RBM ONLINE

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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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http://dx.doi.org/10.1016/j.rbmo.2017.02.003

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

Table 1 – Breast cancer risk studies in infertile women.

Author	Location	Study population	Sample	Results/findings	Follow-up	Key limitations
Brinton et al., 2014	NA	9892	Evaluated for infertility 38.10% who took clomiphene High clomiphene use and more than six cycles 9.6% who took gonadtrophins (usually in combination with clomiphene)	749 with breast cancer Somewhat elevated risk (HR = 1.05) Statistically significant elevated risk (HR = 1.27) Risk increased significantly only in women who remained nulligravid.	Median 30 years	
Stewart et al., 2012	Australia	21,025	Age 20–44 years seeking treatment between 1983 and 2002 Woman who had IVF at a young age (about 24 years)	384 cases of breast cancer (236 did not have IVF and 148 did); mean age for those who did not have IVF was 46.4 and those who did 47.1. HR = 1.59, significantly increased compared with infertile women who began IVF at age 40 years.	Mean 16 years	
Li et al., 2012 Meta-analysis	NA	746,455	Participants from eight cohorts, seven of which included examination of breast cancer risk. General population used as control in five out of the seven studies. Women who had live births used as control in two of the seven studies.	No overall increase in cancer risk, significant increase in ovarian cancer risk, and no increase in breast cancer risk.	Largest group (Kristiansson et al., 2007) had a mean follow-up of 6.2 years for 89.8% of total cohort.	Follow-up was too short, only 3.6–10 years.
Sergentanis et al., 2014 Meta-analysis	NA	1,554,332	Included five of the same studies as Li et al. (2012) but added three more recent studies.	14,961 cases of breast cancer, including 576 among woman exposed to IVF. No significant increase in breast cancer compared with general population or infertile women.	Largest group (Källén et al., 2011), mean follow-up was 8.3 years for 89% of total cohort.	Follow-up was too short. Only one of the eight studies (Stewart et al., 2012) had more than 8.3 years.
Van den Belt-Dusebout et al., 2016	Netherlands	25,1008	25,108 infertile women, of whom 19,158 were treated with IVF between 1983 and 1995	839 cases of invasive breast cancer and 109 in-situ breast cancer. No significant increased risk of breast cancer compared with non-IVF infertile women nor with general population.	Median 21 years	

HR, hazard ratio; RR, relative risk; SIR, standardized incidence ratio.

III breast cancer and had a mastectomy followed by chemotherapy and radiation. Pathology report showed invasive ductal carcinoma, and two out of eight axillary lymph nodes were positive. The tumour was oestrogen-receptor positive, progesterone-receptor positive (ER+/PR+). She was *BRCA* negative and *HER-2* negative. There was no family history of breast cancer.

Patient C

At age 34 years, married to a man who had undergone a vasectomy, Patient C underwent ovarian stimulation for intracytoplasmic sperm injection (ICSI) and IVF. The hormonal regimen included the GnRH agonist nafarelin acetate. The first cycle had no complications. A second cycle, with retrieval of 33 eggs, resulted in hospitalization for severe OHSS. The last cycle, at age 35 years, was successful, resulting in a live birth. . At that point she decided to donate eggs altruistically to infertile women, and underwent three more cycles between the ages of 37 and 39 years. Eight years later, at age 47 years, she was diagnosed with a grade 1 tubular breast carcinoma. She had no family history of breast cancer and genetic testing was reported as negative as well. The tumour was ER+/PR+, *HER-2* negative.

Patient D

At age 25 years, Patient D underwent the first of three cycles of ovarian stimulation, using leuprolide, FSH and then HCG. At age 33 years, she was diagnosed with Stage 1–2 breast cancer. The tumour was ER+/PR+, one of four lymph nodes was positive. Genetic testing was reported as negative for *BRCA* and other genes, and she had no family history of breast cancer.

Patient E

At age 21, Patient E underwent hormonal stimulation and egg retrieval for the first of 10 cycles. After three cycles at one IVF clinic, she had an additional seven cycles at a second clinic, the last being at age 32 years. She underwent several different hormonal regimens, which included at various times leuprolide, FSH and Ganirelix acetate, a GnRH antagonist, and HCG. She experienced OHSS three times. The number of eggs retrieved in those 10 cycles varied between 12 and 33. A physical examination conducted before her final cycle, at age 33 years, revealed a mass in her left breast. Four months later, a biopsy showed invasive ductal carcinoma. The tumour was ER+PR+, Ki-67 intermediate (17%), and *HER2* negative. She had multiple bone and hepatic metastases. Two relatives had breast cancer: a great aunt diagnosed at age 38 years and her grandmother at age 60 years. Patient E was negative for the *BRCA* gene but positive for a *P13KCA* mutation.

Discussion

The individuals in this report were aged between 21 and 35 years at the time of their first egg donation cycle and underwent between one and 10 egg retrieval cycles. One patient (C) initially underwent three cycles for ICSI for herself only because her husband had undergone a vasectomy, and then altruistically for donation; she was not herself an infertile woman. The hormonal regimens varied among patients and also, among those who had multiple cycles in more than one clinic, between clinics. Two of the five women developed severe OHSS requiring hospitalization. One cannot rule out the possibility that this complication itself may increase subsequent chances for breast cancer, but there is no evidence at present about this. The five women were diagnosed with breast cancer 4, 5, 8, 12, and 13 years after their first or only cycle. Four of the five women were in their 30s (33, 33, 34, and 37 years) at the time of their breast cancer diagnosis. All were ER+/PR+. Because about 80% of breast cancers are ER+/PR+, the significance of this finding cannot be evaluated. All five women had negative genetic testing, and four out of five had no family history of breast cancer; one had two relatives with breast cancer. The information on the specific genes tested was limited by what the medical records provided. The early age of breast cancer diagnosis in these egg donors certainly hints at the possibility that the hormonal hyperstimulation of their ovaries was a factor.

We know of the five patients only because they contacted the authors over a several-year period. To estimate the prevalence of breast cancer among egg donors, we would need some information on the total number of donors who developed breast cancer as well as the total number of women donating eggs. Four of the five patients resided in the USA, so the authors sought information on US donors. According to the American Society for Reproductive Medicine, this information has not been collected in the USA. The only available information is the number of donor oocyte cycles in the USA. The annual number of cycles increased from 10,801 in 2000 to 18,306 in 2010 (Kawwass et al., 2013). Without information on the average number of cycles per donor, the number of donors whose oocytes were not used, and donors who did not complete their injection cycle, one cannot determine the total number of US egg donors.

A case series is historically the first step toward more high-quality medical studies. Such studies will be required to answer definitively whether hormonal stimulation of egg donors does or does not increase the risk of various cancers. Single cases, of course, provide an insufficient basis for inferring cause and effect. What is needed is a systematic long-term follow-up of egg donors.

Given the absence of long-term follow-up of egg donors in the USA, it is impossible to even gather information to estimate the prevalence of breast cancer, or of any other cancer, in this group, nor draw any conclusion about the possibility of an increased risk compared with the general population.

This leaves the issue of informed consent. None of the five patients, having asked about the risks, were given any information about long-term risks. It is all too easy to equate the absence of information about long-term risks with the absence of long-term risks. In the USA, the informed consent agreements that IVF clinics give to potential donors provide minimal information on long-term risks, and any that is provided is based on studies of infertile women rather than donors, without explaining that this is a different group.

The absence of information has also led to inadequate attention to potential health risks in a new group, young women who seek to benefit from cryopreservation of their oocytes in order to defer pregnancy. In discussing the options for a 32-year old single woman seeking to maximize her future fertility, Schattman (2015), in the *New England Journal of Medicine*, describes the process of cryopreservation, the outcome for preserved oocytes, the increased risk of pregnancy complications among older women and the immediate risk of OHSS. He recommends discussing the possibility of elective cryopreservation of oocytes with all women who are in their early 30s. (Indeed, some large companies, in an attempt to keep their female employees in the work force, now offer to pay for this procedure for those who wish

to defer pregnancy (National Public Radio, 2014; Time Magazine, 2015). But, as Schneider (2016) pointed out in a Letter to the Editor of the *New England Journal of Medicine*, there is no mention in the paper of potential long-term health risks such as malignancy in women who undergo ovarian stimulation. She concluded: 'All women who undergo ovarian stimulation, especially more than once, should be told that their long-term health risks are unknown.' As the Schattman paper illustrates, the absence of information in the USA makes it more likely that healthcare providers will present the long-term risks as minimal to potential donors.

Conclusions

In 1998, in their report on a young British egg donor with subsequently fatal colon cancer, Ahuja and Simon concluded: 'In egg donation, non-patient volunteers are exposed to unknown risks for the benefit of others. . .. Until epidemiological studies on the safety of egg donors are available, cases can provide the only guidance for safe recruitment.' Almost 20 years later, the long-term risks for egg donors are still largely unknown, and case reports (Ahuja and Simons, 1998; Schneider, 2008) are still the only clues to these possible risks. Studies on a related cohort, infertile women who undergo ovarian stimulation to produce eggs used for their own IVF treatment, have yielded mixed results, with some suggesting a possible increased risk of breast cancer and others not. These follow-up studies of women who had different causes of infertility and drug exposure have had many methodological complexities.

The case reports presented in this paper were provided as an illustration of a possible link between hormonal stimulation and breast cancer. It is tempting to conclude that because we cannot clearly demonstrate, in advance, that ovarian stimulation results in an increased risk of breast cancer, or other cancer, in infertile women, there is no need to follow up actual oocyte donors. Yet, the clear and ethical solution to extrapolating from infertile women is to actually carry out long-term studies of egg donors. It is time to create egg donor registries, and to use them to follow up these women to determine any long-term health risks. With real data on risks, young women will finally be able to make truly informed choices about undergoing ovarian stimulation. Depending on the results of long-term studies, they will know that they are either risking their health by pursuing egg donation, or else they can be reassured that there are no significant long-term medical risks. In the meantime, rather than providing information in their informed consent form only about infertile women, a different group, IVF clinics are ethically obligated to disclose to potential egg donors in a more transparent manner that the long-term risks are currently unknown because they have not been studied.

ARTICLE INFO

Article history:
Received 11 August 2016
Received in revised form 7 February 2017
Accepted 7 February 2017
Declaration: This research did not receive any specific grant from funding agencies in the public commercial, or not-for-profit sections. None of the authors report any conflict of interest.

Keywords:
Breast cancer
Egg donors
Informed consent
Long-term risks
Ovarian stimulation

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