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

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ABSTRACT

Background A common treatment for infertility or genetic issues today is assisted reproductive technology (ART), which includes in vitro fertilization (IVF). Numerous studies have been done in this area in order to better understand the potential effects of this technique on women who undergo in vitro fertilization (IVF) and children born through IVF. This study is an updated meta-analysis to determine whether there is a causal relationship between different fertility treatments and ovarian, 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) has been used as a method to treat infertility issues since the birth of the first "test-tube" child in the early 1980s. These issues include ovulation disorders, fallopian tube damage or blockage, endometriosis, uterine fibroids, impaired sperm production or function, unexplained infertility, and a genetic disorder (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). Therefore, the continued therapy cycles may increase the likelihood of breast cancer growth in the foreseeable future. Women are more likely to acquire breast cancer after IVF than other women to have a family history of the disease or to have first-degree female relatives who have been diagnosed with it. As a result, when doing this process, it is also important to analyze the risk of breast cancer in the family. Because of this, raising patients' understanding of the treatment process is crucial, and women considering IVF should be made aware of the potential repercussions of the link between breast cancer and reproductive therapy methods (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 influences have a significant impact on breast cancer. Any dosage of gonadotropin hormones and fertility medicines that cause ovaries to multiply ovulation can also affect the breast since the ovary influences breast function by producing steroid hormones. In a typical IVF technique, clomiphene citrate and gonadotropins, such as human chorionic gonadotropin (HCG) and human menopausal gonadotropin (HMG), are utilized to induce ovulation and boost the formation of many follicles (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).

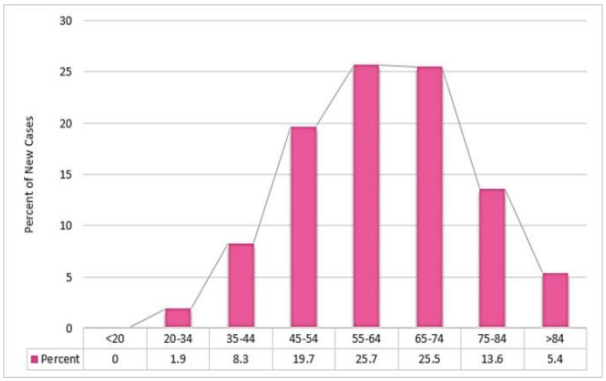

Figure 1. Cases of breast cancer in women of all races from period (2013 – 2017). Females between the ages of 55 and 64 are the most likely to be diagnosed with breast cancer (median age at diagnosis: 62 years)

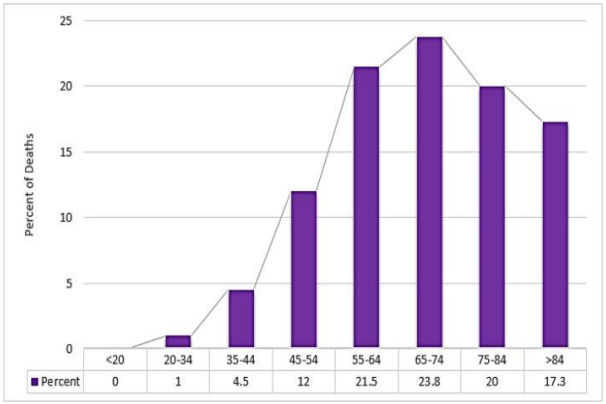

Figure .2 By age group, the mortality rate for women with breast cancer in the United States from 2014 to 2018. Women between the ages of 65 and 74 account for the majority of breast cancer deaths (median age at death: 69 years).

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

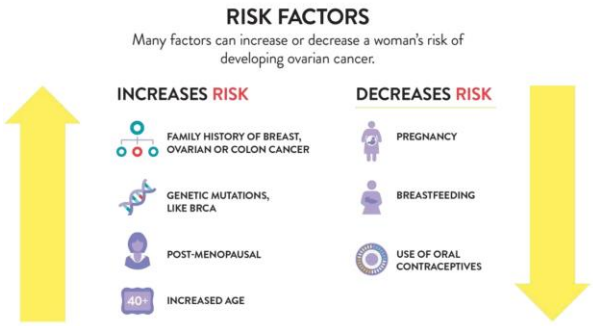

Figure 3. risks factors on ovarian cancer

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). A potential side effect of in vitro fertilization is the ovarian hyperstimulation syndrome (OHSS) (IVF). The ovaries expand and fluid spills into the body when this illness is present. In women with polycystic ovarian syndrome who are undergoing reproductive treatments, this condition is more prevalent. Due to the large doses of drugs used at each step of the IVF, women who had not given birth to a live child by the end of therapy were at a significantly higher risk of developing ovarian cancer (Hughes et al., 2010, Petrangelo et al., 2018). There is no link between IVF and cancer risk. There is no link between ovulation stimulation medication and cancer risk. The risk of ovarian cancer was increased among women who underwent 4 or more IVF cycles, although it was not statistically significant (Taheripanah et al., 2018).

1.3 In Vitro Fertilization (IVF)

One of the methods available to help people with fertility issues conceive a baby is in vitro fertilization (IVF). IVF involves taking an egg out of the woman's ovaries and fertilizing it with sperm in a lab. A woman's womb is where the fertilized egg, also known as an embryo, is placed to continue growing and developing (Lerner-Geva et al., 2003; Lerner-Geva et al., 2006) . In IVF, mature eggs are removed from the ovaries and fertilized in a laboratory using sperm. The fertilized egg (embryo) or eggs (embryos) are then put into a uterus. IVF takes roughly three weeks to complete one cycle (Stewart et al., 2012). When these steps are divided into separate steps, the procedure can take longer. Natural cycle IVF, moderate stimulation IVF, and in vitro maturation are the three basic IVF procedures that use no or minimal amounts of medications (IVM). To stimulate and develop follicles and hence boost ovulation, drugs like Clomiphene citrate and gonadotropins are utilized during the IVF treatment (Pappo et al., 2008; Katz et al., 2008). The risk of premature birth, high blood pressure, placental anomalies, and other issues are all increased by IVF, which also raises the possibility of twins, triplets, or high-order multiples. The chance of miscarriage and birth abnormalities increases with increasing maternal age, a common justification for IVF. If more than one embryo is transplanted to the uterus during IVF, the possibility of multiple births increases (Burkman et al., 2003; Mneimneh et al., 2013). Figure 4 describe steps of IVF.

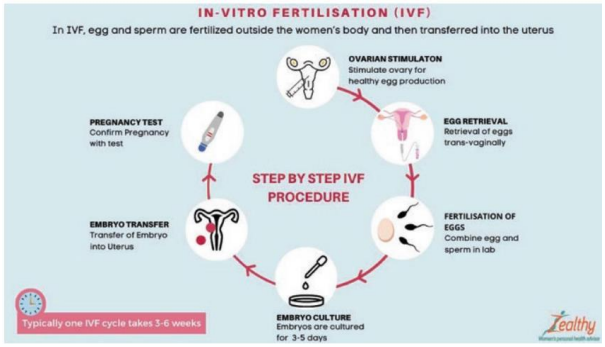

Figure 4. Steps of IVF

Compared to pregnancies with a single foetus, pregnancies with multiple foetuses have a higher risk of early labor and low birth weight. 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).

2.0 Materials and Methods

Members of the cohort's HFEA fertility data were connected to nationwide cancer registries. Members of the cohort's actual initial diagnoses of ovarian, breast, and corpus uteri cancer were compared to expectations for their age, sex, and period. Utilizing national incidence rates for a certain age, sex, and time period, standardized incidence ratios (SIRs) were computed.

2.1 Study Population

"Treatments or procedures that entail in vitro handling of both human oocytes and sperm or embryo's , for the purpose of reproduction," according to the definition of assisted reproduction. The Human Fertilization and Embryology Authority provided records for all women who underwent assisted reproduction between January 1991 and September 2009, as well as those who underwent it between October 2009 and December 2010 and provided prospective consent. These records - as examples - covered England, Wales, and Scotland (HFEA). HFEA records were connected to the Central Registers of the National Health Service of England, Wales, and Scotland (from which emigrations, deaths, and cancer registrations are reported to authorize medical researchers).

2.2 Statistical Analyses

The intended duration of the follow-up period was to begin at the starting point of the first treatment cycle, which is about halfway through the first treatment year, and end on the date of the cancer diagnosis, emigration, death, or study termination, whichever came first. The person's years at risk for analyses involving the number of cycles, the duration of infertility, and live and multiple births were calculated from the date of the last treatment (estimated as the halfway point) because the HFEA failed to record the intermediate dates required for time-dependent analyses. To calculate the expected number of cancer cases

3.0 Results and Discussion

3.1 Breast Cancer

There was no difference in the risks at premenopausal and postmenopausal specifically (age), but there was no overall increase in the risk of breast cancer or other cancers. 50 years, 0.97 (0.89 to 1.06); data not shown; 50 years, standardized incidence ratio 0.98 (95% confidence interval 0.94 to 1.02). Also we noticed significant risk reductions in women regardless of the female factor or just male factor or both, as well as with increasing duration after treatment completion (P=0.01). After the first 12 months of follow-up were left out, the risk of breast cancer was significantly lower than the age-standardized expectation (standardized incidence ratio 0.95 (0.92 to 0.99), P=0.02). Taheripanah et al. (2018) and Dos Santos et al. (2017).

3.2 Ovarian cancer

Our study population was shown to have an overall elevated risk of ovarian cancer (standardized incidence ratio 1.39 (95% confidence interval 1.26 to 1.53); absolute excess risk 5.0 cases per 100 000 person years (95% confidence interval 3.3 to 6.9); table 2). Most age groups at first treatment showed increased risks, but there was a highly significant trend toward risk escalation with advancing age (P< 0.001). Women who had any type of female factor infertility diagnosis had significantly higher chances. The risk did not change significantly with the number of cycles (P=0.29), the length of the infertility (P=0.25), or the amount of time since the end of treatment (P=0.44). It also did not change significantly for women who were only receiving treatment for infertility caused by the male factor. Excluding the initial year of follow-up did not substantially change results (Taheripanah et al., 2018; Nindrea et al., 2019.

3.3 Corpus Uteri Cancer

There was no appreciable increase in the risk of corpus uteri cancer (standardized incidence ratio 1.12 (95% confidence interval 0.95 to 1.30); absolute excess risk 0.8 cases per 100 000 person years (95% confidence interval 0.3 to 2.0). There was a highly significant tendency toward increased risk with declining parity (P< 0.001) and a trend toward significantly lowered risk with women having multiple births (standardized incidence ratio 0.42 (0.14 to 0.99); table 3). The number of cycles, age at starting treatment, or time after treatment completion did not significantly affect risk (P=0.93, P=0.28, or P=0.12). The results were unaffected significantly when the first year of follow-up was excluded (Nindrea et al., 2019).

4. Conclusion

No elevated incidence of corpus uteri or invasive breast cancer was found in this analysis of women who had had treatment with assisted reproductive technology. As the number of treatment cycles rose, the chance of in situ breast cancer increased as well. 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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