IVF, Egg Donation, and Women's Health
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Ovarian stimulation and oocyte retrieval are used most often for couples attempting to use in vitro fertilization to have a biologically related child. In IVF, oocytes (eggs) are removed from a woman's body after she has taken drugs to stimulate egg production. Eggs are fertilized in a laboratory dish, and one or more resulting embryos are transferred to the woman's uterus to initiate a pregnancy.

To date, more than one million babies have been born worldwide as a result of IVF and in 2003 U.S fertility clinics reported 112,872 IVF cycles. Although there has been considerable medical literature exploring the possible health effects of in vitro fertilization to babies born from this technology, the potential health risks to the women who undergo this process have been less extensively studied.

No medical procedure is without risks, and ovarian stimulation and oocyte retrieval is no exception. Possible short-term risks include excessive hyperstimulation resulting from the drugs used to stimulate ovulation. Possible longer-term risks include reproductive or gynecological cancers. It is clear from the rapid growth of IVF that, for many women and couples, the potential risks of IVF are outweighed by the benefit of being able to give birth to a biologically related child or children.

IVF techniques have been used not only to help couples have their own children, but also to provide oocytes that can be donated to an infertile couple seeking to have a baby using a donor egg. More recently, ovarian stimulation and oocyte retrieval have been used to collect oocytes for use in embryonic stem cell research.

Each of these procedures raises issues about the impact and risk of ovarian stimulation and oocyte retrieval for women. This paper explores what is and what is not known about the risks of ovarian stimulation and oocyte retrieval, for both a prospective mother and a prospective egg donor. However, as this white paper describes, more conclusive data about the risks of ovarian stimulation and oocyte retrieval to women are needed.

Short-Term Risks

The primary known short-term risk of ovarian stimulation is ovarian hyperstimulation syndrome (OHSS). Controlled ovarian hyperstimulation (also know as COH) modulates the woman's follicular development cycle with hormones to induce the ovary to produce more than one follicle simultaneously and therefore produce more eggs. Women react differently to the many different drug protocols that are used, and for some, the drugs cause OHSS, which brings severe and sudden health risks to the patient, ranging from mild symptoms of abdominal discomfort to renal failure and death.

All women who undergo ovarian stimulation are at risk for this condition. However, some data demonstrate that OHSS may occur less frequently among women who undergo COH for oocyte donation, as compared to those who continue on with IVF for the purpose of having children. Sauer et al (1996) found that fewer than 2 percent of oocyte donors developed severe OHSS following a standard stimulation cycle, less than the rate of OHSS among IVF patients, which ranges from 2 percent to 50 percent. Other research has supported this finding. (Morris et al., 1995). It has been suggested that the subsequent development of OHSS is directly related to the presence of a hormone called human chorionic gonadotropin (HCG) and that the production of endogenous HCG by a

woman following embryo transfer may increase the risk of OHSS (Sauer et al., 1996; Morris et al., 1995).

OHSS is generally classified into three categories based on severity, from mild to severe (Navot et al, 2001). Mild OHSS is associated with only minimal pain and other mild symptoms and is often regarded as an acceptable endpoint of the controlled ovarian hyperstimulation. "Mild OHSS is routinely inflicted on a large proportion of women undergoing so called COH, thus mild OHSS is nothing more than an acknowledgement that COH has indeed been achieved" (Navot et al, 2001). Moderate OHSS involves abdominal pain and bloating, nausea, and diarrhea. Clinically, any indications of fluid shifts are detectable only with an ultrasound. This stands in contrast to severe OHSS in which fluid shifts are apparent in the abdomen and throughout the body tissues and organs. Symptoms include severe abdominal bloating, distention and pain, shortness of breath, abnormally low blood pressure and high pulse rate. This massive shift in volume out of the blood vessels and into the surrounding tissue results in impaired organ function, most notably in the liver and kidney. Hospital management is indicated for moderate OHSS, with the strategy of preventing further escalation of clinical signs and symptoms, and additional care measures offered by an intensive care unit are often required for the management of OHSS. OHSS management includes supportive therapy for decreased blood volume and organ dysfunction until these systems return to normal function (Gardner et al., 2001).

New drug protocols are being developed to decrease the risk of OHSS. One example is the use of drugs such as gonadotropin releasing hormone (GnRH) antagonists. This class of drugs directly blocks cellular receptors and prevents an initial hormonal surge thought to induce the OHSS cascade of events. Another technique that may reduce the risk of OHSS is withholding the administration of HCG to trigger final oocyte maturation before retrieval (Orvieto et al 2005; Navot et al, 2001). In addition, recent research has resulted in the discovery of a gene that codes for the Follicle Stimulating Hormone (FSH) receptor. Identification of this gene may provide important predictive information about an individual patient's response to ovarian stimulating drugs and allow for better dosing to prevent OHSS (Greb et al., 2005; Daelmans et al., 2004). In the future, knowing more about this gene may help identify women who are at increased risk for OHSS and help reduce occurrence of OHSS.

There are also short-term health risks associated with the oocyte retrieval process, including those from bleeding, infection, and anesthesia. (Sauer, 2001). Pain and anxiety are other issues that have been less well studied (Jordan et al., 2004).

Long-Term Risks

Some studies have followed women who have undergone ovarian stimulation and oocyte retrieval for long periods of time to assess the long-term increased health risks of these procedures. These studies have focused on whether there is an increased risk for gynecological malignancies such as ovarian, breast, or endometrial cancer. Though some studies have focused on egg donors, most of these data have been collected from infertile women undergoing these procedures as a part of IVF in order to have a child. Although the procedures involved in ovarian stimulation and oocyte retrieval are the same regardless of the purpose, women undergoing these procedures as a part of IVF may have underlying physiological differences from fertile women who undergo the procedures to donate eggs either to an infertile couple or to embryonic stem cell research. For example, as a

result of the underlying infertility, infertile women may be at greater risk for long-term health issues, such as gynecological cancers. Thus, it is unclear whether the risks identified in women undergoing IVF may be translatable to fertile women going through ovarian stimulation and oocyte donation for other reasons.

Studies on the risk of gynecological cancers—such as breast, ovarian, and uterine malignancies—dominate the literature about the potential long-term risk of COH. However, the association with non-gynecological malignancies also has become an area of growing interest. There has been very limited discussion of the other long-term medical risks (e.g. the development of hypertension or diabetes).

Gynecologic Cancer

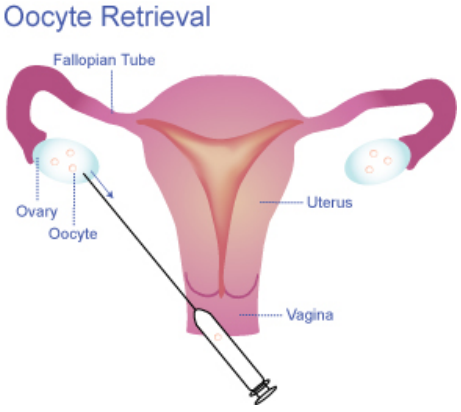
Much of the discussion to date about ovulation induction drugs and cancer addresses the risks associated with the use of one drug in particular, clomiphene citrate. Clomiphene is used for ovulation induction among women who have stopped ovulating or those undergoing artificial insemination but which is not commonly used for oocyte donation or IVF. Some, but not all studies have identified a positive association

Table 1: IVF Drugs

Drugs that may be used before oocyte retrieval	
Kind of Drug:	**Purpose of Drug:**
GnRH (gonadotropin releasing hormone) agonist and GnRH antagonist	Preparatory - Prevent early ovulation - Improve follicular response
Combined hormone oral contraceptives	Preparatory - Prevent functional cyst development that have been associated with decreased pregnancy rates - Used as contraceptive to prevent pregnancy before GnRH agonist/antagonist administration
hMG (Human Menopausal gonadotropin)	*Superovulation* - Induce multiple follicular development
FSH (Follicle Stimulating Hormone)	*Superovulation* - Enhance early follicle cell development
LH (Luteinizing Hormone)	*Superovulation* -Assist in follicular development
HCG (human chorionic gonadotropin)	*Preovulation* - Used to trigger final follicular maturation and ovulation
Drugs that may be used before embryo transfer	
Kind of Drug:	**Purpose of Drug:**
Progesterone	- Used to prepare the uterine lining for embryo transfer, implantation, and early pregnancy - Supplement endogenous hormones
Estrogen	- Required to induce receptors for progesterone
Drugs that may be used after embryo transfer	
Kind of Drug:	**Purpose of Drug:**
Progesterone	- Maintain optimal levels to permit pregnancy
Estrogen	- Maintain optimal levels to permit pregnancy

between clomiphene and malignancies, both gynecologic and non-gynecologic. (Rossing et al., 1994; Whittemore et al., 1994). Concerns about clomiphene often have carried over to a similar concern about gonadoptropins, a separate set of drugs used to induce controlled ovarian hyperstimulation.

In 2005, a systematic review of nearly 100 studies examined the incidence of breast, ovarian, endometrial, melanoma, and other malignancies. (Brinton et al., 2005). In general, that review concluded that while some studies had shown a link between ovarian stimulation drugs (both those used to induce ovulation and those used to stimulate the ovaries for IVF purposes) and cancer risk, many of these studies had significant shortcomings. Two later studies similarly concluded that there is no clear evidence that infertility treatment causes cancer but that additional data are needed to thoroughly investigate this issue. (Salahab et al., 2005; Mohdavi et al., 2006)



Ovarian Cancer

The data concerning the link between infertility treatment and ovarian cancer are limited by several factors. First, sample groups in the studies have been small. Second, there has not been long-term follow-up with patients. Third, many of these investigations have been conducted as cohort studies, which are not considered as reliable as randomized controlled trials. (Gordis, 2004).

Brinton et al. (2005) concluded from a systematic review of multiple studies that there "is no conclusive link between fertility drug use and ovarian cancer." A few trends did exist among the studies. First, ovarian cancer occurred predominantly among nulliparous women (women who have borne no children). However, this group already is at an increased baseline risk of malignancies because of their reproductive histories. Second, some studies found an increase in borderline ovarian tumors among women who underwent IVF. However, it has been proposed that the gonadotropins used might have induced the growth of already existing borderline tumors and that these women, because of their increased awareness of health issues, are more likely to be diagnosed at an earlier stage.

Breast Cancer

Studies addressing the risk of breast cancer from infertility treatment are somewhat conflicting. Some studies suggest an increased breast cancer risk while others do not. For instance, a study by Burkman noted that, in general, infertility drug use is not associated with an increased risk of breast cancer. However, those women who used a specific hormone, Human Menopausal gonadotropin (hMG), for at least six treatment cycles or months had a two to three-fold increased risk of breast cancer (Burkman et al, 2003). However, the investigators make note that these data should be approached with caution, given the number of limiting and confounding elements to the study. In another investigation, Brinton and collegues concluded that the data about the risk of breast cancer following infertility treatment are inconsistent. It is particularly difficult to tease out the effects of gonadotropins on breast cancer risk. Breast cancer is a malignancy often directly related to the hormonal environment of the women, an environment that can be temporarily increased by gonadotropin administration. In addition, many of the studies on this topic relied on the

patient to report her fertility drug dosage and duration many years after the initial treatment for infertility, raising questions about accuracy and utility of the data. Finally, as is the case with ovarian cancer, any increased incidence of breast cancer may be linked with the effects of fertility agents on an existing tumor that may be detected earlier because of the patient's increased awareness of and attention to her health.

Endometrial Cancer

The data regarding endometrial cancer is not as robust as that for breast and ovarian cancer. In addition, the majority of research in this area pertains to the use of clomiphene and the risk of cancer. Though there is evidence that there is a two-fold increase in relative risk of endometrial cancer among clomiphene users, this same trend was not noted among IVF patients (Althuis et al., 2005a). There have been very few studies that have looked directly at the effect of IVF-specific agents. Most cohort studies have not identified an increase risk of endometrial cancer *specifically* with IVF agents. However, some of the studies that have identified an increased risk of endometrial cancer interpret this more as a function of long-term unopposed estrogen exposure, a hormonal state associated with infertility and endometrial cancer, than the use of fertility drugs alone. At the same time, the investigators comment that more definitive evidence is required before dismissing this potential association (Modan et al., 1998).

Could the Underlying Cause of Infertility Raise the Risk of Malignancies?

An analysis of the risk of gynecological cancers resulting from infertility treatment must take into account whether the underlying medical conditions that contribute to infertility may independently place women at higher risk for gynecological malignancies. Many studies have demonstrated that women with primary (never able to conceive) and secondary (previously able to conceive before experiencing infertility) infertility have a higher risk of gynecologic malignancies than the average population (Brinton et al., 2004; Modan et al., 1998; Rossing et al., 1994; Althuis et al., 2005a). Notably, the increased risk has been found among women with infertility who have undergone infertility treatment and those who have not (Brinton et al, 2004). One study documented this as a 23 percent increased risk of cancer among women with infertility, providing consistent findings with other authors (Brinton et al., 2005).

There are numerous examples of the underlying causes of infertility being linked to gynecological malignancies. Breast, endometrial, and ovarian malignancies all can be caused by chronic exposure to reproductive hormones arising from within the woman's body, which can happen as part of infertility. The absence of ovulation (anovulation) and polycystic ovarian syndrome (PCOS), two medical conditions implicated in infertility, also have been associated with an increased risk of breast and endometrial cancer (Brinton et al., 2005; Baron et al., 2001; Pierpoint et al., 1998; Dahlgren et al., 1991; Escobedo et al., 1991). Endometriosis, another factor in infertility, also has been linked with an increased risk of ovarian cancer and malignant melanoma (Brinton et al., 2004; Stern et al., 2001; Modesitt et al., 2002; Ness 2003). Hydrosalpinx, a collection of fluid in the fallopian tubes, has been linked with infertility resulting from implantation failure and ovarian cancer (Brinton et al., 2005).

Non-Gynecologic Cancer

There has been limited research into any link between infertility treatment and the risk of non-gynecologic cancers. A 20-year retrospective study of the risk of classically hormone-sensitive, non-gynecologic

malignancies—including thyroid cancer, colon cancer, and malignant melanoma—found that there was little to no association of these specific cancers and common ovulation stimulating drugs: gonadotropins, Pergonal, Humegon, and Metrodin. (Althuis et al., 2005b).

Other Medical Considerations

Little research to date has focused on the risk of non-malignant medical conditions following ovarian stimulation and oocyte retrieval. Medical conditions, such hypertension or diabetes, or gynecologic conditions, such as uterine fibroids or pelvic pain, have not been robustly examined. One study that looked specifically at the risk of gynecologic diseases following IVF did not identify a positive association (Klip, 2003). Another study that examined the theoretic possibility of accelerated menopause following IVF also did not identify a negative outcome among these women (de Boer, 2005). Additional research is indicated in this area.

Several case reports have described women who have been treated with the GnRH agonist Lupron who have reported symptoms including musculoskeletal weakness and pain, depression, memory impairment, loss of libido and other psychological conditions (Norsigian, 2005; Lazar, 1999.) Most of these cases have not been reported or evaluated with formal research protocols. Many of the circulated case reports lack specific and essential information about the cause of the initial gynecological condition warranting treatment with Lupron, medication dosage and duration of treatment (Lazar, 1999, entries from the Infertility Network). From a review of the available reports of these women, it appears as if many were treated with Lupron for endometriosis or uterine fibroids, conditions that require higher doses of GnRH agonist for treatment than used for ovarian stimulation and oocyte retrieval (Lazar, 1999). Similar findings have not been observed among patients who undergo GnRH agonist treatment for other conditions. For instance, the musculoskeletal symptoms reported among these women who have been treated with large doses of a GnRH agonist have not been observed among men with prostate cancer or children with precocious puberty who undergo therapy with the same medication (Tanaka, 2005; Almeida, 2004). There have not been rigorous studies on these outcomes in large enough study populations to be able to quantify any possible risk.

Future Research

More research in the areas of ovarian stimulation and health outcomes must be completed before definitive conclusions can be drawn about the risks for women. Existing studies have been limited in a variety of ways, yet there has been some evidence that the drugs used in ovarian stimulation and oocyte retrieval may be associated with increased risk of cancer. Priorities for future research ought to include:

- Reducing the risk of OHSS without impaired pregnancy rates and developing the means to identify women who are at a increased risk of OHSS before initiating treatment.
- Long-term evaluation of larger populations of women who have undergone infertility treatment, with more accurate information about the patients' specific infertility treatments (e.g., dosages, durations, drug name).
- Studies examining the long-term health outcomes of women undergoing ovarian stimulation and oocyte retrieval for oocyte donation as compared to the outcomes of women undergoing stimulation and retrieval for IVF, to better understand whether other factors, such as a woman's underlying infertility, play a role in the long-term risks of cancer or other diseases.

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