

REVIEW

FERTILITY PRESERVATION IN YOUNG WOMEN WITH BREAST CANCER: UPTAKE, DETERMINANTS OF ACCESS, AND LONG-TERM REPRODUCTIVE OUTCOMES: A REVIEW

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ABSTRACT: This narrative review addresses how evidence on treatment-related fertility risk, fertility-preservation strategies, inequities in access, and post-treatment reproductive outcomes can be integrated into individualized and equitable care for young women with breast cancer. Its objective is not to restate existing guideline recommendations, but to identify where their implementation fails in routine practice and to synthesize clinically actionable strategies across the care continuum, from diagnosis to survivorship. Fertility preservation (FP) has emerged as a critical component of comprehensive care for young women diagnosed with breast cancer. Advances in reproductive technologies, including oocyte and embryo cryopreservation, alongside growing evidence on ovarian protection strategies and prospective trials such as the POSITIVE (Pregnancy Outcome and Safety of Interrupting Therapy for Women with Endocrine-Responsive Breast Cancer) study, have expanded both counseling and reproductive options for survivors. Observational data and meta-analyses consistently demonstrate that pregnancy after breast cancer is generally safe, including in hormone receptor-positive disease and among BRCA mutation carriers, without increasing recurrence risk when appropriately timed. Nevertheless, substantial disparities persist in FP access, influenced by socioeconomic status, race/ethnicity, insurance coverage, and geographic location. System-level interventions – such as automatic referrals to oncofertility specialists, dedicated FP navigation programs, and mandated or publicly funded coverage – have improved uptake and patient satisfaction. Psychosocial interventions and structured decision aids further reduce decisional conflict and regret, supporting informed reproductive choices. Emerging challenges include understanding the impact of newer oncologic therapies, such as PARP (Poly (ADP-ribose) polymerase) inhibitors, immune checkpoint inhibitors, and antibody-drug conjugates, on fertility potential. By bringing together evidence that is usually dispersed across oncology, reproductive medicine, health-services research, and survivorship studies, this review highlights practical actions for clinicians: early risk-based counselling, prompt referral, multidisciplinary coordination, navigation support, and attention to financial and geographic barriers. Long-term survivorship registries capturing ovarian reserve, FP utilization, pregnancy outcomes, child health, and psychosocial metrics are essential for evaluating real-world effectiveness and equity. Integrating FP into routine breast cancer care requires a dual strategy: implementation of evidence-based clinical pathways and system-level support, combined with research to refine guidance as therapies evolve. This approach has the potential to safeguard reproductive potential, reduce psychosocial burden, and enhance quality of life for young breast cancer survivors.

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Impact statement: This review highlights clinically actionable strategies for timely fertility counselling and preservation in young women with breast cancer, addressing treatment-related risks, access disparities, and reproductive outcomes to improve survivorship care.

Key words: *Fertility preservation; breast cancer; oncofertility; reproductive outcomes; health disparities.*

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INTRODUCTION

Breast cancer diagnosed during the reproductive years represents both a clinical and psychosocial challenge. While age cutoffs vary, many studies and guidelines define “young” as ≤ 40 years (some use ≤ 45) because fertility considerations, hormonal milieu, and life plans differ substantially from older patients. In many high-income settings, breast cancer before age 40 accounts for a small but clinically important minority of all cases, generally estimated at approximately 5% (1, 2). In contrast, data from certain low- and middle-income countries report substantially higher proportions – for instance, up to 10-20% of breast cancers in women under 40 (2). This higher proportional burden partly reflects the younger underlying population age structure in many low- and middle-income countries, in addition to differences in incidence patterns, reproductive risk factors, and access to early detection; proportional comparisons should therefore not be interpreted as direct evidence of a uniformly higher age-specific risk. Survivorship improvements make reproductive questions central to care planning; fertility preservation (FP) counseling at diagnosis is now standard-of-care in most oncology guidelines (3, 4). Young patients often face a compressed timeline:

diagnosis → need for rapid treatment initiation → complex fertility decisions that require specialist input.

The cancer treatment itself (chemotherapy, ovarian suppression, certain targeted agents) can reduce ovarian reserve and increase the risk of premature ovarian insufficiency (POI). Beyond biological risk, disparities in awareness, referral, and access lead to unequal uptake of preserving options across socioeconomic strata – an issue of reproductive justice (4, 5). Although international guidelines consistently recommend timely discussion of infertility risk and referral for FP, they necessarily provide broad recommendations and do not fully resolve how treatment-related risk, patient preferences, access barriers, and subsequent reproductive plans should be integrated in routine breast cancer care. The evidence is dispersed across oncology, reproductive medicine, health-services research, and survivorship studies, often using different populations, outcomes, and definitions. Consequently, clinicians may know that FP should be discussed, yet still lack an integrated framework for identifying where implementation fails, which patients are most likely to encounter barriers, and how counsel-

ling should extend beyond gamete cryopreservation to pregnancy planning and long-term reproductive health. This review therefore addresses the following question: how can current evidence on gonadotoxic risk, fertility-preservation strategies, inequities in access, and reproductive outcomes after breast cancer be integrated to support equitable, individualized clinical decision-making in young women? Our objective is to provide a clinically oriented synthesis of the care continuum – from diagnosis and treatment planning to survivorship – and to identify actionable system-level interventions and priority evidence gaps.

METHODS

This article was designed as a narrative review supported by a structured literature search. The aim was to address a broad, clinically integrative question spanning treatment-related gonadotoxicity, fertility-preservation interventions, health-care access, social determinants, pregnancy after breast cancer, and long-term survivorship outcomes. Because these domains include heterogeneous study designs, populations, exposures, outcome definitions, and health-system contexts, a systematic review focused on a single, prespecified outcome was not considered suitable. Rather than estimate a pooled effect, we aimed to interpret how evidence across these domains can inform individualized counselling and equitable clinical pathways.

We searched PubMed/MEDLINE and Embase for English-language articles published up to March 2026 using combinations of the terms “breast neoplasms”, “fertility preservation”, “oncofertility”, “premature ovarian insufficiency”, “pregnancy after breast cancer”, and “socioeconomic factors”. We used the search to identify influential and contemporary evidence, prioritising clinical practice guidelines, prospective cohorts, registry-based studies, clinical trials, systematic reviews, and studies reporting fertility-related outcomes in women diagnosed at ≤ 40 -45 years. Reference lists of key studies and guidelines were also reviewed. This was not a systematic review: we did not conduct duplicate screening, a formal risk-of-bias assessment, PRISMA-based study selection, or quantitative pooling. The resulting evidence was organised into a structured qualitative synthesis around four clinically connected domains: treatment-related fertility risk, available preservation strategies, determinants of access and uptake, and reproductive outcomes during survivorship.

FERTILITY RISK ASSOCIATED WITH BREAST CANCER THERAPY

Advances in systemic therapy have markedly improved survival outcomes for young women with breast cancer, yet many of these same treatments pose a threat to reproductive function. The degree of gonadal toxicity varies widely by drug class, cumulative dose, patient age, and baseline ovarian reserve, but the potential for POI or long-term infertility remains a central survivorship concern.

Chemotherapy and ovarian failure

Contemporary anthracycline-cyclophosphamide regimens, with or without taxanes, are integral to early breast cancer therapy but confer a measurable risk of chemotherapy-induced ovarian dysfunction and POI. Although individual studies vary in methodology and outcome definitions, the collective evidence from prospective trials and meta-analyses confirms that the majority of premenopausal women experience transient ovarian failure during treatment, and that a substantial subset develop persistent dysfunction thereafter. In a large pooled prospective analysis of 696 women aged ≤ 45 years treated with anthracycline/taxane-based chemotherapy, Furlanetto *et al.* reported that 85.1% met criteria for chemotherapy-induced ovarian failure at the end of treatment. Among those with longitudinal follow-up, most subsequently regained premenopausal hormone levels, but a clinically relevant minority had persistent ovarian dysfunction at 24 months (6). These findings underscore the distinction between transient treatment-related amenorrhea and long-term POI. Complementary evidence from biochemical studies underscores the extent of gonadal damage: a systematic review and meta-analysis by Romito *et al.* documented consistent and clinically meaningful declines in anti-Müllerian hormone (AMH) following standard breast cancer chemotherapy in women under 40, reflecting substantial depletion of ovarian reserve (7). In clinical practice, AMH is a widely used biomarker of ovarian reserve and a robust predictor of ovarian response to stimulation for oocyte or embryo cryopreservation, but AMH alone is a limited predictor of natural fertility and time to spontaneous conception. At the population level, a comprehensive meta-analysis including 68 studies and more than 26,000 patients estimated that approximately 64% of women experienced chemotherapy-induced amenorrhea at the reported follow-up time points, with substantial heterogeneity in defini-

tions and timing across studies (8). This figure therefore reflects a high overall burden of treatment-related amenorrhea rather than a precise estimate of permanent POI.

These findings collectively indicate that while most younger women eventually recover ovarian function, anthracycline- and taxane-based regimens carry a clinically relevant long-term risk of ovarian insufficiency, particularly in those approaching the late reproductive years. Consistent data from AMH-based longitudinal analyses further reinforce that the risk of sustained ovarian dysfunction rises sharply with age and cumulative cyclophosphamide exposure. Although women under 35 years often retain some degree of ovarian reserve, they nevertheless experience pronounced AMH declines, signifying subclinical gonadotoxicity and reduced reproductive potential. These observations highlight the importance of integrating structured FP counseling into treatment planning for all premenopausal patients, irrespective of apparent low-risk age or regimen intensity.

Endocrine therapy

In hormone receptor-positive (HR+) breast cancer, adjuvant endocrine therapy remains fundamental, typically extending over 5-10 years. Standard approaches include tamoxifen alone or aromatase inhibitors combined with ovarian function suppression (OFS), depending on menopausal status and recurrence risk. Although these drugs are not directly cytotoxic to ovarian follicles, their prolonged use substantially delays childbearing, creating a unique challenge for young women with reproductive aspirations. The central dilemma is balancing oncologic safety against fertility goals. Long-term endocrine therapy effectively reduces recurrence risk but overlaps with a woman's most fertile years, often compelling difficult decisions regarding pregnancy timing and the risks associated with therapy interruption or deferral (9). The landmark POSITIVE trial (Pregnancy Outcome and Safety of Interrupting Therapy for Women with Endocrine-Responsive Breast Cancer) directly addressed this issue. The study enrolled premenopausal women with HR+ early breast cancer who had completed 18-30 months of adjuvant endocrine therapy and desired pregnancy. Participants temporarily paused treatment for up to two years to attempt conception. The results demonstrated no excess short-term recurrence risk compared with historical controls and favorable pregnancy outcomes among participants who interrupted therapy under close monitoring (10).

Table 1. Fertility-related impact of systemic therapies used in young women with breast cancer.

THERAPY CLASS	MECHANISM AND CLINICAL CONTEXT	EVIDENCE OF FERTILITY IMPACT	MAIN MODIFIERS OF RISK OR CLINICAL CONSIDERATIONS	KEY REFERENCES
Chemotherapy: anthracycline-cyclophosphamide regimens with or without taxanes	Cytotoxic therapy damages growing and resting ovarian follicles and remains a major component of treatment for early breast cancer.	High risk of transient amenorrhea and clinically relevant risk of persistent ovarian dysfunction or premature ovarian insufficiency. In prospective studies, ovarian failure was common at the end of treatment, while a smaller proportion had persistent dysfunction during follow-up. Chemotherapy is also associated with substantial declines in anti-Müllerian hormone, reflecting reduced ovarian reserve.	Older age, especially >40 years; cumulative cyclophosphamide dose; baseline ovarian reserve; and concomitant ovarian suppression. Resumption of menstruation does not necessarily indicate full recovery of fertility potential.	[6-8]
Endocrine therapy: tamoxifen with or without ovarian function suppression; aromatase inhibitors plus ovarian function suppression	Endocrine therapy is not directly cytotoxic to ovarian follicles but may delay pregnancy because treatment is usually prescribed for 5-10 years.	The principal fertility-related effect is postponement of childbearing during the years of highest natural fertility. In selected women with hormone receptor-positive early breast cancer, temporary interruption of endocrine therapy after 18-30 months to attempt pregnancy did not increase short-term recurrence risk.	Duration of planned endocrine therapy; residual recurrence risk; age and ovarian reserve; reproductive plans; and the feasibility of a monitored treatment interruption.	[9-11]
HER2-directed monoclonal antibodies: trastuzumab and pertuzumab	Targeted anti-HER2 therapies are commonly administered with chemotherapy in HER2-positive breast cancer.	HER2-directed monoclonal antibodies alone are not considered directly gonadotoxic, and there is no established evidence that they independently cause premature ovarian insufficiency.	Fertility risk is primarily determined by accompanying chemotherapy, patient age, and baseline ovarian reserve. Pregnancy should be avoided during treatment because of fetal risk.	[13]
Antibody-drug conjugates: trastuzumab emtansine and trastuzumab deruxtecan	HER2-targeted antibodies conjugated to cytotoxic payloads.	Human data on ovarian toxicity are limited. The cytotoxic payload creates a plausible risk of off-target ovarian injury; therefore, fertility risk should be considered uncertain rather than absent.	Cumulative exposure; concurrent or previous chemotherapy; patient age; and treatment setting. Fertility preservation counselling should be offered before treatment whenever feasible.	[13,14]
PARP inhibitors: olaparib and talazoparib	DNA-repair inhibitors used mainly in germline BRCA-mutated breast cancer.	Preclinical studies indicate embryotoxicity and teratogenicity. Their effect on human ovarian reserve and long-term fertility remains uncertain.	Duration of treatment; previous exposure to chemotherapy; BRCA status; and planned pregnancy. Effective contraception is required during treatment and for the recommended period after treatment discontinuation.	[14,15]
Immune checkpoint inhibitors: pembrolizumab and atezolizumab	Anti-PD-1/PD-L1 therapies increasingly used in triple-negative and high-risk early breast cancer.	Definitive clinical data on ovarian reserve, fertility, pregnancy, and offspring outcomes are lacking. Potential effects include immune-mediated ovarian inflammation and disruption of reproductive immune tolerance, but current evidence remains limited.	Pre-existing autoimmune disease; duration of exposure; concomitant chemotherapy; endocrine immune-related adverse events; and the need for long-term reproductive monitoring.	[16]

AMH: anti-Müllerian hormone; HER2: human epidermal growth factor receptor 2; PARP: poly(ADP-ribose) polymerase; PD-1: programmed cell death protein 1; PD-L1: programmed death-ligand 1.

These findings have reshaped clinical counseling, providing evidence-based reassurance that temporary interruption of endocrine therapy can be feasible and oncologically safe in carefully selected patients. Recent expert consensus and guideline updates emphasize a multidisciplinary approach – encompassing oncology, reproductive endocrinology, and psycho-oncology – to ensure that fertility goals are addressed without compromising disease control (11, 9). This collaborative framework enhances reproductive autonomy while maintaining adherence to oncologic principles, marking a major step toward patient-centered survivorship care in HR+ disease.

Targeted and novel agents

The rapid evolution of targeted and immune-based therapies in breast cancer has introduced new uncertainties about their reproductive safety. HER2-directed monoclonal antibodies such as trastuzumab and pertuzumab, integral to HER2-positive regimens, are not classically gonadotoxic and have not been associated with POI (12). However, newer antibody-drug conjugates (ADCs), including trastuzumab emtansine (T-DM1) and trastuzumab deruxtecan, deliver cytotoxic payloads that may induce off-target ovarian injury, though clinical data remain limited (13, 14). Similarly, poly (ADP-ribose) polymerase (PARP) inhibitors such as olaparib and talazoparib – now standard for germline *BRCA*-mutated early and metastatic disease – show embryotoxic and teratogenic effects in preclinical models. Their effect on ovarian reserve in humans remains uncertain, but animal studies suggest potential sublethal follicular injury, warranting strict contraception during and after therapy (13, 14). Immune checkpoint inhibitors, including pembrolizumab and atezolizumab, increasingly used in triple-negative and high-risk early breast cancer, may influence fertility indirectly through immune-mediated ovarian inflammation or interference with placental immune tolerance. Current evidence is limited to preclinical findings and isolated clinical reports, but systematic reproductive monitoring in ongoing trials is warranted (14, 15). Despite the widespread adoption of these agents, fertility-related outcomes remain poorly captured in pivotal clinical studies. Consequently, major societies such as ASCO (4), ESMO (16), and ESHRE (17) underscore the need to discuss FP with all women of reproductive age before initiating treatments with uncertain gonadotoxic profiles. Until robust human data are

available, a precautionary approach should prevail, ensuring that oocyte or embryo cryopreservation is offered whenever feasible, especially for those receiving experimental or high-risk regimens. This gap between oncologic innovation and reproductive survivorship highlights the urgency of incorporating fertility and pregnancy outcomes as pre-defined endpoints in future clinical trials. Doing so will align precision oncology with reproductive health equity for young women with breast cancer (18, 19).

Table 1 summarizes the variable impact of breast cancer therapies on fertility, highlighting chemotherapy as the main cause of ovarian damage, the timing challenges posed by endocrine therapy, and the uncertain gonadotoxicity of newer targeted and immune agents. Early, individualized fertility counseling remains essential.

FP IN YOUNG BREAST CANCER PATIENTS: CURRENT TECHNIQUES, IMPLEMENTATION, AND UPTAKE

FP has become a fundamental component of comprehensive cancer care for reproductive-age women, reflecting both the increasing survival of young patients and the recognition of reproductive health as a key determinant of long-term quality of life. Current international guidelines from ASCO, ESMO, and ESHRE unanimously recommend that all women of reproductive age who are candidates for gonadotoxic therapy receive prompt counselling on fertility risks and timely referral to FP services (16, 17, 20).

Established FP techniques

Among established strategies, embryo cryopreservation remains the gold standard for women with a partner or those willing to use donor sperm. The process involves controlled ovarian stimulation (COS), oocyte retrieval, *in vitro* fertilization, and vitrification of embryos, achieving the highest cumulative live-birth rates (CLBRs) when performed at younger ages and with more embryos preserved (21, 22). The introduction of random-start COS protocols has revolutionized practice, allowing ovarian stimulation at any point in the menstrual cycle and enabling FP even in patients requiring urgent chemotherapy initiation (23). For women without a partner or those preferring to avoid embryo creation, oocyte cryopreservation represents an equally

effective and ethically acceptable alternative. Population-based data confirm that live-birth rates following oocyte vitrification now approximate those of embryo cryopreservation, especially when FP is undertaken before age 35 (24, 25). The technical reliability and efficiency of modern vitrification have consolidated oocyte cryopreservation as a cornerstone of oncofertility practice. Ovarian tissue cryopreservation (OTC) occupies a unique role for patients unable to undergo ovarian stimulation or for prepubertal girls. The procedure entails laparoscopic retrieval and storage of ovarian cortical tissue, followed by reimplantation after cancer therapy. More than 200 live births have been reported worldwide, demonstrating the capacity of OTC to restore both endocrine function and fertility (26). Nonetheless, the potential for malignant cell reintroduction – particularly in hematologic malignancies – remains a concern, mandating strict patient selection and rigorous tissue screening. Gonadotropin-releasing hormone agonists (GnRHa) during chemotherapy offer a non-invasive adjunctive measure to reduce ovarian toxicity. An individual patient-level meta-analysis confirmed that GnRHa co-treatment significantly decreases the risk of chemotherapy-induced POI and increases post-treatment pregnancies (27, 28). Although GnRHa do not preserve gametes, they serve as a valuable option when cryopreservation is not feasible. Additional surgical approaches, such as ovarian transposition prior to pelvic irradiation, can safeguard ovarian function by repositioning the ovaries outside the radiation field (29). Emerging experimental techniques, including *in vitro* follicle maturation and artificial ovary bioengineering, are under investigation and hold promise for expanding FP options in high-risk or time-constrained scenarios.

Ethical and legal considerations

Ethical and legal frameworks governing FP vary substantially across countries, necessitating explicit informed consent for embryo creation, storage, and potential disposition (30). In Italy, for example, regulatory changes since the enactment of Law 40/2004 have progressively expanded the permissibility of assisted reproduction techniques, reflecting evolving societal and clinical perspectives (31).

Counselling and uptake in clinical practice

Despite clear guideline recommendations, real-world uptake of fertility counselling and preservation remains limited. Across large observational

and registry-based cohorts, reported fertility counselling rates among eligible young breast cancer patients have ranged from approximately 40% to 70%, depending on country, insurance coverage, institutional resources, and the presence of dedicated oncofertility pathways. In these same settings, uptake of fertility-preservation strategies has generally remained substantially lower, often around 10-30% of eligible patients. These figures illustrate a persistent unmet need but should not be interpreted as universal benchmarks, given the marked heterogeneity across healthcare systems and study populations (32-34). Barriers include inadequate referral systems, lack of interdisciplinary coordination, time constraints, and unequal regional availability of FP services. Within this context, the women who proceed with active FP – most commonly oocyte or embryo cryopreservation – tend to be younger, nulliparous, and of higher socioeconomic status or with private insurance coverage, while financial and logistical barriers continue to deter participation, particularly in settings without public reimbursement (16, 35). Encouragingly, recent years have witnessed gradual improvements in both counselling and FP uptake, reflecting wider awareness, dissemination of international guidelines, and technological advances such as vitrification and random-start COS. Nonetheless, persistent inequities related to socioeconomic status, geography, and ethnicity remain. Overcoming these disparities will require system-level strategies including standardized referral protocols, integration of fertility specialists within oncology teams, and policy frameworks ensuring equitable access. In conclusion, FP is now recognized as an essential element of multidisciplinary care for young breast cancer patients. Embryo and oocyte cryopreservation remain the most effective and widely accessible techniques, while OTC and GnRHa co-treatment extend the spectrum of options. Although significant progress has been achieved, consistent implementation and equitable access remain challenges. Embedding fertility counselling and preservation into standard oncologic pathways is crucial to ensure that all women facing breast cancer can make informed, autonomous reproductive decisions.

Figure 1 illustrates current FP techniques, ethical frameworks, and real-world uptake among young breast cancer patients, emphasizing the gap between guideline recommendations and clinical implementation.

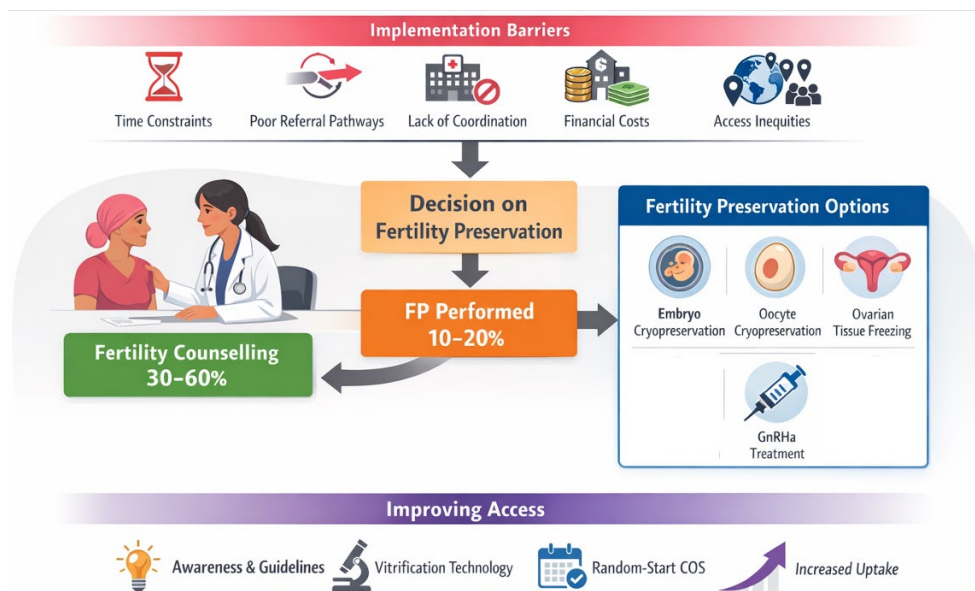


Figure 1. Fertility preservation in young breast cancer patients: counselling, uptake, and implementation barriers.

This schematic illustrates the clinical pathway from diagnosis of breast cancer in reproductive-age women to FP decision-making. Although international guidelines recommend fertility counselling for all eligible patients, only 40-70% of women receive counselling in routine practice. Among those counselled, approximately 10-20% proceed with active FP, highlighting a substantial gap between recommendations and real-world uptake. Available FP strategies include embryo cryopreservation, oocyte cryopreservation, ovarian tissue cryopreservation, and ovarian suppression with GnRHa during chemotherapy. Multiple barriers contribute to limited implementation, including time constraints before treatment initiation, inadequate referral pathways, limited interdisciplinary coordination, financial costs, and geographic disparities in access to fertility services. At the same time, increasing awareness, wider dissemination of international guidelines, and technological advances such as vitrification and random-start controlled ovarian stimulation (COS) are progressively improving access and uptake of FP among young women with breast cancer.

DETERMINANTS OF DECISION-MAKING

FP represents a critical yet unevenly accessible component of oncofertility care, where persistent disparities across racial, socioeconomic, and systemic lines profoundly shape reproductive outcomes for young women with cancer. Understanding why some women receive fertility counseling and pursue cryopreservation while others do not require a multidimensional perspective encompassing patient, provider, and system-level determinants. Evidence consistently shows that socioeconomic status, education, race and ethnicity, geographic access, physician attitudes, and psychosocial characteristics jointly influence FP decision-making in oncology.

Inequities in FP access

The landmark study by Letourneau *et al.* (36) highlighted these disparities, showing that minority women and those with lower socioeconomic status were substantially less likely to receive fertility counseling or pursue FP. Among 1,041 reproductive-age women diagnosed with cancer, White and

privately insured patients were disproportionately represented among those who received counseling and underwent oocyte or embryo cryopreservation. Even after controlling for age, parity, and cancer type, racial and socioeconomic factors remained independently predictive of FP uptake, indicating systemic inequities embedded in oncology care delivery. Building on these findings, Tierney *et al.* (5) demonstrated that disparities begin even earlier, at the level of disease incidence. Their population-based analysis revealed that young Black and Hispanic women had higher incidence rates of fertility-impacting malignancies, yet were less likely to receive counseling or preservation services. These inequities are compounded by broader social determinants of health, including insurance gaps, environmental risk exposures, and geographic barriers to specialty care. Despite increasing awareness and dissemination of ASCO and ESMO FP guidelines, access to FP services remains uneven across patient populations. Recent evidence indicates that referral and uptake of FP interventions are frequently suboptimal, with marked disparities linked to race,

socioeconomic status, and geography. Turner *et al.* reported persistent gaps in oncofertility care in the United States, highlighting that guideline dissemination alone has not resolved inequities in counseling or service utilization (37). Structural barriers further compound these disparities: Peipert *et al.* showed through geospatial analysis that distance to fertility centers and limited regional availability of reproductive specialists disproportionately affect women in rural or economically disadvantaged areas (38). Similarly, Coker Appiah *et al.* identified ongoing unmet needs among pediatric, adolescent, and young adult female patients, emphasizing the role of provider awareness and institutional resources alongside sociodemographic factors in shaping access (39). Population-based analyses corroborate these findings, demonstrating that minority and low-income women are less likely to receive timely referrals to reproductive specialists, with persistent barriers including limited provider knowledge, inconsistent insurance coverage, and cultural or communication gaps between patients and oncology teams (40). A recent narrative review also highlighted structural inequities such as cost barriers, differential clinic availability, and underrepresentation in clinical research as contributors to ongoing racial disparities in both FP and assisted reproductive technology (ART) utilization (41). Together, these data underscore that translating FP guidelines into equitable clinical practice remains incomplete and call for coordinated policy initiatives, insurance reform, and culturally tailored counseling strategies to ensure all women with cancer can access fertility-preserving care.

LONG-TERM REPRODUCTIVE OUTCOMES ACROSS SOCIOECONOMIC STRATA

Most studies of social determinants in oncofertility have focused on counselling, referral, and FP uptake, whereas fewer have reported long-term reproductive outcomes stratified by socioeconomic position. Existing data, although limited, suggest that social gradients in access to FP may extend to subsequent pregnancies and live births. For example, registry-based cohorts and insurance-claims analyses have shown that women with private or comprehensive insurance are more likely to undergo FP and to achieve post-treatment pregnancies than those with public or no insurance, even after accounting for

age and tumor characteristics (39, 40, 42). Similarly, studies from racially and ethnically diverse health systems indicate lower cumulative live-birth rates and higher rates of treatment-related amenorrhea among Black and Hispanic survivors compared with White survivors, patterns that likely reflect intersecting effects of structural racism, differential access to specialist care, and financial barriers (5, 36, 37). At the same time, robust data on child health outcomes and on ovarian-reserve trajectories by socioeconomic strata remain scarce. Closing these evidence gaps – through prospective survivorship registries that capture both social determinants and reproductive endpoints – should be considered a priority for future research.

SOCIOECONOMIC STATUS AND INSURANCE COVERAGE

Socioeconomic status and insurance coverage are among the strongest predictors of FP utilization. Multiple studies show that higher income, private insurance, and residence in states with FP benefit mandates correlate with increased FP uptake. Sauerbrun-Cutler *et al.* (43) reported that expanding insurance mandates and employer-based fertility benefits significantly improved utilization. Similarly, Flores Ortega *et al.* (44) demonstrated that cost remains the predominant barrier in systems reliant on out-of-pocket payment, while Peipert *et al.* (38) showed that FP benefit mandates led to measurable increases in service utilization. Collectively, these data affirm that financial policy reform can materially reduce inequities in FP access.

Education and health literacy

Educational attainment and health literacy strongly influence understanding of infertility risks and subsequent decisions regarding FP. Women with higher levels of education are more likely to appreciate the gonadotoxic potential of cancer therapy and to seek timely counselling. A systematic review of interventions to improve FP decision-making among young women with cancer found that structured counselling, decision aids, and educational tools can enhance patient knowledge and reduce decisional conflict, particularly mitigating disparities linked to limited health literacy (45, 46). Similarly, evidence from decision aid trials in breast cancer patients demonstrated that these tools increase knowledge, confidence, and satisfaction with fertility-related decisions,

with the greatest benefit observed among women with higher baseline health literacy (47, 48). However, persistent gaps remain among socioeconomically disadvantaged groups, emphasizing the need for tailored communication strategies.

Race and ethnicity

Racial and ethnic disparities in FP counselling and utilization are consistently documented across oncology care. Minority women – including Black and Hispanic/Latina patients – are less likely to receive FP counselling or to undergo fertility-preserving procedures, even when adjusting for income, insurance status and other sociodemographic factors. A New York City cohort study by Voigt *et al.* found that, among 107 patients who underwent medically indicated FP between 2017 and 2018, only 3 patients (2.8%) identified as Black and 6 (5.6%) as Hispanic. In the subgroup with available comparator data, these observed numbers were substantially lower than those expected from the racial and ethnic distribution of reproductive-age women with cancer in New York City: 3 observed *versus* 15 expected Black patients and 6 observed *versus* 15 expected Hispanic patients ($p < 0.001$) (42).

More broadly, Turner *et al.* analyzed national oncofertility data and reported significantly lower referral and utilization rates for minority women, implicating structural and cultural barriers, language differences and implicit clinician biases as critical drivers of inequity (37). A narrative review by Gadson, Sauerbrun-Cutler and Eaton highlighted the persistent gap in FP access among minority populations and emphasized that culturally tailored education, interpreter services and systematic monitoring of referral pathways are essential to ensure equitable utilization (41).

Geographic access

Geographic location exerts a profound influence on access to FP. Women treated at rural, community, or regional oncology centers often face delayed or absent referral to oncofertility specialists, limiting timely access to FP counselling and services. A systematic review by Pathak *et al.* found that clinics with limited local reproductive-specialty resources and fragmented referral pathways were associated with markedly lower FP uptake among eligible patients (49). In parallel, a national geospatial analysis by Peipert *et al.* showed that 3.63 million female individuals aged 15-44 years – corresponding to 5.70% of the reproductive-age female population in the

continental United States – lived outside a two-hour travel radius of an oncofertility center, particularly in states lacking FP insurance mandates, highlighting structural geographic inequities (38).

Interventions such as tele-medicine linkage to fertility specialists, standardized referral algorithms embedded in oncology workflow, and travel-support programs have shown promise in mitigating these geographic disparities.

Physician-related factors

Physician engagement and institutional support play a critical role in FP access. Oncologists vary substantially in how frequently, how early, and how comprehensively they address fertility risks with reproductive-age patients. In their systematic review, Deshpande *et al.* found that many women who were clearly eligible for FP never received counselling, underscoring failure at the provider- or system-level rather than solely patient choice (50). Provider knowledge, comfort with fertility discussions, competing workflow demands, and lack of standardized referral pathways all influence the likelihood of FP-counselling and referral. The use of dedicated fertility navigators – specialized coordinators embedded within oncology or oncofertility clinics – has emerged as a promising strategy. In a qualitative evaluation at an academic center, van den Berg *et al.* found that fertility navigators improved patient satisfaction, offered consistent information and emotional support, and strengthened collaboration between oncology and fertility teams (51). Centers that integrate navigators, standardized electronic-health-record prompts, and routine fertility referral-checklists report higher rates of timely FP discussion and uptake. However, enhancing physician-related factors requires institutional commitment to fertility pathways: mandatory referral triggers at diagnosis, training modules on oncofertility for oncology teams, and inter-disciplinary coordination with reproductive specialists. Only when counselling and referral become system-standard rather than optional will FP access approach equity across age, race, and socioeconomic strata.

Psychosocial determinants

Psychosocial factors play a significant role in fertility-preservation decision-making. Emotional distress at diagnosis, the perceived urgency to initiate oncologic treatment, relationship status, and partner support all influence whether a woman chooses to pursue FP. Time pressure, information overload, and

uncertainty often lead cancer patients to defer fertility-preservation decisions (52). Yuen *et al.* reported that patients who received oncofertility counselling were younger, with a median age of 35 compared with 38 years for those not counselled, and were more likely to be nulliparous, 45 percent *versus* 18.5 percent (32). A systematic review of fertility-preservation patient decision aids demonstrated that structured tools significantly increased fertility-preservation knowledge and reduced decisional conflict (53). Together, these findings emphasize the need to integrate psychosocial assessment and support into fertility-preservation counselling to facilitate informed, value-congruent choices.

Figure 2 provides a clear, visually intuitive summary of the complex interplay of patient, provider, and system determinants affecting FP decisions.

PREGNANCY AFTER BREAST CANCER

Pregnancy represents an important and often complex consideration for young breast-cancer survivors. Advances in oncologic care and fertility-preservation strategies mean that an increasing number of women diagnosed with breast cancer in reproductive years are contemplating conception after treatment. Clinicians and patients alike confront key questions about the safety of pregnancy, optimal timing, reproductive outcomes, and breastfeeding – all within the context of tumor biology, prior treatment exposures, ovarian reserve, and personal reproductive goals. This section synthesizes current evidence and guidelines to support informed decision-making in this population.

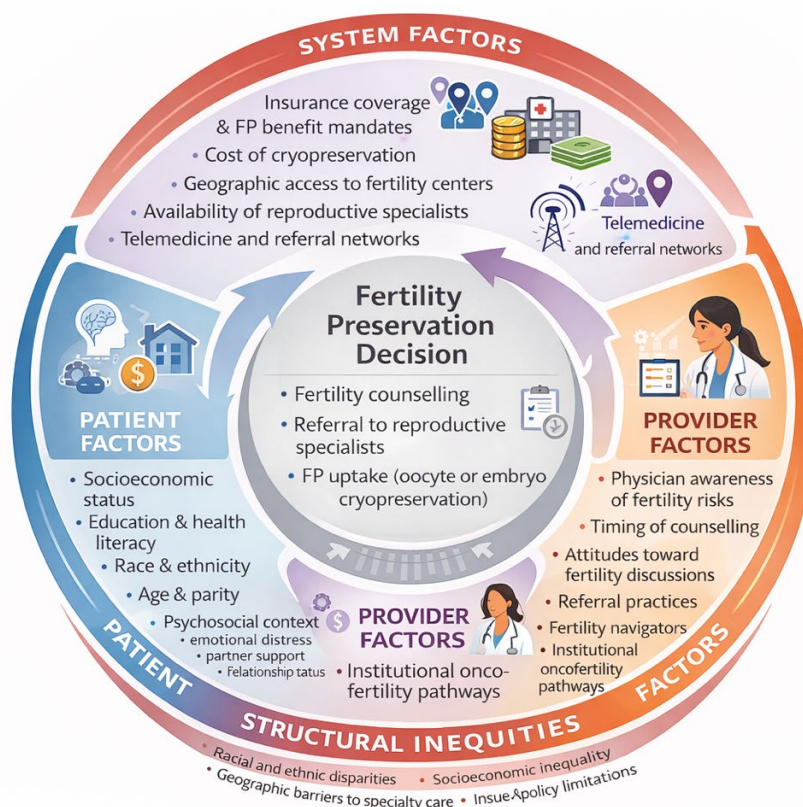


Figure 2. Multilevel determinants of fertility preservation decision-making in young women with cancer.

FP utilization is shaped by the interaction of patient-, provider-, and system-level determinants. Patient factors include socioeconomic status, education and health literacy, race and ethnicity, reproductive history, and psychosocial context. Provider determinants encompass clinician awareness of fertility risks, timing of counselling, referral practices, and the availability of fertility navigators or institutional oncofertility pathways. System-level influences include insurance coverage, cost barriers, geographic access to fertility centers, and the availability of reproductive specialists. These determinants operate within a broader context of structural inequities – including racial, socioeconomic, and geographic disparities – which collectively influence whether young women with cancer receive timely fertility counselling and ultimately pursue FP interventions.

Safety of pregnancy

The preponderance of observational evidence – from meta-analyses, registries, and narrative reviews – indicates that pregnancy after breast cancer does not increase the risk of recurrence; indeed, in many studies, survivors who become pregnant demonstrate similar or even apparently improved survival outcomes compared with those who do not, although these findings are likely influenced by the selection of women who remain recurrence-free and well enough to conceive. For example, in the narrative review by Carneiro *et al.*, the authors concluded that “the best published evidence suggests pregnancy after breast cancer does not increase the risk of disease recurrence, thus pregnancy should not be forbidden once treatment is completed” (54). Large systematic reviews further support this: Nolan *et al.* found no detrimental effect of pregnancy on Disease-Free Survival (DFS) or Overall Survival (OS) in patients with hormone-receptor (HR)-positive disease (55) and Arecco *et al.*, in a meta-analysis of young women with HR-positive early breast cancer, reported no adverse effect of pregnancy on DFS (HR 0.96, 95%CI 0.79-1.16) and an apparently improved OS (HR 0.46, 95%CI 0.24-0.87) (56); however, the latter is likely driven by strong selection of women who survived, remained recurrence-free, and subsequently pursued pregnancy (the “healthy mother effect”) rather than a causal protective effect of pregnancy.

More recently, a large cohort study of 4,732 women with germline BRCA1/2 pathogenic variants diagnosed with invasive breast cancer before age 40 found, among the 659 who became pregnant, an adjusted hazard ratio for DFS of 0.99 (95%CI 0.81-1.20) compared to those who did not become pregnant – indicating no increased risk in this high-risk genetic subgroup (57).

Taken together, these data provide robust reassurance that, in selected survivors (especially those in remission, with favorable tumor characteristics, and preserved fertility potential), pregnancy can be pursued safely. Some meta-analytic data even suggest superior survival outcomes in women who become pregnant (for example, pooled HR for DFS ~0.66; 95%CI 0.49-0.89) (3, 58). However, caution remains warranted due to potential selection bias (“healthy mother effect”), shorter follow-up in many studies, and the predominance of lower-risk patients in published cohorts.

Timing of pregnancy after breast cancer: evidence-based recommendations

Historically, clinicians advised delaying pregnancy for at least 2 years after treatment, coinciding with the

period of highest risk for recurrence. Emerging evidence now supports the possibility of earlier conception in carefully selected women, particularly when tumor characteristics, stage, and patient preferences are favorable. This question has been most rigorously evaluated in the POSITIVE trial, in which temporary interruption of endocrine therapy after 18-30 months to allow pregnancy did not increase short-term recurrence risk in carefully selected women with HR-positive disease (10) (see Endocrine Therapy section). Counseling should be individualized, taking into account tumor biology, stage, duration of endocrine therapy, fertility potential, and patient preferences. This evidence underscores the importance of early, multidisciplinary oncofertility consultation to guide timing, optimize outcomes, and support informed reproductive decisions.

Fertility, pregnancy, and postpartum outcomes

Pregnancy after breast cancer, whether achieved spontaneously or via FP strategies, is generally feasible, and many survivors successfully deliver healthy infants. Pregnancy rates in survivors remain lower than in age-matched general populations, but ART using cryopreserved gametes yields satisfactory conception and live birth rates. Slight increases in preterm birth or low birthweight have been reported in some series, yet overall neonatal outcomes are reassuring (59). Breastfeeding is generally safe and feasible, with no evidence of increased recurrence risk, though prior surgery or radiotherapy may limit lactation capacity. Importantly, breastfeeding preserves benefits for maternal-infant bonding, and structured postpartum support is recommended to optimize both maternal and neonatal outcomes (54). However, practical ability to breastfeed may be limited by prior breast surgery (e.g., mastectomy or extensive lumpectomy), radiotherapy involving the breast and axilla, or adjuvant systemic therapy. Clinicians should support survivors’ interest in breastfeeding with realistic counselling about potential anatomical/physiologic limitations.

Long-term reproductive and psychosocial outcomes

Long-term reproductive health remains a central concern for young breast cancer survivors. Anti-Müllerian hormone (AMH) is a widely used biomarker of ovarian reserve in clinical practice, and chemotherapy-related declines in AMH – particularly in older premenopausal women – underline the risk of sus-

tained ovarian dysfunction (see Chemotherapy and ovarian failure) (7, 60). Serial AMH monitoring may assist clinicians in counselling survivors about residual fertility potential and in planning the timing of conception attempts, although AMH alone is a limited predictor of natural fertility and time to spontaneous conception.

Among survivors of breast cancer who did not use cryopreserved gametes, spontaneous conception rates remain substantially lower than in age-matched controls. For example, one prospective cohort found that among women who returned to ovarian function after chemotherapy, ~65% attempted conception and about half achieved pregnancy through intercourse alone (61). In the oncofertility series more broadly, the rates of spontaneous pregnancy appear to cluster roughly in the range of ~10%-30% depending on age at diagnosis, treatment type, and duration of follow-up. Patients who banked oocytes or embryos before therapy demonstrate higher live-birth or pregnancy success rates, particularly when cryopreservation occurred at younger ages. Nevertheless, even when menstrual function resumes post-treatment, a diminished ovarian reserve may restrict the long-term fertility window. Fertility concerns in cancer survivors carry major psychosocial consequences. Pre-treatment fertility-preservation counselling has been associated with lower decisional regret, improved quality of life, and better satisfaction with fertility outcomes (50, 62). While direct data on structured decision-aid tools and peer-support programs for oncofertility remain relatively limited, emerging evidence supports their role in reducing decisional conflict and regret in reproductive-aged cancer survivors (62). Although much of the published work has focused on the safety and outcomes of pregnancy after breast cancer, the longer-term reproductive lifespan of survivors – including time to menopause, the residual fertility window beyond the first post-treatment conception, and the psychosocial sequelae across years of survivorship – remains under-investigated and deserves dedicated prospective research.

CONCLUSIONS

FP is an essential component of comprehensive care for young women with breast cancer. Advances over the past decade – including optimized oocyte and embryo cryopreservation, accumulation of meta-analytic evidence on ovarian-protection strategies, and

prospective trials such as the POSITIVE trial – have significantly expanded counseling and reproductive options (63). Despite these advances, substantial inequities persist, driven by socioeconomic status, race/ethnicity, insurance coverage, and geography, which limit equitable access to FP (64). System-level interventions can help bridge these gaps: automatic referrals to onco-fertility specialists, dedicated FP navigation programs, and mandated or publicly funded coverage for medically indicated FP have demonstrated effectiveness in improving uptake and patient satisfaction (65). Long-term survivorship registries capturing harmonized data on FP procedures, ovarian reserve markers, pregnancy attempts and outcomes, child health, and psychosocial metrics are crucial for evaluating real-world effectiveness and disparities, with international collaboration maximizing statistical power for subgroup analyses such as BRCA mutation carriers (66). Emerging evidence indicates that BRCA pathogenic variants may independently reduce ovarian reserve, emphasizing the need for tailored counselling and early FP in this population (67). Furthermore, the fertility effects of newer oncologic agents – including PARP inhibitors, immune-checkpoint inhibitors, antibody-drug conjugates, and other targeted therapies – remain largely uncharacterized, highlighting an urgent research priority for trials enrolling premenopausal women to include fertility endpoints and biologic sampling (4). Psychosocial interventions and structured decision aids are increasingly recognized as critical to reduce decisional regret, improve quality of life, and address anxiety and distress related to fertility concerns (53). Finally, health-economic research incorporating quality-of-life outcomes and the societal value of parenthood can inform policy and coverage decisions, ensuring equitable access to FP (68).

This review has several limitations. First, it is a narrative rather than a systematic review, and we may therefore have missed some relevant studies despite a broad search strategy. Second, most of the available evidence comes from high-income countries with well-resourced oncology and fertility services, limiting the generalizability of our conclusions to low- and middle-income settings. Third, long-term data on ovarian reserve, live-birth rates, and child health after FP remain sparse, particularly when stratified by socioeconomic status, race/ethnicity, or insurance coverage. Fourth, evidence on the gonadotoxicity and reproductive safety of newer agents – such as PARP inhibitors, antibody-drug conjugates,

and immune checkpoint inhibitors – is still evolving. Finally, pregnancy-after-cancer cohorts are inherently affected by selection bias, as only women who have survived, remained recurrence-free, and actively pursued pregnancy are captured, complicating causal inference regarding the impact of pregnancy on prognosis.

In conclusion, integrating FP into routine breast-cancer care requires a dual approach: implementing evidence-based clinical pathways and system-level support while pursuing targeted research to refine guidance as oncologic therapies evolve. Such an approach promises to safeguard reproductive potential, mitigate psychosocial burden, and enhance long-term quality of life for young breast-cancer survivors.

COMPLIANCE WITH ETHICAL STANDARDS

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Conflicts of interest

The authors declare no competing interests.

Availability of data and materials

The data presented in this study are available on request from the corresponding author.

Authors' contributions

AP: conceptualization, investigation, writing – original draft, visualization, supervision. IB: writing – review & editing, visualization, investigation, supervision. FMa: investigation, supervision. MBB: supervision. FMo: investigation, visualization. LM: conceptualization, writing – original draft, investigation, supervision.

Publication ethics

Plagiarism

This is a review article, and all original studies are cited as appropriate. Figures were generated with the help of AI.

Data falsification and fabrication

The contents of the article are original, and any overlaps with other articles are by the authors themselves and appropriately cited.

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