

# Fatal colon cancer in a young egg donor: A physician mother's call for follow-up and research on the long-term risks of ovarian stimulation

Jennifer Schneider, M.D., Ph.D.

Arizona Community Physicians, Tucson, Arizona

**Objective:** To present a case report of fatal colon cancer in a young, previously healthy woman 4 years after repeated ovarian stimulation for egg donation, review previous publications on the risks of ovarian stimulation, and make recommendations for further egg donor follow-up, research, and actions by professional associations and regulatory agencies.

**Design:** Case report and review of the literature.

**Setting:** Case report and review of the literature.

**Patient(s):** One patient and published cases.

**Intervention(s):** None.

**Main Outcome Measure(s):** None.

**Result(s):** There has been no systematic study of the long-term risk of cancer or other adverse outcomes in healthy egg donors.

**Conclusion(s):** At present, potential egg donors cannot give truly informed consent because insufficient information exists about their long-term risks. (Fertil Steril® 2008; ■: ■–■. ©2008 by American Society for Reproductive Medicine.)

## CASE REPORT

"I've decided to be an egg donor," my daughter told me on the phone. She had read posters and newspaper advertisements on campus seeking egg donors and thought it would be a good way to assert her financial independence. Also, she had always hoped to have children and was drawn to the idea of helping other women. Jessica was precisely the kind of young woman the advertisers were targeting. She was an honors student at an elite university, multitalented, athletic, tall, attractive, and had a healthy lifestyle. She did not smoke, she exercised and danced, and she was a vegetarian. I was concerned, but after all, she was an adult, free to make her own choices. "The most important thing is your safety," I told her, responding both as her mother and as a physician. "Don't worry, Mom," she assured me. "The agency told me it's safe, and they use a reputable IVF clinic and experienced doctors. I know there's the usual small risk of bleeding or infection from the egg retrieval, but otherwise they say there's no problem." The protocol used was a typical one for that time; it included leuprolide 250  $\mu$ g subcutaneously twice

a day for 2–3 weeks, pergonal 3 amps per day, and hCG 10,000 units IM.

The first cycle went smoothly, and a pregnancy resulted from it. Shortly thereafter, the agency contacted her about a second recipient. Jessica was about to move from one coast of the United States to the other, so she initially declined. But this time, because she was a "proven" egg donor, the agency offered her significantly more money. It was too good to turn down. In all, she did three egg retrieval cycles in a few months. Other pregnancies resulted.

Fast-forward 4 years. Jessica was now a graduate student in filmmaking, as well as a composer. Returning from a holiday in Japan, she began to complain of abdominal cramps. An attempted colonoscopy failed because of severe intestinal obstruction. A computed tomography scan of her abdomen revealed tumor involvement of her colon and both ovaries as well as peritoneal carcinomatosis. Histologic analysis of biopsy specimens confirmed widespread colon cancer. Two years later, after chemotherapy, surgery, and palliative radiation for bone and brain metastases, Jessica died, in July 2003. She was 31 years old. Subsequent DNA testing of her tissue revealed no genetic predisposition to colon cancer.

Jessica had spent the 2 years of her illness composing an opera, racing the clock to complete it in time to see it performed. She almost made it. Her opera opened in New York City 3 weeks after her death. Jessica's story was covered

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Dr. Schneider reports being the mother of an egg donor who subsequently died at age 31 of colon cancer.

Reprint requests: Jennifer P. Schneider, M.D., Arizona Community Physicians, 1500 North Wilmot Road, Suite B 250, Tucson, AZ 85712 (FAX: 520-290-0596; E-mail: [Jennifer@jenniferschneider.com](mailto:Jennifer@jenniferschneider.com)).

on television and in the *New York Times* (1). In these stories Jessica was not identified as a past egg donor. Instead, it was another tragic cancer death of a talented young person.

## LITERATURE REVIEW AND DISCUSSION

With time, I have tried to learn the answers to three disturbing questions. First, why did a previously healthy woman, with no family history of colon cancer, present with advanced disease at the unusually young age of 29? DNA analysis of Jessica's tissue revealed no sign of any predisposition to colon cancer. Of course, of the many people who die of cancer in the United States each year, only a small percent (primarily those with breast or ovarian cancer) are evaluated for any genetic basis for their cancer. Second, if Jessica did have a predisposition to develop the disease, was it prematurely and inadvertently triggered by repeated large doses of hormones used for stimulation of her ovaries? The answer is, we don't know. Finally, did Jessica receive enough information from the donor egg agency and assisted reproductive technologies (ART) clinics about her long-term risks to enable her to make an informed decision at the time her agreement was obtained? The broker of the egg agency stated that she had already destroyed Jessica's records and did not remember anything.

The Society for Assisted Reproductive Technology (SART) currently has 400 member ART clinics, and probably 100% of them advertise (2). There are approximately 470 IVF clinics in total in the United States (3). The Web sites of brokers and IVF clinics extol the joys of helping others and the financial gain to the donor but barely make any meaningful reference to possible long-term risks. Jessica and thousands of other women like her never received the information that would have been useful before their agreement to donate eggs. The reason is that the necessary studies have never been done.

The Institute of Medicine (IOM) and the National Research Council of the National Academies of Science (NAS) recently published the outcome of a conference they held in September 2006 on the risks of IVF (4). Potential acute risks to egg donors included ovarian hyperstimulation syndrome (OHSS), anesthesia/surgical mishaps, and psychological problems. Another risk is arterial thrombosis (5). The potential long-term risks identified were breast, ovarian, and endometrial cancers (all of which involve tissues that have estrogen receptors) and perhaps problems with long-term infertility. Cancer of the colon was not reviewed in the IOM report. However, the report acknowledged that there are several reasons to be concerned that the hormones used in ovarian hyperstimulation might make a number of cancers more likely.

One cannot rule out the possibility that my daughter's cancer may have been one of the unfortunate consequences of her decision to donate her eggs. As a medical professional I understand that a single case provides an insufficient basis for inferring cause and effect, but recent medical research

has multiple examples where a single adverse outcome led to policy changes. For example, the 1999 death of 18-year-old Arizona resident Jesse Gelsinger during experimental treatment in a clinical trial of gene therapy for a rare genetic disorder immediately resulted in cessation of human experiments with genetic alterations until additional studies could be done, per order of the U.S. Food and Drug Administration (FDA) (6). Subsequently the National Institutes of Health (NIH) organized a committee to study the youth's death and the safety of adenovirus vectors and to review gene therapy protocols. A single tragic case led to significant institutional involvement in efforts to prevent recurrences.

There are other reports of adverse consequences of egg donation, and in at least one previously published paper there are striking similarities to Jessica's circumstances. This involved the case of 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 (7). It is possible that other women have died or experienced serious illness after egg donation that may be related to egg retrieval but have not been identified by the clinics or their brokers because they do not have the responsibility to do so.

The lack of egg donor studies is reflected in the dearth of studies of even short-term adverse consequences of egg donation. For example, in 2007, Jayaprakasan and colleagues reported on a prospective study of the risk of OHSS in 339 infertile women undergoing a superovulation protocol for IVF. Citing the need for such data because it "is an essential prerequisite for appropriate informed consent" in egg donors, they used infertile women as surrogates for egg donors because of "the absence of sufficiently large numbers of egg donors to assess the risk." In this study, hospital admission for OHSS was needed for 49 (14.5%) of women, a sizable risk, with similar rates in pregnant and nonpregnant women. This risk is high enough that the investigators recommend active monitoring for the first week after egg collection in all egg donors who develop at least 20 follicles (8).

The small number of published reports about the long-term effects of ovarian stimulation, which have been based on infertile women rather than young egg donors, have often drawn ambiguous conclusions. For example, a meta-analysis of ovarian cancer in women treated with fertility drugs was inconclusive (9). A retrospective cohort study of over 12,000 infertile women concluded that women who had taken fertility drugs did have a higher rate of uterine cancer than the general population (10). When the same cohort was analyzed for risk of breast cancer, there was a slight increase in hormone-treated women, especially in those followed for at least 20 years (11). Unfortunately, the number of cancers in these studies was small. The studies were retrospective, and the time elapsed since egg retrieval was often not long enough. To provide sufficient statistical power to assess cancer risk, large numbers of women are needed, along with lengthy follow-up periods. Virtually all of the published reports have suggested that given time, an association between the exogenous gonadotropins and various cancers may eventually be demonstrated.

With regard specifically to colon cancer, a 2002 paper by Burkman reviewed what was known at the time about the effect of [1] oral contraceptives and [2] postmenopausal hormone therapy on the risk of ovarian and colon cancer (12). The paper cites a study demonstrating estrogen receptors in both normal and cancerous colorectal cells, a study that indicates that estrogen promotes growth of colonic tumor cells, and another study suggesting growth inhibition. The Burkman review concluded that there is some evidence that oral contraceptives have a favorable impact on the risk of colorectal cancer and that there is growing evidence that hormone therapy reduces the risk of colorectal cancer.

Very relevant to this discussion are studies of estrogen effects on the proliferation of colon cancer cells. Di Domenico et al. (13) demonstrated a small but significant increase in the proliferation of colon cancer-derived cells after the patients were treated orally with the estrogen  $E_2$ , whereas a different estrogen, estrone ( $E_1$ ), inhibited cell proliferation. In a subsequent *in vitro* study of estrogen metabolism in cancerous and noncancerous colon specimens from 24 patients with colon cancer, different estrogens had different effects on the proliferation of these cancer cells:  $E_1$  significantly decreased proliferation (implying a protective effect), whereas  $E_2$  did not (14). The investigators suggest that it is possible that epidemiological data on the risk of colon cancer are attributable to the beneficial effects of  $E_1$ , together with deleterious effects of  $E_2$ .

In other words, different estrogenic compounds have different effects on colon cells. Studies on the specific stimulatory or inhibitory effects on colon cells of gonadotropins and estrogenic compounds used in ovarian stimulation remain to be done. When the author of the 2002 paper on the effects of oral contraceptives and hormone therapy on colon cancer was recently asked about effects of hormones used in egg retrieval, he said, "I am unaware of any information on the risk of colon cancer with ovarian stimulation etc. However, I have not searched the literature extensively" (15).

In her recent review article in *Reproductive Bio Medicine Online (RBM Online)* (16), Dr. Louise Brinton states, "There has been little attention focused on the long-term effects of assisted reproductive technologies, which often involve much higher exposures to gonadotrophins than were received by women in previous eras. In addition, most IVF protocols include luteal phase support for several weeks with supplemental progestogens, which raises concern since these agents have been linked in several studies to increase in breast cancer risk." The implication clearly is that the results of earlier studies on the effects of dosages used in contraception or postmenopausal hormone replacement cannot be assumed to apply to dosages and drugs used in ovarian stimulation.

The observational evidence already available has given rise to the growing feeling that the existing studies may have missed the increased cancer risk because they have not closely followed their subjects for long enough (17). Professional bodies worldwide have long been suspicious of the

longer term risks of ovarian stimulation. Some countries (including Canada, Israel, United Kingdom, and Belgium) do not allow paid egg donation on the grounds that a nonpatient should not be converted into a patient for monetary gain. Yet egg donation in the United States is thriving, and the financial incentives keep growing. At many Ivy League colleges, women are typically offered \$8,000–\$15,000 per egg retrieval cycle, more if they are "proven" donors. And now the use of oocytes for stem cell research further increases the demand for egg retrieval. All this is in the absence of any valid, empirical information on the long-term risks.

The American Society for Reproductive Medicine (ASRM) periodically issues new ethical directives for egg donation, but they largely comprise fairly benign recommendations on the appropriateness of the level of financial incentives for donor volunteers rather than concentrating on their protection (18). The problem with this approach is that it creates the myth of providing an ethical framework for the practice; yet price setting for donating eggs is not equivalent to providing guidance for risk taking. Egg donors are often paid by their brokers sums of money that exceed the limits suggested in the ASRM guidelines. The ASRM recommendations are evidently not binding on clinicians.

Despite growing concerns, no professional body in the United States has taken any initiative to conduct a systematic follow-up of paid or altruistically motivated volunteer egg donors. Based on the published data on the number of cycles of egg donation (13,000 in 2003 alone, according to the IOC [4] and 123,200 in the United States by 2005 according to SART [19]), one can estimate that up to 100,000 young American women have donated or sold their eggs to fertility clinics. Very few would have received any information that would have enabled them to make an informed decision about their risks. Most would not have understood that there is a huge difference between being told, "We don't know of any significant long-term risks" and "There are no significant long-term risks." Women recruited at university campuses all over the United States clearly need protection from the coercive influences of the marketplace. It would be counterproductive for the profession to be seen to be complicit in denying that safety to them.

Beeson and Lippman (20), writing on the medical risks and ethical problems of egg harvesting for stem cell research, call for professionals in the field "to consider more seriously the welfare of the egg provider, to do the kind of serious research on long-term consequences of egg harvesting that is needed and to establish appropriate enforceable international oversight and regulation before encouraging more young women to put themselves at risk." The practice guidelines of ASRM stated in 1998, "It is necessary that the physician cautions the woman that the use of exogenous gonadotrophins may increase her life time risk of malignant ovarian tumors."

In 2006, the IOM and National Research Council of the National Academy stated, "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 women who have participated in IVF may not be directly applicable to oocyte donors. It will be important in the coming years to accumulate extensive health data from the women whose eggs are harvested and to monitor them for long-term effects.”

Dr. Suzanne Parisian, former chief medical officer of the FDA wrote in 2005, “Many of the drugs used during [IVF] procedures have not been monitored for long-term safety. Pharmaceutical firms have not been required by either government or physicians to collect safety data for IVF drugs regarding the risk of cancer or other serious health conditions despite the drugs being available in the United States for several decades” (21).

At present, at least in the United States, once an egg donor walks out of the IVF clinic, any further medical attention to or follow-up of that donor ceases. This is unconscionable. The interests of women eager to have children and the need for oocytes for stem cell research (perhaps less urgent now that stem cells have been created from skin cells [22]) have clearly been put ahead of the health of the women donating the eggs. It is unrealistic to expect ART clinics, researchers interested in harvesting oocytes, or organizations of reproductive medicine specialists to voluntarily institute systematic follow-up of egg donors. Even less should one expect them to initiate and complete the prospective studies necessary to obtain long overdue risk information. They clearly have a conflict of interest—their concern about the egg donors versus the financial benefit of harvesting eggs. Additionally, many egg donors, especially college students who use the payment for tuition, may want to remain anonymous; later, when they are in a stable relationship, they may not want their partner to know that they already have biological children.

## RECOMMENDATIONS

I believe it is time for the professional egg donor community to take the necessary steps to ensure the safety of egg donors. If this does not happen soon, then federal regulations are sure to follow. Initially, I would make the following recommendations:

The Centers for Disease Control and Prevention (CDC) collect data on the outcome of ART from several hundred clinics in the United States (23). Their report, however, excludes any of the drug types and regimens used, and it also lacks information on the health of egg donors or of the babies resulting from IVF. The CDC should immediately start a registry of egg donors, including both infertile women seeking to become pregnant (or becoming pregnant) and women who are selling or donating eggs, whether to produce a baby or for stem cell research. The type and quantity of the stimulatory drugs must be included. Leuprolide (Lupron), for example, which is widely used in the United States, is not approved by the FDA for ovarian stimulation (24). The FDA should maintain a drug-specific registry of egg donors so that these donors can be followed up; this may require

a mandate and funding from Congress. The egg donor registry will of course require prospective egg donors to give permission for the appropriate agency to contact them for future follow-up. Some women may not wish to do this, but if it becomes part of the requirements for egg donation it will soon cease to be an issue. An alternative would be for ASRM and SART to set up a centralized egg donor registry, and I would challenge every ART clinic to contribute \$10,000 to initiate and maintain such a registry.

With an egg registry in place, long-term prospective studies of egg donors should be undertaken, preferably under the aegis of an agency such as the NIH. Simultaneous retrospective studies can yield results more quickly and should be launched without delay. Attempts should be made to contact tens of thousands of past egg donors and obtain information on their health since the egg donation(s). Analysis of the data will allow the issuing of meaningful guidelines about the risks to egg donors.

Government agencies such as the NIH should become involved in funding prospective research on egg donor health. The National Cancer Institute is probably the most appropriate group to do the study of cancer outcome. Prospective studies will take time to complete. The responsibility for obtaining the consent for egg donation treatment should not entirely rest with the recruiting agencies, the clinics, or other marketing agents until such time that the federal authorities have reviewed this ethical process in egg donation. Professional bodies such as the ASRM should become responsible for providing verifiable information about risks to consenting volunteers. The egg retrieval “industry” earning large profits should also fund such research on the outcome for the women who are making this industry possible.

Finally, the print and electronic media, which are now crucial in recruiting potential donors, should be approached by the regulatory authorities to include mention of the likelihood of the short- and long-term risks that are inherent in egg donation.

It is entirely plausible that with more explicit warnings about the risks some volunteers may be deterred, leading to a delay in providing eggs to infertile women who need them. However, recipients can still use the surplus eggs from consenting IVF patients in the so-called egg-sharing programs available in other countries in many clinics (25). This would largely rule out the need to recruit nonpatient volunteers (and recruiting agencies) because the eggs would be sourced from women who themselves need IVF treatment.

It will take some years, but within a decade we will know whether in fact egg 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 might reduce the risk. One alternative being intensively restudied is natural-cycle IVF without the use of LH down-regulation, with or without terminal hCG to make the natural cycle fit convenient clinical practice (26). The first “test-tube baby,” Louise Brown,

was conceived using natural-cycle IVF, and recently Dr. R. G. Edwards, one of the physicians responsible for her birth, summarized alternatives to “usual IVF” in his review, “IVF, IVM, natural cycle IVF, minimal stimulation IVF—time for a rethink” (27), pointing out that these three approaches are now practiced in increasing numbers of IVF clinics and may well eventually replace routine IVF.

I am very much in favor of IVF, which makes it possible for many families to have children who would otherwise be unable to do so. At this point, it is unclear whether my daughter’s colon cancer had anything to do with her ovarian stimulation or whether it was simply an unfortunate chance event. We could evaluate this better if there was more information on what the long-term risks to the egg donors might be. With real data on risks, young women will finally be able to make truly informed choices about egg retrieval.

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