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Review Article

In-Vitro Fertilization Impact on the Risk of Breast Cancer: A Review Article

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Abstract

Background: Due to the increasing prevalence of infertility, the number of referrals to infertility treatment centers has also increased. Nowadays, assisted reproductive technology (ART), including in vitro fertilization (IVF), is a treatment for infertility or genetic problems. Considering the possible consequences of this method among women undergoing in vitro fertilization (IVF) and kids conceived by IVF, extensive research has been conducted in this regard.

Methods: Overall, 100 articles were entered into the study, and relevant articles were searched and extracted from PubMed, Springer, and Google Scholar databases. In IVF procedure, medications such as Clomiphene citrate and gonadotropins are used to stimulate and mature follicles and thus increase ovulation.

Results: There are conflicting opinions on this issue. Some findings report a slight increase in cancer risk for hormone-sensitive cancers including breast cancer. The long-term use of IVF medications can increase estrogen hormones and cause excessive expression of genes, resulting in an increased risk of breast cancer, which is one of the most frequent cancers among women.

Conclusion: There are some risks to be aware of, which followed the hypothesis that long IVF treatment process may lead to breast cancer among IVF candidates. Furthermore, the risk of breast cancer may be increased in those women with a positive family history and related inherited genes. Therefore, women candidates for IVF should be informed of the probable implications of the reproductive therapy techniques.

Keywords: Breast cancer; In vitro fertilization (IVF); Clomiphene citrate; Gonadotropins; Infertility; Personalized medicine

Introduction

Since the birth of the first 'test-tube' baby in the early 1980s, in-vitro fertilization (IVF) has been used as a method for solving infertility problems including ovulation disorders, fallopian tube damage or blockage, endometriosis, uterine fibroids, impaired sperm production or function, unex-

plained infertility, and a genetic disorder (1, 2). According to global statistics, a large number of couples annually visit IVF centers to carry out infertility treatment due to the fertility problems. Moreover, ovulation-inducing drugs have been used for various types of infertility (3-9).

Infertility problems can be cured through use of several methods including assisted reproductive technology (ART), surgery and medication, or intrauterine insemination (IUI) (10). Studies conducted in the Netherlands and the United States showed a high consumption of fertility drugs and a sudden increase in referrals of patients to fertility health care centers between the 1980s and 90s (11, 12). Many studies, especially retrospective cohorts, have long focused on the future effects of ART in women undergoing these treatments and their offspring (13). Parity and increased breastfeeding may reduce some subtypes of breast and gynecologic cancers (14-16), but with regard to research on the effects of IVF treatment, this method can increase the risk of developing breast cancer (17). Contrary to the result of studies with small sample sizes (18-20), there are speculations that the risk of cancer in women has increased after IVF (21, 22). In particular, an association has been found between ovulation induction and a significant increase in the risk of breast cancer, which appears to be stronger among women waiting more than one year to conceive (14, 23-29).

Women who have infertility problems and are undergoing hormone therapy are more likely to have dense breasts, a factor that may raise the risk of developing breast cancer. In a study of 43,313 women, the association between ovulation stimulant drugs and mammographic breast density was investigated. Women reporting infertility had more dense tissue in the breast as a result of controlled ovarian stimulation, which can affect the risk of getting breast cancer (17). Some important risk factors for breast cancer such as age are beyond control. Thus, there may be a possible association between the age of IVF-treated women and breast cancer development. Women over 30 yr old are increasingly at risk for breast cancer by initiating IVF cycles (30). Moreover, I Pappo et al. demonstrated the incidence of breast cancer in women age >or=40 yr after controlled ovarian stimulation in their retrospective cohort study (31). In Western Australia, a different outcome was reported. Young IVF-treated women were more likely to have an increased risk of breast cancer compared to those who did not perform IVF, as well as those of other ages (32).

Breast cancer is strongly influenced by hormonal factors (25, 33-38). As the ovary affects the breast function by producing steroid hormones, any dose of gonadotropin hormones and fertility drugs that affect ovaries to multiply ovulation can also affect the breast (5). In a typical IVF procedure, clomiphene citrate and gonadotropins, including human chorionic gonadotropin (HCG) and human menopausal gonadotropin (HMG), are used to stimulate the growth of multiple follicles and induce ovulation (39). Ovarian stimulation can affect the levels of endogenous estrogen, which may cause cancer risk (13, 22, 40, 41). The probability of this cancer is also greater in women who have previously used IVF several times but did not get pregnant, usually more than six months, because of persistent exposure to HMG (20).

Breast Cancer

Female breast cancer is an invasive malignancy that is highly influenced by female steroids. It is the most common cancer in women worldwide, particularly in middle-aged and older women and the rate of new cases of female with breast cancer is 128.5 per 100,000 women per year (42, 43) (Fig. 1) (44). In some countries such as Iran, the extent of cancer and its spread has increased, although the age of breast cancer incidence has sharply decreased. Breast cancer death rate is about 20.1 per 100,000 women in the United States, with an average age of 69 yr (Fig. 2) (44). The mortality of breast cancer declined due to improvements in screening and effective treatments (45). Known and suspected factors such as lifestyle, age, race, geographical location, and exposure to ionizing radiation are effective in developing breast cancer (46). According to studies, null parity (47), advanced maternal age (AMA) (48), early menarche (49), late menopause (50), and longtime hormone

therapy are risk factors of breast cancers (51-53), which are probably to be affected by progesterone and estrogen hormones secretion (38, 54). At the same age, the risk of breast cancer is higher in premenopausal women than postmenopausal women (55, 56).

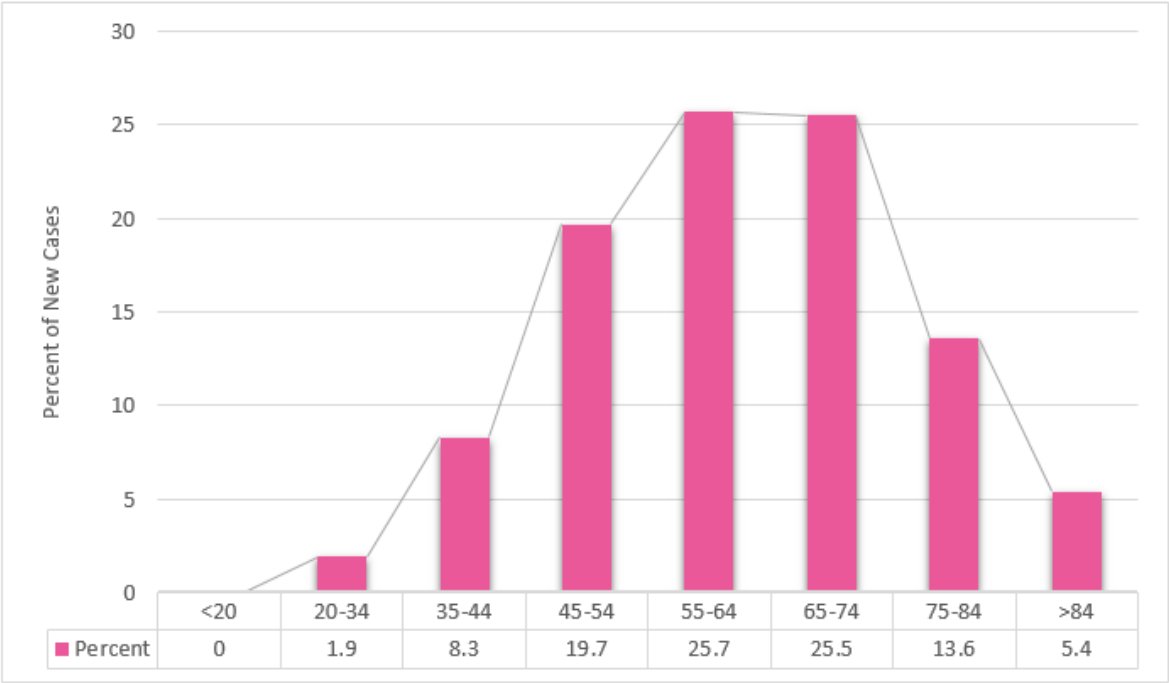

Fig. 1: New cases of female with breast cancer of all races, 2013–2017. Breast cancer is most frequently diagnosed among females aged 55–64 (median age at diagnosis = 62 years) (44)

Besides, lactation in parous women for a longer duration can be associated with a lower risk of breast cancer (57). This cancer may also be inherited (58). However, family history plays a minor role in most cases. Hereditary mutations in the BRCA1 or BRCA2 gene, play the most important role in hereditary breast cancer occurrence (59, 60). In addition, mutations in several other genes, including CDH1, PTEN, TP53, STK11, MLH1 and MLH2 have been associated with hereditary breast cancer (61). Women with the mutation in the BRCA1 and BRCA2 genes, located on the long arms of chromosomes 17 and 13 respectively, are especially susceptible to the breast cancer but represent only 5% to 10% of cases (62). Another important consideration is the genetic polymorphism (63) associated with the synthesis and metabolism of estrogen on the risk of developing breast cancer that is under investigation (64). Polymorphisms in the cytochrome P450 family (CYPs) and in the glutathione S-transferase (GSTs) enzymes are associated with breast cancer, because of their effect on the metabolism of environmental carcinogens and estrogen (62, 65-69). Therefore, hormones play a key role in the development of this cancer by influencing the proliferation of breast epithelial cells (70). Early menarche and late menopause affect the risk of breast cancer, because, during the reproductive period, secretion of ovarian steroid hormones affects breast function (56).

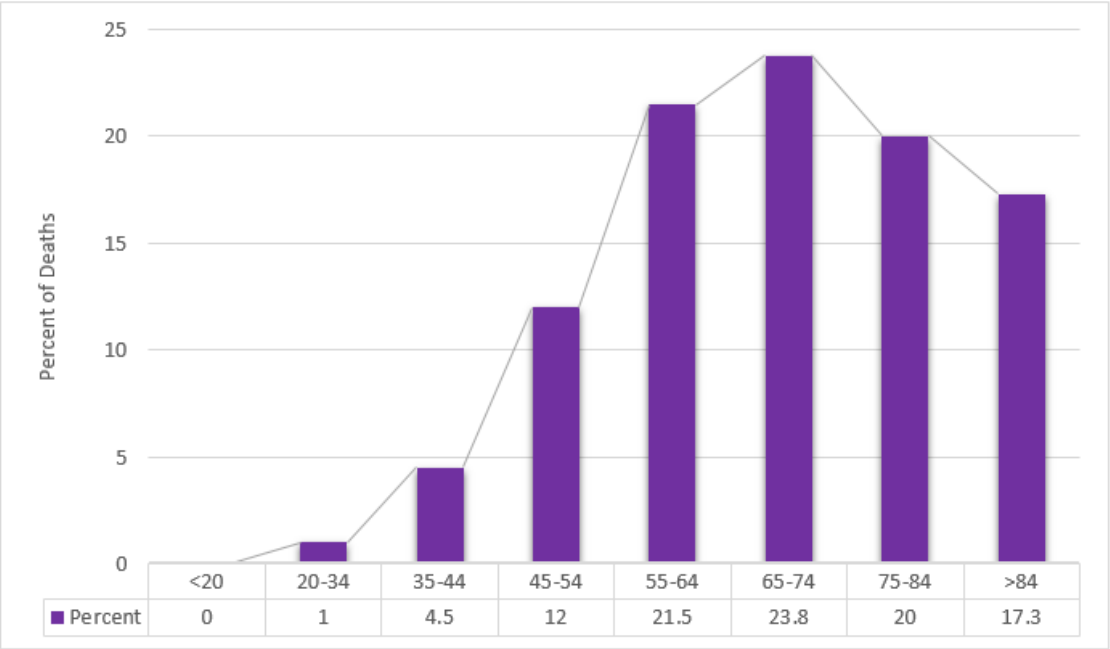

Fig. 2: Mortality rate in women with breast cancer by age group, U.S, 2014–2018. The breast cancer deaths is highest among women aged 65–74 (median age at death = 69 years) (44)

Estradiol hormone and its mechanism of action

Estradiol hormone is an estrogen steroid hormone that prepares the body for reproductive cycles. (71), stimulates the proliferation of mammary gland (72), and it can be synthesized in the breast, ovary, and extraglandular tissues. Estradiol affects the breast cells with paracrine, autocrine, and intracrine mechanisms. Moreover, this hormone can cause various chromosomal and genetic lesions, including aneuploidy (73), and more exposure to Estradiol (E2) or other estrogenic compounds can accelerate the development of breast carcinomas from early mutation to tumor metastasis, by increasing cell proliferation or genotoxic effects (42, 69). The estradiol hormone interacts with two nuclear receptors and crucial transcriptional regulators in breast called ER α (estrogen receptor α) and ERβ (estrogen receptor β), to affect its target tissue. The binding of estrogen to the nuclear estrogen receptor α promotes breast cancer growth (74). The complexation of these receptors and their attachment to a specific DNA sequence require the binding of estradiol to the ERs, but this connection can cause damage to the DNA, followed by increased DNA replication and cell division (75, 76).

Fertility Stimulant Drugs

In general, this study aimed to evaluate the effects of drugs used in IVF, clomiphene citrate and gonadotropins on breast cancer risk, and several studies have been conducted on its potential risk (18, 41, 77, 78). However, these drugs are not reviewed alone and the effect of medication dosing and duration and family history of the individuals should also be considered (80).

Clomiphene citrate (CC) or clomifene is an ovulatory stimulant drug and its action in women leads to multiple ovulation to cure unexplained subfertility, polycystic ovary syndrome, or oligo-ovulatory infertility (80-82). Clomiphene citrate along with IUI (Intrauterine insemination) has been determined an effective treatment for infertility (83). CC contains a mixture of enclomiphene and zuclomiphene isomers. Zuclomiphene is much more effective for induction of ovulation. The exact

mechanism of this drug is unknownbut it has been determined with both estrogenic and anti-estrogenic attributes. It competes with estrogen to bind to estrogen receptors in cells containing these receptors, including the ovaries, pituitary, and hypothalamus. By affecting these organs, such as the hypothalamus, it increases the GnRH secretion, thus acting as a selective estrogen receptor modulator. In contrast to estrogen, clomiphene citrate binds nuclear ER for a longer time. By stimulating the release of gonadotropins, like luteinizing hormone (LH), and follicle-stimulating hormone (FSH), it helps to develop the maturation of follicles, induces ovulation, and thus pregnancy (84-88). Therefore, clomiphene citrate is an estrogenic agonist and increases ovulation. When it binds to estrogen receptors in breast cells, it increases the expression of the relevant genes, cell proliferation, and ultimately breast cancer. Probable side effects of taking CC include hot flashes, mood swings, headaches, abnormal vaginal/uterine bleeding, vaginal dryness or thick cervical mucus, breast tenderness or discomfort, ovarian enlargement and visual disturbances. But there are concerns about the potential risks of taking clomiphene citrate on the ovarian hyperstimulation syndrome, and both ovarian and breast cancer (89, 90).

Gonadotropins, including LH, FSH, and HCG (91, 92), are made in the gonadotropic cells in the anterior pituitary gland, and this action is stimulated by Gonadotropin-releasing hormones (GnRH), secreted from the hypothalamus (93). Gonadotropins are essential for reproduction, sexual development, and also ovarian stimulation in women undergoing ART.

To stimulate ovary, an injectable medication containing a FSH, a LH, or a combination of both might be used, which stimulate more than one egg to develop at a time. Excessive use of gonadotropins in this procedure can suddenly increase the level of FSH and LH hormones, stimulate and mature follicles, and can also increase estrogen secretion, which in turn increases gene expression and possibly the risk of breast cancer (94), as was mentioned before.

During the oocyte maturation phase, when the follicles are ready for egg retrieval, HCG or other medications are applied to help the egg mature. Most women who had received more than 6 cycles of HCG or HMG) in IVF process, are generally at an estimated 40% risk of developing breast cancer, especially those with positive family history of breast cancer (20, 31, 95). HCG, a peptide hormone, is found physiologically in both female and male sexes. It is specially produced during pregnancy by the embryo (92), and not only plays an important role in pregnancy but also affects tumor formation and stimulation in the presence of estrogen and estrogen response elements (ERE) (96). Malignant breast cancer cells produce HCG, especially its β-subunit (97), and also contain a relatively high level of the HCG receptors (98), therefore, it can be recognized as a tumor marker in breast (99, 100). In brief, in the absence of pregnancy, increasing the presence of this molecule in the body can increase the growth of cancer cells.

Duration and Dose Effects

Overall, the medication dose and duration of use are considered to have an impact on breast cancer which is noteworthy. The highest rate of cancer incidence has been among women with an average of more than three cycles who were exposed to drugs or treated for more than a year and were unable to conceive (77, 78, 101). Studies with greater years of follow-up have provided better results on the effects of these drugs on breast cancer (31). For instance, in a study with more than 10 years of follow up, the potential impact of clomiphene citrate on breast cancer has been cited among cohort studies (41).

Conclusion

IVF is a treatment for infertility or genetic problems. The breast cancer risk in women receiving fertility treatment is increased especially among those older than age 40. Some breast cancer cases are thought to be hereditary and some develop due to a problem involving hormones. Medications used in IVF including clomiphene citrate and gonadotropins, increase the level of LH and FSH, which in turn raises estrogen levels. This sudden increase in estrogen level, an important female sex

hormone, can increase the expression of genes and follow that the risk of breast cancer. Findings from studies with large sample size show that women who had received fertility therapy for a long time, especially more than a year, are more prone to the disadvantages of fertility drugs. Thus, the repeated therapeutic cycles can probably raise the development of breast cancer in the next future. Women with a family history of breast cancer or those with first-degree female relatives who have been diagnosed with breast cancer are more susceptible to develop breast cancer after IVF procedure than others. Therefore, breast cancer family history risk assessment should also be considered in this process. Hence, the awareness surrounding the treatment process is incredibly important, and women candidates for IVF should be informed of the probable implications of the association between breast cancer and reproductive therapy techniques.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Not applicable.

Conflict of interest

The authors declare that they have no conflict of interest.

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