Breast Cancer in Young Egg Donors: A Call for Follow-up, Research, and Transparency on the Long-Term Risks of Ovarian Stimulation

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Abstract [197 words]

In the United States, prospective egg donors are usually told there are no known long-term risks of the hormonal stimulation or egg retrieval process (for example, cancer or infertility). They often interpret this to mean that there *are* no risks. The reason for the lack of knowledge, however, is that to date there have been no long-term outcome studies of the health risks to such young women. The only information we have are (1) case reports, and (2) population studies of a *different* group, infertile women who underwent hormonal stimulation for IVF, women already known to have differential risks of various cancers. This report describes 5 individual cases of egg donors who developed breast cancer (4/5 in their 30s) despite negative genetic testing. Additionally, we summarize available studies of breast cancer in infertile women who experienced IVF, some with too-short a

follow-up. We emphasize the need to create egg donor registries that will facilitate long-term studies on these women. Finally, after reviewing the informed consent agreements in several large U.S. IVF organizations, we call for more transparent explanations to egg donors about the lack of knowledge of long-term risks as well as more transparent informed consent documents.

Keywords: egg donors, breast cancer; ovarian stimulation, long-term risks, informed consent

Introduction

The absence of long-term follow-up studies of health risks to egg donors has been apparent for many years, and is still true today. In 2001, 5 years after the first of 3 cycles of ovarian stimulation for oocyte donation, a previously healthy 29-year old woman was diagnosed with metastatic colon cancer. She had no family history of colon cancer, and DNA analysis done after her death at age 31 confirmed the absence of any genetic predisposition to this cancer (Schneider, 2008). An attempt at the time to find information regarding a possible connection between ovarian stimulation and colon cancer yielded only one report (Ahuja and Simons, 1998), a 33-year old egg donor in England who was diagnosed with advanced colon cancer some 4 years after altruistic egg donation and died at age 39. She underwent 2 cycles of ovarian stimulation.

More recently, Spaan et al (2016) wrote, “Sex hormones seem to have a role in the etiology of colorectal cancer. This raises interest in the possible effects of fertility drugs.” In 1996 they set up a nationwide cohort study in the Netherlands to examine colon cancer risk in 19,158 infertile women who underwent hormonal stimulation for in vitro fertilization (IVF), and 5,950 unexposed infertile women. They compared colorectal cancer risk in the IVF group with (1) the general population and (2) infertile women who did not get IVF. After a median follow-up of 21 years, they observed 109 cases of colorectal cancer, which was no greater than the risk in the general population, but was significantly *decreased* in the non-IVF infertile women. The infertile IVF-treated

women had a significantly *increased* colon cancer risk compared with infertile non-IVF-treated women. The authors concluded, “Further research is warranted to examine whether ovarian stimulation for IVF contributes to development of colorectal cancer.” Of course, the same is true for other cancers.

More than two decades after the beginning of ovarian stimulation of young women for oocyte retrieval, there has still been no research on the long-term cancer risks of hormonal stimulation of egg donors. Surprisingly, the *only* information we have is case reports, plus population studies of a very different group, infertile women undergoing hormonal stimulation for IVF in an attempt to get pregnant. Infertility and nulliparity in themselves have differential risks of various cancers. All too often the results of these studies (which are often confusing because of the coexisting infertility, different age, etc.) are extrapolated to young, presumably fertile women without understanding that these are different cohorts.

The reality is that the potential risks to egg donors have not been studied -- not only the potential risks of colon cancer, but of any other malignancy. Specifically endometrial and breast cancers are related to total endogenous estrogen exposure; ovarian cancer is less certain, but hyperstimulation of any tissue can lead to malignant transformation. Historically there have been other examples of the use of hormones which, only after many years, when outcome studies were finally done, were found to have had significant negative consequences. One of these was the use of diethylstilbestrol for over 30 years to reduce adverse pregnancy outcomes in women who’d experienced miscarriages. Only after a report of several cases of vaginal clear cell carcinoma in girls previously exposed in utero to DES was published in 1971 (Herbst, 1971), were serious outcome studies done, and these resulted in confirmation of the risk and cessation of the use of DES for this indication.

A case series is historically the first step toward more high-quality studies of the efficacy and risks of a medical procedure. Such studies will be required in order to answer definitively whether hormonal stimulation of egg donors does or does not increase the risk of various cancers. The outcome, whether positive or

negative, will be of benefit to egg donors as it will provide them with clinically useful information. If there is an increased long-term risk of cancer, potential egg donors will be able to make a truly informed decision about whether to proceed; if there is no risk, donors will be able to be told clearly that there is no risk and will be very relieved, as many of them do question what the long-term risks are.

Until that time, we are left with case reports. In this paper, following an updated review of the literature, we present several cases of breast cancer in young women following egg donation,

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 in order to obtain data on any long-term health risks. Currently, however, the existing studies on health risks to egg donors describe only short-term adverse events of oocyte retrieval such as hemorrhage or ovarian hyperstimulation syndrome (OHSS). The emphasis on immediate complications are evident, for example, in a study by Sauer (2001) titled, “Defining the incidence of serious complications experienced by oocyte donors: a review of 1000 cases.” This retrospective analysis reviewed 1,000 women at the time of egg retrieval and at a follow-up exam one week later. A low incidence of “significant morbidity” requiring hospitalization, 0.7%, was found. There were 3 cases of serious OHSS, 2 cases of hemorrhage, and 2 of hypotension related to anesthesia. Complications beyond 1 week were not studied. In addition to cancer, long-term complications might include infertility. Because oocyte retrieval may result in ovarian adhesion formation, thus reducing future fertility (Levens et al, 2008), a need exists to follow up egg donors in order to obtain information on potential infertility (unfortunately this has not yet been done). Among 155 egg donors who completed a survey a mean of 9.4 years (range 1-22 years) after their first egg donation, 15 (9.6%) experienced a new infertility problem and only 4 of the15 became pregnant after donation, despite attempts to conceive (Kramer et al, 2009).

In 2007 the Institute of Medicine (IOM) and the National Research Council of the National Academies of Science (NAS) published the outcome of a

conference on the risks of human oocyte donation for stem cell research (Giudice et al, 2007). Potential acute risks to egg donors included ovarian hyperstimulation syndrome (OHSS), anesthesia/surgical mishaps, and psychological problems. Another risk was arterial thrombosis leading to stroke. The potential long-term risks of ovarian hyperstimulation were of hormone-dependent cancers, in particular of breast, ovarian, and endometrial cancers, as well as possible problems with long-term infertility. The report concluded, "The evidence to date is limited, but does not support a relationship between fertility drugs and an increased prevalence of breast or ovarian cancer. More research is required to examine what the long-term impact fertility drugs may be on breast and ovarian cancer prevalence rates." Unfortunately, many readers may perceive the *lack of evidence* of cancer risks as evidence of no danger (Jain, 2013).

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 of another group of women who undergo ovarian stimulation in order to produce multiple oocytes for IVF– infertile women who have had difficulty conceiving. Before presenting our cases of breast cancer following egg donation, it is instructive to review the literature on the relationship between the use of fertility drugs (by infertile women) and breast cancer, since those are the only available studies.

The problem with equating these two groups is that they differ in several ways. First, at the time of their egg retrieval, infertile women are generally older than altruistic or commercial egg donors. Second, infertility itself has shown to affect the risk of various cancers. For example, Brinton et al (2004) found that infertile women had an approximately 30% higher risk of developing breast cancer than did fertile women. The IOM report (Giudice, 2007) addressed this, saying, "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." (p.24).

Third, in most studies, the cohort of "infertile" women is a collection of women who have different biological causes, which may thus produce differential risks of various cancers. "The "infertility" category usually includes women whose infertility is mechanical (e.g. tubal obstruction pelvic adhesions, or anatomical variations), hormonal, or "male-factor infertility." However, each of these groups may itself have differential cancer risks. A retrospective study of 12,193 women who had been evaluated for infertility specifically addressed the causes of infertility as predictors of subsequent cancer risk (Brinton et al, 2005). The cohort of infertile women had a 23% higher overall risk of cancer than women in the general population. Infertile woman were at an increased risk of uterine and ovarian cancer. Women whose infertility was due to endometriosis had a relative risk (RR) of colon cancer of 2.3, ovarian cancer of 2.88, and thyroid cancer of 4.65.

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; yet others 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.

With regard to breast cancer, there have been several population studies on the risk in infertile women who underwent hormonal stimulation to produce multiple oocytes. Many of them did not have a sufficiently lengthy follow-up period. Table 1 summarizes four studies with long-term follow-up and two recent meta-analyses. Brinton et al (2014) performed an extended follow-up (median

30 years) of women who underwent hormonal stimulation for infertility. Among those who had >6 cycles of clomiphene, especially with persistent nulligravid status, were at a significantly higher risk of breast cancer.

[INSERT TABLE 1 NEAR HERE]

Older studies had mixed results. In a retrospective Israeli study of infertile women followed for a mean of 20.9 years (Lerner-Geva et al, 2006), hormonal stimulation significantly increased the risk of breast cancer, compared to the general population, only when clomiphene had been used. Another Israeli study (Calderon-Margalit et al, 2008), this one of parous women followed up for a median of 29 years found that among women were treated with hormones for IVF), there was a significantly increased overall cancer risk but only a borderline increased risk of breast cancer

In an Australian population study (Stewart et al, 2012), of women seeking infertility treatment followed up for a mean of 16 years, there was no overall increased risk with IVF treatment, but women who had IVF at a young age (about 24) had a hazard ratio (HR) of 1.59 compared with those who began IVF at age 40. The authors concluded, “Commencing IVF treatment at a young age is associated with an increased risk of breast cancer.” Considering that egg donors are usually in their 20s when they undergo ovarian stimulation, this study suggests that the relatively young age of egg donors at the time of ovarian stimulation might in itself be a risk factor for breast cancer.

Li et al (2012) did a meta-analysis of 8 cohort studies comprising a total of 746,455 participants; 7 of the studies included examination of breast cancer risk (Venn,1995; Venn, 1999; Dor, 2002; Lerner-Geva, 2003; Kristiansson, 2007; Pappo 2008; Kallen, 2011). The results showed no overall increase in cancer risk, a significant increase in risk of ovarian cancer, and no increase in breast cancer risk. However, a significant limitation was that the follow-up periods ranged only from 3.6 to 10 years; by far the largest study (Kristiansson et al 2007), which comprised 89.8% of the entire population in the Li meta-analysis, had a mean follow-up of only 6.2 years. Such a short study interval is clearly

inadequate to determine whether ovarian stimulation causes cancer.

A more recent meta-analysis (Sergentanis et al, 2016) included 5 of the same studies as in the Li meta-analysis, but also 3 more recent studies (Yi-Kuhn, 2012; Stewart, 2012, and Brinton 2013). Like the Li meta-analysis, they too found no significant association between IVF and breast cancer either in comparison with the general population or in comparison with infertile women. However, only one of the 8 studies had a follow-up of more than 8.3 years. In studies designed to detect the risk of diseases that often take many years to manifest, follow-ups of less than 10 years are clearly inadequate. However, the finding in several long-term population studies of an increased risk of breast cancer following 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.

Materials and Methods

In the absence of registries and of studies, and years after the event, it is not easy to locate individuals who developed breast cancer after egg donation. The 5 women in this report all initiated their involvement: One originally wrote the first author (JS) in 2008 after reading a summary of the author's U.S. Congressional briefing about egg donors. Another originally wrote JS in 2011 after reading her published papers. Two women had contacted the second author (JL) who is a well-known advocate for women's reproductive health issues. The fifth responded to the third author (WK) after reading an announcement on that author's website, Donor Sibling Registry, seeking egg donors who had subsequently been diagnosed with cancer. All patients provided medical records gave permission to publish their de-identified information. This report is not a study of these cases, but rather a brief summary of each.

Results

Patient A. At age 29, Patient A underwent one cycle of ovarian stimulation (with leuprolide, hCG,etc.) and egg retrieval for egg donation. She was told that the

risks of donation were “very low.” She developed mild ovarian hyperstimulation syndrome (OHSS), and 28 eggs were retrieved from her right ovary. A few days later, she had severe OHSS, massive swelling and torsion of the right ovary, and was hospitalized for 2 weeks. Five years later, at age 34, she was diagnosed with stage IIB breast cancer and underwent a left mastectomy. Pathology report showed a 2.8 cm poorly differentiated in situ ductal carcinoma, and 2 of 6 positive lymph nodes. The cancer was estrogen and progesterone positive, and HER-2/neu. She then underwent chemotherapy followed by radiation. One year later she underwent a right mastectomy because of atypical hyperplasia; pathology showed mostly atypical ductal hyperplasia, with rare cells showing features of low-grade carcinoma in situ, as well as negative cervical lymph nodes. She had no family history of breast cancer, and genetic analysis was negative for the BRCA gene. At follow-up at age 43 there is no evidence of recurrence.

Patient B: At age 32, Patient B underwent one cycle of ovarian stimulation and egg retrieval for altruistic donation to a family member. When she asked about risks, she was informed of short-term risks but not long-term. Four years later, at age 37, she was diagnosed with stage III cancer of the left breast and had a mastectomy followed by chemotherapy and radiation. Pathology report showed invasive ductal carcinoma, and 2 of 8 axillary lymph nodes were positive for metastatic adenocarcinoma. The tumor was estrogen-receptor positive, progesterone-receptor positive (ER+/PR+). She was BRCA negative and HER-2 negative. Subsequently she underwent a hysterectomy and prophylactic mastectomy of the contralateral breast. She had no family history of breast cancer. At follow-up at age 47 there is no evidence of recurrence.

Patient C: At age 34, having married a man who’d had a vasectomy, Patient C underwent the first of 2 ovarian stimulation cycles for ICSI and IVF. The second cycle resulted in retrieval of 33 eggs, as well as hospitalization for OHSS. The last one, when she was 35, was successful. At that point she decided to donate

eggs altruistically to infertile women, and did 3 more cycles of hormonal stimulation between ages 37 and 39. Eight years later, at age 47, she was diagnosed with a grade 1 tubular carcinoma of her left breast and underwent lumpectomy. She had no family history of breast cancer and genetic testing was negative as well. The tumor wasER+/PR+, HER-2 negative, with 3 of 3 lymph nodes negative. She also underwent radiation therapy. At age 53 she has no evidence of recurrence.

Patient D (At age 25, patient D underwent the first of 3 cycles of ovarian stimulation, producing 11-14 eggs per cycle. She was treated with leuprolide, FSH, and then hCG at the end of the cycle with about 6 months between cycles. At age 33**,** about 8 years after the last donation, she was diagnosed with Stage 1-2 cancer of her left breast. The tumor was ER+/PR+, surrounded by 11 cm of ductal carcinoma in situ (DCIS) around it. One lymph node of 4 was positive for metastatic cancer. Genetic testing was negative for BRCA and other genes, and the tumor was slow growing so that she did not need chemotherapy. She did undergo bilateral mastectomy and subsequently radiation, followed by several months of leuprolide. Patient D reports that she was informed about possible infertility but not about any possible cancer risk.

Patient E At age 21, patient E underwent hormonal stimulation and egg retrieval for the first of 10 times. After 3 cycles at one IVF clinic, she underwent an additional 7 cycles at a second clinic, the last being at age 32. The number of eggs retrieved in those 10 cycles varied from 12 to 33. A physical examination done prior to her final cycle revealed a mass in her left breast. She was 33 years old. Although the mass was palpable, a diagnostic mammogram showed no abnormalities. Four months later a biopsy showed invasive ductal carcinoma. The tumor was ER+PR+,, Ki-67 intermediate (17%), and HER2 negative. A PET/CT scan of her body showed multiple osseous metastases throughout her axial and appendicular skeleton, multiple hepatic metastases and 2 positive left axial lymph nodes. Two relatives on her father’s side had breast cancer – her

great aunt diagnosed at age 38 and her grandmother at age 60. Genetic testing of Patient E showed she was negative for the BRCA gene but positive for a P13KCA mutation. She underwent chemotherapy with Taxol (paclitaxel) with excellent results, and then letrozole (Femara), which resulted in bone pain so that anastrozole (Arimidex) was substituted. She did not have any radiation, and no lymph nodes were removed. Patient E also underwent a hysterectomy and bilateral oophorectomy. Her bone metastases have resolved and the liver metastases have decreased.

Patient E recalls being told there were no risks to donors other than OHSS, which she experienced 3 times. A detailed and lengthy informed consent form was in her medical record, which she signed in 2011 and also, she recalls, several other years. In the section describing risks of egg donation, a paragraph titled “Bloating” ended with the following reassuring statement unrelated to bloating:

> One study has raised the possibility of an association (as distinct from a cause and effect relationship) between the use of fertility drugs and ovarian cancer. The study was based on a very small number of subjects and many, including the study author, have agreed that the presumed association is very tenuous.

This was the only mention of any potential long-term risk. Additionally, she was never informed of the ASRM guideline limiting donation to a total of 6 cycles,

Discussion

The individuals in this report were aged 21-35 at the time of their first egg donation cycle, and underwent 1-10 egg retrieval cycles. Two of the 5 women (who underwent 1 and 5 cycles) developed severe OHSS requiring hospitalization. The 5 women were diagnosed with breast cancer 4,5,8,12, and 13 years after their first or only cycle. These few cases point up the need for long-term follow-up, in contrast to so many of the currently available studies on infertile women, where risk is assessed on the basis of follow-up of only 10 years or less.

Four of the 5 were in their 30s (33, 33, 34, and 37) at the time of their breast cancer diagnosis. All were ER+/PR+. Because most breast cancers are ER+/PR+ and there were only 5 cases, the significance of this finding cannot be evaluated. All 5 had negative genetic testing, and 4 of the 5 had no family history of breast cancer; one had 2 relatives with breast cancer. All 5 had tumors that were estrogen and progesterone positive. It is striking that so many of these egg donors developed breast cancer at such a young age, and certainly this hints at the possibility that the hormonal hyperstimulation of their ovaries was a factor. Clearly one cannot draw conclusions about risks on the basis of a small number of case reports, but these results simply highlight the need for more research on egg donors.

In contrast to extensive studies of the short- and long-term health risks of infertile women who undergo ovulation induction with fertility drugs, egg donors are rarely followed beyond the first week after egg retrieval, and studies of their long-term risks are rare. The authors of the 2007 Institute of Medicine paper (Giudice et al, 2007) concluded,

> One of the most striking facts about in vitro fertilization is just how little is known with certainty about the long-term health outcomes for the women who undergo the procedure*. There are no registries that track the health of the people who have taken part in IVF, and much of what is known about the risks for women participating in IVF may not be directly applicable to oocyte donors* [Italics added]. . . Thus it will be important in the coming years to accumulate extensive health data for women whose eggs are harvested and to monitor them for long-term effects. With more data it will be possible to quantify the various risks of oocyte donation much better than can be done today and to put numbers to the risks that a donor may face.

Regarding the quality of the data, they wrote,

> The only way to know for sure, is to perform studies of women who have taken the hormones in the course of assisted reproduction therapy and

> compare their risk of cancer with controls who did not have the hormone therapy but who were similar in all other ways. [p.24]

Ten years after this report, there is still a lack of high-quality studies on the cancer risks of hormonal stimulation of egg donors. The Institute of Medicine (IOM) conference (Giudice, 2007) concluded, “The evidence to date does not support a relationship between fertility drugs ad an increased prevalence of breast or ovarian cancer.” Too many reports cite a *lack* of evidence as evidence of no danger rather than acknowledging that no data exist on the long-term effects of IVF drugs on young fertile women (Jain, 2013). In the page on side effects of egg donation, the infertility website IHR (Infertility Resources, 2016) states, that “empirical studies have not demonstrated any definitive link between egg donation and infertility, cancer, or any other significant long-term health problems. Since egg donation is a relatively new procedure, we hope to learn more about the long-term effects of egg donation in the future when additional research becomes available.”

In reality, egg donation with hormonal stimulation of the donor has been done since the late 1980s, and the possibility of an association with cancer was raised many times beginning in 1989 (Ahuja and Simons, 1996). Already in 1996, Robert Edwards, who in 1983, along with Patrick Steptoe, helped create the first “test-tube baby,” questioned the use of high-dose ovarian stimulation protocols used in IVF treatments. Thus, egg donation is hardly a “relatively new” procedure, and the need for information about potential health risks to donors has been recognized for over 25 years. The lack of long-term follow-up of egg donors to determine their risks has made it easy for prospective egg donors, as well as for those who counsel them, to equate the *absence of information* about long-term risks with *the absence of long-term risks.* This attitude is evident in the United States in information that assisted reproductive technology (ART) organizations present to prospective donors, both in fact sheets that they produce and in the standardized informed consent agreement that they provide to their clinics.

For example, the American Society for Reproductive Medicine (ASRM), in their one-page Fact Sheet titled “In vitro fertilization (IVF): what are the risks?” provides the following statement in the section called “Possible side effects of the injectable fertility medicines”: ”Earlier reports from several decades ago suggested a link between ovarian cancer and the use of fertility medicines. However, more recent and well done studies no longer show clear associations between ovarian cancer and the use of fertility medications.” (ASRM, Fact Sheet, www.sart.org/oocyte_Retrieval_and_Embryo_Transfer, retrieved 4/15/16). This is the sum total of the information they provide regarding the multiple published studies on risks of any cancer following ovarian stimulation, whether for infertile women or for egg donors.

The U.S.-based Society for Assisted Reproductive Technology (SART), in their current ASRM/SART 17-page document “Egg Donation: Process, Risk, Consent and Agreement,” under the title “Risks of Egg Donation” which consist of hyperstimulation, cyst formation, ovarian hyperstimulation syndrome, cancer, and adnexal torsion (ovarian twisting), they say this about the cancer risk:

> Many have worried that the use of fertility drugs could lead to an increased risk of cancer – in particular, breast, ovarian, and uterine (including endometrial) cancers. Since all of these cancers are more common in women with infertility, simply comparing women taking fertility drugs with women in the general population inevitably shows an increased incidence of cancer. When the analysis takes into account the increased cancer risk due to infertility per se, the evidence does not support a relationship between fertility drugs and an increased prevalence of breast or ovarian cancer. More research is required to examine the long-term impact fertility drugs may have on breast and ovarian cancer prevalence rates. For uterine cancer, the numbers are too small to draw conclusions. (SART, version 6/27/13, retrieved 3/27/16).

This explanation is specifically focused on infertile women, although the stated population of women to be given this document are egg donors. Moreover, the

conclusion that the “evidence does not support a relationship between fertility drugs and an increased prevalence of breast or ovarian cancer” minimizes the risk while omitting the very relevant fact that there have been no long-term studies specifically on egg donors. Once again, there is a conflation of purported *absence of risk* when the reality is the *absence of information.* This cannot be considered a document that provides informed consent.

A more straightforward, albeit very brief, disclosure about cancer risk was found in a 2006 guidebook from the New York State Department of Health Advisory Group on Assisted Reproductive Technologies (accessed 5/3/16), which stated,

> The long term risks of fertility drugs are unknown. A few studies suggest that fertility drugs might increase a woman’s risk for developing ovarian cancer later in life. Others do not show this link. At this time, no one knows for sure.

The absence of information has also led to inadequate attention to potential health risks in another population, young women who seek to benefit from a technological advance – the cryopreservation of 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) describes the process of cryopreservation, the outcome for preserved oocytes, the increased risk of pregnancy among older women, and the immediate risk of OHSS. He recommends, “The possibility of elective cryopreservation of oocytes should be discussed with all women who are in their early 30s, since the number of available and genetically normal eggs continually decreases over time.” (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.) 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, concluding, “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 makes it more likely that health care providers will minimize the risks.

There are only two ways to gather long-term data on egg donors. One is to initiate retrospective studies on egg donors in countries in which records and registries are maintained, the type of studies that currently abound on infertile women undergoing IVF. In the U.S., attempts could be made to contact tens of thousands of past egg donors and obtain information on their health in the years following the egg donation(s). The second, especially in the U.S., is to begin keeping records of egg donors and follow them over the years, in the same way that other organ donors are followed. Of course, it will be many years before this approach yields data, but analysis of the data will eventually allow the issuing of meaningful guidelines about the risks to egg donors.

Currently in the U.S., the Centers for Disease Control and Prevention (CDC) collects data on the outcome of ART from several hundred clinics in the United States. Clinics provide information such as "diagnosis frequency" of infertile women, "percentage of recipient starts resulting in live births", "average number of transfers resulting in live births," and "number of embryos transferred." Cycles are counted, not women; even those undergoing IVF are invisible. The focus is on the success rate of IVF interventions, not on the drug and regimens used, nor on the health of egg donors or their genetic offspring. The Society for Assisted Reproductive Technologies (SART) states that they keep track and have accurate records about the children born from egg donation, but in a study of 109 parents of egg-donor-conceived children, more than 40% stated that they were never asked to report the birth of their child (Blyth, 2013). SART provides information online about IVF outcomes (https://www.sartcorsonline.com/rptCSR_PublicMultYear.aspx?ClinicPKID=0) but no information about donor health. The CDC needs to broaden their perspective and begin a registry of egg donors, including those whose oocytes are intended for research. The type and dosages of the stimulatory drugs must be included. Leuprolide (Lupron), for example, which is widely used in the United States, is

still not approved by the Food and Drug Association (FDA) for ovarian stimulation; information about health outcomes of its use is very much needed.

An alternative to a national CDC registry would be for ASRM/SART to set up a centralized egg donor registry. In March 2008 DePaul University College of Law sponsored a symposium to discuss this issue, called, “Tracking change: The feasibility of a voluntary gamete donor registry in the United States.” The outcome was a decision to create a study committee, but no action came out of it. With an egg donor registry in place, long-term prospective studies of egg donors could be undertaken, preferably under the aegis of an agency such as the National Institutes of Health (NIH). In addition, retrospective studies, which will yield results more quickly, should be launched without delay. The goal will be to discern whether in fact oocyte retrieval engenders an increased risk of various cancers and what factors are likely to increase or decrease the risk. For example, using lower doses of hormones for ovarian stimulation, or actually limiting the total number of cycles, might reduce the risk. One alternative being intensively restudied is natural-cycle IVF without the use of luteinizing hormone (LH) down-regulation, with or without terminal hCG to make the natural cycle fit convenient clinical practice (Lenton, 2007). Although this approach yields fewer eggs, there is evidence that they are of higher quality.

Conclusions:

In 1998, Ahuja and Simon concluded in their report on a young British egg donor with subsequently fatal colon cancer, “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, case reports can provide the only guidance for safe recruitment.” Almost 20 years later, the long-term risks are still largely unknown, and case reports are still the most potent exemplars of these possible risks. It is time to create egg donor registries, and to use them to follow up these women for decades to determine what are the 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 indeed risking their long-term health by pursuing egg donation, or else they can be reassured that there are no significant long-term medical risks. This information will be very useful either way. In the meantime, rather than providing information in their informed consent form about *infertile* women, who are a different group with documented different risks, 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.

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Table 1: Summary of breast cancer risk studies in infertile women

HR = Hazard Ratio; RR = Relative Risk; SIR = Standardized Incidence Ratio

Author	Location	Study Population	Sample	Results/Findings	Follow-Up	Key Limitations
Brinton et al, 2014	NA	9,892	Evaluated for infertility	749 with breast cancer	Median 30 years	
			38.10% who took clomiphene	Somewhat elevated risk (HR=1.05)		
			High clomiphene use and >6 cycles	Statistically significant elevated risk (HR=1.27)		
			9.6% who took gonadtropins (usually in combination with clomiphene)	Risk increased significantly only in women who remained nulligravid.		
Lerner-Geva et al, 2006	Israel	5,788	Attended infertility clinic 1964-1984	131 cases of breast cancer with mean age at diagnosis 47.2 years. Compared to general population, SIR was not significantly increased.	20 years; Mean follow-up after 1st visit 20.9+6.6 years; Mean time between 1st visit and breast diagnosis, 19 years.	Women who were deceased, some from cancer, were not included.
				Subgroup analysis - clomiphene significantly increased risk of breast cancer (SIR=1.4) compared with unexposed women.		
Calderon-Margalit et al, 2008	Israel	15,030	Parous women gave birth in 1974-1976 and 567 used drugs to induce ovulation	Significantly increased breast cancer risk HR=1.65. Significantly increased overall cancer risk, HR=1.36. Median age of breast cancer diagnosis 49.4 (lower than general population).	Median 29 years	
			Those who waited 12 months to conceive	Twice the risk as general population		
Stewart et al, 2012	Australia	21,025	Age 20-44 seeking treatment 1983-2002	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.	Mean 16 years	
			Woman who had IVF at young age (about 24)	HR=1.59, significantly increased compared with infertile women who began IVF at age 40.		

Author	Location	Study Population	Sample	Results/Findings	Follow-Up	Key Limitations
Li et al, 2012 **Meta-analysis**	NA	746,455	Participants from 8 cohorts, 7 of which included examination of breast cancer risk. General population used as control in 5 of the 7 studies. Women who had live births used as control in 2 of the 7 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 f/u of 6.2 years for 89.8% of total cohort.	Follow-up was too short, only 3.6-10 years.
Sergentanis et al, 2016 **Meta-analysis**	NA	1,554,332	Included 5 of the same studies as Li et al but added 3 more recent studies.	14,961 cases of breast cancer, including 576 among woman exposed to IVF. No significant increase in breast cancer compared to general population or infertile women.	Largest group (Kallen et al, 2011), mean follow-up was 8.3 years for 89% of total cohort.	Follow-up was too short. Only 1 of the 8 studies (Stewart,[2012]) had more than 8.3 years.