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Commentary

Long-term breast cancer risk following ovarian stimulation in young egg donors: a call for follow-up, research and informed consent

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A B S T R A C T

In the USA and other countries, oocyte donation is gaining increasing importance. Although sufficient data exist on procedure-associated short-term risks for oocyte donors, such as ovarian hyperstimulation syndrome, long-term follow-up studies of egg donors are lacking and their health risks are unknown. The lack of information may be misleadingly interpreted as lack of risk. Long-term hormone replacement therapy is recognized as a risk factor for breast cancer; the breast cancer risk of ovarian stimulation for egg donors is unknown but is a possibility. This commentary describes five individual cases of egg donors who developed breast cancer (four out of five women in their 30s) despite negative genetic testing results. Additionally, we summarize available studies of breast cancer in infertile women who experienced IVF. We emphasize the need to create egg donor registries that will facilitate long-term studies on egg donors. Until this information is available, we call for more realistic explanations to egg donors about the lack of knowledge of long-term risks as well as more transparent informed consent documents.

Introduction

More than 2 decades after the beginning of ovarian stimulation of healthy young women for oocyte retrieval for egg donation, research has still not been conducted on their potential increased long-term risks, such as cancer and infertility. The existing studies on health risks to egg donors describe only short-term adverse events of oocyte retrieval such as haemorrhage or ovarian hyperstimulation syndrome (OHSS).

In this commentary, we focus on breast cancer, the leading cause of cancer death among women worldwide (American Cancer Society, 2015; World Cancer Research Fund International, 2012). Hyperstimulation of any tissue can lead to malignant transformation. Breast and endometrial cancers are known to be related to total endogenous oestrogen exposure. A pooled analysis of data from seven studies found 'a positive association between [endogenous] sex hormones and breast cancer risk in premenopausal women. Whether or not this association is causal is not known, but plausible biological mechanisms exist that could explain such an effect.' (Endogenous Hormones and Breast Cancer Collaborative Group, 2013). In the Million Women Study in the UK, it was found that 'current use of HRT [hormone replacement therapy] is associated with an increased risk of incident and fatal breast cancer.' (Beral et al., 2003). The risk increased with years of use, and was greatest for those who had taken an oestrogen–progesterone combination for 10 years or more. Of course, breast cancer risk is also increased if various inherited gene mutations are present, including mutations in the *BRCA1*, *BRCA2*, *CHEK2*, *ATM*, and *PALB2*,

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as well as tumour suppressor gene *TP53* (p53) germ line mutations, and other unknown genes. Lifetime risk in the general population of getting breast cancer by the age of 70 years is about 8–12%, whereas, in BRCA carriers, the risk in *BRCA 1* carriers is 55–65% and in *BRCA2* carriers 45% (Antoniou et al., 2008). About 5–10% of breast cancers can be linked to gene mutations (Breastcancer.org, 2016). Age is also a significant risk factor for breast cancer. According to the US National Cancer Institute's SEER program (Surveillance, Epidemiology and End Results), the incidence at diagnosis of invasive breast cancer gradually increased, from 13.0/100,000 for women aged 30–34 years, 29.6 at ages 35–39 years, 61.6 at 40–44 years, and 221.8 at ages 65–69 years (a 17-fold increase from ages 30–34 years), and 233.6 at 75–79 years (Howlader et al., 2012).

In the absence of high-quality, long-term studies of egg donors, conclusions about their cancer risks have been extrapolated from the increasingly large number of studies of long-term risks in another group, infertile women who undergo ovarian stimulation in order to produce multiple eggs for their personal use for IVF. The problem with equating these two groups is that they differ in several ways; for example, at the time of their egg retrieval, infertile women are generally older than altruistic or commercial egg donors.

Infertility itself has been shown to affect the risk of various cancers. For example, Brinton et al. (2004) found that infertile women had about a 30% higher risk of developing breast cancer compared with the general population. 'This undoubtedly reflects unique attributes of infertile women, including higher rates of nulliparity, a recognized breast cancer risk.' (Brinton et al., 2004). An Institute of Medicine report (Giudice et al., 2007) stated that 'Infertility increases the risk of all three cancers [breast, ovarian, and endometrial], so a study that compared women undergoing IVF with women in the general population might find the IVF group with a higher rate of cancer – but not because of the fertility drugs they had taken but rather because the infertility that led them to try IVF also made them more likely to develop these cancers.' Therefore, infertile women have different underlying cancer risks than do egg donors.

The populations in the published studies varied in age at IVF treatment, in parity, in hormonal regimen and in years of follow-up. In most studies, the cohort of 'infertile' women is heterogeneous, including various biological causes, as well as mechanical (e.g. tubal obstruction, pelvic adhesions, or anatomical variations), hormonal, or male-factor infertility. Each of these groups may itself have differential cancer risks, as shown by Brinton et al. (2005). Theoretically, the female partners of infertile males would be expected to be biologically similar to fertile egg donors, but, in reality, a significant proportion of them have their own infertility issues. For example, Liberty et al. (2014) retrospectively analysed 376 hysterosalpingograms of couples with severe male-factor infertility, and found that 25.5% of them had mechanical abnormalities and therefore their own cause of infertility.

Another difficulty is finding the appropriate control group. Some studies use cancer risks in the general population as a comparator, others use infertile women who did not *undergo* hormonal stimulation as controls; others have used both types of control groups. Not surprisingly, different studies have yielded different findings and conclusions.

Brinton (2007) summarized existing studies on the long-term effects of ovulation-stimulating drugs on cancer risk in infertile women. She found the results of various studies to be conflicting, with some showing no association and others showing possible increases in risk of one or another type of cancer, or in cancer risk in varying subgroups. In contrast, two studies clearly showed increased risk of endometrial cancer with clomiphene use.

Several recent population studies reported on the risk in infertile women who underwent hormonal stimulation to produce multiple oocytes and its association with breast cancer. Three studies and two meta-analyses are presented in **Table 1**.

Two of the three studies found significant increases in breast cancer risk among certain subpopulations, such as those who took clomiphene or those who remained nulligravid (Brinton et al., 2014) or only in those who had IVF at a young age (Stewart et al., 2012). A recent study by Van den Belt-Dusebout et al. (2016), however, found no significant increase in breast cancer risk. In this study, among women undergoing fertility treatment in the Netherlands between 1983 and 1995, IVF treatment compared with non-IVF treatment was not associated with increased risk of breast cancer after a median follow-up of 21 years. Breast cancer risk among IVF-treated women was also not significantly different from that in the general population. These findings are consistent with absence of a significant increase in long-term risk of breast cancer among IVF-treated women.

Of the two meta-analyses, the study by Li et al. (2012) found no significant increase in breast cancer risk, but did find a significant increase in ovarian cancer risk. Their follow-up, however, was too short, only 3.6–10 years, and the largest study included, constituting 89.8% of the cohort, had a mean follow-up of only 6.2 years. A meta-analysis by Sergentanis et al. (2014) found no significant increase in breast cancer, but only one of the eight included studies had a follow-up of more than 8.3 years.

Therefore, there is still some uncertainty about the long-term cancer risks for infertile women who undergo hormonal stimulation, or for some subgroups of infertile women. The finding in several (but not all) long-term population studies of an increased risk of breast cancer after ovarian stimulation makes it imperative to study this potential risk among egg donors. Until this is actually possible, we can at least present some individual cases.

Cases

In recent years, five women contacted the three authors to report their breast cancer after egg donation. All patients provided medical records and gave permission to publish their de-identified information. In some cases, the patients were unable to provide the specifics of the ovarian stimulation protocols.

Patient A

At age 29 years, Patient A underwent one cycle of ovarian stimulation with the gonadotrophin releasing hormone (GnRH) leuprolide as well as HCG, yielding 28 eggs. She experienced severe ovarian hyperstimulation syndrome (OHSS), with massive swelling and torsion of the right ovary. Five years later, at age 34 years, she was diagnosed with stage IIB breast cancer. Pathology report showed a poorly differentiated in-situ ductal carcinoma, and two out of six positive lymph nodes. The cancer was oestrogen and progesterone positive, and HER-2/neu. negative. She had no family history of breast cancer, and genetic analysis was negative for the *BRCA* gene.

Patient B

At age 32 years, Patient B underwent one cycle of ovarian stimulation. Four years later, at age 37 years, she was diagnosed with stage