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Risks of Ovarian, Breast and Uterine Corpus Cancer in Women Receiving IVF Treatment

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ABSTRACT

Background Assisted reproductive technologies (ART), such as in vitro fertilization (IVF), have become common treatments for infertility and genetic conditions. While these methods have helped countless couples build families, concerns about potential long-term health consequences have emerged. This meta-analysis aims to investigate the link between various fertility treatments and the development of ovarian and breast cancer.

Methods To reflect contemporary in vitro fertilization (IVF) practice, studies written during the last 20 years were included. Finding out whether women who receive hormonal reproductive treatment have an elevated risk of ovarian, breast cancer was the study's main objective. To find out if individual fertility therapies increased the risk of breast cancer, one of the secondary outcomes was to do so. Researcher observed first cancer diagnoses for ovarian, breast, and corpus uteri were compared to expected rates for each age, sex, and period. With the help of age, sex, and time-specific incidence rates, standardized incidence ratios (SIRs) were computed.

Results

On this subject, there are opposing viewpoints. According to some research, the risk of developing hormone-sensitive malignancies, such as ovarian, breast cancer, has somewhat increased. Breast cancer is one of the most common malignancies in women and the long-term use of IVF drugs can raise estrogen hormones and lead to excessive gene expression, increasing the risk of the disease.

Conclusion There are a few dangers to be aware of as a result of the theory that lengthy IVF treatments may cause breast cancer in IVF candidates. Additionally, ovarian, breast cancer risk may be elevated in women with a favorable family history and associated inherited genes. The likely effects of the reproductive therapy approaches should therefore be explained to women who are candidates for IVF. Explained to women who are candidates for IVF..

1.0 Inroduction

In vitro fertilization (IVF) emerged in the early 1980s as a groundbreaking treatment for infertility. Following the birth of the first "test-tube" baby, IVF became a viable option for individuals facing fertility challenges such as ovulation disorders, blocked fallopian tubes, endometriosis, uterine fibroids, male infertility, unexplained infertility, and genetic conditions. (Farhud *et al*., 2019). Numerous couples seek infertility treatment at IVF clinics each year as a result of fertility issues, according to statistics from throughout the world. Additionally, ovulation-inducing medications have been utilized for a variety of infertility issues.

Many techniques can be used to treat infertility issues, including intrauterine insemination, surgery, and assisted reproductive technology (ART) (Kroener *et al*., 2017).

The long-term consequences of ART on both the children of women receiving these therapies and their offspring have been the subject of numerous researches, particularly retrospective cohorts. According to research on the consequences of IVF treatment, this procedure can increase the risk of getting breast cancer; however parity and enhanced nursing may lessen specific subtypes of breast and gynecologic malignancies. There are theories that, in contrast to the findings of research with small sample sizes, the risk of cancer in women has increased following IVF (Lundberg *et al*., 2016; Anstey *et al*., 2017). Particularly, it has been discovered that women who wait more than a year to get pregnant are more likely to experience breast cancer as a result of ovulation induction. Genetic or infertility issues can be treated with IVF. In particular, women over 40 years old who are having reproductive treatment are at higher risk for breast cancer. Both hereditary breast cancer and hormone-related problems are thought to contribute to some incidences of the disease (Jensen *et al*., 2008). The LH and FSH levels are raised by drugs used in IVF, such as clomiphene citrate and gonadotropins, which also raise the estrogen levels. This

abrupt rise in estrogen, a key female sex hormone, can boost gene expression and, as a result, the risk of breast cancer (Reigstad *et al*., 2015). According to results from studies with a sizable sample size, women who have undergone reproductive treatment for a long period, particularly for longer than a year, are more vulnerable to the negative effects of fertility medicines (Petrangelo *et al*., 2018). Repeated IVF cycles may increase the long-term risk of developing breast cancer. Women undergoing IVF are more likely to develop breast cancer if they have a family history of the disease. It's crucial to assess a woman's family history before starting IVF and to inform her about the potential increased risk. To make informed decisions, women considering IVF should fully understand the potential link between fertility treatments and breast cancer. (Williams *et al*., 2018; NIH, 2018).

1.1. Breast Cancer

Female steroids have a significant impact on the invasive malignancy known as female breast cancer. Breast cancer is the most prevalent cancer in women globally, especially in middle-aged and older women, with a new case rate of 128.5 per 100,000 women per year as showed at Figure 1 and Figure 2. Due to advancements in screening methods and efficient therapies, the death rate for breast cancer has decreased (Surakasula et al., 2014). Hormonal factors play a crucial role in breast cancer development. The ovaries influence breast function through the production of steroid hormones. Consequently, any hormonal treatments that stimulate ovulation, such as those used in IVF, may impact breast tissue. IVF procedures typically involve clomiphene citrate and gonadotropins like HCG and HMG to induce ovulation and foster the growth of multiple follicles, which can lead to increased hormone levels. (Collaborative Group on Hormonal Factors in Breast Cancer, 2002; Cole, 2014). Endogenous estrogen levels may be impacted by ovarian stimulation, raising the risk of cancer. Additionally, due to prolonged exposure to HMG, the risk of developing this malignancy is higher in women who have used IVF multiple times in the past but were unable to conceive, typically for longer than six months. A number of risk factors have a role in the development of breast cancer, which is a complex disease. Hormonal factors are a factor in the majority of breast cancers (Collaborative Group on Hormonal Factors in Breast Cancer, 2012). Exogenous and endogenous hormones have both been shown to have a part in the etiology of breast cancer, according to numerous studies. Because of this, experts have talked about a potential connection between ovulation-inducing medicines and a higher risk of breast cancer. Estradiol concentration can increase up to ten times more during an ovulation stimulation cycle than during a typical ovulation cycle. An elevated risk of breast cancer diagnosis in the first year following treatment with reproductive medications is linked to this practice (Liehr, 2000; Ayhan, 2004; Bulzomi et al., 2010; Nindrea et al., 2019).

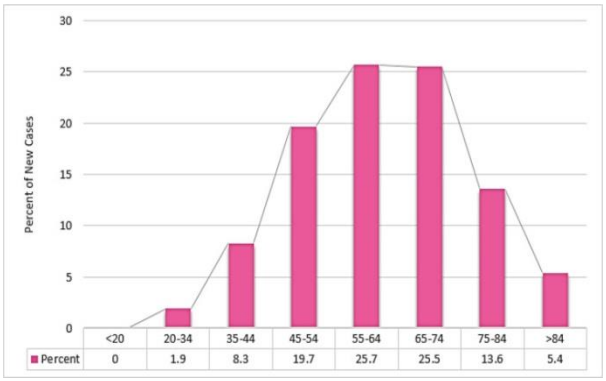

Figure 1. Breast cancer affected women of all racial backgrounds between 2013 and 2017. The age group most commonly diagnosed with breast cancer was women aged 55 to 64, with an average age of 62 at diagnosis

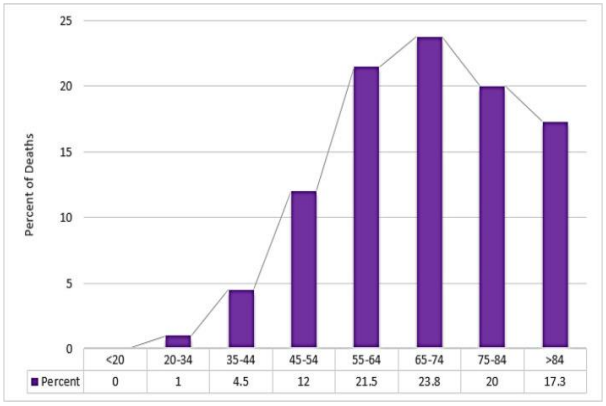

Figure .2 By age group, the mortality rate for women with breast cancer in the United States from 2014 to 2018. Women between the ages of 65 and 74 account for the majority of breast cancer deaths (median age at death: 69 years).

1.2 Ovarian and Uterine Corpus Cancer

Corpus of the ovary and uterus The female reproductive system has several locations where cancer might develop: Ovarian cancer develops in the fallopian tubes and occurs in the ovaries, which are the female reproductive organs on either side; cervical cancer is located in the cervix, the little, lower portion of the uterus where it joins the upper end of the vagina; and ovarian cancer develops in the cervix (Brekelmans, 2003; Brown et al., 2009). Figure 3 illustrated risks factors on ovarian cancer.

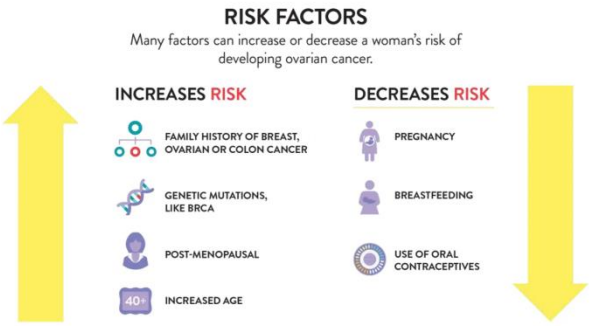

Figure 3. Risks factors on ovarian cancer

Contrary to popular belief, ovarian cancer is a more lethal form of the disease than endometrial cancer. In terms of the number of female fatalities from gynecologic cancers, ovarian cancer takes the lead. Ovarian cancer is frequently not discovered until it has progressed to other parts of the body, unlike endometrial cancer (Calderon-Margalit et al., 2009). The rectum or bladder can both become affected by uterine cancer on a general basis. In addition, the fallopian tubes, ovaries, and vagina may all become affected. It is common for this type of cancer to grow slowly and to be discovered before it has spread to other parts of the body (Ramalhinho et al., 2012; Dos Santos et al., 2017). Patients with multiple gynecological cancers are more likely to have synchronized ovarian and uterine cancers. When opposed to a single advanced cancer, synchronous malignancies are typically identified at an earlier stage, have a lower grading, and have a better prognosis (Sreeja et al., 2012). Ovarian hyperstimulation syndrome (OHSS) is a potential complication of IVF. This condition involves enlarged ovaries and fluid buildup in the body. Women with polycystic ovary syndrome (PCOS) undergoing fertility treatments are at higher risk. Additionally, women who have undergone multiple IVF cycles without a successful pregnancy may face an increased risk of ovarian cancer due to the high doses of fertility drugs involved in the process. (Hughes et al., 2010, Petrangelo et al., 2018). There is no established link between IVF or ovulation stimulation medication and an increased risk of cancer. While there was a suggestion of a slightly higher ovarian cancer risk in women undergoing four or more IVF cycles, this finding was not statistically significant. (Taheripanah et al., 2018).

1.3 In Vitro Fertilization (IVF)

IVF is a fertility treatment. It involves retrieving eggs from a woman's ovaries, fertilizing them with sperm in a lab, and then transferring the resulting embryo into the woman's uterus to develop. (Lerner-Geva et al., 2003; Lerner-Geva et al., 2006). During IVF, mature eggs are taken out from the ovaries and combined with sperm in a lab for fertilization. The fertilized egg (embryo) or eggs (embryos) are subsequently transferred into the uterus. It typically takes around three weeks to finish one cycle of IVF. (Stewart et al., 2012). When these steps are divided into separate steps, the procedure can take longer. There are three main types of IVF: natural cycle, mild stimulation, and in vitro maturation (IVM). These approaches use minimal or no medication. Traditional IVF, on the other hand, employs drugs like clomiphene citrate and gonadotropins to stimulate follicle growth and increase ovulation. (Pappo et al., 2008; Katz et al., 2008). IVF increases the risk of complications such as premature birth, high blood pressure, placental abnormalities, and multiples (twins, triplets, etc.). The likelihood of miscarriage and birth defects also rises with advanced maternal age, a common reason for pursuing IVF. Transferring multiple embryos during IVF significantly increases the chance of multiple births. (Burkman et al., 2003; Mneimneh et al., 2013). Figure 4 describe steps of IVF.
Multiple pregnancies are associated with a higher risk of premature birth and babies with low birth weight compared to single pregnancies. Children born through in vitro fertilization (IVF) were more than four times more likely to have cancer than those without birth defects due to chromosomal abnormalities (Boivin et al., 2007).

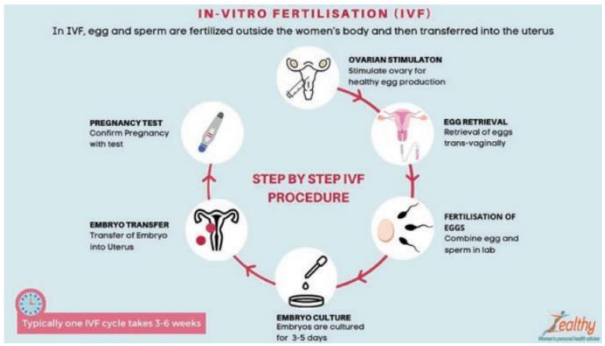

Figure 4. Steps of IVF

2.0 Materials and Methods

The cohort's HFEA fertility data participants were linked to cancer registries across the country. Comparisons were made between the cohort's actual initial diagnoses of ovarian, breast, and corpus uteri cancer and the expected diagnoses based on their age, sex, and period. Standardized incidence ratios (SIRs) were calculated by using national incidence rates for a specific age, gender, and timeframe.

2.1 Study Population

According to the definition of assisted reproduction, procedures involving the manipulation of human eggs, sperm,

or embryos in a laboratory for the purpose of reproduction are considered treatments. The Human Fertilization and Embryology Authority gave data on women who had assisted reproduction from January 1991 to September 2009 and from October 2009 to December 2010 with prior consent. The records, for instance, included England, Wales, and Scotland (HFEA). HFEA data was linked to the Central Registers of the NHS in England, Wales, and Scotland to provide information for medical research on emigrations, deaths, and cancer registrations.

2.2 Statistical Analyses

The follow-up duration was planned to start during the first treatment cycle (around midway through the first year of treatment) and continue until the earliest of the following: cancer diagnosis, death, migration, or end of study. Since the HFEA did not document the specific dates needed for time-based studies, the total person years at risk for analyzing cycle numbers, infertility duration, and live/multiple births were determined from the last treatment date (approximated as the midpoint of the final treatment year). To estimate expected cancer incidences.

3.0 Results and Discussion

3.1 Breast Cancer

The study found no overall increased risk of breast or other cancers following treatment. This held true for both premenopausal and postmenopausal women. However, the risk of breast cancer significantly decreased over time since treatment completion. This reduction was particularly evident when the first 12 months of follow-up were excluded. Women with a history of fertility issues, regardless of whether the partner's factor was involved, also showed a reduced breast cancer risk compared to expected rates. (standardized incidence ratio 0.95 (0.92 to 0.99), P=0.02) (Dos Santos et al., 2017; Taheripanah et al., 2018).

3.2 Ovarian cancer

Our study identified a significantly increased risk of ovarian cancer among the study group (1.39 times higher risk). This equates to an extra 5 cases per 100,000 women per year. While the risk was elevated across most age groups, it notably increased with younger age at initial treatment. Women with female factor infertility were at a significantly higher risk compared to those without. Importantly, the risk was not influenced by the number of IVF cycles, duration of infertility, time since treatment, or male factor infertility. Removing the first year of follow-up did not alter these findings. (Taheripanah *et al*., 2018; Nindrea *et al*., 2019

3.3 Corpus Uteri Cancer

The study found no significant increase in the risk of uterine corpus cancer. However, a strong link between lower fertility and a higher cancer risk was observed. Interestingly, women with multiple births seemed to have a lower risk, although this finding needs further investigation. Factors such as the number of IVF cycles, age at treatment, and time since treatment did not impact the risk of uterine corpus cancer. (Nindrea *et al*., 2019).

4. Conclusion

No increased occurrence of uterine or breast cancer was discovered in this study of women who underwent treatment with assisted reproductive technology. As the number of treatment cycles increased, so did the likelihood of developing in situ breast cancer. A surplus of ovarian cancer of all sorts was also noted. Our findings, however, imply that underlying patient traits, as opposed to assisted reproduction itself, are more likely to be the cause of this discovery. We were unable to discern between an actual rise in the probability of borderline ovarian tumors and alternative possibilities, such as surveillance bias. To keep track of these significant effects in light of the expanding population, more research and longer follow-up are required.

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