidence.
- Women may be counseled that there is no clear evidence that the use of fertility drugs for IVF increases the risk of cancers.

Answers to questions patients ask

Q1 ***Does IVF treatment increase the risk of cancer?***

A1. No it doesn't. There were initial worries about this issue because we use hormones to stimulate the ovaries in IVF, but subsequently many studies looked at the effect of having IVF on cancers of the breast, ovary and womb, and their conclusions were that there is no increased risk.

Q2 ***My aunt had IVF in the past and now she developed cancer. Do you think it was the IVF that caused it?***

A2. Unfortunately, cancer is not uncommon, and it is estimated that about one in three people will develop cancer in their lifetime. The good news is that many of these cancers are diagnosed early enough to treat them, but the point is that cancer could happen whether the woman had IVF or not. Many studies looked at the effect of having IVF on cancers of the breast, ovary and womb, and their conclusions were that there is no increased risk. Sometimes, having conditions that make the woman more likely to need IVF (such as PCOS) in itself increases the risk of cancer.

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