

***More ART than Science:
What We Still Don't Know About the Long-Term Health Risks of
Ovarian Stimulation and Egg Retrieval***

Introduction

Assisted reproductive technologies (ARTs) help people build families in a variety of ways. Like all health interventions, ARTs have risks and benefits. The risks and benefits of ARTs depend not only on an *individual's* particular health status and fertility needs and desires, but also on many other factors that shape health status and wellbeing such as age, income level, race, ethnicity, sexual orientation, and gender identity.

The Reproductive Health Technologies Project (RHTP) is committed to ensuring that all women have the information they need to make their own informed decisions about the use of new and emerging reproductive technologies. Reproductive technologies mean not only those necessary to prevent or terminate a pregnancy, but those developed to assist in the creation and maintenance of healthy pregnancies as well.

This white paper provides an overview of recent scientific literature on the long-term health effects of ovarian stimulation and egg retrieval, a specific component of ART used during in vitro fertilization (IVF), egg donation, and egg freezing. These processes have become increasingly common in human reproduction.

This paper is not a complete literature review, but rather an overall assessment of what is and what is not currently known, followed by recommendations for how to improve the information available about this aspect of reproductive health care. Beyond the scope of this paper there is much work to do in related areas to ensure that all individuals and couples pursuing pregnancy have the information and resources they need.

This paper builds on work that RHTP began in 2003 when we convened leaders from reproductive health, rights, and justice organizations and women's health advocacy organizations to consider issues related to assisted reproduction techniques and emerging technologies. Shortly after that convening, RHTP produced a white paper about ovarian stimulation and egg retrieval, which participants had identified as an area of particular interest. The paper included an overview of what was then known and not known about the long-term health effects on women undergoing these procedures.ⁱ

Since then, researchers have conducted numerous studies – many of them large-scale and involving thousands of women – on the health effects of ovarian stimulation and egg retrieval. These studies focus primarily on whether ovarian stimulation and egg retrieval might raise the risk of reproductive cancers such as breast, ovarian, and uterine (endometrial) cancer. This white paper provides an update,

ⁱ This paper and the 2003 paper use the terms “woman” and “women” because those terms are used universally in the research in this area. Of course, LGBTQ and gender non-conforming individuals undergo ovarian stimulation and egg retrieval and are most likely among the hundreds of thousands of research subjects in the studies discussed here, although they were not specifically mentioned in the literature. To our knowledge, no data exist yet about long-term health risks to transgender men who stop testosterone hormonal therapy in order to undergo ovarian stimulation and egg retrieval.

to reflect the additional knowledge gained from the research that has taken place since RHTP's earlier exploration of the field.

In sum, the most important finding of RHTP's analysis is that all of the studies and all of the researchers highlight the need for more ongoing research. The results of these studies are generally reassuring, but also complicated and sometimes conflicting.

Ovarian stimulation and egg retrieval: the basic facts

During a typical natural menstrual cycle, one egg matures and is released during ovulation. *Ovarian stimulation*, sometimes referred to as "controlled ovarian hyperstimulation," involves a series of medications designed to:

- Suppress a woman's normal ovarian function (using oral contraceptives and/or hormone suppressors such as leuprolide acetate);
- Stimulate the pituitary gland to direct the ovary to mature and release multiple follicles instead of one (using gonadotropins which contain follicle-stimulating hormone alone or combined with luteinizing hormone); and
- Ensure final maturation of the eggs and trigger ovulation (using human chorionic gonadotropin).

The *egg retrieval* process removes the matured eggs from the ovarian follicle using an ultrasound-guided needle. Ovarian stimulation and egg retrieval are necessary for three reproductive health technologies discussed in this white paper:

- *In vitro fertilization*, which means mixing eggs and sperm in a petri dish for fertilization and then transferring resulting embryos to a woman's uterus;
- *Egg "donation,"* which means providing one's eggs for another's reproduction or for research purposes. This commonly used phrase (also used in this paper) implies that a woman gives her eggs for free; however, she may or may not receive compensation. Some IVF clinics provide a discount on IVF if a woman agrees to donate some of her eggs; and
- *Egg freezing* or oocyte cryopreservation, which allows a woman to preserve her own eggs for future use. Her eggs are extracted and then frozen. When she is ready to become pregnant they are thawed, fertilized, and transferred to her uterus.

What we know

Most research into the long-term health risks of ovarian stimulation and egg retrieval has analyzed women's risk for reproductive cancers. The focus has been on the risk of reproductive cancers because drugs involved in ovarian stimulation manipulate the body's hormone levels and many forms of reproductive cancers are generally believed to respond to changes in hormone levels. Some scientists have suggested that the puncturing of the ovarian tissue in order to retrieve eggs also might increase the risk of cancer in that tissue.

Cancer causation is poorly understood generally and there are multiple factors to sort out in studying how ovarian stimulation and egg retrieval may or may not contribute. The research suggests that there are many “confounding factors” that muddy results and underscore the need for larger and longer studies. Leading researchers acknowledge that it is difficult to tease apart causation and understand which factors raise a woman’s risk of reproductive cancers.

For example, although some research suggests that women who undergo ovarian stimulation and egg retrieval develop reproductive cancers more often, many researchers note that it may be the underlying fertility issue, such as premature ovarian failure, that causes the increase in cancer risk. Scientists also know that other factors (such as a woman’s age, genetics, and weight) may play a role in her cancer risk levels. Recent research seems to suggest that women who received higher doses of certain medications, completed more cycles of IVF, or started IVF younger (i.e., in their 20s or early 30s), may be at increased risk. However, all or some of these factors may also correlate with, contribute to, or reflect an underlying infertility problem that itself brings additional risk.

Where research has shown an increase in risk, the numbers involved are often very small and the occurrence of cancer may still be rare. For instance, a woman’s risk may “double” by increasing from 1% to 2%, a level at which a patient might readily weigh the risks and benefits and decide to proceed with the reproductive technology that would allow her to have a baby. Indeed pregnancy itself has been shown to be protective against some forms of reproductive cancerⁱⁱ whether occurring after IVF or not, making relative risk levels difficult to calculate.

The ideal, gold-standard research would require following very large numbers of diverse patients for many years. Large numbers allow analysis of numerous subgroups and give researchers the chance to tease apart how ovarian stimulation and egg retrieval might contribute to cancer risk. The best research would also require many years of patient follow-up to see if patients who undergo ovarian stimulation and retrieval in their 20s and 30s might have an increased risk of cancer, not just in the years following the process, but especially decades later when reproductive cancers are more likely to develop. However, recruiting large numbers of people who are undergoing fertility treatments and following them over a long period of time is logistically difficult, particularly in the United States (U.S.) where there is no centralized health care system.

The most recent research does include some large-scale studies of hundreds of thousands of women; but most IVF patients and other users of ovarian stimulation and egg retrieval have not yet reached the decades of their lives when they are most vulnerable to reproductive cancers. Thus it is critical to continue to study and follow participants for years to come.

Generally speaking, “we do not have enough evidence to draw any firm conclusions about the potential association between IVF treatment and hormone-related cancers.”ⁱⁱⁱ However, this lack of evidence of an association may sometimes be presented to or heard by potential patients as, “there is no evidence of increased risk of cancer.” Patients may interpret this statement as a promise of no increased risk of cancer – something we simply do not yet know. The gaps in knowledge and misunderstandings

ⁱⁱ Kyung Hee Han et al., “Protective Effect of Progesterone during Pregnancy against Ovarian Cancer,” *Journal of Cancer Prevention* 18, no. 2 (2013): 113-22, doi:10.15430/JCP.2013.18.2.113.

ⁱⁱⁱ Louise M. Stewart and Roger Hart, “Long-term cancer risks in women after treatment with IVF: do we have any answers yet?,” *Women’s Health* 11, no. 1 (2015): 10, doi:10.2217/whe.14.58.

surrounding the knowledge we do have thus far are frustrating to people considering IVF, egg donation or egg freezing, and to advocates working on their behalf.

The Big Picture

The largest recent studies and meta-analyses looking at overall cancer risk are simultaneously reassuring, confusing, and conflicting.

For example, a 2013 meta-analysis of the association between IVF and cancer included eight earlier cohort studies and a total of 746,455 participants. It found “no significant association between IVF and cancer risk.” IVF seemed to have a possible beneficial effect on the risk of breast cancer, perhaps because of the beneficial effect of pregnancy on overall breast cancer risk. Some increased risk of ovarian cancer was observed in the analysis of all the studies and subgroups. The authors called for further studies of higher methodological quality with larger populations and longer follow-up.^{iv}

A comprehensive 2013 Cochrane review of 25 studies of over 180,000 women looking at various possible risks found “no evidence that the risk of ovarian cancer was increased in women treated with fertility drugs, compared with subfertile women untreated with fertility drugs, or women in the general population.”^v The reviewers believed that most studies showing an increase in the risk of ovarian cancer had a high overall risk of bias due to retrospective study design, lack of accounting for potential confounding factors, and estimates based on a small number of cases. The researchers said there may be an increase in risk of borderline ovarian tumors in infertile women treated with IVF. Borderline ovarian tumors are low-grade ovarian malignancies with less aggressive behavior than invasive ovarian cancer. They grow slowly and are often found at an early stage.

A 2015 study of more than 100,000 women in New York, Texas, and Illinois concluded that women initiating ART treatment have no greater risk for developing cancer after nearly five years of follow-up compared with the general population and with other women treated with ART. However, this study is notable for its short follow-up time. Continued follow-up of these same women would provide valuable additional information about women as they enter the years when they are more vulnerable to cancer.^{vi}

Studies Specific to Ovarian Cancer

Recent studies examining the links between ovarian stimulation and egg retrieval and the risk of ovarian cancer have reached a range of conclusions:

- A 2011 Dutch study of more than 19,000 women concluded that ovarian stimulation for IVF may increase the risk of ovarian cancer, particularly borderline ovarian tumors. This study compared three groups: women with fertility issues treated with IVF, women with fertility issues not treated with IVF, and women in the general population. Borderline ovarian tumors were more frequent in the IVF group than in the general population. The risk for invasive ovarian cancer

^{iv} LL Li et al., “Meta-analysis on the possible association between in vitro fertilization and cancer risk,” *International Journal of Gynecological Cancer* 23, no. 1 (2013): 16-24, doi:10.1097/IGC.0b013e318277608b.

^v Ivana Rizzuto, Renee F. Behrens, and Lesley A. Smith, “Risk of ovarian cancer in women treated with ovarian stimulating drugs for infertility,” *Cochrane Database of Systematic Reviews*, no. 8 (2013): 2, doi:10.1002/14651858.CD008215.pub2.

^{vi} Barbara Luke et al., “Cancer in women after assisted reproductive technology,” *Fertility and Sterility* 104, no. 5 (2015): 1218-26, doi:10.1016/j.fertnstert.2015.07.1135.

was not significantly elevated, but increased with longer follow-up after first treatment of IVF. The median follow-up period was less than 15 years. The study found an increased risk of invasive ovarian cancer in the IVF group after more than 15 years of follow-up, which was not observed in the non-IVF group. The authors called for a longer follow-up period and larger prospective cohort studies of IVF-treated women with a comparison group of women with fertility issues not treated with IVF.^{vii}

- A 2013 U.S. study of 9,825 women evaluated for infertility between 1965 and 1988 found no evidence of increased ovarian cancer among these women overall, regardless of treatment. They did find that women who used ovulation-inducing drugs and did not become pregnant demonstrated higher risk of ovarian cancer than those who did become pregnant. The authors called for ongoing monitoring of women treated with these drugs who do not become pregnant.^{viii}
- A 2013 retrospective cohort study of more than 87,000 women in Israel found no significant relationship between IVF exposures and the risks of breast, endometrial, or ovarian cancers. The study had a shorter follow-up period than another Israeli study described below. However, the authors stated, “Our findings of a trend of increasing risk of ovarian cancer related to number of IVF cycles, albeit nonsignificant, may be noteworthy.”^{ix}
- A 2013 study of more than 21,000 women in Australia found no evidence of an increased risk of ovarian cancer following IVF in women who give birth. For women who had never given birth, there was uncertainty about the increased risk of having undergone IVF. In the subpopulation of women who were diagnosed with endometriosis, those who had given birth may have had a slightly increased risk of ovarian cancer, while those who had never given birth showed a marked increase in risk.^x
- A 2014 review of scientific literature concerning the association between the use of fertility treatments and the risk of ovarian cancer found that “[s]ome works suggest the hypothesis that fertility drugs do not significantly contribute to ovarian cancer risk” while “[o]ther studies have reported an increased risk of ovarian cancer in women treated with fertility drugs.” The review noted that “some studies have reported an increased risk especially for borderline ovarian tumors.”^{xi} Finally, it argued that more recent studies are both more reassuring regarding the potential risk of ovarian cancer and more accurate because they are designed to avoid a variety of complicating factors.

^{vii} Flora van Leeuwen et al., “Risk of borderline and invasive ovarian tumours after ovarian stimulation for in vitro fertilization in a large Dutch cohort,” *Human Reproduction* 26, no. 12 (2011): 3456-65, doi:10.1093/humrep/der322.

^{viii} Britton Trabert et al., “Ovulation-inducing drugs and ovarian cancer risk: results from an extended follow-up of a large United States infertility cohort,” *Fertility and Sterility* 100, no. 6 (2013): 1660-66, doi:10.1016/j.fertnstert.2013.08.008.

^{ix} Louise A. Brinton et al., “In vitro fertilization and risk of breast and gynecologic cancers: a retrospective cohort study within the Israeli Maccabi Healthcare Services,” *Fertility and Sterility* 99, no. 5 (2013): 1193, doi:10.1016/j.fertnstert.2012.12.029.

^x Louise Stewart et al., “In vitro fertilization, endometriosis, nulliparity and ovarian cancer risk,” *Gynecologic Oncology* 128, no. 2 (2013): 260-64, doi:10.1016/j.ygyno.2012.10.023.

^{xi} Federica Tomao et al., “Fertility drugs, reproductive strategies and ovarian cancer risk,” *Journal of Ovarian Research* 7, no. 51 (2014): 6, doi:10.1186/1757-2215-7-51.

- A 2015 study of over 100,000 women in Israel found IVF treatments pose a significant risk of ovarian and uterine cancer. The study examined long-term female malignancies in a cohort of women with and without a history of fertility treatments including IVF and non-IVF treatments that also included medications. The study had a mean follow-up duration of 12 years, longer than the follow-up period in the 2013 Israeli study summarized above. Patients with a history of IVF treatments had a higher risk of ovarian and uterine cancer compared to patients who received other fertility treatments, as well as compared to patients with no history of fertility treatments.^{xii}
- Most recently at the 2015 American Society of Reproductive Medicine (ASRM) conference, researchers presented data from a study of every IVF procedure in Britain between 1991 and 2010. The procedures had been recorded by the Human Fertilization and Embryology Authority and involved over 250,000 women. Researchers found that compared to the general population, ART patients had a 30% greater likelihood of developing ovarian cancer. However, the researchers noted that the numbers were very small: out of more than 250,000 women who underwent IVF, there were 386 ovarian cancers. In addition, increased risk appeared to be associated with younger age at first exposure, a diagnosis of female factor infertility (especially endometriosis), and the number of children the women had. Patients with fewer live births were at greater risk and those who had no live births after treatment were at the greatest risk. The risk of cancer was highest during the first three years of treatment. The women were still relatively young at the conclusion of the study. The researchers stated, “continuing research is needed to further elucidate the associations between underlying causes of infertility, the impact of successful pregnancies or the lack of them, ART treatments, and cancer.”^{xiii}

Studies Specific to Breast Cancer

In the largest studies looking specifically at whether ovarian stimulation and egg retrieval raise the risk of breast cancer, the results have varied, with the most recent study providing some reassurance:

- A 2012 Australian study examined more than 21,000 women and compared those undergoing IVF with those receiving other treatment for fertility issues. There was an increased rate of breast cancer in women who commenced IVF at age 24 and younger. The study also found an association between women who deliver their first child later in their reproductive lives and an increased risk of breast cancer. The authors observed that additional studies could help confirm both these links by contributing to “an important part of the process of informed consent for younger women commencing IVF to appreciate the trade-off in lifetime objectives and risks that they may face.”^{xiv}
- A 2014 U.S. study of more than 12,000 women found that women who used fertility drugs did not appear to have an increased risk of breast cancer. The study included women who had

^{xii} Roy Kessous et al., “The risk of female malignancies after fertility treatments: a cohort study with 25-year follow-up,” *Journal of Cancer Research and Clinical Oncology* 142, no. 1 (2016): 287-93, doi:10.1007/s00432-015-2035-x.

^{xiii} American Society for Reproductive Medicine, “For Women Having IVF, Infertility Status and Diagnosis Determine Ovarian Cancer Risk,” news release, October 20, 2015, https://www.asrm.org/For_Women_Having_IVF_Infertility_Status_and_Diagnosis_Determine_Ovarian_Cancer_Risk/.

^{xiv} Louise Stewart et al., “In vitro fertilization and breast cancer: is there cause for concern?,” *Fertility and Sterility* 98, no. 2 (2012): 339, doi:10.1016/j.fertnstert.2012.04.019.

undergone IVF and other fertility treatments, such as ovarian stimulation, using various medications. There was a somewhat higher risk for women who underwent multiple cycles at medication doses far higher than the doses used today. There was also a higher risk for women who used a particular set of drugs (gonadotropins) and never became pregnant. This may reflect the fact that pregnancy typically provides some protection from breast cancer and never being pregnant increases a woman's risk. Women who were still unable to become pregnant after being treated with clomiphene and gonadotropins had twice the risk of breast cancer, and at younger-than-average ages (53), compared to women who were not prescribed these drugs. The authors noted that the population they studied was still relatively young and recommended additional follow-up as they age.^{xv}

- In 2015, a study of more than 800,000 Norwegian women, all of whom had given birth, found the risk of breast cancer was 20% higher among the women who gave birth after IVF than among those who got pregnant without IVF. However, where IVF was used but the cause of infertility was male factor, there was no increased risk of breast cancer, suggesting that the underlying cause of female infertility was the likely cause of the risk increase rather than the hormone treatment itself. Women followed for at least 10 years showed an increased risk. The population of the study was young (maximum age at the end of follow-up time was 45) and the follow-up time was relatively short. This study included only women who had children. The authors recommended that women who underwent IVF should be followed as they advance into more typical cancer age ranges. Therefore, the authors suggested that future studies should examine risks in women who received IVF but never became pregnant compared to women who did not receive IVF and did not become pregnant.^{xvi}
- A 2016 Swedish study of more than 40,000 women aged 40 to 69 found that women who have undergone ovarian stimulation show increased density of breast tissue, which is a risk factor for breast cancer. The authors noted that it is difficult to know if the density is an effect of ovarian stimulation or of underlying infertility and recommended additional monitoring.^{xvii}
- Most recently, a 2016 Dutch study of more than 25,000 women found that undergoing IVF does not increase the risk of breast cancer. Women undergoing fertility treatment in the Netherlands between 1980 and 1995 were followed for a median time of 21 years. Those who underwent IVF did not have a significantly higher rate of breast cancer than women who underwent other fertility-related medical care. They also did not have a significantly higher rate of breast cancer than women in the general population. The study is one of the first to continue follow-up into the decades when women are most vulnerable to reproductive cancers. The median age at end of follow-up was 53.8 years for the IVF group and 55.3 years for the non-IVF group. The researchers have recruited additional women and will be continuing follow-up into post-menopausal years as well.^{xviii}

^{xv} Louise Brinton et al., "Long-term relationship of ovulation-stimulating drugs to breast cancer risk," *Cancer Epidemiology, Biomarkers and Prevention* 23, no. 4 (2014): 584-93, doi:10.1158/1055-9965.EPI-13-0996.

^{xvi} Marte M. Reigstad et al., "Risk of breast cancer following fertility treatment--a registry based cohort study of parous women in Norway," *International Journal of Cancer* 136, no. 5 (2015): 1140-48, doi:10.1002/ijc.29069.

^{xvii} Frida E. Lundberg et al., "Association of infertility and fertility treatment with mammographic density in a large screening-based cohort of women: a cross-sectional study," *Breast Cancer Research* 18 (2016): 36, doi:10.1186/s13058-016-0693-5.

^{xviii} Alexandra W. van den Belt-Dusebout et al., "Ovarian Stimulation for In Vitro Fertilization and Long-term Risk of Breast Cancer," *Journal of the American Medical Association* 316, no. 3 (2016): 330-12, doi:10.1001/jama.2016.9389.

Studies Related to Other Forms of Cancer

- A 2013 study of 12,000 women found a slightly elevated risk of endometrial cancer associated with both clomiphene and gonadotropins, two medications used in ovarian stimulation. The authors noted that the women appeared to be at higher risk if they were under 30 when treated, although the risk may have come from the underlying cause of infertility that indicated a need for treatment at a young age. They found no convincing evidence of increased risk with cumulative exposures or more cycles of use. The authors called for more research that included a longer follow-up period.^{xix}

Other studies have investigated whether there is a heightened risk of melanoma, thyroid cancer, colorectal cancer, and ophthalmic complications such as retinal detachment after IVF. None have resulted in strong or conclusive evidence of increased risk but the researchers have called for additional research and monitoring.^{xx}

What we don't know

1. We do not know enough to tease apart confounding factors.

A myriad of possible confounding factors complicate our understanding of the long-term impact of ovarian stimulation and egg retrieval:

- *Underlying cause of the infertility:* Many researchers have noted that the conditions that cause or contribute to infertility, such as premature ovarian failure, could raise the risk of developing cancer later. Some studies find that women who received higher doses of certain medications, completed more cycles of IVF, or started IVF younger may be at increased risk. However, all or some of these factors may also correlate with, contribute to, or reflect underlying infertility. An increasing body of research shows that exposure to chemicals and endocrine disruptors, in particular, may contribute to both infertility and reproductive cancers later in life. Some studies show an increased risk of reproductive cancer only when the underlying cause of infertility is female, rather than male, further suggesting that increased risk may come from the infertility rather than the treatment.
- *Varied comparison groups:* Some studies compare women who have received IVF to women with fertility issues treated without IVF. Other studies compare women who received IVF to the general population of all women. Some do both.

^{xix} Louise A. Brinton et al., "Fertility drugs and endometrial cancer risk: results from an extended follow-up of a large infertility cohort," *Human Reproduction* 28, no. 10 (2013): 2813-21, doi:10.1093/humrep/det323.

^{xx} Louise A. Brinton et al., "Effects of fertility drugs on cancers other than breast and gynecologic malignancies," *Fertility and Sterility* 104, no. 4 (2015): 980-88, doi:10.1016/j.fertnstert.2015.06.045; Mandy Spaan et al., "Melanoma risk after ovarian stimulation for in vitro fertilization," *Human Reproduction* 30, no. 5 (2015): 1216-28, doi:10.1093/humrep/dev023; Mandy Spaan et al., "Risk of colorectal cancer after ovarian stimulation for in vitro fertilization," *Clinical Gastroenterology and Hepatology* 14, no. 5 (2016): 729-37.e5, doi:10.1016/j.cgh.2015.12.018; Roy Ratson et al., "Fertility treatments and the risk for ophthalmic complications: a cohort study with 25-year follow-up," *Journal of Maternal-Fetal and Neonatal Medicine* 29, no. 19 (2016): 2094-97, doi:10.3109/14767058.2015.1120717.

- *Short follow-up period:* The earliest IVF baby, Louise Brown, was born in 1978. Even women who underwent the process in the 1980s are just now reaching their 50s and 60s, the more vulnerable decades of life for reproductive cancers. Few studies have followed women into the years when reproductive cancers are more likely to appear.
- *Changing drug protocols:* Most fertility patients in the 70s and 80s underwent very different drug regimens than those used today. Some researchers have looked at the long-term health outcomes of women treated with pre-IVF fertility treatments that use some of the drugs now used in IVF.
- *Varying drug protocols:* Even at any one particular moment in time, drug protocols vary tremendously from patient to patient, cycle to cycle, across clinics, and in different countries.
- *Drug dose:* The cumulative amount of exposure of any individual woman depends on her total number of IVF cycles or other treatments, the type and dosage of medications, as well as whether she has taken other medications such as hormonal contraceptives or hormone replacement therapy. There is no data on the long-term health impact of transgender men or other gender non-conforming individuals taking ART hormone medications after taking testosterone or other hormonal treatment.
- *Low numbers, low statistical power:* A woman's risk may "double" but increase only from 1% to 2%. Many reproductive cancers such as ovarian cancer are quite rare. Even the largest studies have few women who actually have developed cancer. Many patients must be followed in order to have enough information to tease out any confounding factors. In recent studies, most evidence of higher risk is found in small subgroups, such as women who began IVF at a young age or women who completed multiple cycles of ovarian stimulation and egg retrieval.
- *Parity:* Factors known to be relevant to reproductive cancer risk include how many, if any, children a woman has had and her age at the first delivery. All these factors may affect risk, possibly because of the protective benefit of pregnancy on some forms of cancer.
- *Age:* A woman's age when starting treatment may be independently relevant or it may be correlated with some causes of infertility that may themselves affect risk.
- *Socioeconomic factors:* Some research suggests a higher risk of reproductive cancers can be found in lower-income women. This increased risk could be attributable to many factors, including a statistically higher frequency of chronic diseases such as obesity and diabetes, higher exposure to toxic chemicals, and the lack of time and resources to pursue regular health screenings or other health-seeking behaviors. In addition, IVF is expensive. Given how infrequently health insurance pays for fertility care, lower-income women who may piece together resources to pay for IVF may be more vulnerable to being exposed to higher levels of drugs in order to produce as many eggs as possible. There may be similar incentives to over-stimulate women participating in egg sharing programs in which the cost of IVF is reduced for women who are willing to donate some of the eggs they produce.

2. We know little about specific health risks for egg donors and egg freezers.

Most of the limited research that does exist has been on women with fertility issues who undergo IVF in order to become pregnant at that time. With the exception of anecdotal reports and case studies,^{xxi} there has been virtually no research into the long-term health risks of women who underwent ovarian stimulation and egg retrieval in order to become egg donors or to freeze their own eggs for later use. These are women who do not intend to become pregnant immediately following the ovarian stimulation and egg retrieval.

Ovarian stimulation and egg retrieval are believed to prepare the body hormonally to sustain a pregnancy (e.g., by increasing uterine receptivity to implantation). Generally speaking, pregnancy is also believed to protect the woman from some of the short-term side effects of ovarian stimulation and egg retrieval. Thus there are several areas of particular concern for egg donors and egg freezers:

- Some studies show increased health risks over a lifetime when an individual first undergoes ovarian stimulation and egg retrieval at a young age or undergoes multiple cycles. This is of concern because the “ideal” egg donor is young, often in her 20s, and many egg donors wish to donate multiple times.
- Some long-term risks are higher if a woman does not ultimately become pregnant. Studies also show that advanced age at first birth may increase a woman’s risk for certain cancers. Egg freezers are often already in their 30s, want to increase their chances of having a child later in life, and are using a still relatively untested technology in their efforts to do so.
- Some studies suggest that the higher medication doses used in the past raised risks more than current protocols. Many egg donors believe that doctors choose more aggressive protocols, including higher doses of medication, for women who are producing eggs for someone else (either for reproductive use or research). As one egg donor advocacy group has put it:

[M]any donors believe fertility doctors are deliberately pushing our bodies harder than those of their “real,” paying patients. For an IVF patient, 10-15 eggs in a single retrieval is a good number. But many egg donors in our group have had well over 15 eggs retrieved in a single cycle – in one case, 50.^{xxii}

When some donors have expressed concern upon learning their hormone levels are higher than recommended levels, they “have been reminded that their compensation is contingent upon following instructions.”^{xxiii}

Like egg donors, women intending to freeze their eggs for later use may undergo particularly aggressive protocols in order to produce as many eggs as possible to increase their odds of success. In part that is because there is very little information about how successful today’s egg freezers – often women in

^{xxi} Jennifer Schneider, “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,” *Fertility and Sterility* 90, no. 5 (2008): 2016.e1-5-2016.e5, doi:10.1016/j.fertnstert.2007.12.074.

^{xxii} “Can egg donations cause cancer?,” We Are Egg Donors, November 13, 2015, <http://www.weareeggdonors.com/blog/2015/11/13/can-egg-donation-cause-cancer>.

^{xxiii} Ibid.

their late 30s and early 40s – are likely to be in the future. Egg freezing has a success rate of 30% when women are 25 or younger when eggs are frozen. The success rates decrease as a woman approaches 40. To date, most frozen eggs that resulted in live births had not been frozen for long and were provided by young women screened to be “ideal,” healthy egg donors. Few, if any, babies actually have been born using eggs retrieved from women in their later reproductive years.^{xxiv}

Many clinics and private egg freezing companies heavily market egg freezing to professional women. Some employers, such as Apple and Facebook, offer it as an employee benefit. EggBanxx, a company offering egg freezing directly to women, estimates that by 2018 the number of women freezing their eggs in the U.S. will be close to 76,000.^{xxv} The growth of egg freezing both illuminates and reinforces the fear women have that whether for professional or personal reasons, they will not be having children during their most fertile years.

It is ironic that women feel particularly pressured to worry about their fertility when nearly half of infertility cases are caused in whole or in part by male factor infertility. It is a much larger and more complicated societal dilemma that people are expected to be most productive in their work during the years when they are most fertile. Marketers argue that the smart, responsible thing for women with professional aspirations to do is freeze their eggs. Advocates argue that this provides false reassurance to women about the possible consequences of postponing childbearing and lets employers off the hook for establishing policies and practices that would make it possible for employees to continue their careers while starting a family.

Egg freezing was initially developed as a last resort for young women facing cancer and chemotherapy to preserve their chances of having a child with their own egg in later years. The American College of Obstetricians and Gynecologists does not endorse egg freezing for the “sole purpose of circumventing reproductive aging in healthy women.”^{xxvi} In 2012, ASRM announced that it no longer considered egg freezing “experimental” but stressed that it did not endorse the practice of healthy women freezing their eggs for future use. Representatives of ASRM have stated that “while a careful review of the literature indicates egg freezing is a valid technique for young women for whom it is medically indicated, we cannot at this time endorse its widespread elective use to delay childbearing”^{xxvii} and “marketing this technology for the purpose of deferring childbearing may give women false hope.”^{xxviii} Despite ASRM’s stance, many leading clinics and fertility doctors offer egg freezing to women as a way to delay childbearing for professional or personal reasons.

^{xxiv} Robin Marantz Henig, “Freezing eggs may reduce a woman’s odds of success with IVF,” *National Public Radio*, August 28, 2015, <http://www.npr.org/sections/health-shots/2015/08/28/435251307/freezing-eggs-may-reduce-a-womans-odds-of-success-with-ivf>.

^{xxv} Eva Wiseman, “We need to talk about egg freezing,” *The Guardian*, February 7, 2016, <https://www.theguardian.com/society/2016/feb/07/life-on-hold-with-frozen-eggs>.

^{xxvi} “Oocyte Cryopreservation,” American College of Obstetricians and Gynecologists Committee Opinion No. 584, updated January 2014, reaffirmed 2016, <http://www.acog.org/Resources-And-Publications/Committee-Opinions/Committee-on-Gynecologic-Practice/Oocyte-Cryopreservation>.

^{xxvii} Miriam Zoll, “Freezing Eggs Puts Women and Infants’ Health at Stake,” *New York Times*, October 16, 2014, <http://www.nytimes.com/roomfordebate/2014/10/15/freezing-plans-for-motherhood-and-staying-on-the-job/freezing-eggs-puts-women-and-infants-health-at-stake>.

^{xxviii} The Practice Committees of the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology, “Mature oocyte cryopreservation: a guideline,” *Fertility and Sterility* 99, no. 1 (2013): 42, doi:10.1016/j.fertnstert.2012.09.028.

3. We do not know enough about safer, more affordable alternatives to current ovarian stimulation practices.

Worldwide, “natural cycle IVF,” also known as “low ovarian stimulation techniques,” are used to provide fertility care with fewer drugs, lower doses, and often lower cost.

Natural cycle IVF does not typically involve stimulation. Patients usually have very few or one follicle(s) and one egg is retrieved. This can be a good alternative for patients with regular menstrual cycles who are 35 or younger and have typical ovarian reserve and function. Appropriateness may also depend on the cause of infertility.

These are not new techniques. The mother of the first IVF baby did not receive any stimulating medications. In that case, a single egg was retrieved and fertilized and the embryo resulted in a successful birth. Many European fertility centers routinely use low stimulation IVF with good success rates, but it is not as widely available in the U.S.

“Light IVF” or minimal stimulation IVF typically produces fewer (3-5) eggs. Some evidence suggests that the eggs from minimal stimulation IVF are better suited for fertilization and are more likely to result in live births.^{xxix}

According to ASRM, there are no universal minimal stimulation protocols for IVF. Minimal stimulation protocols have a lower overall success rate; however, certain patient populations may benefit from this approach. It is typically used with women for whom even full stimulation does not stimulate many follicles, women at high risk for ovarian hyperstimulation syndrome,^{xxx} and women who do not want to freeze eggs or want to limit the number of eggs to be fertilized for ethical or religious reasons.

Conventional IVF uses injectable drugs, which are particularly expensive and require more office visits than forms of IVF that do not use injectable drugs. Some clinics offer IVF without injectable drugs, thus decreasing the total cost of the procedure. Some clinics are also experimenting with lower-cost cultures in which to fertilize the egg and grow the embryos. For example, an organization known as the Walking Egg Foundation reported promising interim results at a European Society for Human Reproduction and Embryology meeting in 2013.^{xxxi}

To be sure, these alternatives have disadvantages. They can be both less effective and more costly in the long run if providers have to go through several attempts of other protocols before concluding that they should use full stimulation IVF. Unfortunately, there has been little research comparing the effectiveness and safety of alternative protocols to full stimulation IVF, which means that women must weigh their options without reliable information.

^{xxix} Thomas Allersma, Cindy Farquhar, and Astrid EP Cantineau, “Natural cycle in vitro fertilisation (IVF) for subfertile couples,” *Cochrane Database of Systematic Reviews* 8, no. CD010550 (2013), doi:10.1002/14651858.CD010550.pub2.

^{xxx} Ovarian hyperstimulation syndrome is an occasional serious complication of taking fertility medications, resulting in swollen, painful ovaries, rapid weight gain, shortness of breath, nausea, vomiting, or diarrhea. It rarely can lead to life-threatening complications.

^{xxxi} “Infertility,” World Health Organization, last updated June 2015, <http://www.who.int/reproductivehealth/topics/infertility/new/en/>.

It is also critical to recognize that these alternatives are unlikely to be offered to egg donors and egg freezers, who are pressured to maximize the number of eggs produced.

Recommendations: a call for research now

Nearly every article published in this area has concluded with a call for more research with longer follow-up periods and larger numbers of women. RHTP believes that *now* is a critical time to expand our research efforts in this area for three primary reasons.

First, IVF use is widespread and shows no sign of decreasing its rate of growth. It is estimated that in the 38 years since the first use of IVF in 1978, more than five million IVF babies have been born worldwide, with half of them born since 2007.^{xxxii} The Centers for Disease Control and Prevention reports that in the U.S., 1.6% of all babies born each year are conceived using ARTs.^{xxxiii}

The earliest IVF patients are just now entering the decades of life when women tend to develop reproductive cancers. Most published research has not followed women beyond their mid-40s. Every passing year represents a tremendous missed opportunity to follow women into their more vulnerable decades.

Second, the use of donor eggs and the availability and popularity of egg freezing has increased dramatically in recent years.^{xxxiv} There is essentially no research focused specifically on the long-term health risks to egg donors or egg freezers. Increasingly, donors themselves are advocating for better information.^{xxxv} Without improved information, the counseling and informed consent processes for both egg donors and egg freezers lacks critical substance.

Third, we live in a time of unprecedented opportunity for innovative collaboration in large-scale health research. Careful analysis of the anonymized data of millions of people around the world can rapidly provide information about the effects of particular aspects of patient care. For example, the “Precision Medicine Initiative” at the National Institutes of Health will rely on recruitment of over a million people in the U.S. in order to build a base of evidence to support greater understanding of many different conditions and their treatments. Researchers and policymakers leading the “Cancer Moonshot” at the National Cancer Institute have said that the use of “big data” will be critical in improving cancer care and seeking a cure for the disease. Although there are privacy and security concerns to address, RHTP believes that researchers could and should develop long-term, large-scale international studies of millions of women as part of an effort to tease apart the data related to long-term health risks and ovarian stimulation and egg retrieval.

^{xxxii} “ART Fact Sheet,” European Society of Human Reproduction and Embryology, last updated July 2014, <https://www.eshre.eu/Guidelines-and-Legal/ART-fact-sheet.aspx>.

^{xxxiii} “ART Success Rates. Preliminary Data,” Centers for Disease Control and Prevention, last updated 2014, <http://www.cdc.gov/art/reports/>.

^{xxxiv} Jennifer F. Kawwass et al., “Trends and Outcomes for Donor Oocyte Cycles in the United States, 2000-2010,” *Journal of the American Medical Association* 310, no. 22 (2013): 2426-34, doi:10.1001/jama.2013.280924.

^{xxxv} “Research Opportunities for Egg Donors,” We Are Egg Donors, November 13, 2013, <http://www.weareeggdonors.com/blog/2015/11/13/research-opportunities-for-egg-donors>.

It is clear that we do not yet know enough about the long-term health effects of ovarian stimulation and egg retrieval and that now is a critical time to pursue more information. RHTP recommends increased investigation in this area through a comprehensive process involving patients, providers, professional societies, researchers, and government entities alike.

We believe any ongoing research process should include:

- 1) *A survey of women* who have undergone ovarian stimulation and egg retrieval for the purposes of IVF, egg donation, or egg freezing. The goal of the survey would be to better understand women's experiences, explore attitudes towards the process and the questions related to health risks, and understand the motivation behind individuals' willingness or hesitation to participate in long-term follow-up research;
- 2) *A research summit* including international leaders in the field and experts in patient-centered research. The summit would address past and anticipated obstacles to large-scale international collaborative research and explore ideas for overcoming such obstacles, possibilities for funding and other resources, and the use of "big data" to aid this work; and
- 3) *Development and publication of a blueprint* for how, when, and by whom the necessary research could be done.

RHTP encourages global collaboration and partnerships aimed at accomplishing this work. Additionally, we note that the National Academy of Medicine (NAM - formerly the Institute of Medicine) convened a panel in 2007 to consider the ethical issues that would arise in the context of creating embryos for stem cell research. The panel's report primarily addressed short-term risks and what little was then known about longer-term risks.^{xxxvi} Perhaps it is time for NAM or a similar body to address this issue once again.

Conclusion

ARTs have allowed millions of people worldwide to build their families. As an integral part of ART, ovarian stimulation and egg retrieval will continue to be a part of the life experience of many individuals, couples, and families.

Given the complexity of assessing the long-term health effects of these procedures and how little we presently know, it is currently unlikely that an individual could feel informed and confident in thoroughly considering the risks and benefits involved in these procedures. RHTP is committed to ensuring that the research necessary to fill our knowledge gaps takes place as quickly as possible. Ongoing studies and better data in this area are crucial to fulfill the promise of life-long reproductive health.

^{xxxvi} Linda Giudice, Eileen Santa, and Robert Pool, *Assessing the Medical Risks of Human Oocyte Donation for Stem Cell Research: Workshop Report* (Institute of Medicine and National Research Council of the National Academies Press 2007), 31-40, <http://www.nap.edu/catalog/11832/assessing-the-medical-risks-of-human-oocyte-donation-for-stem-cell-research>.