International Journal of Reproduction, Contraception, Obstetrics and Gynecology
Chadha S. Int J Reprod Contracept Obstet Gynecol. 2025 Jul;14(7):2416-2423
www.ijrcog.org
pISSN 2320-1770 | eISSN 2320-1789

DOI: https://dx.doi.org/10.18203/2320-1770.ijrcog20252004

Review Article

Breast cancer in reproductive-age women: oncofertility perspectives, treatment impact, and fertility preservation strategies

Saloni Chadha*

Department of Obstetrics and Gynecology, VMMC and Safdarjung Hospital, New Delhi, India

Received: 19 May 2025
Accepted: 17 June 2025

***Correspondence:**
Dr. Saloni Chadha,
E-mail: Chadha.saloni@gmail.com

ABSTRACT

Breast cancer remains the most prevalent malignancy among females globally, comprising 12.5% of all cancer cases. While the median age of diagnosis in Western populations is 62 years, India reports a significantly younger median age of approximately 49 years, correlating with its youthful demographic profile. The incidence of breast cancer in women of reproductive age- approximately 19.3 per 100,000- has been rising steadily, necessitating urgent attention to fertility preservation in this population. Cancer treatments such as gonadotoxic chemotherapy, endocrine therapy, and radiation can adversely affect ovarian reserve, delay childbearing, or induce premature ovarian insufficiency. Consequently, fertility preservation has emerged as a crucial component of cancer care for young survivors. Oncofertility, an evolving interdisciplinary field, integrates oncology and reproductive medicine to provide comprehensive fertility counselling and interventions for cancer patients. Despite the growing importance of fertility preservation, barriers such as inadequate referral, limited awareness, financial constraints, and concerns regarding delays in cancer treatment or hormonal stimulation in hormone-positive cases hinder access. The impact of treatment on fertility varies depending on age, ovarian reserve, and treatment modality. Options for fertility preservation include embryo cryopreservation, mature and immature oocyte freezing, ovarian tissue cryopreservation, and temporary ovarian suppression using GnRH agonists. The National Comprehensive Cancer Network (NCCN) recommends early fertility discussions for all premenopausal breast cancer patients. In addition, pregnancy-associated breast cancer (PABC), though rare, presents a clinical challenge due to diagnostic delays and treatment limitations during gestation. As survival rates improve, safeguarding reproductive potential becomes vital to the quality of life of young survivors. Individualized, timely fertility preservation strategies supported by national and international guidelines are key to improving outcomes in reproductive-age women with breast cancer.

Keywords: Oncofertility, Fertility preservation, Reproductive-age women, Breast cancer, Chemotherapy-induced gonadotoxicity

INTRODUCTION

Breast cancer accounts for 12.5% of all cancer cases, is the most common cancer globally among females. The median age for a breast cancer diagnosis is 62 years. Despite significant advances in early detection and treatment, the incidence of breast cancer among women under 50 years has been rising steadily by about 0.2% per year since the 1990s.[1] The epidemiology of breast cancer in India highlights a distinct pattern compared to Western countries. The median age at diagnosis in India is approximately 49 years, notably younger than the 62 years observed in Western populations. This difference is partly attributable to India's predominantly younger demographic, with nearly 75% of the population below 50 years of age.[2]

Urbanization and lifestyle changes contribute significantly to rising risks in urban areas, such as Mumbai, where the

lifetime risk is estimated at 1 in 28, compared to 1 in 60 in rural regions- reflecting a much lower threat than Western countries.[2]

Breast cancer can develop in various parts of the breast, including the ducts, lobules, or connective tissues, and is classified into different types based on its molecular and histological characteristics. Risk factors include genetic predispositions such as BRCA1 and BRCA2 mutations, lifestyle factors like alcohol consumption and obesity, and hormonal influences.[3]

Breast cancers in people under 45 may also be aggressive and harder to treat. Young individuals can develop any type of breast cancer. However, the most common breast cancers in this age group are invasive ductal carcinoma and triple-negative breast cancer. Invasive ductal carcinoma, the most prevalent type of breast cancer across all age groups, originates in the milk ducts and then invades the surrounding breast tissue. Triple-negative breast cancer, a rarer form of invasive breast cancer, lacks estrogen, progesterone, and HER2 receptors, making it more challenging to treat.

The symptoms of breast cancer in young women mirror those experienced by individuals of other age groups. These symptoms can include palpable breast lumps or lumps in the axillary region, mastalgia (breast pain), and alterations in breast skin such as erythema, dimpling, or rashes. Additionally, patients may present with nipple inversion, nipple discharge (which may or may not be accompanied by pain), and swollen lymph nodes. Other signs include thickening or swelling of the breast skin or nipple. Recognizing these symptoms early is crucial for timely diagnosis and treatment.[4]

Early detection through regular mammograms and advancements in targeted therapies have improved survival rates, yet ongoing research is crucial to address the rising incidence and develop more effective treatments. A novel medical discipline known as 'oncofertility' has emerged from the intersection of oncology and reproductive medicine. This field is dedicated to addressing the reproductive needs and fertility preservation of cancer patients, integrating the expertise of both oncology and reproductive health specialists.

BREAST CANCER IN REPRODUCTIVE AGE WOMEN

The incidence rate of breast cancer in women of reproductive age is approximately 19.3 per 100,000.[5] This statistic underscores the importance of addressing fertility preservation in this demographic, as a significant number of young women are diagnosed with breast cancer during their prime reproductive years. Consequently, understanding the potential gonadotoxic effects of breast cancer treatments and implementing effective fertility preservation strategies is crucial for maintaining future reproductive options for these patients.

Breast cancer in young women exhibits distinct biological characteristics compared to that in older women. Tumors in younger patients tend to be more aggressive, often demonstrating higher proliferation rates, as indicated by increased Ki-67 expression, higher histologic grades (grades 3 and 4), and a greater likelihood of being estrogen receptor (ER)-negative. Molecular profiling further highlights these differences, with younger women's tumors showing elevated expression of proliferation-related genes and reduced ER expression, as reflected in higher oncotype DX recurrence scores. Gene expression analyses also reveal unique tumor signatures in women aged 40 and below, characterized by enrichment of pathways associated with immature mammary epithelial cells, growth factor signaling, and stem cell-like properties. Additionally, younger patients have a higher frequency of germline mutations in key susceptibility genes such as BRCA1 and BRCA2, particularly in those diagnosed before age 35 or 40, contributing to early onset and distinctive tumor biology. Overall, breast cancers in young women tend to be more proliferative, less differentiated, hormone receptor-negative, and genetically distinct, with a greater prevalence of high-risk mutations compared to those in older women.[6]

Breast cancer in these women is frequently diagnosed at a more advanced stage, primarily due to delayed detection. This delay arises from a combination of lower awareness among young women regarding breast cancer symptoms and reduced clinical suspicion among physicians, given the relatively low incidence in this age group. Furthermore, the high breast density commonly seen in younger women reduces the sensitivity of mammography, posing additional challenges to early and accurate diagnosis.[7]

NEED FOR FERTILITY PRESERVATION

The necessity for fertility preservation in breast cancer patients is underscored by the use of various treatments that can adversely impact reproductive potential. Gonadotoxic chemotherapy, long-lasting adjuvant therapies, non-pharmacologic ovarian suppression, and radiation therapy are integral components of breast cancer treatment that pose significant risks to fertility. Gonadotoxic chemotherapy can directly harm ovarian reserve, while prolonged adjuvant therapies often involve hormonal manipulation that can delay childbearing. Non-pharmacologic ovarian suppression and radiation therapy can also lead to decreased ovarian function or damage to reproductive organs.

Receiving specialized counselling about reproductive loss and the option of fertility preservation is significantly correlated with reduced regret ($p<0.0001$) and improved quality of life (QOL) among breast cancer survivors. However, many patients do not have access to these beneficial resources. It is essential that women of reproductive age receive expert guidance and the opportunity to make informed decisions regarding fertility

preservation. Providing such support enables patients to make choices that align with their future reproductive desires, ultimately enhancing their post-treatment quality of life.[8]

The impact of breast cancer treatment on fertility is a significant concern for young women, influencing their decision-making process. A survey of 657 young breast cancer survivors revealed that 57% were substantially worried about infertility at diagnosis, with 29% reporting that these concerns affected their treatment choices. Despite 72% discussing fertility issues with their doctors, only 51% felt adequately addressed. The findings highlight the need for better communication and education about fertility preservation options and underscore the importance of continued research in this area.[5]

ONCOFERTILITY

Oncofertility is a specialized subfield that integrates oncology and reproductive medicine to investigate and enhance reproductive options for cancer survivors. This multidisciplinary approach encompasses collaboration between oncology and fertility healthcare providers (HCPs) to address fertility preservation (FP) and related issues. Oncofertility involves comprehensive discussions about fertility risks and preservation strategies, as well as the management of complications such as pubertal delay, menstrual irregularities, hormonal deficiencies, and sexual dysfunction (Figure 1). This field aims to ensure that cancer survivors have the opportunity to make informed decisions about their reproductive futures.[9]

Several barriers to fertility preservation in breast cancer patients have been identified. These include a lack of referrals from oncologists, insufficient time for patients to make informed decisions, and a general lack of information regarding fertility preservation options. Additionally, concerns about potential delays in cancer treatment, uncertainty about the effects of ovarian stimulation on hormone-positive tumors, and apprehensions regarding the safety of pregnancy following treatment further complicate decision-making. The high cost of fertility preservation procedures and individual personal circumstances also contribute to the challenges faced by patients considering these options. Addressing these barriers is essential to improving access to fertility preservation services for cancer patients.[10] Inherited pathogenic genetic variations in the BRCA1 and BRCA2 genes, which are the most extensively studied breast cancer susceptibility genes, are responsible for approximately 5%-10% of all female breast cancers and 15%-20% of all familial breast cancer cases.[11] Women with BRCA1 or BRCA2 mutations have a markedly increased risk of developing breast cancer, with an estimated lifetime risk of about 70% by the age of 80, compared to a 10% risk in the general female population. These statistics underscore the importance of genetic screening and counselling in managing breast cancer risk among individuals with a family history of the disease.

Women at very high risk of breast cancer, such as those with pathogenic BRCA gene variants, may opt for prophylactic salpingo-oophorectomy (surgical removal of the fallopian tubes and ovaries) to reduce the risk of ovarian cancer. However, the benefit of this procedure for breast cancer prevention is less clear and may be primarily limited when done at 35-40 years. Importantly, it should be noted that not all women who choose prophylactic surgery would have developed cancer, and for some, regular surveillance may be equally effective in reducing breast cancer mortality. This highlights the necessity of personalized risk assessment and decision-making in managing cancer prevention strategies among high-risk individuals.[12] A primary fertility concern for women at high risk of breast cancer is the challenging decision of balancing the desire for pregnancy against the potential benefits of risk-reducing surgery. This decision-making process involves careful consideration of the risks associated with delaying prophylactic procedures to preserve fertility, alongside the potential impact on future reproductive outcomes.

Thus, timely counselling is essential. Oncologists should discuss fertility risks and preservation options with patients before initiating treatment. Multidisciplinary collaboration between oncologists, reproductive specialists, and mental health professionals ensures comprehensive care. Barriers such as lack of awareness, time constraints, and financial considerations need to be addressed to facilitate informed decisions.

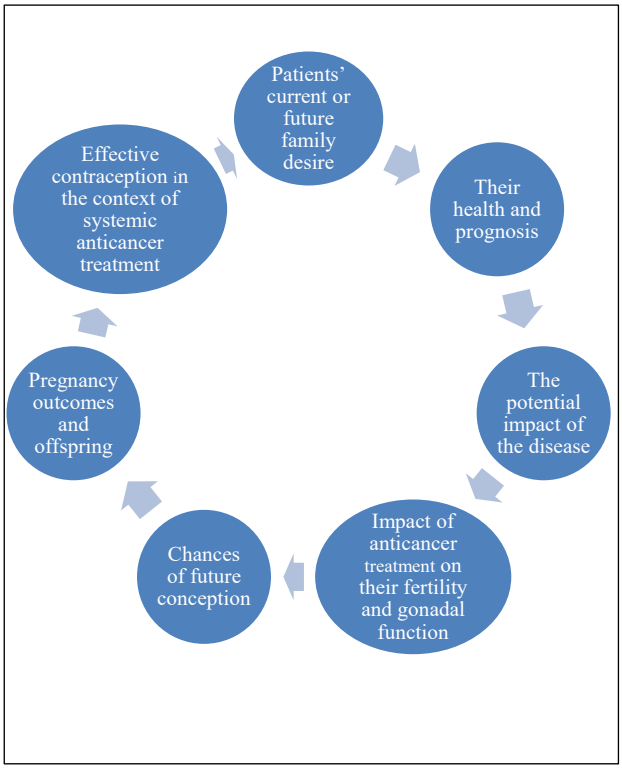

Figure 1: Oncofertility components.

IMPACT OF BREAST CANCER TREATMENT ON FERTILITY

Chemotherapy-induced gonadotoxicity

The effects of chemotherapy on fertility are influenced by multiple factors, including the patient's age, familial history of ovarian function, and existing ovarian follicle reserve. A history of previous ovarian or pelvic surgery, as well as prior chemotherapy, pelvic, or abdominal radiotherapy, can also impact ovarian function. Elevated levels of follicle-stimulating hormone (FSH) persistently indicate diminished ovarian reserve. Additionally, the specific class of chemotherapeutic agents, particularly the distinction between alkylating and non-alkylating agents, plays a crucial role in determining the extent of gonadotoxicity. Other contributing factors include the presence of concomitant diseases, the dosing regimen, and the duration of chemotherapy. Understanding these variables is essential for assessing the reproductive risks and developing strategies for fertility preservation in young cancer patients. The risk of irreversible and permanent amenorrhea in women treated for breast cancer varies depending on both age and chemotherapy regimen. Women aged 40 and older face a high risk when treated with CMF (cyclophosphamide, methotrexate, and fluorouracil), CEF (cyclophosphamide, epirubicin, and fluorouracil), or CAF (cyclophosphamide, adriamycin, and fluorouracil) for six cycles. Those aged 30-39 also encounter an intermediate risk with these regimens. Younger women, particularly those under 30, face a lower risk, even when receiving similar chemotherapy protocols. The risk of amenorrhea remains very low (less than 20%) for chemotherapeutic agents such as Vincristine, Methotrexate, and Fluorouracil. However, the impact of other agents, including Taxanes, Oxaliplatin, Irinotecan, monoclonal antibodies, and tyrosine kinase inhibitors, remains uncertain.[13]

The ovarian reserve, primarily composed of primordial follicles (PMFs), declines over a woman's reproductive life, with its maintenance dependent on a balance between follicular activation and inhibition factors like anti-Müllerian hormone (AMH). Cyclophosphamide, an alkylating agent used in breast cancer treatment, disrupts this balance by triggering premature PMF activation and leading to ovarian insufficiency. In a study on Cy-treated pubertal mice, AMH administration was shown to prevent PMF depletion and reduce PI3K pathway activation, suggesting its potential role in protecting fertility during chemotherapy.[14]

In a study on mice, co-treatment with rapamycin significantly reduced primordial follicle loss by inhibiting this pathway, maintaining serum AMH levels, and preventing premature follicle activation. These findings suggest that rapamycin could protect ovarian function and preserve fertility in female patients undergoing chemotherapy, offering a nonsurgical approach to preventing premature ovarian failure.[15]

Hormonal therapy and ovarian suppression

Young women with breast cancer are more likely to present with triple-negative (TN) or HER2-amplified subtypes; however, a substantial proportion of them still develop estrogen receptor-positive (ER+) breast cancer. For these patients, endocrine therapy has been shown to significantly improve both disease-free survival and overall survival, offering an effective treatment option in this specific subset of breast cancer.

A study aimed to assess the impact of tamoxifen therapy on fertility in breast cancer survivors and found that women who had used tamoxifen were significantly less likely to have a child after their breast cancer diagnosis compared to non-users, with a hazard ratio of 0.29. However, despite the reduced likelihood of childbirth, tamoxifen users did not show a decreased ovarian reserve. In fact, they had higher levels of antimüllerian hormone (AMH) and antral follicle count (AFC), suggesting that tamoxifen use may preserve ovarian function despite its association with lower fertility rates.[16]

In a study by A.H. Partridge it was found that temporarily interrupting endocrine therapy for pregnancy in young women with hormone receptor-positive early breast cancer did not significantly increase short-term breast cancer recurrence. Among 516 women, 74% achieved pregnancy, and 63.8% had live births, with 365 babies born. The breast cancer recurrence risk was comparable to an external control group, indicating that pausing therapy for pregnancy is safe in the short term.[17]

In hormone receptor-positive breast cancers, adjuvant endocrine therapy (like tamoxifen or aromatase inhibitors) is usually prescribed for 5–10 years, delaying pregnancy plans. Although not directly gonadotoxic, this significantly narrows the fertility window.[18]

Radiation

While radiotherapy is a cornerstone in the management of breast cancer, especially in breast-conserving therapy or postmastectomy chest wall irradiation, the radiation scatter to the pelvic organs- including the ovaries- is minimal and not clinically significant. Studies have shown that the dose of ionizing radiation reaching the ovaries during breast cancer radiotherapy is generally insufficient to compromise ovarian function or to induce ovarian malignancies in women of reproductive age. This makes fertility preservation and ovarian health in breast cancer patients primarily a concern of systemic treatments like chemotherapy, rather than radiotherapy.

The occurrence of ovarian cancer in women with a prior history of breast cancer is relatively rare and is more strongly linked to hereditary cancer syndromes, especially mutations in the BRCA1 and BRCA2 genes.[19]

Fertility preservation

The National Comprehensive Cancer Network (NCCN) Guidelines emphasize the importance of addressing fertility preservation early in the treatment planning process for all premenopausal women diagnosed with breast cancer, regardless of cancer subtype or stage.

This recommendation reflects a growing recognition that: (a) cancer treatments such as chemotherapy, targeted therapies, and endocrine therapy can cause temporary or permanent ovarian failure; and (b) breast cancer survivors are increasingly young women with curative potential, and preserving their quality of life- including fertility- is crucial.[20]

FERTILITY PRESERVATION OPTIONS

Embryo cryopreservation

Embryo cryopreservation is a well-established method for fertility preservation. It involves controlled ovarian stimulation to retrieve mature oocytes, which are then fertilized with sperm to create embryos that are subsequently frozen for future use. This technique is particularly suitable for women who have a male partner or are willing to use donor sperm.

Embryo cryopreservation has demonstrated high success rates, with live birth rates per transfer reaching approximately 35.6% in women under 35 years of age. The limitation associated with this technique is that the process requires a delay in cancer treatment to allow for ovarian stimulation, which may not be feasible for all patients. Additionally, it necessitates the availability of sperm at the time of oocyte retrieval.[21]

Oocyte (egg) cryopreservation

Oocyte cryopreservation, commonly known as egg freezing, is an alternative for women who do not have a current male partner or prefer not to use donor sperm. Similar to embryo cryopreservation, it involves ovarian stimulation and retrieval of mature oocytes, which are then vitrified (rapidly frozen) for future use. Advancements in vitrification techniques have significantly improved oocyte survival rates post-thaw, leading to increased pregnancy and live birth rates.

A large historical cohort study encompassing 290 newly diagnosed breast cancer patients undergoing 354 fertility preservation cycles (2000-2022) at two tertiary centers evaluated ovarian stimulation using FSH in conjunction with either Letrozole or Tamoxifen. The study revealed that Letrozole co-treatment was associated with the administration of higher total FSH doses and a shorter stimulation period, alongside significantly reduced peak estradiol levels and endometrial thickness compared to Tamoxifen. Importantly, despite these differences in stimulation parameters, both co-treatment groups exhibited comparable fertility outcomes, including the number of oocytes retrieved, the quantity of oocytes and embryos cryopreserved, and oocyte maturation and fertilization rates. Multivariate analysis corroborated the absence of a significant association between the type of co-treatment and fertility parameters. These findings indicate that the incorporation of either Letrozole or Tamoxifen into ovarian stimulation protocols for breast cancer patients yields equivalent and safe fertility preservation outcomes.[22]

Oocyte cryopreservation can be broadly categorized into two approaches: mature oocyte cryopreservation and in vitro maturation (IVM) of immature oocytes.

Mature oocyte cryopreservation is especially suited for women who can afford to delay chemotherapy by approximately 10 to 14 days to allow for ovarian stimulation and egg retrieval. This technique has demonstrated success rates comparable to embryo cryopreservation, particularly in young women under the age of 35, due to advancements in vitrification techniques. However, a key limitation is the requirement for high estrogen levels during controlled ovarian stimulation, which may be of concern in patients with estrogen receptor-positive (ER+) breast cancer. To mitigate this risk, aromatase inhibitors such as letrozole are commonly co-administered during stimulation protocols to reduce systemic estrogen exposure without compromising oocyte yield or maturation.[23]

Immature oocyte cryopreservation using in vitro maturation (IVM) is an evolving fertility preservation technique particularly suitable for breast cancer patients who require urgent initiation of treatment or have contraindications to ovarian stimulation. In this approach, oocytes are retrieved at an immature stage- typically at the germinal vesicle or metaphase I stage-without the need for prior ovarian stimulation or with only minimal stimulation. These immature oocytes are then matured in vitro under controlled laboratory conditions using specialized culture media containing FSH, hCG, and growth factors. Once matured to the metaphase II stage, the oocytes are either vitrified for future use or fertilized and the resulting embryos are frozen.[24]

One of the key advantages of IVM is that it can be initiated at any point in the menstrual cycle, eliminating the need for cycle synchronization and allowing fertility preservation to proceed without delaying cancer therapy. Additionally, since ovarian stimulation is not required, there is minimal estrogen exposure, making this technique particularly favorable for patients with estrogen receptor-positive (ER+) breast cancer. The reduced medication burden also translates to lower costs and fewer side effects compared to conventional IVF. However, IVM has some limitations. Maturation rates range from 60-70%, and fertilization and pregnancy rates are generally lower compared to conventional IVF using in vivo matured oocytes. As such, the technique is still considered

experimental in many guidelines, although it is gaining wider acceptance in the field of oncofertility.[25] Clinical studies, such as one by Shalom-Paz et al. (2010) published in *Fertility & Sterility*, have demonstrated that IVM is both feasible and safe in breast cancer patients needing urgent fertility preservation.[26] Moreover, new research indicates that pregnancy and live birth outcomes with IVM are steadily improving due to advances in culture media and laboratory protocols.[24]

OVARIAN TISSUE CRYOPRESERVATION

Ovarian tissue cryopreservation has emerged as a globally adopted fertility preservation strategy, particularly beneficial for young girls and women with cancer who cannot afford delays in treatment, as well as those with benign conditions at risk of premature ovarian insufficiency. To date, over 130 live births have been reported following transplantation of cryopreserved ovarian tissue, with most patients regaining ovarian function post-reimplantation. The most commonly used technique is slow freezing followed by rapid thawing, often adapted from protocols developed for sheep ovarian tissue. However, because freezing can adversely affect the ovarian stroma and granulosa cells, some centers have explored vitrification as an alternative. While vitrification shows promise, only two live births have been reported using this method, highlighting the need for further optimization of both cryopreservation and warming protocols to enhance follicular survival. Additionally, this technique holds future potential not only for fertility preservation but also as a means to delay menopause or childbearing in healthy women.[27]

Gonadotropin-releasing hormone (GNRH) agonists

With improved cancer survival rates due to advances in screening, diagnostics, and treatment, young women facing radiation therapy are at risk of long-term reproductive damage. This includes ovarian insufficiency, pubertal arrest, and potential infertility, particularly with cranial irradiation affecting the hypothalamic-pituitary-gonadal axis. Uterine damage, such as reduced vascularization, fibrosis, and endometrial atrophy, is also a concern. Given these risks, fertility preservation should be considered before or during treatment.[28]

Gonadotropin-releasing hormone (GnRH) analogues-including both agonists and antagonists-are increasingly being explored as potential agents to preserve ovarian function during chemotherapy and radiotherapy due to their ovarian suppressive effects. By mimicking a prepubertal hormonal state, these agents may reduce the gonadotoxicity of cancer treatments by inhibiting the rapid turnover of growing follicles, which are particularly vulnerable to cytotoxic damage. GnRH agonists have demonstrated efficacy in preserving ovarian function, especially in breast and hematological cancers, though data for gynecologic malignancies like ovarian, endometrial, and cervical cancers remain limited. Antagonists, which act more rapidly and avoid the flare effect seen with agonists, may be beneficial in urgent treatment scenarios, although evidence is still emerging, with most studies conducted in animal models. Combined agonist-antagonist protocols are also largely experimental.

Fertility loss remains a major concern in reproductive-age women undergoing cancer therapy, with premature ovarian failure affecting 15-50% of premenopausal patients depending on age, treatment type, and cancer diagnosis. While various fertility preservation options exist-including oocyte/embryo cryopreservation, in vitro maturation, ovarian tissue cryopreservation, and ovarian transposition-GnRH analogues can serve as adjuncts, especially when time or medical conditions limit other interventions.[29]

Current guidelines reflect this nuance. The European Society of Human Reproduction and Embryology (ESHRE) prefers GnRH antagonist protocols for ovarian stimulation due to shorter stimulation duration and reduced risk of OHSS. The American Society for Reproductive Medicine (ASRM) supports the off-label use of GnRH agonists for ovarian protection in breast cancer patients but emphasizes they should not replace established fertility preservation methods.[30] The National Comprehensive Cancer Network (NCCN) also does not recognize GnRH agonists as standalone fertility preservation. More high-quality research, particularly focusing on ovarian reserve outcomes like AMH levels and live birth rates, is needed to clearly define the protective role of GnRH analogues during gonadotoxic cancer therapies.[29]

Pregnancy-associated breast cancer

Although relatively rare-affecting approximately 1 in 3,000 to 1 in 10,000 pregnancies-PABC is the most frequently diagnosed malignancy in pregnant women, with an estimated incidence ranging from 2.4 to 7.3 per 100,000 pregnancies. However, its occurrence is expected to rise due to increasing breast cancer rates in young women and the growing trend in Western countries of delayed childbearing; for instance, a recent Italian study reported a mean maternal age of 33 years, with around 40% of pregnancies occurring after age 35. The diagnosis of PABC presents unique clinical, ethical, and psychosocial challenges for patients, families, and healthcare providers. Over the past decade, significant progress has been made, particularly in establishing the safety of administering chemotherapy during pregnancy, leading to the development of tailored clinical guidelines. Nonetheless, given its rarity, many aspects of PABC management still rely on limited data, highlighting the need for continued research to strengthen evidence-based care in this complex setting.[31]

The Italian Gruppo Italiano Mammella (GIM) initiated the prospective, national Prefer study to specifically investigate the fertility and pregnancy-related challenges

faced by young breast cancer patients. This comprehensive initiative encompasses two distinct sub-studies: Prefer-Fertility ad Prefer-Pregnancy. Prefer-Fertility focuses on premenopausal women (aged 18-45) with non-metastatic breast cancer undergoing (neo)adjuvant chemotherapy, prospectively collecting data on their preferences, utilization, and outcomes of fertility preservation, as well as hormonal fluctuations during and after therapy. The prefer-pregnancy arm follows survivors who become pregnant post-treatment and individuals diagnosed with Pregnancy-associated breast cancer (PABC), with an emphasis on clinical management and maternal, fetal, obstetric, and pediatric outcomes. with a five-year enrollment period and a 15-year follow-up, the prefer program, launched in 2012 and 2013, aims to improve oncofertility counseling, support personalized treatment decisions, and establish long-term evidence regarding the safety and efficacy of fertility and pregnancy management in this specific patient group.[32]

CONCLUSION

Breast cancer in women of reproductive age presents unique challenges due to the intersection of oncologic and reproductive health concerns. With a rising incidence of aggressive tumors in younger women and advancements in cancer treatment leading to improved survival, fertility preservation has become an essential component of comprehensive cancer care. Oncofertility, a multidisciplinary field bridging oncology and reproductive medicine, plays a pivotal role in ensuring that young breast cancer patients are informed about and have access to fertility preservation options such as embryo cryopreservation and GnRH analogues. Timely counseling and individualized fertility preservation strategies, guided by established protocols and guidelines, are critical to safeguarding future reproductive potential and enhancing quality of life among survivors.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Hampe ME, Rhoton-Vlasak AS. Fertility preservation in breast cancer with case-based examples for guidance. J Assist Reprod Genet. 2020;37(3):717-29.
2. Parmar V. Rising Incidence of Breast Cancer in the Young Fertile Indian Population-a Reality Check. Indian J Surg Oncol. 2018;9(3):296-9.
3. Majeed W, Aslam B, Javed I, Khaliq T, Muhammad F, Ali A, Raza A. Breast cancer: major risk factors and recent developments in treatment. Asian Pac J Cancer Prev. 2014;15(8):3353-8.
4. Koo MM, Wagner C, Abel GA, McPhail S, Rubin GP, Lyratzopoulos G. Typical and atypical presenting symptoms of breast cancer and their associations with diagnostic intervals: Evidence from a national audit of cancer diagnosis. Cancer Epidemiol. 2017;48:140-6.
5. Mehejabin F, Rahman MS. Knowledge and perception of breast cancer among women of reproductive age in Chattogram, Bangladesh: A cross-sectional survey. Health Sci Rep. 2022;5(5):e840.
6. Lee HB, Han W. Unique features of young age breast cancer and its management. J Breast Cancer. 2014;17(4):301-7.
7. Jassem J, Ozmen V, Bacanu F, Drobniene M, Eglitis J, Lakshmaiah KC, Kahan Z, et al. Delays in diagnosis and treatment of breast cancer: a multinational analysis. Eur J Public Health. 2014;24(5):761-7.
8. Letourneau JM, Ebbel EE, Katz PP, Katz A, Ai WZ, Chien AJ, et al. Pretreatment fertility counseling and fertility preservation improve quality of life in reproductive age women with cancer. Cancer. 2012;118(6):1710-7.
9. Anazodo A, Ataman-Millhouse L, Jayasinghe Y, Woodruff TK. Oncofertility-An emerging discipline rather than a special consideration. Pediatr Blood Cancer. 2018;65(11):e27297.
10. Hill KA, Nadler T, Mandel R, Burlein-Hall S, Librach C, Glass K, et al. Experience of young women diagnosed with breast cancer who undergo fertility preservation consultation. Clin Breast Cancer. 2012;12(2):127-32.
11. Tung N, Lin NU, Kidd J, Allen BA, Singh N, Wenstrup RJ, et al. Frequency of Germline Mutations in 25 Cancer Susceptibility Genes in a Sequential Series of Patients With Breast Cancer. J Clin Oncol. 2016;34(13):1460-8.
12. Kotsopoulos J, Lubinski J, Gronwald J, Menkiszak J, McCuaig J, Metcalfe K, et al. Bilateral Oophorectomy and the Risk of Breast Cancer in BRCA1 Mutation Carriers: A Reappraisal. Cancer Epidemiol Biomarkers Prev. 2022;31(7):1351-8.
13. Zhao J, Liu J, Chen K, Li S, Wang Y, Yang Y, et al. What lies behind chemotherapy-induced amenorrhea for breast cancer patients: a meta-analysis. Breast Cancer Res Treat. 2014;145(1):113-28.
14. Sonigo C, Beau I, Grynberg M, Binart N. AMH prevents primordial ovarian follicle loss and fertility alteration in cyclophosphamide-treated mice. FASEB J. 2019;33(1):1278-87.
15. Zhou L, Xie Y, Li S, Liang Y, Qiu Q, Lin H, et al. Rapamycin Prevents cyclophosphamide-induced Over-activation of Primordial Follicle pool through PI3K/Akt/mTOR Signaling Pathway in vivo. J Ovarian Res. 2017;10(1):56.
16. Shandley LM, Spencer JB, Fothergill A, Mertens AC, Manatunga A, Paplomata E, et al. Impact of tamoxifen therapy on fertility in breast cancer survivors. Fertil Steril. 2017;107(1):243-52.
17. Partridge AH, Niman SM, Ruggeri M, Peccatori FA, Azim HA, Colleoni M, et al. Interrupting Endocrine Therapy to Attempt Pregnancy after Breast Cancer. N Engl J Med. 2023;388(18):1645-56.
18. Azim HA, Michiels S, Bedard PL, Singhal SK, Criscitiello C, Ignatiadis M, et al. Elucidating Prognosis and Biology of Breast Cancer Arising in

Young Women Using Gene Expression Profiling. Clin Cancer Res. 2012;18(5):1341-51.
19. Marcu LG, Santos A, Bezak E. Risk of second primary cancer after breast cancer treatment. Eur J Cancer Care (Engl). 2014;23(1):51-64.
20. Carlson RW, Jonasch E. NCCN Evidence Blocks. J Natl Compr Cancer Netw. 2016;14(5S):616-9.
21. Kim SS, Klemp J, Fabian C. Breast cancer and fertility preservation. Fertil Steril. 2011;95(5):1535-43.
22. Lifshitz D, Ben-Haroush A, Meirow D, Orvieto R, Meirman DV, Elbaz L, et al. Letrozole or Tamoxifen co-administration during fertility preservation for patients affected by breast cancer. Reprod Biomed Online. 2025;104878.
23. Oktay K, Buyuk E, Libertella N, Akar M, Rosenwaks Z. Fertility Preservation in Breast Cancer Patients: A Prospective Controlled Comparison of Ovarian Stimulation With Tamoxifen and Letrozole for Embryo Cryopreservation. J Clin Oncol. 2005;23(19):4347-53.
24. De Roo C, Tilleman K. In Vitro Maturation of Oocytes Retrieved from Ovarian Tissue: Outcomes from Current Approaches and Future Perspectives. J Clin Med. 2021;10(20):4680.
25. Gotschel F, Sonigo C, Becquart C, Sellami I, Mayeur A, Grynberg M. New Insights on In Vitro Maturation of Oocytes for Fertility Preservation. Int J Mol Sci. 2024;25(19):10605.
26. Gotschel F, Sonigo C, Becquart C, Sellami I, Mayeur A, Grynberg M. New Insights on In Vitro Maturation of Oocytes for Fertility Preservation. Int J Mol Sci. 2024;25(19):10605.
27. Rivas Leonel EC, Lucci CM, Amorim CA. Cryopreservation of Human Ovarian Tissue: A Review. Transfus Med Hemotherapy. 2019;46(3):173-81.
28. Marci R, Mallozzi M, Di Benedetto L, Schimberni M, Mossa S, Soave I, et al. Radiations and female fertility. Reprod Biol Endocrinol. 2018;16(1):112.
29. Valsamakis G, Valtetsiotis K, Charmandari E, Lambrinoudaki I, Vlahos NF. GnRH Analogues as a Co-Treatment to Therapy in Women of Reproductive Age with Cancer and Fertility Preservation. Int J Mol Sci. 2022;23(4):2287.
30. Practice Committee of the American Society for Reproductive Medicine. Fertility preservation in patients undergoing gonadotoxic therapy or gonadectomy: a committee opinion. Fertil Steril. 2019;112(6):1022-33.
31. Loibl S, Schmidt A, Gentilini O, Kaufman B, Kuhl C, Denkert C, et al. Breast Cancer Diagnosed During Pregnancy: Adapting Recent Advances in Breast Cancer Care for Pregnant Patients. JAMA Oncol. 2015;1(8):1145-53.
32. Lambertini M, Anserini P, Fontana V, Poggio F, Iacono G, Abate A, Levaggi A, et al. The PREgnancy and FERtility (PREFER) study: an Italian multicenter prospective cohort study on fertility preservation and pregnancy issues in young breast cancer patients. BMC Cancer. 2017;17(1):346.

Cite this article as: Chadha S. Breast cancer in reproductive-age women: oncofertility perspectives, treatment impact, and fertility preservation strategies. Int J Reprod Contracept Obstet Gynecol 2025;14:2416-23.