

Review

Fertility Preservation for Young Women with Breast Cancer: Review and Perspective

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Abstract

Objectives: Breast cancer is a common malignancy that poses a significant danger to women. Recently the risks of breast cancer have been increasing in younger populations, and treatments may affect the ability to conceive, requiring options for fertility preservation. The clinical management of breast cancer typically involves surgery, chemotherapy, and radiotherapy, all of which may present detrimental effects on fertility. Thus, it is crucial to consider fertility preservation when formulating treatment plans. **Mechanism:** A narrative review was conducted to analyze the available literature regarding the impact of breast cancer treatment modalities on fertility, as well as strategies for fertility preservation. **Findings in Brief:** Various breast cancer treatment modalities can result in varying degrees of damage to a patient's ovaries, potentially compromising their ovarian function and subsequently affecting their fertility. This article reviews various fertility preservation methods, including oocyte and embryo cryopreservation, controlled ovarian stimulation (COS), *in vitro* maturation (IVM), cryopreservation, and ovarian tissue transplantation. Additionally, we discuss several potential strategies, such as 3D bioprinting, Traditional Chinese Medicine (TCM), and Artificial Intelligence (AI) assisted treatment. **Conclusions:** The impact of breast cancer treatment modalities and fertility preservation strategies exhibits individual variability, necessitating the clinical selection of treatment based on the specific circumstances of each patient. The integration of 3D bioprinting, TCM, and AI is expected to provide a new perspective for young breast cancer patients seeking to maintain their fertility.

Keywords: breast cancer; *in vitro* maturation; fertility preservation; 3D bioprinting; traditional Chinese medicine

1. Introduction

Breast cancer is a common malignancy among women and a leading cause of female mortality worldwide [1–3]. With advancements in integrated treatments for breast cancer, an increasing number of women of reproductive age are surviving this pathology. However, these treatments can impact a woman's reproductive endocrine system. Chemotherapy, commonly used in treating breast cancer patients, is known to present cytotoxic effects on the ovaries [4]. Radiation therapy used in treating breast cancer can affect fertility by damaging germs cells or by altering the reproductive environment [5]. Some endocrine therapy drugs, such as tamoxifen (TAM), may interfere with fertility. In fact, TAM can lead to irregular menstruation cycles, ovulation disorders, and possibly premature ovarian failure [6]. Furthermore, the prolonged use of TAM over 5 to 10 years can impact fertility. Due to its described teratogenic effects, patients are advised against becoming pregnant while taking the drug [7]. These adverse effects become more pronounced as young female breast cancer patient's age, often putting them at risk impaired fertility in the future. These effects may not only lead to significant

psychological and emotional stress, but may also impact their family and social relationships. Therefore, it is imperative to thoroughly consider these potential risks when formulating breast cancer treatment plans, with the focus to implement fertility preservation strategies [8,9].

Currently, a range of fertility preservation strategies have been proposed and implemented in clinical practice. These include oocytes and embryos cryopreservation, control of ovarian stimulation, *in vitro* maturation (IVM), and ovarian tissue transplantation. The emergence of these techniques offers hope for young breast cancer patients to preserve fertility while undergoing treatment. Various treatments impact fertility to differing extents, with individual patient conditions exhibiting substantial variation. Therefore, providers should carefully assess and select the most appropriate fertility preservation method based on factors such as the patients age, pathological characteristics present, and fertility intention manifested by the patient.

Young patients, especially those who have not yet been pregnant, are particularly concerned about the impact of anti-tumor treatment modalities on their reproductive function. According to Ruddy *et al.* [10], in a study involving women under the age of 40 diagnosed with breast



cancer, 26% of the patients reported concerns about fertility affecting their treatment decisions. These concerns included refusing chemotherapy, choosing one treatment regimen over another, declining endocrine therapy, or discontinuing endocrine therapy before the recommended five-year period [10]. While pursuing the therapeutic effects of treatment, it is imperative to prioritize and protect the fertility of these patients [11–13]. In this review, we will discuss the impact of antitumor therapy on reproductive function, along with various strategies available for fertility preservation. Our aim is to provide tailored fertility preservation strategy options for young breast cancer patients.

2. Breast Cancer Treatment and Its Effect on Fertility

Patients undergoing antitumor therapy may experience various effects on fertility, such as decreased libido, sexual dysfunction, and increased infertility rates.

2.1 Cytotoxic Chemotherapy

Cytotoxic chemotherapy is a fundamental component of adjuvant therapy for individuals with breast cancer. Extensive evidence supports its efficacy in significantly improving patient prognosis [14–16]. Commonly used chemotherapy drugs include anthracyclines, alkylating agents, platinum compounds, and 5-fluorouracil [17–20]. These drugs can cause damage to a patient's ovaries, potentially impacting their fertility. Studies have shown that chemotherapy induces ovarian dysfunction mainly through two main mechanisms: direct damage to the DNA of primordial follicle oocytes and the induction of primordial follicle activation, ultimately leading to the depletion of the primordial follicle reserve [21].

Doxorubicin, epirubicin, and pirarubicin are among the most frequently employed anthracycline drugs. Owumi *et al.* [22] discovered that doxorubicin treatment in mice increased the levels of oxidative and inflammatory stress biomarkers in the ovaries. Wang *et al.* [23] demonstrated that the application of epirubicin in mice could induce oxidative stress, inflammation, and ovarian damage by promoting cell apoptosis. Cyclophosphamide is also recognized for its ability to induce significant ovarian damage [24]. Specifically, cyclophosphamide triggers primordial follicle activation, cell apoptosis, and ovarian follicle damage, thereby promoting premature ovarian failure [25]. As a result, patients may experience menstrual irregularities, amenorrhea, and infertility [26]. Xu *et al.* [21] observed that cyclophosphamide may increase the secretion of transforming growth factor- β 1 (TGF- β 1) in the ovaries by inducing cellular senescence, thereby contributing to ovarian dysfunction. Some studies have reported that the toxicity of cyclophosphamide is significantly influenced by its administration schedule and dose, and it is closely associated with patient's age [27,28]. Interestingly enough, higher doses of cyclophosphamide are more likely to induce ovarian fail-

ure in older patients [29]. Cisplatin exerts its anticancer effects by inducing DNA damage during the G1/S phase and subsequently promoting apoptosis. Notably, the ovarian toxicity associated with platinum drugs is significantly less pronounced compared to that of more commonly used drugs such as cyclophosphamide. Cisplatin is associated with amenorrhea, reduced fertility, and an increased risk of premature menopause in women [30]. However, due to the limited clinical data on the use of cisplatin alone, it is difficult to explain the specific mechanism of cisplatin-induced ovarian toxicity in humans. Studies have shown that cisplatin adversely affects oocyte survival in rats by causing the depletion of follicular reserves, which in turn reduces fertility [31,32]. Additionally, the decreased level of anti-Müllerian hormone (AMH) is related to cisplatin exposure and may affect fertility by reducing the number of circulating AMH and AMH-positive follicles [33,34].

In current clinical practice, the combined administration of anthracyclines and taxanes is often employed to enhance therapeutic efficacy. Although the addition of taxanes to anthracycline-based/cyclophosphamide chemotherapy can further increase the risk of inducing amenorrhea, recent studies have found that there was no significant difference in the impact on amenorrhea between chemotherapy regimens with and without paclitaxel [35]. Hence, further investigation into the efficacy of combining anthracyclines with taxanes is warranted. Studies have demonstrated that melatonin can mitigate the fertility damage caused by chemotherapy drugs through the suppression of PTEN/AKT/FOXO3a pathway or reducing reactive oxygen species (ROS)-induced endoplasmic reticulum stress (ERS) [23,36].

2.2 Hormone Therapy: TAM and Aromatase Inhibitors

Breast cancer is characterized by abnormal expression of estrogen, progesterone, and human epidermal growth factor receptor 2 (HER2). Hormone disruptors are frequently employed in the treatment management of breast cancer patients who test positive for estrogen/progesterone receptors [37]. TAM is a non-steroidal anti-estrogenic drug [38]. *In vitro* experiments have demonstrated that TAM can prevent the loss of ovarian follicle reserves by inhibiting apoptosis, without compromising the anti-tumor effects of breast cancer treatment [39]. Nynca *et al.* [40] conducted a proteomics and transcriptomics study in a rat model treated with TAM. The authors observed that TAM alters the expression of genes associated with the activation or arrest of primordial follicles, thereby emphasizing the importance of preventing the loss of ovarian follicle reserves [40]. In clinical trials involving 1067 patients with breast cancer who received over 5 years of TAM treatment following chemotherapy, the results showed that 69% of patients resumed menstruation. Additionally, 98% and 74% of patients met the predefined criteria for ovarian function restoration based on serum follicle-stimulating hormone

(FSH) and estradiol levels, respectively [41]. The aforementioned results indicate that TAM effectively fulfills its function in breast cancer treatment and possesses gonadal protective properties.

Aromatase inhibitors constitute a class of pharmaceuticals capable of suppressing the activity of aromatase, an enzyme responsible for the conversion of androgens to estrogen [42]. In hormone receptor (HR)-positive breast cancer, estrogen can promote the growth of tumor cells. Therefore, by inhibiting aromatase, these inhibitors can reduce estrogen production within the body, thereby inhibiting tumor growth. Compared with TAM, aromatase inhibitors can more directly reduce estrogen levels, leading to a more effective tumor growth control. However, the use of aromatase inhibitors requires attention to potential risks and side effects. Since these drugs reduce estrogen levels, they may induce symptoms associated with estrogen deficiency, such as hot flashes, joint pain, and osteoporosis. Moreover, for younger patients, long-term estrogen deficiency may impact their reproductive system, including fertility, and bone health. Aromatase inhibitors, combined with gonadotropin-releasing hormone (GnRH) antagonists, are widely used in premenopausal breast cancer patients with HR-positive breast cancer. The Suppression Ovarian Function Trial (SOFT) and the TAM and Exemestane Trial (TEXT) demonstrated superior patient outcomes when ovarian suppression was added to anti-hormonal therapy for premenopausal patients with breast cancer [43]. Overall, aromatase inhibitors represent an effective therapeutic choice for young patients diagnosed with HR-positive breast cancer [44]. However, their administration requires careful consideration to strike a balance between maximizing efficacy and mitigating potential risks. Further investigation of the combination or sequential treatment strategies of aromatase inhibitors and other drugs, such as TAM, could offer insights into optimizing treatment outcomes.

2.3 Immunotherapy: Programmed Cell Death Protein 1/Programmed Death-Ligand 1 (PD-1/PD-L1) Immune Checkpoint Inhibitors

Pembrolizumab, Nivolumab, Atezolizumab, and Camrelizumab are among the common anti-PD-1 drugs employed in breast cancer treatment. Among these drugs, Pembrolizumab and Nivolumab are clinically approved PD-1 inhibitors, primarily employed in the management of advanced and metastatic tumors. They have exhibited promising efficacy in the treatment of advanced triple-negative breast cancer [45]. However, some studies suggest that these drugs may potentially induce adverse effects on the ovaries [46,47]. Xu *et al.* [46] discovered, through experiments conducted on prepubertal female mice with normal immune function and immunodeficiency, that the administration of Pembrolizumab or anti-mouse PD-1 antibody led to a significant reduction in the number of primor-

dial follicles in mice with normal immune function. However, no change in the number of follicles was observed in immunodeficient nude mice. No differences were observed in the number of cumulus-oocyte complexes (COCs) and the onset of puberty between the control group and the anti-mouse PD-1 antibody treatment group, indicating no impact on short-term fertility. These results demonstrated that injecting Pembrolizumab into immunocompetent mice significantly reduced the number of their primordial follicles [46]. PD-L1 inhibitors commonly used in breast cancer treatment include Atezolizumab and Avelumab. Atezolizumab was the first PD-L1 inhibitor to receive approval, but there have been reports of its excessive use leading to menstrual irregularities and anovulation in female monkeys [47].

2.4 Molecular Targeted Therapy: Olaparib, Palbociclib, and HER2-Targeted Therapy

Olaparib, an ADP-ribose polymerase inhibitor, has been approved for the treatment of HER2-negative metastatic breast cancer in patients with germline *BRCA1/2* mutations [48]. *In vitro* experiments have demonstrated that although the use of Olaparib as adjuvant therapy after chemotherapy does not significantly affect the number of oocytes, direct treatment with Olaparib can reduce the number of oocytes, potentially impacting the fertility of mice [49]. Although Olaparib may modestly improve the prognosis of breast cancer patients, it is better suited as an adjuvant therapy when fertility preservation is a concern [50,51]. Cyclin-dependent kinases (CDK) 4/6 play crucial roles in the tumor cell cycle [52] and can also exert influence on meiosis in oocytes [53]. Palbociclib is one of the selective CDK4/6 inhibitors. Catlin *et al.* [54] found that Palbociclib does not affect the fertility of female or male mice or rabbits. The study also observed that the drug led to reduced maternal weight gain and food consumption, along with the observations of low fetal weight in rats and small forelimb digit bones in rabbits [54].

In the management of patients with HER2-positive breast cancer, the preferred treatment approach often involves the utilization of HER2-targeted therapy [55]. Key medications for HER2-targeted treatment include Trastuzumab, Pertuzumab, Ado-trastuzumab emtansine (T-DM1), and Lapatinib [56]. Levi *et al.* [57] observed a significant decrease in AMH levels among HER2-positive patients following chemotherapy administration. Nevertheless, treatment with Trastuzumab led to a restoration of AMH levels to baseline, suggesting a potential mitigation of chemotherapy-induced ovarian toxicity by Trastuzumab [57]. Additionally, other studies have proposed that the incidence of amenorrhea following adjuvant ado-trastuzumab emtansine (T-DM1) therapy is reduced by 26% compared to patients treated with Paclitaxel-Trastuzumab (TH) post-chemotherapy [58]. Lambertini *et al.* [59] con-

Table 1. Breast cancer treatments and their effects on fertility.

Treatment methods	Pharmaceutical drug	Effects on fertility
Cytotoxic therapy	Doxorubicin, Epirubicin, Pirarubicin, Cyclophosphamide, Cisplatin	Direct damage to oocytes DNA and follicular function may occur. Temporary or permanent amenorrhea may occur.
Hormone therapy	TAM	It may preserve ovarian follicular reserve function.
Immunotherapy	Pembrolizumab, Nivolumab, Atezolizumab, Camrelizumab, Atezolizumab, Avemulab	It damages ovarian function and decreases the follicle count.
Molecular targeted therapy	Olaparib, Palbociclib	It may affect the oocytes meiosis.
	Trastuzumab, Pertuzumab, Lapatinib, Ado-trastuzumab	HER2 targeted therapy can mitigate chemotherapy-induced damage to the ovary and reduce the amenorrhea rate.

TAM, tamoxifen; HER2, human epidermal growth factor receptor 2.

ducted a comprehensive analysis of research involving premenopausal women undergoing various treatment regimens, including single-agent Trastuzumab, single-agent Lapatinib, and combination or sequential therapy with Trastuzumab and Lapatinib. These findings suggest a potentially favorable gonadal safety profile associated with the aforementioned medications.

Table 1 provides a summary of breast cancer treatments and their effects on fertility.

3. Fertility Preservation Strategies

Medical infertility poses a significant challenge for patients diagnosed with malignancies. Chemotherapy-induced ovarian damage and the postponement of pregnancy due to adjuvant endocrine therapy contribute to unsatisfactory fertility outcomes among breast cancer patients [60]. Furthermore, for patients who have undergone chemotherapy, even if they have been cured of cancer, certain risks may exist during pregnancy, including fetal abnormalities, premature birth, and miscarriage. Medications can also contribute to postnatal complications, such as birth defects and developmental issues [61–64]. It is crucial to prioritize fertility preservation for cancer patients before initiating treatment, a consideration often neglected in many conventional tumor treatments. It highlights the need for increased attention and comprehensive improvement in this area [65]. Currently, standard techniques for preserving fertility include oocyte cryopreservation, embryo cryopreservation, and ovarian tissue cryopreservation. Determining the most suitable preservation method requires careful consideration of factors such as the patient's tumor stage, age, marital status, treatment regimen, physical well-being, and personal preferences [66].

3.1 Oocyte Acquisition and Maturation in Fertility Preservation

Controlled ovarian stimulation (COS) represents a pivotal aspect of reproductive technology, entailing the administration of exogenous gonadotropins under rigorous

monitoring to stimulate the development of multiple follicles, thereby aiming to obtain an appropriate number of high-quality oocytes. Traditional COS protocols initiate during the follicular phase and may not be adequate for preserving fertility in patients requiring immediate cancer therapy. However, progress in the understanding the menstrual cycle has led to the development of innovative random-start COS methods, enabling ovarian stimulation at any phase of the cycle [66]. Research by Baerwald and Pierson [62] has demonstrated that the efficacy of random-start COS in preserving fertility is comparable to that of conventional COS. As a result, a larger cohort of patients can preserve their fertility and proceed with tumor treatment after a brief delay of only 2–3 weeks through random-start COS, thereby effectively minimizing any potential setbacks in their tumor treatment [67]. Ovarian stimulation can induce a short-term elevation in estrogen levels, consequently increasing the risk of breast cancer tumor recurrence [68,69]. Consequently, certain breast cancer treatment protocols incorporate the use of adjuvant drugs alongside standard ovarian stimulation medications. Commonly utilized options include the estrogen receptor modulator TAM and the aromatase inhibitor Letrozole. Randomized controlled trials have demonstrated no significant differences in oocyte quality among breast cancer patients undergoing standard ovarian stimulation, those receiving standard stimulation plus TAM, and those receiving standard stimulation plus Letrozole. This suggests that the addition of TAM or Letrozole to the standard ovarian stimulation regimen does not impact survival rates [70]. Importantly, studies have revealed no significant difference in the risk of breast cancer recurrence or disease-free survival between breast cancer patients undergoing fertility preservation using COS with Letrozole and those who do not pursue fertility preservation [71,72]. COS typically culminates with a trigger to induce oocyte maturation. Common trigger options include human chorionic gonadotropin (hCG), FSH, luteinizing hormone (LH), and GnRH agonist (GnRHa). Single triggering refers to the administration of a single COS trigger medica-

tion to induce maturation of multiple ovarian follicles, with the goal of inducing ovulation using only one drug. Dual triggering refers to the utilization of a combination of trigger medications, commonly involving the administration of both GnRHa and hCG [73]. Reddy *et al.* [74] have demonstrated that in breast cancer patients treated with Letrozole and gonadotropin stimulation, with the use of GnRHa trigger not only improves treatment cycle outcomes but also significantly reduces the risk of ovarian hyperstimulation syndrome.

IVM is classified as an adjunctive reproductive technology, wherein immature oocytes are retrieved without COS and subsequently matured through *in vitro* experimentation. This technique also represents a viable approach for breast cancer patients seeking to preserve their fertility [75]. Studies have shown that the retrieval of immature oocytes without COS, followed by IVM and vitrification of oocytes or embryos, neither increased serum estradiol levels nor delayed treatment for patients with breast cancer [75]. Shalom-Paz *et al.* [76] reviewed 66 patients with breast cancer who underwent extraction of immature oocytes without COS and subsequent IVM. Consequently, the maturity rate of oocytes was 64.2%, and the fertilization rate was 77.8%. Overall, IVM emerges as a more favorable strategy for fertility preservation in patients with breast cancer.

3.2 Cryopreservation in Fertility Preservation

Cryopreservation of oocytes or embryos constitutes a pivotal element of assisted reproductive technology (ART) and represents a fundamental method for preserving fertility in females diagnosed with cancer-related reproductive syndromes. For single female patients, oocyte cryopreservation serves as a crucial method for preserving fertility. Furthermore, for individuals with partners, embryo cryopreservation carries significant significance. Unlike oocyte cryopreservation, embryo cryopreservation involves periodic *in vitro* fertilization (IVF) or intracytoplasmic sperm injection (ICSI) subsequent to oocyte retrieval. Cryopreservation methods, such as slow freezing and vitrification, allow for the storage of oocytes or embryos for extended periods of time, sometimes spanning many years [77]. Oocyte cryopreservation is slower compared to embryo cryopreservation, requiring the use of additional cryoprotectants for the slow freezing process [78]. One study compiled data from 8824 cryopreserved embryos, comprising 7482 vitrified embryos and 1342 slow-frozen embryos, all fertilized through IVF or ICSI. These results indicated that compared with slow-freezing, the post-thaw survival rate of cleavage-stage embryos and blastocysts was significantly higher following vitrification [79]. However, the majority of vitrification methods employ an open system, wherein oocytes are directly exposed to liquid nitrogen to facilitate ultra-rapid cooling and minimize ice crystal formation. Nevertheless, there remains a risk of contamination in liquid ni-

trogen as a consequence of the direct exposure of oocytes. Hence, the development of methods for disinfecting liquid nitrogen disinfection is critical. Currently, certain methods such as microfiltration or ultraviolet light are being employed [80]. Guidelines from the American Society for Reproductive Medicine and the Society for ART indicate that following vitrification, the survival rate of oocytes ranges from 90% to 97%, the fertilization rate from 71% to 79%, the implantation rate from 17% to 41%, and the estimated clinical pregnancy rate per thawed oocyte from 4.5% to 12% [81]. Overall, vitrification offers robust technical support for fertility preservation in cancer patients.

The primary aim of ovarian tissue cryopreservation is to preserve and maintain a woman's fertility, enabling her to utilize her oocytes for future conception. This is particularly critical for pre-adolescent girls diagnosed with malignant tumors before experiencing their first menstrual cycle, as well as for patients who are unable to undergo COS due to urgent cancer treatment requirements. Typically, follicles or ovarian tissue are obtained from the patient's ovaries through surgery, promptly frozen in specialized cryoprotectant solutions, and then stored long-term in liquid nitrogen. Following the patient's treatment, when the decision to conceive is made, the tissue is thawed and re-implanted into the patient's body to restore fertility. The success of ovarian tissue cryopreservation may be influenced by various factors, including patient's age, tumor grade, storage duration, and tissue quality. Although clinical experience remains limited, numerous successful cases have been reported. Over 130 instances of full-term pregnancies have been documented following autotransplantation of cryopreserved ovarian tissue [82,83].

3.3 Function of GnRHa in Fertility Preservation

GnRHa plays several key roles in fertility conservation. Primarily, understanding the fundamental mechanism of GnRHa is essential. GnRHa primarily mimics the action of GnRH to regulate the secretion of gonadotropin in the pituitary gland, particularly FSH and LH [84].

In the fertility preservation of breast cancer patients, GnRHa is mainly employed in the following aspects: (1) Blocking FSH secretion: continuous administration of GnRHa inhibits the pituitary gland, thus reducing ovarian stimulation [85]. This is particularly important during chemotherapy, as chemotherapeutic drugs often exert toxic effects on the ovary. By reducing FSH secretion, GnRHa can decrease the ovarian sensitivity to these drugs, thus helping to protect the ovary from injury. (2) Reducing uterine-ovarian stimulation: GnRHa also reduces the uterus and ovary stimulation by lowering estrogen levels. This helps in creating more favorable conditions for subsequent fertility preservation procedures, such as cryopreservation of oocytes or embryos [86]. Furthermore, GnRHa can activate GnRH receptors on the ovary, despite its usual inhibitory effect. This activation may help 'prime' the ovary

Table 2. Viable fertility preservation techniques for breast cancer patients.

Technique name	Applicable user	Key points	Live birth rate/ fertilization rate
Oocyte cryopreservation	Single patient	It serves as the foundation for subsequent IVF-assisted reproduction.	34%~42%
Embryo cryopreservation	Patients with partner	Currently, it is the most advanced and optimal fertility preservation method.	14%~34%
Ovarian tissue cryopreservation	Pre-adolescent girls/Patients requiring emergency treatment	It does not delay treatment time, does not affect the changes of hormone levels in the body, and can restore ovarian endocrine function. The survival rate of tissue transplantation is as high as 96 %, and presents a large fertility reserve.	40%~43.3%
Random-start ovarian stimulation	Non-prepubertal patient	It can start COS at any time and does not delay treatment time.	-
IVM	Non-prepubertal patient	It does not delay tumor treatment and does not affect changes in hormone levels for patients.	77.8%

Note: The corresponding index for oocyte cryopreservation, embryo cryopreservation, and ovarian tissue cryopreservation is the live birth rate; the index corresponding to the IVM of oocytes is the fertilization rate.

IVM, *in vitro* maturation; IVF, *in vitro* fertilization; COS, controlled ovarian stimulation.

before chemotherapy, increasing its sensitivity to subsequent fertility preservation measures. (3) Up-regulation of anti-apoptotic molecules in the gonad: chemotherapeutic drugs often impair ovarian function by inducing apoptosis. However, GnRHa can upregulate anti-apoptotic molecules such as Bcl-2 within the ovary. This action helps counteract apoptosis induced by chemotherapeutic agents, thus protecting ovarian cells from damage. (4) Protecting undifferentiated germline stem cells: preserving undifferentiated germline stem cells in the ovary is crucial for young women, as these cells are critical for future fertility. GnRHa can protect these stem cells from the damage caused by chemotherapy drugs through mechanisms mentioned before.

Overall, GnRHa plays multiple protective roles in fertility conservation in breast cancer patients. It not only directly protects the ovary from chemotherapeutic agents [87], but also creates more favorable conditions for subsequent fertility preservation measures by regulating the endocrine environment. This renders GnRHa an essential component of breast cancer treatment, particularly in young female patients aiming to preserve their fertility. Table 2 provides a synopsis of viable fertility preservation techniques for breast cancer patients.

4. Prospect of Potential Strategies for Fertility Preservation

Preservation of fertility is of paramount importance when addressing the treatment needs of young patients with breast cancer. Given contemporary clinical approaches, several potential strategies can be utilized for fertility preservation or to improve fertility outcome. This include

3D bioprinting and Traditional Chinese Medicine (TCM)-assisted treatment [66].

4.1 3D Bioprinting Technology

With advancements in 3D bioprinting technology and cell biology, it has become possible to create artificial organs or tissues that are biocompatible, biodegradable, and functional [88]. In the field of female reproductive therapy, 3D bioprinting technology has been extensively explored. In 2017, Laronda *et al.* [89] attempted to 3D bioprint ovaries, reporting that the 3D manufacturing of ovarian tissue could partially restore ovarian hormone secretion and oocyte production functionality. In 2022, Wu *et al.* [90] used gelatin-methacrylate for the 3D bioprinting of artificial ovaries, suggesting that it exhibited good moisture absorbency, degradation kinetics, and shape fidelity. This artificial ovary provided a suitable microenvironment for ovarian follicles, enabling their successful growth and ovulation [90]. Li *et al.* [91] demonstrated that 3D bioprinted artificial ovaries, devoid of drug-based *in vitro* activation technology and comprised of fat-derived stem cells, successfully restored ovarian insufficiency and ovarian dysfunction in mice. Their study further suggested that 3D bioprinting extends the viability of fat-derived stem cells, initiates early vascular microenvironment, regulates hormone levels, promotes follicle maturation, and ultimately improves premature ovarian insufficiency (POI) [91].

4.2 TCM Adjuvant Therapy

TCM has emerged as a prominent treatment approach for various health conditions in China and other Asian countries, including for POI, which is characterized by a decline ovarian function before the age 40 [92,93]. Breast can-

cer survivors experiencing ovarian damage resulting from chemotherapy may find potential benefits from insights derived from TCM approaches employed in the clinical management of POI. According to TCM principles, the kidneys are considered the foundation of innate essence, playing a crucial role in regulating the body's growth, development, and reproductive functions. Kidney essence is believed to transform into blood, which subsequently nourishes all bodily organs and systems in the body. Deficiencies in kidney essence can result in compromised female reproductive capabilities. Hence, TCM frequently employs kidney-tonifying herbal remedies to address disorders associated with ovarian dysfunction. Zhang *et al.* [94] administered an herbal formulation called the “Yi Shen Yang Lvan Formula”, specifically designed to nourish both the kidneys and ovaries in the treatment of POI. After a three-month treatment regimen, patients exhibited increased AMH levels, accompanied by decreased levels of FSH and LH. Additionally, the treatment resulted in the inhibition of apoptosis in ovarian granulosa cells, thereby enhancing ovarian reserve function in the patients [94]. Xie *et al.* [95] conducted a study suggesting that the “Hu Yang Yang Kun Formula” might inhibit granulosa cell apoptosis, decrease follicle atresia, and restore ovarian function by the Hippo-JAK2/STAT3 signaling pathway. Furthermore, other TCM treatments have been employed to restore ovarian function. Zhang *et al.* [96] applied moxibustion to the “Guan Yuan” and “San Yin Jiao” acupoints in rats with POI. This intervention was observed to inhibit the phosphorylation of the PI3K/Akt/mTOR signaling pathway in ovarian tissues, decrease Akt activation, suppress premature development and excessive apoptosis of primordial follicles, and enhance ovarian hormone levels while reducing inflammatory responses [96]. A meta-analysis revealed that combined treatment involving acupuncture alongside other therapies (TCM/Western Medicine) for POI is more effective compared to utilizing TCM or Western Medicine alone [97]. A recent meta-analysis has revealed that the combined treatment of acupuncture and Chinese herbal medicine for POI exhibits significantly greater overall efficacy in contrast to Western Medicine [98]. In summary, it appears feasible to develop innovative strategies based on TCM treatment methods for restoring ovarian function and preserving fertility among breast cancer patients.

4.3 Artificial Intelligence (AI)

AI is employed across diverse domains of the medical field, including image diagnostics, prediction of disease risk, and the development of new drugs. The careful selection of embryos for transplantation during the IVF treatment process is paramount, as it can significantly enhance the success rate of live births while mitigating potential complications. Embryologists frequently rely on their expertise when selecting embryos, resulting in significant variability. Introducing AI technology into the field of IVF facilitated

automated and standardized processes for assessing the success rate of fertilized embryos. This helps reduce current errors and inaccuracies in manual selection judgments, ultimately improving the success rate of IVF [99–101]. Hariton *et al.* [102] revealed that machine learning algorithms can optimize the timing of trigger injections to achieve the maximum yield of available oocytes and improve fertilization rates. Letterie and Mac Donald [103] developed a computer algorithm designed for IVF management, showcasing remarkable accuracy in decision-making across various stages: continuing or stopping ovulation stimulation (0.92), triggering and scheduling egg retrieval or canceling the cycle (0.96), adjusting medication dosage (0.82), and determining follow-up days (0.87). These advancements collectively contribute to the improvement of the success rate of IVF [103].

5. Conclusions

While the survival of cancer patients have notably improved, the ramifications of reduced fertility on the cancer survivors remain a complex and multifaceted issue. Cancer survivors encounter a multitude of challenges, including physical difficulties, the risk of disease recurrence, long-term side effects, as well as psychological, social, and emotional stress [104]. Among these challenges, the issue of fertility holds particularly importance for young female cancer survivors. Although there is currently no evidence suggesting that fertility impacts the prognosis of breast cancer patients, a significant proportion of young breast cancer patients express a strong desire to preserve their fertility [105,106]. The POSITIVE trial (NCT02308085) demonstrated that temporary interruption of endocrine therapy in women with previous hormone receptor-positive in early breast cancer, aimed at attempting pregnancy, did not result in a higher short-term risk of breast cancer events [107]. Therefore, it is crucial for doctors to actively explore appropriate treatment modalities and incorporate fertility preservation strategies to align the preferences of these patients [108].

Young female cancer patients should actively pursue approaches for preserving fertility during their treatment. This involves consulting a healthcare provider before starting treatment to understand the impact of chemotherapy on fertility and potential protective measures. Implementing appropriate measures during treatment, such as preserving ovarian function with hormone medications; and actively seeking fertility counseling and support prior treatment to determine the fertility program best suited for their individual needs. Moreover, social and family support is critical for cancer survivors. It is necessary to increase the research efforts and publicize fertility preservation for cancer survivors, aiming to improve the public awareness and attention toward this issue. Additionally, medical practitioners should be knowledgeable in diverse approaches, considering the unique clinical presentation of each patient, to attain

optimal outcomes. Integrating existing technologies with emerging ones, such as 3D bioprinting, TCM, and AI, is crucial in advancing the development of breast cancer treatment and fertility preservation methods.

Abbreviations

TAM, tamoxifen; HER2, human epidermal growth factor receptor 2; T-DM1, ado-trastuzumab emtansine; AMH, anti-Müllerian hormone; TH, paclitaxel-trastuzumab; TRA, treatment-related amenorrhea; CDK, cyclin-dependent kinases; HR, hormone receptor; COS, controlled ovarian stimulation; hCG, human chorionic gonadotropin; FSH, follicle-stimulating hormone; LH, luteinising hormone; GnRHa, gonadotropin-releasing hormone antagonists; SOFT, Suppression Ovarian Function Trial; TEXT, Exemestane Trial; COCs, cumulus-oocyte complexes; ART, assisted reproductive technology; IVF, *in vitro* fertilization; ICSI, intracytoplasmic sperm injection; TCM, Traditional Chinese Medicine; POI, premature ovarian insufficiency; AI, artificial intelligence.

Author Contributions

SZ, LC, ZM conducted the literature review and wrote the manuscript. YY contributed to the conceptualization of the review. YY also significantly revised and approved the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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