REVIEW

In vitro fertilization impact on the risk of breast cancer

Ana-Maria Mihai[1,*], Laura Maria Ianculescu[2], Dragoş Creţoiu[3], Nicolae Suciu[1,3]

[1] Alessandrescu-Rusescu National Institute for Mother and Child Health, Bucharest, Romania. [2] Ponderas Academic Hospital, Regina Maria Private Healthcare Network, Bucharest, Romania. [3] Carol Davila University of Medicine and Pharmacy, Bucharest, Romania.

[*]Correspondence: Ana-Maria Mihai, Alessandrescu-Rusescu National Institute for Mother and Child Health, 120 Lacul Tei Blvd., Bucharest, 20382, Romania. Email: anamaria.mihai@drd.umfcd.ro

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ABSTRACT

Breast cancer, with its increasing incidence and high mortality rates, remains a major global health challenge, significantly impacting individuals, families, and societies. Understanding the multifactorial risk factors contributing to its development is crucial for effective prevention and management. Hormonal factors play a significant role in breast cancer development. Given that ovarian steroid hormones influence breast function, any gonadotropin hormone or fertility drug that stimulates ovulation may also impact breast tissue. Contrary to the findings of studies with smaller sample sizes, concerns have emerged regarding the potential increased risk of breast cancer following in vitro fertilization (IVF) treatments. This article explores the potential risk of breast cancer associated with hormonal cycles during IVF, supported by a literature review and a case study conducted in a tertiary hospital in Bucharest, Romania. The case involves a 38-year-old patient with a history of hormonally treated endometriosis and five IVF cycles, who presented for mammographic and ultrasound screening. The screening revealed multicentric and multifocal BIRADS-5 lesions, with histopathological and immunohistochemical analysis confirming invasive breast carcinoma of no special type with ductal carcinoma in situ, HER2 positive (3+), estrogen receptor and progesterone receptor negative, and a Ki-67 proliferation index of 50%.

KEYWORDS: breast cancer; mammography; screening; IVF; increased risk

BACKGROUND

Breast cancer stands as the foremost diagnosed cancer among women, representing approximately 25% of all cancer cases globally. In 2020 alone, there were approximately 2.26 million reported cases, underscoring its profound impact. Tragically, breast cancer also holds the grim distinction of being the leading cause of cancer-related deaths in women [1]. The International Agency for Research on Cancer (IARC) has highlighted a staggering 66% rise in global cancer deaths since 1960, underscoring the urgency of addressing this escalating trend. In the United States, statistics reveal that roughly one in eight women will face a diagnosis of invasive breast cancer at some stage in their lives [2].

The latest Globocan data from 2020 highlight that breast cancer constituted 26.9% of all cancer cases diagnosed among women in Romania. This statistic underscores its status as the most commonly diagnosed cancer in women in the country (Figure 1) [3].

Breast cancer is a complex, multifaceted disease requiring a thorough understanding of its risk factors for effective management and prevention. Recognizing and addressing these factors are paramount for achieving early detection, optimal treatment outcomes, and improved patient prognosis.

Certain risk factors for breast cancer are beyond individual control, yet they play a significant role in assessing overall risk. These include being female, advancing age, and a family history of breast or ovarian cancer, all of which are well-established risk determinants. Additionally, genetic mutations, particularly in the BRCA1 and BRCA2 genes, significantly heighten the risk. Race and ethnicity also influence susceptibility, with certain groups showing higher prevalence rates. Reproductive history, such as nulliparity or having a first pregnancy at an older age, combined with early menarche or late menopause, further increase risk. Moreover, dense breast tissue, a previous diagnosis of breast cancer, or a history of non-cancerous breast diseases, as well as prior radiation therapy, are all factors that elevate breast cancer risk [4].

Unlike the non-modifiable risks, there are several factors within an individual's control that can be adjusted to potentially reduce breast cancer risk. Hormonal therapy, particularly long-term use, and exposure to diethylstilbestrol (DES) are known to increase risk. Lifestyle choices also play a crucial role; for example, regular physical activity is associated with a lower risk, while overweight or obesity,

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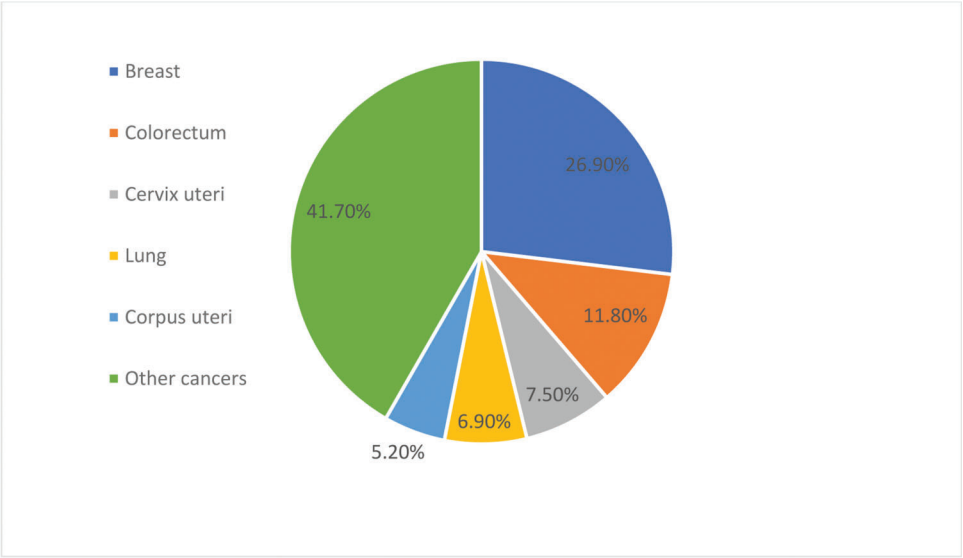

Fig. 1. Number of breast cancer new cases in 2020, females, all ages - adapted after Globocan 2020 [3].

particularly after menopause, is linked to higher risk. Alcohol consumption and smoking are additional risk factors that have been well-documented, while inadequate vitamin intake and excessive exposure to artificial light, such as from night shifts, have also been implicated. Dietary choices, such as the intake of processed foods, along with exposure to certain chemicals and other drugs, are areas where behavioral changes could make a meaningful impact [4]. Understanding the interplay between these various risk factors is vital for developing personalized prevention strategies. While non-modifiable factors cannot be changed, awareness of them allows for closer monitoring and early intervention. On the other hand, addressing modifiable risk factors presents an opportunity for individuals to take proactive steps toward reducing their risk of developing breast cancer.

Hormonal factors are central to the development of breast cancer, with prolonged estrogen exposure being a well-recognized risk factor, particularly for estrogen receptor-positive forms of the disease [5]. The link between nulliparity and delayed childbearing with increased breast cancer risk is well-documented, largely due to the extended exposure to endogenous estrogen. This association naturally raises concerns about the potential confounding risks associated with in vitro fertilization (IVF) [6]. Given the role of the ovaries in regulating breast function through the production of steroid hormones, it is reasonable to consider that any intervention, such as the administration of gonadotropin hormones and fertility drugs to stimulate ovulation, could also have an impact on breast tissue. While the evidence remains a subject of ongoing research, it is imperative to approach these concerns with a nuanced perspective. On one hand, IVF offers hope and the possibility of motherhood to many women; on the other, the potential risks, however minimal, cannot be entirely dismissed. This duality underscores the importance of personalized medical advice, where the benefits and risks of fertility treatments are carefully weighed, particularly in women who may already be at an elevated risk for breast cancer [7]. In contrast to findings from studies with limited sample sizes, there is growing speculation that the risk of cancer in women has increased after IVF [8,9].

ESTRADIOL HORMONE AND ITS MECHANISM OF ACTION

Estradiol, a potent estrogen steroid hormone, plays a central role in the development and function of the reproductive system, including the preparation of the body for reproductive cycles. It is synthesized not only in the ovaries but also in breast and extraglandular tissues, exerting its influence on breast cells through paracrine, autocrine, and intracrine mechanisms. Estradiol is essential for the proliferation of mammary glands; however, its role in breast cancer development is concerning due to its capacity to induce various chromosomal and genetic alterations, including aneuploidy. Prolonged exposure to estradiol or other estrogenic compounds significantly escalates the risk of breast cancer by promoting cell proliferation and exerting genotoxic effects. This hormone drives the progression of breast carcinomas from early mutations to tumor metastasis, highlighting its dual role as both a necessary factor for normal breast development and a potential catalyst for malignancy [10].

Estrogen influences breast cancer through multiple pathways: stimulating cell proliferation, leading to potential DNA replication errors; generating reactive oxygen species that can damage DNA; and altering cellular homeostasis. The balance of estrogen metabolites, especially the ratio between 2-hydroxyestradiol and 4-hydroxyestradiol, is critical in determining breast cancer risk. Additionally, some effects of estrogen on breast cancer occur independently of estrogen receptors, suggesting that reducing estrogen metabolite formation may lower breast cancer risk [11].

Estradiol, a critical hormone, exerts its effects on breast tissue through its interaction with two key nuclear receptors, ERα (estrogen receptor α) and ERβ (estrogen receptor β). These receptors function as vital transcriptional regulators, modulating gene expression within the target tissue. When estrogen binds to ERα, it significantly influences the growth

of breast cancer cells. The formation of this receptor-ligand complex allows the receptors to attach to specific DNA sequences, initiating a cascade of genetic activities. However, this interaction is not without risks. The binding of estradiol to these receptors can lead to DNA damage, which in turn, can trigger an increase in DNA replication and cell division, potentially accelerating tumorigenesis. This dual role of estradiol - necessary for normal cellular function but also a contributor to cancer development - underscores the complexity of hormone-driven processes in breast cancer. The intricate balance between estradiol's physiological roles and its potential to induce harmful genetic changes is a crucial area of focus in understanding and managing breast cancer [12].

The balance of estrogen metabolites and the regulation of estradiol's interaction with its receptors are crucial in maintaining breast tissue homeostasis. Disruptions in this balance may push the tissue toward malignancy, underscoring the importance of understanding estradiol's role in both normal breast development and cancer progression. The potential for estradiol to act independently of its receptors further complicates the picture, suggesting that strategies aimed at reducing the formation of estrogen metabolites could be key in lowering the risk of breast cancer. This duality of estradiol's role highlights the delicate balance that exists in breast tissue, where a hormone vital for normal function can also become a driving force behind cancer development.

FERTILITY STIMULANT DRUGS

IVF stimulant drugs play a critical role in optimizing the success of egg retrieval in the in vitro fertilization process. These medications, such as gonadotropins (which include follicle-stimulating hormone, FSH, and luteinizing hormone, LH), as well as GnRH agonists/antagonists and human chorionic gonadotropin (hCG), are designed to enhance ovarian activity. By stimulating the ovaries, these drugs encourage the production of multiple mature eggs within a single cycle, significantly boosting the potential for successful fertilization and the subsequent selection of viable embryos. The strategic use of these stimulants is essential in overcoming the natural limitation of single-egg ovulation, thereby offering a greater pool of embryos from which to choose. This is particularly crucial for patients who may have difficulties with egg production or who are seeking to maximize their chances of conception in a limited number of cycles. However, while these drugs are powerful tools in assisted reproductive technology, their administration must be carefully monitored to avoid complications such as ovarian hyperstimulation syndrome (OHSS), which can arise from excessive ovarian response. The balance between efficacy and safety in the use of IVF stimulant drugs highlights the delicate nature of fertility treatments and the need for personalized medical approaches to meet the unique needs of each patient [13].

Clomiphene citrate (CC) is a key ovulatory stimulant, effective in inducing multiple ovulation cycles to address unexplained subfertility and conditions like polycystic ovary syndrome (PCOS) [14]. CC contains a blend of enclomiphene and zuclomiphene isomers, with zuclomiphene being particularly effective at inducing ovulation. Although the precise mechanism of CC remains partially understood, it exhibits both estrogenic and anti-estrogenic properties. CC functions by competing with estrogen for binding to estrogen receptors in the ovaries, pituitary, and hypothalamus. This interaction disrupts normal estrogen signaling and enhances the release of gonadotropins such as luteinizing hormone (LH) and follicle-stimulating hormone (FSH), ultimately promoting follicle maturation and ovulation [15]. Therefore, clomiphene citrate is an estrogenic agonist and increases ovulation. By binding to estrogen receptors in breast tissue, it can amplify gene expression associated with cellular growth, potentially leading to increased breast cancer risk. The drug's side effects include hot flashes, mood fluctuations, headaches, irregular bleeding, vaginal dryness, thickened cervical mucus, breast tenderness, ovarian enlargement, and visual disturbances. However, there are growing concerns about the drug's role in ovarian hyperstimulation syndrome and its potential link to both ovarian and breast cancers [16]. From a personal perspective, it is fascinating how CC's dual action - both as an estrogen antagonist and agonist - can lead to significant therapeutic outcomes in fertility treatments. Its ability to modulate the endocrine system and stimulate ovulation underscores its value in addressing various fertility issues, though it also highlights the complex balance required to optimize its effectiveness while managing potential side effects. The drug's role in enhancing reproductive success reflects the ongoing advancements in reproductive medicine, yet it also reminds us of the intricate interplay between hormones and their broader implications for health.

Gonadotropins, including luteinizing hormone (LH), follicle-stimulating hormone (FSH), and human chorionic gonadotropin (hCG), are essential for ovarian stimulation during assisted reproductive technology (ART). Administered as injectable medications, these hormones promote the development of multiple follicles and increase estrogen secretion. Elevated estrogen levels can upregulate gene expression involved in cell proliferation, potentially increasing the risk of breast cancer, particularly in women with predisposing factors. Additionally, studies have shown that the prolonged use of gonadotropins may lead to higher circulating estrogen concentrations, which have been linked to breast tissue changes that could predispose patients to malignancy over time. Moreover, the repeated ovarian stimulation cycles associated with ART could contribute to cumulative estrogen exposure, thereby amplifying the risk of breast cancer in susceptible individuals [17,18].

During the phase of oocyte maturation, when follicles reach the point of readiness for egg retrieval, human chorionic gonadotropin (hCG) or other similar medications are administered to facilitate the final maturation of the eggs. Research indicates that women who have undergone more than six cycles of hCG or human menopausal gonadotropin (hMG) during the IVF process may face an estimated 40% increased risk of developing breast cancer, especially if they have a family history of the disease [19]. Human chorionic gonadotropin (hCG), a peptide hormone produced by the embryo during pregnancy, plays a pivotal role in maintaining pregnancy by supporting the corpus luteum and ensuring progesterone production. However, its role extends beyond reproductive functions, as hCG is also involved in cancer biology [20,21]. Interestingly, malignant breast cancer cells can produce hCG, particularly its β-subunit, and display elevated levels of hCG receptors, making it a potential tumor marker in breast cancer diagnostics. The presence of hCG in breast tissue, particularly in the absence of pregnancy, raises concerns about its potential to stimulate the growth of cancer

cells, suggesting that hCG could have oncogenic effects when artificially introduced into the body [12,22]. This aspect of hCG's function warrants further investigation, as it underscores a possible link between fertility treatments and an increased risk of breast cancer, especially in genetically predisposed individuals. The broader implications of hCG in cancer development necessitate careful consideration and more comprehensive studies to better understand the balance between its therapeutic benefits in fertility treatments and its potential risks in cancer progression.

STUDIES RESULTS ON EVALUATING IVF IMPACT ON THE RISK OF BREAST CANCER

When examining the impact of in vitro fertilization (IVF) on the risk of breast cancer, several key studies have been published, providing insights into this complex issue.

A large cohort study from Denmark followed IVF patients over several decades. The results suggested that IVF itself does not significantly increase the risk of breast cancer compared to the general population. However, the study highlighted that patients with a high number of IVF cycles or those who underwent ovarian stimulation might have a slightly higher risk, underscoring the need for ongoing surveillance [23].

A case-control study that investigated the impact of clomiphene citrate on breast cancer risk found that prolonged use of clomiphene citrate might be associated with a modestly increased risk of breast cancer. The study suggested that the risk could be linked to the estrogenic effects of clomiphene citrate [12]. Similar results were indicated in Grodstein F et al. study [24]. Schmidt L et al. concluded, through a review article compiled evidence from multiple studies, that while there is some concern about the long-term impact of hormonal treatments on cancer risk, including breast cancer, current evidence does not show a clear and consistent increase in risk. The review recommended continued monitoring and research to confirm these findings [25]. Tzeng JI et al. conducted a systematic review focused on the cancer risks associated with ovarian stimulation protocols used in IVF. The study found a slightly increased risk of breast cancer with certain stimulation protocols but emphasized that the overall risk remains low. The authors highlighted the importance of individualized treatment plans and ongoing research to address these concerns [26]. In the largest meta-analysis in the past 20 years on the incidence of breast cancer associated with fertility treatment, analyzing 25 studies, including 617,479 participants, there was no significant association demonstrated between fertility treatments and excess breast-cancer risk [27].

In 2007, Jensen and his team uncovered a striking four-fold increase in the risk of developing ductal breast cancer following the use of progesterone, sparking considerable concern about the potential carcinogenic effects of hormonal therapies in reproductive medicine. Despite the significance of these findings, subsequent studies have struggled to replicate these results, casting doubt on the consistency and generalizability of this association [28-31].

Building on this foundation, Katz and his colleagues conducted an extensive cohort study examining women who underwent a similar IVF regimen, seeking to understand whether the incidence of breast cancer was higher among those who developed the disease compared to those who did not. Their analysis revealed a crucial insight: women who began their first IVF cycle after the age of 30 faced a markedly higher risk of developing breast cancer, even after adjusting for the age at first pregnancy. This finding highlights the potential vulnerability of older women undergoing fertility treatments, suggesting that age at the start of IVF may play a critical role in modulating cancer risk [32].

Similarly, Pappo and his team observed an increased incidence of breast cancer in women over the age of 40 who underwent four or more cycles of IVF, particularly among those with a history of hormonal infertility. However, their study did not account for key factors such as age at first pregnancy, nor did it address the likelihood that these women, many of whom were nulliparous, might already have an elevated baseline risk for breast cancer. The omission of these variables complicates the interpretation of their findings and raises questions about whether the increased cancer risk is truly attributable to IVF or is instead a reflection of underlying demographic factors [33].

Comparing these studies reveals a complex and nuanced picture of the relationship between IVF, hormonal therapy, and breast cancer risk. While Jensen's initial findings suggested a clear link between progesterone use and increased cancer risk, the lack of reproducibility in subsequent studies underscores the need for caution in drawing definitive conclusions. Katz's and Pappo's research, on the other hand, highlights the importance of considering patient age, both at the time of IVF and at first pregnancy, as significant factors in assessing cancer risk. These studies collectively suggest that while IVF and associated hormonal treatments may contribute to breast cancer risk, particularly in older women or those with preexisting risk factors, the full extent of this relationship remains unclear and warrants further investigation. Understanding the interplay of age, hormonal exposure, and reproductive history is essential for developing tailored risk assessment strategies for women undergoing fertility treatments.

To explore the potential risk of cancer in women undergoing IVF treatment at an advanced age, Tsafrir and colleagues conducted a comprehensive study involving a cohort of 501 women, with an average age of 42.3 years at the time of their first IVF cycle. The study followed these women for more than a decade, providing a long-term perspective on the relationship between IVF and breast cancer risk. Interestingly, the results revealed that undergoing IVF did not correlate with an elevated risk of breast cancer in the long-term, suggesting that advanced age at the start of IVF may not be as significant a risk factor as previously thought [34]. In contrast, research conducted by Stewart and colleagues offers a different perspective. By comparing breast cancer incidence among women undergoing fertility treatments, they observed a higher rate of breast cancer in those who initiated IVF at a younger age. This finding indicates that early exposure to the hormonal changes associated with IVF might heighten the risk of developing breast cancer, particularly in younger women whose breast tissue might be more susceptible to hormonal fluctuations [35]. Moreover, studies by Burkmann and Taheripanah further complicate the picture by reporting an increased incidence of breast cancer in women who underwent multiple IVF cycles - specifically, more than six cycles or treatments extending beyond six months. These findings suggest that the cumulative hormonal exposure from repeated or prolonged IVF treatments may play a critical

role in increasing breast cancer risk, raising important questions about the long-term safety of extensive fertility treatments [9,36]. Comparing these studies underscores the complexity of understanding breast cancer risk in the context of IVF treatments. While Tsafrir's study provides some reassurance regarding the long-term safety of IVF in older women, the findings from Stewart and others highlight potential risks associated with starting IVF at a younger age or undergoing multiple treatment cycles. These contrasting results suggest that breast cancer risk in IVF patients is influenced by a variety of factors, including age, the number of cycles, and the duration of treatment. As such, these studies emphasize the need for individualized risk assessments and cautious consideration of these variables when planning fertility treatments. The nuanced relationship between IVF and breast cancer risk calls for ongoing research to fully elucidate the mechanisms at play and to develop guidelines that ensure both the safety and success of fertility treatments.

BREAST CANCER SCREENING IN YOUNG WOMEN

Early detection plays a pivotal role in improving breast cancer outcomes and reducing mortality rates. Mammography is established as the sole imaging modality proven to decrease mortality from breast cancer, yet its efficacy in reducing mortality among high-risk patients remains unconfirmed [37]. In high-risk individuals, magnetic resonance imaging (MRI) can complement mammography as a screening tool [38].

Organizations such as the American Cancer Society (ACS) and the U.S. Preventive Services Task Force (USPSTF) advocate distinct imaging protocols tailored to diverse high-risk patient cohorts. For instance, the ACS recommends annual MRI and mammography starting at age 30 for high-risk individuals, with continuation contingent upon the patient's health status. In contrast, the USPSTF advises commencing mammography at age 40 for high-risk patients [39].

In our observational retrospective study conducted in a tertiary hospital in Bucharest, Romania, from which also derived our case report presented through this paper, data were collected from a cohort of 1.704 women who presented for mammography. Among these, 66 patients (3.9%) were younger than 40 years. A significant proportion (63.6%) exhibited symptoms at presentation, with the following distribution: pain (45.5%), palpable breast lumps (40.9%), nipple discharge (12.1%), and changes in breast appearance (4.5%). The remaining patients sought screening due to being classified in a high-risk group. Thirteen patients (19.7%) reported a family medical history of breast or ovarian cancer, with the majority (16.7%) having a family history of breast cancer, one patient (1.5%) having a family history of ovarian cancer, and one patient (1.5%) having both breast and ovarian cancers. Among these 13 patients, six (46.2%) reported that their mothers were diagnosed with breast or ovarian cancer by the age of 50 or younger. Eleven patients (16.7%) had a gynecological medical history, with three patients (4.5%) presenting conditions associated with hyperestrogenism. A substantial majority of patients (74.2%) had undergone previous medical tests, with breast ultrasound scans being the most frequent (45 patients, 68.2%), followed by mammography (17 patients, 25.8%), MRIs (12 patients, 18.2%), and biopsies (12 patients, 18.2%). Notably, 51 patients (77.3%) were receiving their first mammography at the time of presentation. These findings underscore the importance of adhering to established screening guidelines and emphasize the need for tailored screening strategies for high-risk individuals. Regular monitoring and early intervention are essential for improving outcomes in this group. The variation in screening recommendations highlights the need for personalized approaches based on individual risk factors, including family history and previous medical conditions. Enhanced screening protocols, including the integration of MRI for high-risk patients, may improve early detection and ultimately reduce breast cancer mortality.

CASE REPORT – BREAST CANCER AFTER 5 EPISODES OF IVF IN A 38-YEAR-OLD PATIENT

In the context of contradictory and controversial results in the literature regarding IVF hormonal treatments impact on the risk of breast cancer, we report a case of a 38-year-old patient at risk, with a personal history of surgically and hormonally treated endometriosis and five episodes of in vitro fertilization (IVF), who presented for individual mammographic and ultrasound screening. The patient has a notable family history of breast neoplasm, including a paternal aunt diagnosed at the age of 65 and a first cousin diagnosed at the age of 39. Mammographic and ultrasound screening identified multicentric and multifocal BIRADS-5 lesions in the patient's breasts. Histopathological and immunohistochemical analysis confirmed the presence of invasive breast carcinoma of no special type (NST) accompanied by ductal carcinoma in situ. The tumor was classified as HER2 positive (3+), with negative estrogen receptor and progesterone receptor status, and a Ki-67 proliferation index of 50%.

Imaging Studies

The mammographic assessment (Figures 2 and 3) revealed breasts with increased density, classified as type D according to the American College of Radiology (ACR) criteria. A focal aggregation of microcalcifications was detected at the junction of the left external quadrants, extending approximately 1 cm from the nipple. This area encompassed an architectural distortion (Figure 2), with the isolated calcifications exhibiting a segmental pattern. These calcifications were also noted within the nipple and retro-nipple region, prominently visualized on the magnified 2D image, spanning dimensions of 50/30 mm (Figure 3). Subtle asymmetries in breast density were observed on the left side, particularly in the deep prepectoral region, with a maximum depth of 8 mm. These findings warranted supplementary evaluation with ultrasound.

The ultrasound evaluation (Figures 4 and 5) revealed a hypoechoic lesion with irregular contours and microcalcifications inside, located retroareolarly, which was punctured under ultrasound guidance (Figure 4). Additionally, the ultrasound appearance showed axillary adenopathy characterized by a suspicious hypertrophic cortex, which was also subjected to ultrasound-guided core-biopsy, but no signs indicative of malignancy were found (Figure 5). Ultrasound imaging further showed small hypoechoic lesions with irregular contours, which were subsequently biopsied.

Magnetic Resonance Imaging (MRI) depicted masses with multifocal and multicentric contrast enhancements (Figure 6). These findings supported the diagnosis and the extent of the disease.

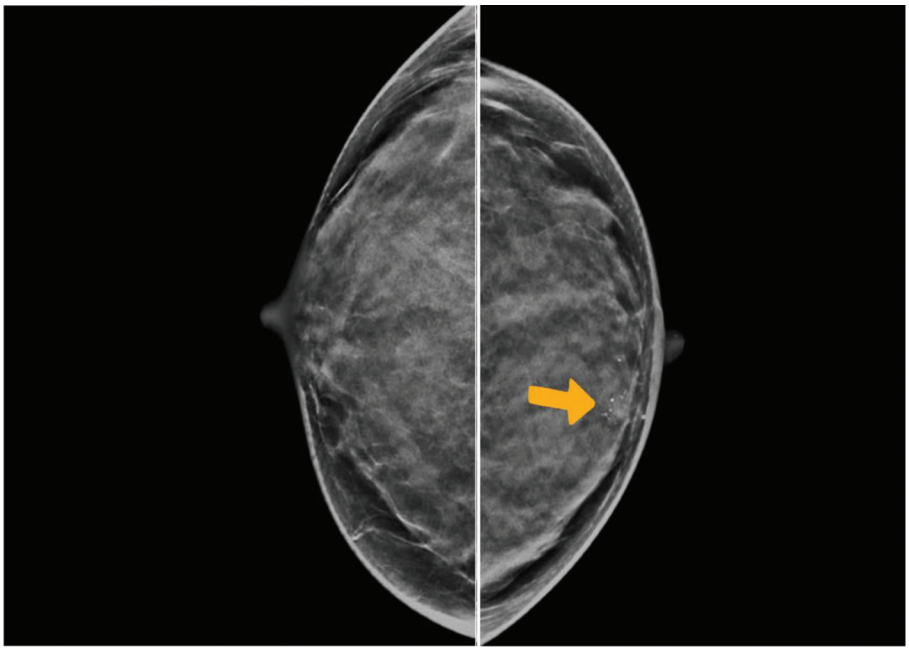

Fig. 2. Mammographic appearance - RCC (left side), LCC (right side): increased density classified as type D according to the American College of Radiology (ACR) criteria; architectural distortion with focal aggregation of microcalcifications (arrow).

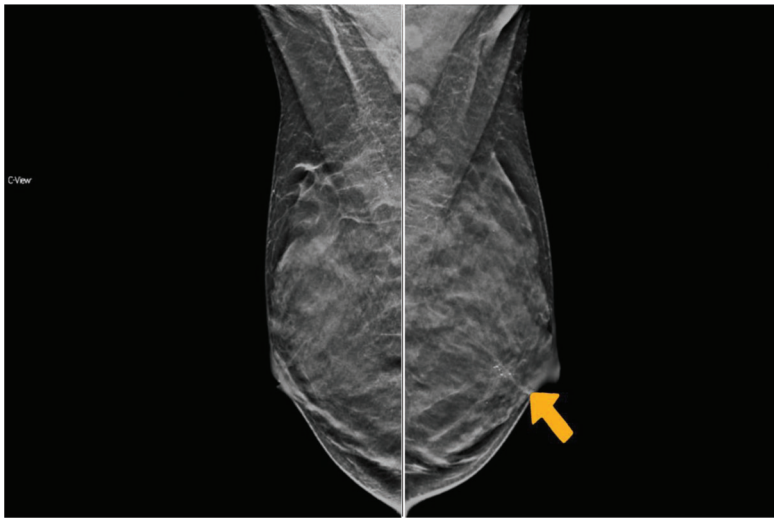

Fig. 3. Mammographic appearance - RMLO (left side), LMLO (right side); isolated calcifications exhibit a segmental pattern and are also present within the nipple and retro-nipple region (arrow); subtle asymmetries in breast density are observed on the left side, particularly in the deep prepectoral region.

Treatment

The patient underwent neoadjuvant anti-HER2 chemotherapy, which resulted in a complete imaging and pathological response, as assessed by MRI. Following chemotherapy, a left radical mastectomy was performed with immediate reconstruction using an implant. A sentinel node biopsy was also performed, revealing no signs of malignancy. Additionally, a prophylactic right mastectomy was performed with immediate reconstruction using an implant.

Post-treatment Imaging

Post-neoadjuvant chemotherapy MRI (dynamic 1) confirmed a complete imaging and pathological response, demonstrating the effectiveness of the neoadjuvant anti-HER2 chemotherapy (Figure 7).

DISCUSSIONS

Understanding the long-term implications of ovarian stimulation for in vitro fertilization (IVF) on breast cancer risk remains limited, given the relatively recent widespread adoption of IVF methodologies since the late 1980s [40,41]. Given the high incidence of breast cancer and the substantial number of women undergoing ovarian stimulation for IVF, even a marginal elevation in risk could have significant public health ramifications.

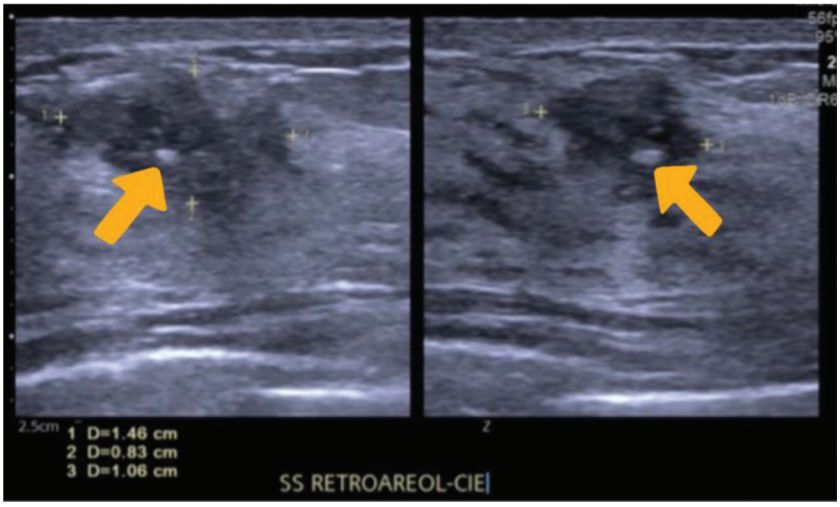

Fig. 4. Ultrasound evaluation reveals a hypoechoic image, with irregular contours, microcalcifications inside (arrow), retroareolar location; we performed core-biopsy under ultrasound guidance (right side).

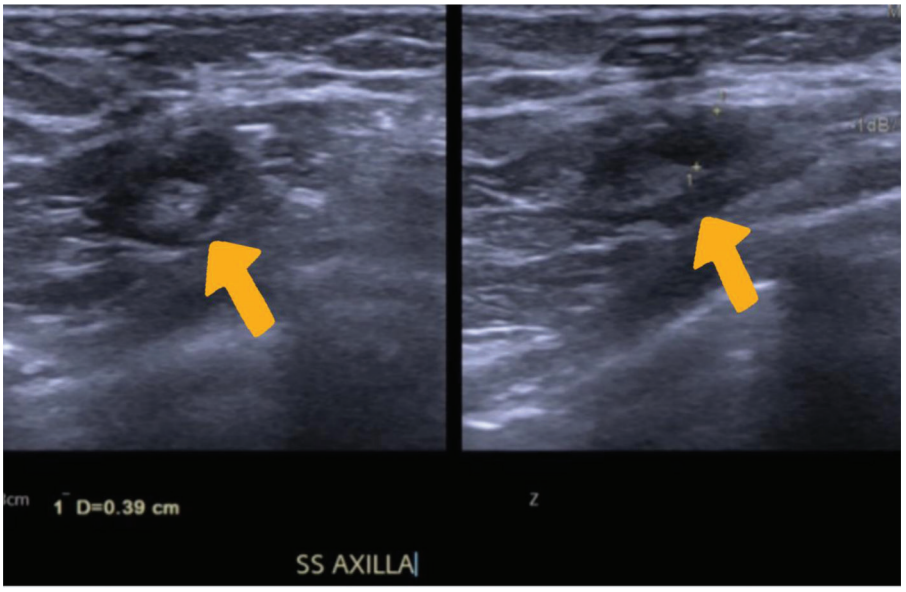

Fig. 5. The ultrasound appearance reveals axillary adenopathy characterized by suspicious hypertrophic cortex (arrow), subsequently subjected to ultrasound-guided puncture (which did not reveal signs indicative for malignancy).

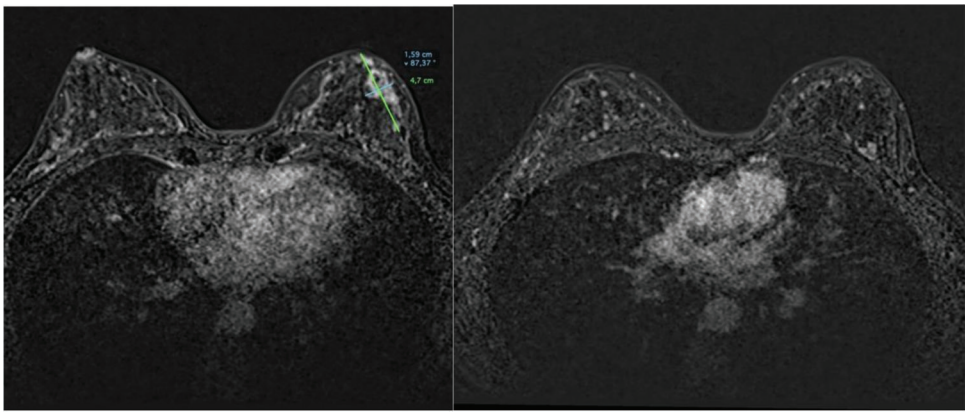

Fig. 6. MRI images depict masses with multifocal and multicentric contrast enhancements (marked by the two lines).

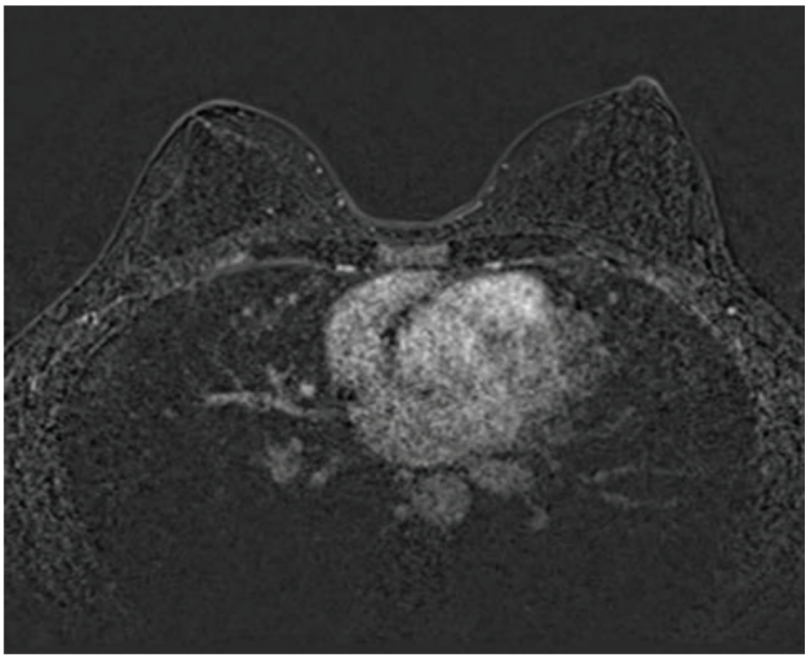

Fig. 7. MRI post NAC – dynamic 1 – complete imaging and pathological response after neoadjuvant chemotherapy.

Debate persists regarding this topic, with some studies suggesting a slight rise in cancer risk, particularly for hormone-sensitive cancers like breast cancer. Prolonged use of IVF medications can elevate estrogen levels and induce aberrant gene expression, potentially heightening breast cancer susceptibility, a prevalent malignancy among women [12].

Findings from a comprehensive Danish study, encompassing a median follow-up of 21.1 years, align with recent reviews indicating no discernible increase in breast cancer risk following IVF procedures [42-44].

Several studies have identified increased breast cancer risks within specific subgroups, such as those undergoing more than 4 cycles [33] or 6 cycles of human menopausal gonadotropin (hMG) [9], or those subjected to treatments exceeding 10 years [45]. Stewart et al. noted heightened breast cancer risks among women commencing IVF treatment at younger ages [41], while others reported elevated risks among those aged over 30 years [32] or 40 years [33] at the onset of IVF treatment.

Women undergoing hormone therapy are often found to have denser breast tissue, a condition that may elevate their risk of developing breast cancer. This correlation was highlighted in a study involving 43,313 women, which explored the effects of ovulation stimulant drugs on mammographic breast density. The research indicated that women who reported infertility and underwent controlled ovarian stimulation exhibited increased breast density. This heightened density can obscure mammographic images and potentially complicate the early detection of breast cancer [46].

Breast tissue density is not static but changes throughout a woman's life. Typically, higher breast density is seen in younger women, those with a lower body mass index, during pregnancy or lactation, and among those on hormone replacement therapy [47,48]. Notably, increased breast density is a significant risk factor for breast cancer, impacting both premenopausal and postmenopausal women [47,48].

One of the significant hurdles in assessing the impact of fertility treatments on breast cancer risk is the confounding effect of infertility itself. Nulliparity and infertility are known risk factors for breast cancer, which means that women undergoing fertility treatments might have an inherently higher risk due to these underlying factors. Consequently, this can lead to misleading conclusions when comparing these women to the general population, making it challenging to isolate the specific impact of fertility treatments on breast cancer risk.

These findings emphasize the need for a more refined approach to breast cancer screening for women undergoing hormone therapy or fertility treatments. Recognizing the dual role of increased breast density as both a risk factor and a complicating factor in imaging is crucial. Therefore, tailored screening strategies that incorporate additional imaging techniques or alternative diagnostic methods should be considered to address the increased density and its potential implications. This nuanced understanding is vital for developing effective screening protocols and improving early detection for women at higher risk [49].

CONCLUSIONS

The relationship between IFV and the risk of breast cancer remains a topic of ongoing research and debate. Current evidence suggests that IVF does not significantly increase the overall risk of breast cancer; however, variations in risk may exist depending on individual factors such as age, genetic predispositions, and hormone exposure levels. While some studies indicate a potential slight increase in risk, particularly in women who undergo multiple IVF cycles or start treatment at an older age, the findings are not definitive. Overall, IVF appears to be a relatively safe procedure concerning breast cancer risk, but further long-term studies are needed to fully understand the potential implications.

These findings of our study underscore the importance of adhering to established screening guidelines and emphasize

the need for tailored screening strategies for high-risk individuals. Regular monitoring and early intervention are essential for improving outcomes in this group. The variation in screening recommendations highlights the need for personalized approaches based on individual risk factors, including family history and previous medical conditions. Enhanced screening protocols, including the integration of MRI for high-risk patients, may improve early detection and ultimately reduce breast cancer mortality.

Conflict of interest

None.

Informed consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

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