# Preservation of fertility in premenopausal patients with breast cancer

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A B S T R A C T

**Introduction:** Cancer survivorship is increasingly important with advances in cancer therapeutics. Minimisation of treatment-related morbidity is an area that requires attention. This situation is most pressing in premenopausal patients with breast cancer, in whom advances in hormonal and targeted therapies have improved mortality rates. However, treatment-related infertility is still poorly addressed, and in East Asia, there is limited discussion regarding management of treatment-related infertility.

**Methods:** A search of the literature was conducted using PubMed, Google Scholar, and Science Direct using the terms "breast cancer", "fertility preservation", "oocyte and embryonic cryopreservation", "GnRH-a co-administration", "ovarian tissue cryopreservation and transplantation", "Japan", "China", "Korea", and 'Singapore". Only studies published in English from 1980-2019 were included. The focus of the review was on identifying the current fertility preservation methods available to premenopausal women with breast cancer and the barriers that impede access.

**Results:** Fertility preservation options include GnRH-a co-administration to minimise treatment-associated infertility, oocyte and embryonic cryopreservation, and emerging treatments such as ovarian tissue cryopreservation and transplantation. In East Asia, the uptake of fertility preservation options has been limited despite it being a major patient concern. A lack of awareness of fertility preservation treatments hinders discussion between patients and clinicians about fertility preservation.

**Conclusion:** Despite progress in fertility preservation technologies, their impact for patients will be minimal if there is a lack of awareness/use of the technology. This review aims to raise awareness of such technologies among clinicians, enabling discussion between patients and clinicians about fertility preservation options.

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## Introduction

Recently, survival among patients with breast cancer has significantly improved. With better understanding of the disease's diverse biology and increased availability of treatments, the 5-year survival rate for women diagnosed with breast cancer has increased from 75.2% between 1975 and 1977 to 88.2% between 2001 and 2008, leading to a substantial increase in breast cancer survivors.[1] More strikingly, over 10% of breast cancer cases occur in women under age 45 years. Among these premenopausal survivors, 50% or more will live 20 years or longer following diagnosis. Thus, there is a need to address survivorship issues pertaining to long-term toxicity associated with breast cancer treatment.[1] A study showed that 20 038 premenopausal women are diagnosed with breast cancer annually in the United States, with an estimated 96% (19 416) of these premenopausal patients at risk of infertility because of chemotherapy or hormonal therapy.[1] Following chemotherapy, the reported incidence of amenorrhea varies between 40% and 68%.[2] The agents most responsible for inducing amenorrhoea and premature ovarian failure (POF) are alkylating agents such as cyclophosphamide, whereas antimetabolites have a lesser effect.[2] A brief summary of the association between infertility risk and type of chemotherapy can be seen in Table 1.[3,4]

Apart from chemotherapy, hormonal modulation with tamoxifen is beneficial for hormone receptor–positive disease, which accounts for 70% of breast cancers. A 5-year course of tamoxifen reduces recurrence by 47% and mortality by 26%.[5] However, tamoxifen is teratogenic, and pregnancy is contra-indicated during treatment; hence, pregnancy is often postponed. Although tamoxifen

 

may not directly damage the ovaries, several studies have reported its association with higher rates of treatment-related amenorrhea, particularly after age 40 years.[5] It is likely that tamoxifen's length of therapy may indirectly contribute to infertility alongside age-related fertility decline.[5] Apart from difficulties with conception, premenopausal patients with breast cancer also experience high rates of spontaneous abortion (29%) and premature deliveries with low birth weight (40%).[2]

Minimising cancer treatment–associated infertility is especially important for premenopausal women who have not yet established a family. Female infertility in premenopausal women can cause these women great distress by preventing them from achieving the important life and social goal of motherhood. A recent study ranks this among the top five concerns among patients with premenopausal breast cancer.[6] Moreover, in addition to impacting patients' mental health, the fear of infertility also impacts treatment compliance.[6] Of all patients, 29% do not comply with treatment because of treatment-associated infertility fears, which impacts patients' prognosis and life expectancy.[7-9]

While these fears are increasingly recognised by doctors, recent literature suggests that 32% of patients do not recall discussing fertility with their doctors. This lack of communication could be caused by a lack of awareness or confidence discussing fertility management in the context of breast cancer. This phenomenon was highlighted by a finding that 37% of oncologists feared delaying chemotherapy for fertility preservation, and 49% of oncologists were concerned about pregnancy safety after breast cancer treatment.[8,10] A Hong Kong study showed that only 45.6% of clinicians from diverse fields such as clinical oncology, haematology, obstetrics and gynaecology, paediatrics, and surgery were familiar with fertility preservation.[11] Unfortunately, this lack of clinicians' awareness is detrimental to premenopausal patients with breast cancer. Modern reproductive medicine can preserve female fertility in these patients.[12] This review aims to summarise the existing fertility preservation options for patients with breast cancer to enable clinicians to have informed discussions with their patients.


## 停經前乳癌患者的生殖保存

尹盛陽、龍浩峰、鍾佩樺、楊明明

**引言：**隨着癌症治療的進展，癌症存活變得越來越重要。將治療相關發病率降至最低應予注視。這種情況在停經前乳癌患者中最為緊迫，而即使激素和靶向療法因取得進展令死亡率有所改善，治療相關不育症仍未得到妥善處理。在東亞，有關治療相關不育症治療的討論仍然有限。

**方法：**使用PubMed、Google Scholar和Science Direct對文獻進行檢索，使用詞彙包括“乳癌”、“生殖保存”、“卵母細胞和胚胎冷凍保存”、“促性腺激素釋放激素激動劑聯合輸注”、“卵巢組織冷凍保存和移植”、“日本”、“中國”、“韓國”和“新加坡”。僅納入1980-2019年間以英文發表的研究。這篇綜述的重點在於確定目前停經前乳癌婦女可用的生殖保存方法以及相關的阻礙。

**結果：**生殖保存選項包括促性腺激素釋放激素激動劑聯合輸注將治療相關不育的機會減至最低、卵母細胞和胚胎的低溫保存以及新興治療方法，例如卵巢組織低溫保存和移植。在東亞，儘管患者對生殖保存非常關注，但有關選項仍有限。對生殖保存療法缺乏了解會阻礙患者和臨床醫生之間在這方面的討論。

**結論：**儘管生殖保存技術取得進展，但若果對這種技術缺乏了解和使用，對患者的影響將非常有限。這篇綜述旨在提高臨床醫生對此類技術的認識，使患者和臨床醫生之間能夠在生殖保存方案上進行討論。


## Methods

A literature search was conducted using PubMed, Google Scholar, and Science Direct using the terms "breast cancer", "fertility preservation", "oocyte and embryonic cryopreservation", "GnRH-a co-administration", and "ovarian tissue cryopreservation and transplantation". Only studies published in English from 1980 to 2019 were included. The focus of the literature review was on identifying the current fertility preservation methods available to premenopausal women with breast cancer and the barriers that impede access.

TABLE 1. List of common chemotherapeutic agents used in breast cancer and the risk of amenorrhoea[3,4]

| Risk of amenorrhoea | Chemotherapeutic agents used in breast cancer |
|---|---|
| High risk: >80% of women develop amenorrhea | CMF, CEF, CAF × 6 cycles in women aged ≥40 years<br>Cyclophosphamide 5 g/m² in women aged ≥40 years |
| Intermediate risk: 30%-70% develop amenorrhoea | AC in women aged ≥40 years<br>CMF or CEF or CAF × 6 cycles in women aged 30-39 years |
| Low risk: <20% develop amenorrhoea | AC aged <40 years<br>CMF, CEF, or CAF × 6 cycles aged <30 years |
| Very low/no risk: negligible risk of developing amenorrhoea | Pure methotrexate, 5-fluorouracil |
| Unknown risk | Paclitaxel, docetaxel (taxanes used in AC protocols) |

Abbreviations: AC = anthracycline, cytarabine; CAF = cyclophosphamide, adriamycin, 5-fluorouracil; CEF = cyclophosphamide, epirubicin, 5-fluorouracil; CMF = cyclophosphamide, methotrexate, 5-fluorouracil

### Co-administration of gonadotropin-releasing hormone agonist during chemotherapy

Chemotherapy accelerates follicular destruction, which reduces synthesis of inhibins and oestrogens. The use of adjuvant gonadotropin-releasing hormone agonist (GnRH-a) to limit chemotherapy-induced ovarian toxicity has been proposed by Glode et al.[13] Gonadotropin-releasing hormone agonist has been shown to be protective against ovarian follicular depletion in mice.[14,15] A current postulate on the protective mechanism of GnRH-a is the creation of a hypogonadotropic state. Reduced oestrogen and inhibin levels increase follicle-stimulating hormone (FSH) secretion via negative feedback. Consequently, supraphysiological FSH levels accelerate preantral follicle maturation and recruitment, which is vulnerable to chemotherapy. Gonadotropin-releasing hormone agonist induces pituitary desensitisation, preventing any increase in FSH concentration and hence minimising chemotherapy-induced follicle destruction.[16,17]

The evidence that GnRH-a reduces chemotherapy-associated POF and improves pregnancy rates is increasing.[18] The use of GnRH-a to preserve ovarian function and fertility has recently been recommended as a reliable strategy for at least breast cancer.[19] A pilot study undertaken by Recchia et al[20] reported that patients <40 years with breast cancer who received chemotherapy with GnRH-a co-treatment of 3.6 mg goserelin every 28 days for 1 year resumed cyclic ovarian function. Following a median follow-up of 79 months, Recchia et al[20] observed amenorrhea in none of the patients aged <40 years and 49% of patients aged >40 years. Four pregnancies were observed, three ended at term, and one was voluntarily terminated. Additionally, such a procedure did not affect the clinical outcomes of patients with breast cancer: after a median follow-up of 55 months, the disease-free survival and overall survival were 84% and 94%, respectively.[20] The limitation of that study was the absence of a parallel control group. However, the observed excellent survival rates lessen the theoretical risk of hormonal manipulation in oestrogen-sensitive cancers. Other studies have also shown reduced onset of POF and no significant disruption of cyclical ovarian function.[21,22]

Subsequent trials such as PROMISE-GIM6 have built upon the work by Del Mastro et al.[23] In the PROMISE-GIM6 trial, GnRH-a triptorelin 3.75 mg was administered intramuscularly at least 1 week prior to chemotherapy and subsequently every 4 weeks for the duration of chemotherapy. Patients were premenopausal women with stage I to III breast cancer who were offered adjuvant or neoadjuvant chemotherapy.[23] The early menopause rate was 25.9% in the control group and 8.9% in the triptorelin group: an absolute difference of -17% (95% confidence interval [95% CI]=-26% to -7.9%; P<0.001) was observed.[23] Another trial showed that in premenopausal women with either hormone-receptor-positive or hormone-receptor-negative breast cancer, concurrent administration of triptorelin and chemotherapy was associated with a higher long-term probability of recovery of ovarian function compared with chemotherapy alone, without a statistically significant difference in pregnancy rate.[24] Another recent prospective, randomised, parallel group study using GnRH-a goserelin administered prior and throughout chemotherapy for patients with stage I-IIIB breast cancer showed a reduction in the rate of POF for women aged <40 years.[7] Goserelin reduced the prevalence of amenorrhoea between 12 and 24 months from 38% in the control group to 22% in the treated group. The prevalence of POF was also reduced to 18.5% from 34.8% in the control group.[7] Finally, a meta-analysis of randomised control trials involving GnRH-a during chemotherapy in patients with premenopausal breast cancer showed a reduced rate of POF and increased pregnancy rate without negative prognostic consequences.[24] The meta-analysis included 12 trials involving 1231 breast cancer patients, and the data showed that GnRH-a was associated with a significantly reduced risk of POF (odds ratio=0.36, 95% CI=0.23-0.57; P<0.001).[25] Among the five trials that reported pregnancies, more patients treated with GnRH-a achieved pregnancy (33 vs 19 women; odds ratio=1.83, 95% CI=1.02-3.28; P=0.041). In the three studies that reported disease-free survival, no between-group difference was observed (hazard ratio=1.00, 95% CI=0.49-2.04; P=0.939).[25] These results suggest that GnRH-a provides improved fertility preservation for female patients with breast cancer without affecting cancer progression and survival rates.[24] However, data regarding live births (which are the primary goal of fertility preservation) following GnRH-a administration have been relatively scant. Currently, it seems that administration of GnRH-a to patients with breast cancer is a potentially beneficial fertility preservation strategy. The ease of GnRH-a co-administration also has the potential to benefit patients outside tertiary and university medical centres.

### Embryo and oocyte cryopreservation

Embryo cryopreservation is the most established fertility preservation technique and has entered routine clinical practice. Following oocyte harvesting, oocytes can be fertilised in vitro by donor or partner sperm and the embryos cryopreserved. The benefit of this technique is that embryos tend to survive cryopreservation better than oocytes. The improvements in vitrification technology have led to an even higher embryo survival rate.

An alternative to embryo cryopreservation is mature oocyte cryopreservation. After embryo cryopreservation, this is the second-most established technique, and it has entered clinical practice. An advantage to this technique over embryo cryopreservation is that it does not require sperm from a donor or partner, which is more suitable for single women.

Vitrification has enabled mature oocyte cryopreservation by improving oocyte survival rates and clinical outcomes.[26] A prospective, randomised study conducted with healthy young oocyte donors showed that a 97% survival rate was obtained through this technology.[26] Traditional cryopreservation exposes cells to low temperatures for prolonged periods causing, cytoplasmic ice crystal formation, which compromises cell survival upon thawing.[27] Vitrification is solidification that occurs without ice crystallisation but through extreme elevation in viscosity. This phenomenon is achieved using high cooling rates from -15 000 to -30 000°C/min, minimising ice crystal formation. Vitrification has been optimised to reduce cryoprotectant concentration and subsequent cytotoxicity.[28]

A study on mature oocyte cryopreservation via vitrification for non-oncological patients yielded 693 oocytes, of which 666 (96.1%) survived.[26] A total of 487 (73.1%) were then successfully fertilised, leading to 117 embryos transferred to 57 recipients. The pregnancy rate and implantation rate per transfer were 63.2% and 38.5%, respectively, resulting in 28 healthy babies born.[26] An overview of the work of several research groups shows that oocyte survival rates using this method have ranged between 91% and 99%, fertilisation rates were between 87% and 91%, and pregnancy rates were between 33% and 57%.[29-31] Subsequent work was done in cancer patients: 357 cancer patients had their oocytes cryopreserved, and 11 patients returned post-treatment for in vitro fertilisation (IVF).[32] The oocyte survival rate was 92.3%, the fertilisation rate was 76.6%, and average number of embryos transferred was 1.8±0.7. Four live births at term were achieved with no malformations.[32] Table 2 summarises some outcomes of the recent studies on oocyte cryopreservation for fertility preservation in cancer.[32,33]

Immature oocyte cryopreservation is another extension of oocyte cryopreservation technology. This technique is far less established, but it enables immature eggs to be removed before chemotherapy and have the eggs matured in vitro. This technique is suitable for single female patients who have oncological emergencies and cannot delay chemotherapy for ovarian stimulation. The benefit

TABLE 2. Compilation of recent studies summarising outcomes of oocyte cryopreservation for fertility preservation in cancer[32,33]

| Type of study | Patient details | Study design | Treatment outcomes |
|---|---|---|---|
| Prospective cohort study | Mean age 31.9 years (range, 15-43 years)<br>All recently diagnosed with cancer and were to start chemotherapy, radiotherapy, or both<br>493 Women who consulted for fertility preservation<br>357 Women had their oocytes cryopreserved<br>11 Women returned after being cured for assisted reproduction treatments<br>Of these 11 women, 8 had breast cancer, 1 Hodgkin lymphoma, 1 endometrial adenocarcinoma, and 1 thyroid cancer | In non-hormone-dependent cancer, ovarian stimulation protocol was started using recombinant FSH or GnRH antagonist protocol. In patients with 'hormone-dependent' cancer, a cycle of letrozole, recombinant FSH, GnRH antagonist, and GnRH agonist triptorelin was used<br>The Cryotop method was used for oocyte vitrification with minimal modifications. Embryos were selected for transfer strictly according to their morphological appearance | Outcomes: ovarian function in terms of preservation, fertility, and pregnancy<br>Ongoing pregnancy rate: No. of patients with at least one fetus with visible heart beating beyond 12 weeks/transfer<br>Oocyte survival: 92.3% (60/65)<br>Fertilisation rate: 76.6% (46/60)<br>Average No. of embryos transferred per patient (mean ± SD): 1.8 ± 0.7 (total: 22)<br>Implantation rate: 31.8% (7/22)<br>Clinical pregnancy rate: 54.5% (6/11)<br>Live births: 36.4% (4/11)<br>Pregnancies were delivered at term with normal birth weight and no congenital malformation<br>There were no multiple pregnancies or pregnancy complications |
| Retrospective cohort study | 1073 Patients with cancer<br>Mean age 32.3 ± 3.5 years<br>Returned to use cryopreserved oocytes: 7.5% (80/1073) | Ovarian stimulation protocol used antagonist and agonist protocols for patients with non-hormone-dependent cancer. Letrozole was added to the antagonist protocol for patients with hormone-responsive breast cancer tumours<br>The Cryotop method was used for oocyte vitrification with minimal modifications | Oocyte survival: 81.8% (495/605)<br>Implantation rate: 32.5% (27/83)<br>Clinical pregnancy rate: 30% (24/80)<br>Live births: 22.5% (18/80) |

Abbreviations: FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; SD = standard deviation

of immature oocytes over mature oocytes is their survivability: immature oocytes are relatively cryo-resistant because of their smaller size and lack of meiotic spindle. The greatest challenge for clinical translation of immature oocyte cryopreservation technology is the difficulties encountered during in vitro maturation of immature oocytes. Currently, only a single live birth has been reported following the slow freezing of immature oocytes.[34]

## Protocols of ovarian stimulation

Embryonic or oocyte cryopreservation is a proven approach in fertility preservation, especially in chemotherapy.[35] For both types of cryopreservation, a period of 8 to 12 days is needed for ovarian stimulation and subsequent oocyte harvesting. Traditionally but now uncommonly performed, the ovarian stimulation protocol begins with GnRH-a administration during the preceding cycle's luteal phase to promote ovarian quiescence followed by daily gonadotropin injections. Serial measurements of oestradiol levels and follicular diameter are taken for monitoring. When there are more than three dominant follicles present, human chorionic gonadotropin is administered to trigger ovulation and oocytes collected.[36] This protocol has many disadvantages, chiefly delay of the commencement of chemotherapy and high oestrogen exposure (which leads to increased risk of breast cancer progression and recurrence, particularly in hormone-sensitive breast cancer). Therefore, various new stimulation protocols have developed to enable either a shorter stimulation period or a lower oestrogen level during stimulation.

Random start protocols have been proposed to minimise the time for oocyte collection by decreasing total duration of the IVF cycle and have been shown to be equally effective as conventional start protocols in terms of the total number of mature oocytes retrieved, oocyte maturity rate, and fertilisation rate.[37-39] Other novel stimulation protocols with tamoxifen or aromatase inhibitors have been developed to increase the safety margin of ovarian stimulation in patients with oestrogen-sensitive tumours. Tamoxifen is a selective oestrogen receptor modulator. In addition to its anti-oestrogenic action in breast tissue, it acts as an antagonist in the central nervous system and interferes with the negative feedback exerted by oestrogen on the hypothalamic/pituitary axis, leading to an increase in GnRH secretion from the hypothalamus. A few studies have explored tamoxifen use for ovarian stimulation in patients with breast cancer.[40-42] A higher number of mature oocytes and subsequent embryos were obtained from the tamoxifen group compared with natural cycle, with at least one embryo generated per tamoxifen patient. Two patients conceived, one miscarried at 8 weeks of pregnancy, but her risk of spontaneous abortion was high at age 42 years. The other patient delivered a healthy set of twins.[40] In a more recent study, co-administration of tamoxifen with ovarian stimulation for fertility preservation did not interfere with IVF results. Comparisons were made between those who did and did not receive concurrent tamoxifen. The mean percentages of oocytes retrieved were 12.65% and 10.2%, respectively, and the numbers of embryos cryopreserved were 8.5 and 6.4, respectively.[42] Patients co-treated with tamoxifen had marginally higher oestradiol levels, but the difference was not statistically significant. However, co-treatment with tamoxifen was considered to be safe, as the long-term recurrence risk at up to 10 years was not increased.[42]

Aromatase inhibitors (eg, letrozole) significantly suppress plasma oestrogen levels by competitively inhibiting aromatase enzyme activity. Centrally, it releases the hypothalamic/pituitary axis from oestrogenic negative feedback, increasing secretion of FSH by the pituitary gland while increasing the FSH sensitivity of the ovarian granulosa cells. Combined letrozole-FSH protocols have resulted in oestradiol levels lower than those seen in natural cycles alongside fertility outcomes similar to standard IVF protocols.[43,44] In a recent trial, 131 women with stage ≤3 breast cancer underwent ovarian stimulation with concurrent daily letrozole 5 mg prior to cryopreserving embryos and subsequent adjuvant chemotherapy. The overall live birth rate per embryo transfer was similar to the United States national mean among infertile women of a similar age without cancer who underwent IVF–embryo transfer (45.0 vs 38.2; P=0.2).[45] Another trial highlighted the safety, feasibility, and utility of two consecutive ovarian stimulation cycles with the use of letrozole-gonadotropin protocol for fertility preservation in patients with breast cancer.[46] The mean total number of oocytes harvested (16.1 ± 13.2 vs 9.1 ± 5.2) and embryos generated (6.4 ± 2.9 vs 3.7 ± 3.1) were significantly higher in patients who underwent two cycles compared with those who underwent one cycle.[46] There was no significant delay in time interval from surgery to chemotherapy between the two-cycle and single-cycle groups (63.7 ± 7.7 vs 58.0 ± 12.1 days, respectively). The recurrence rate was similar between two-cycle (0 of 17) and single-cycle (2 of 49) patients.[46]

## Ovarian tissue cryopreservation and transplantation

Cryopreservation and autotransplantation of ovarian tissue are emerging technologies, and women considering such treatments should do so judiciously under specialised expertise in the setting of clinical trials. These techniques rely upon slow freezing technology used to cryopreserve oocytes and embryos, but it is more difficult to optimise the

procedure because ovaries contain many different cell types. Upon freezing and thawing, problems occur with fertilisation of maturing oocytes.[47] The best follicular survival rate is approximately 70% to 80%, with light microscopy revealing normal follicles. However, electron microscopy has detected ultrastructural changes.[48] The benefits of autotransplantation of ovarian tissue include restoration of endocrine and reproductive function; however, greater clinical evaluation of this technology is needed. Autotransplantation of ovarian tissue can be orthotopic or heterotopic. Orthotopic refers to transplantation of ovarian tissue to the original ovary site, while heterotopic refers to transplanting the ovarian tissue to a foreign site. Currently, the most effective site for graft longevity is still unknown. Orthotopic ovarian transplantation allows for natural conception, while heterotopic transplantation in accessible sites minimises repeated invasive procedures and improves ease of oocyte recovery.[49]

Oktay et al[50] reported restoration of hormonal function, follicular growth, and oocyte retrieval after heterotopic transplantation in a patient with breast cancer. They retrieved 20 oocytes from subcutaneously implanted ovarian tissue 6 years after chemotherapy resulting in one fertilisation, but no pregnancy ensued.[50] There have since been case reports of spontaneous pregnancy and live births after autotransplantation of cryopreserved human ovarian tissue in patients with cancer.[51,52] An early case report described a patient with triple negative medullary breast cancer undergoing ovarian tissue cryopreservation. Following cancer treatment, she underwent an ovarian tissue transplant, and menses occurred 63 days after transplantation. Sixteen mature oocytes were harvested following four sessions of ovarian stimulation. All vitrified oocytes survived thawing, and 77.7% were fertilised. Two day 3 embryos were implanted, and two healthy boys were born at 34 weeks.[53]

As of 2017, there have been an estimated 86 successful births and nine ongoing pregnancies using cryopreserved ovarian tissue internationally.[54] The majority of the patient population that has undergone this procedure has a cancer diagnosis, of which many are haematological malignancies, which require urgent chemotherapy. Furthermore, of the singleton pregnancies, the mean gestational age was 39 weeks, and the mean birth weight was 3168 g, which are within normal standards.[54] These early results suggest that ovarian tissue preservation and subsequent transplantation might become a suitable fertility preservation therapy in premenopausal women. A summary of a large case series of live births from ovarian tissue transplantation is shown in Table 3. It focuses on the perinatal outcomes of 40 live births from 32 women.[54] The reference also briefly compiles the 86 live births and nine ongoing pregnancies after transplantation of frozen-thawed ovarian cortex.[54]

The advantage of ovarian cryopreservation and transplantation is that it does not require an ovarian stimulation protocol, which delays cancer treatment. Additionally, this procedure is especially suitable for prepubescent cancer patients, in whom ovarian stimulation is contra-indicated. Moreover, ovarian cryopreservation and transplantation not only restores fertility but also restores gonadal/endocrine function. Finally, because hundreds of immature oocytes can be harvested at once, a huge ovarian reserve can be preserved. The disadvantage of

TABLE 3. Summary of ovarian tissue cryopreservation live births published in peer-reviewed papers[54]

| Patient demographics | Patient's medical history | Pregnancy details |
|---|---|---|
| No. of patients: 32<br><br>Mean age 25 years (range, 17-37 years) | Neoplastic: Hodgkin lymphoma, non-Hodgkin lymphoma, aplastic anaemia, Ewing's sarcoma, neuroectodermic tumour, granulosa cell tumour, breast cancer, ovarian cancer, bilateral teratoma, molar pregnancy<br><br>Haemoglobinopathies: sickle cell anaemia, thalassemia<br><br>Autoimmune conditions: microscopic polyangiitis, paroxysmal nocturnal haemoglobinuria<br><br>Gynaecological: pelvic inflammatory disease, primary ovarian insufficiency<br><br>All patients were confirmed to be menopausal using FSH, LH, and AMH prior to transplantation. Commonly cited indication for transplantation is poor ovarian function | Time from transplantation to pregnancy: mean 18 months, range 4-85 months<br><br>Gestation details:<br>Gestational age: mean 38 weeks, range 37-41 weeks<br>Pregnancy complications: HELLP syndrome, cholecystolithiasis, mild preeclampsia, hypothyroidism, cervical insufficiency<br><br>Delivery details:<br>Caesarean section: 17<br>Vaginal delivery: 13<br>Not specified: 7<br>Birth weight: mean 3076 g, range: 1650-4015 g<br><br>Birth details:<br>Total No. of births: 40 (male 21, female 19)<br>Natural conception: 17<br>Assisted reproduction techniques: 23<br>Sets of twins: 3 |

Abbreviations: AMH = anti-Mullerian hormone; FSH = follicle-stimulating hormone; HELLP syndrome = haemolysis, elevated liver enzymes, and a low platelet count; LH = luteinising hormone

ovarian tissue cryopreservation and transplantation is that it requires at least two surgical operations: one for removal and another for future re-implantation. Following implantation, there is the challenge of minimising ischaemia, which could lead to follicle loss or initiate maturation of the immature oocytes. To minimise follicle loss post-transplant, the entire ovarian cortex is often cryopreserved. Another potential concern of autotransplantation is the risk of cancer cell transmission, which has the highest probability in cases of haematological cancers. Shaw et al[55] reported lymphoma in mice with fresh or cryobanked grafted ovarian tissue from donor mice with lymphoma. Clinically, however, ovarian metastases are uncommon in cancers affecting young people.[56] Kim et al[57] reported in a mouse model that ovarian tissue from patients with high-grade lymphoma appears safe for autotransplantation, as none of the grafted mice tested positive for lymphoma. Further research is required to assess the optimal site for transplantation, improve methods of detecting residual disease in harvested tissue, ascertain the optimal size of ovarian grafts, optimise freezing/thawing techniques, and promote re-vascularisation of the transplanted tissue.

## Oncofertility in East Asia

In the context of Asia, the Asian Society for Fertility Preservation (ASFP) was established to promote the science and clinical application of fertility preservation techniques. The members of the ASFP include China, Hong Kong, Taiwan, Singapore, Korea, Japan, Vietnam, India, Thailand, Indonesia, the Philippines, and Pakistan. This review will focus broadly on fertility preservation care services in East Asia (ie, China, Singapore, Korea, and Japan), as seen in Table 4.

In Japan, oocyte, embryo, and ovarian tissue cryopreservation are available. However, despite the availability of the technology, uptake of fertility preservation techniques has been limited, as the majority of cancer hospitals do not provide fertility preservation services.[58] This problem is further compounded by the lack of robust coordinated care networks to assist in delivering oncofertility care.[58] To overcome this problem, the Japanese have been aggressively experimenting with various referral service models: (1) a reproductive care centre-led model wherein reproductive care centres reach out to cancer centres, and (2) a cancer centre model in which the cancer centre serves as the basis of the referral network.[59] To facilitate the running of the referral network, the Japanese have focused on harnessing allied health to drive a psychosocial-based care delivery system.[59] They aim to train oncofertility navigators that are able to provide psychosocial care whilst also guiding patients on the technical aspects of their fertility preservation journey.[59]

The efforts of the Korean Society for Fertility Preservation (KSFP) have produced a well-established referral network that even covers regional healthcare centres, rendering high-quality fertility preservation treatments accessible at various institutions.[58,60] Fertility preservation treatments have a multidisciplinary focus incorporating physicians, nurses, mental health professionals, office staff, and laboratory personnel.[58,60] To facilitate patient communication regarding fertility preservation under the time pressure of cancer treatment, print material and web resources are distributed to patients during the fertility preservation consultation.[58,60] However, despite this concerted effort, uptake of fertility preservation treatments has been limited.[60] The main issue raised by the KSFP was access to care: the oncologists noted that there was a lack of discussion of fertility preservation options and referrals to fertility specialists.[60] This may be for several reasons: exclusive focus on cancer treatment and its perceived urgency, the perception of limited options for fertility preservation, the perception that fertility is unimportant to patients, and not knowing the referral pathway for patients interested in fertility preservation.[60]

Like many East Asian countries, China has the technology to perform fertility preservation techniques. However, similarly, the limiting factor for uptake of these technologies is barriers to access. Like in Korea, there is a lack of knowledge and awareness of fertility preservation techniques among healthcare professionals: among obstetrics and gynaecology specialists, despite knowing about cancer therapy

TABLE 4. Broad overview of oncofertility care services across East Asia[58]

| Country | Established fertility preservation society | Local guidelines | Information for patients easily available on the internet | Referral system | Legal involvement | Insurance coverag |
|---|---|---|---|---|---|---|
| Japan | Yes | Yes | Yes | Yes | Yes | Partial |
| Korea | Yes | Yes | Yes | Yes | Yes | Partial |
| China | Yes | No | No | No | No | No |
| Singapore | Yes | No | No | No | No | No |

being gonadotoxic, about 20% of them were not familiar with fertility preservation techniques.[61] Only 50% of obstetrics and gynaecology specialists who were familiar with fertility preservation techniques had been consulted by oncologists about managing a patient's infertility risk.[61] Despite this, 96.6% of obstetrics and gynaecology specialists reported being keen on collaborating with oncologists to preserve the fertility of female patients with cancer.[61] This suggests that despite a willingness to collaborate on fertility preservation, there has been limited communication between oncologists and obstetrics and gynaecology specialists.

Finally, Singapore, being a small city-state, has limited resources for fertility preservation care delivery services: in fact, it does not have a fertility preservation society.[58] All fertility preservation services are concentrated in one large tertiary hospital in Singapore.[58] Reproductive preservation techniques exist in Singapore; however, access to them is again limited by both the patient's and oncologist's knowledge and awareness of the technology.[58]

## Discussion

Fertility preservation is a major concern for premenopausal patients. Hence, at the outset of chemotherapy, its gonadotoxic effects must be discussed by a multidisciplinary team. When discussing fertility preservation options, their nature, success rate, risk, cost, and potential ethical implications should be discussed with the patient.[62] Additionally, it is important to set realistic expectations about the fertility preservation treatment with the patient: factors such as patient age, ovarian reserve, presence of a partner, presence of previous live births, financial status, and religious background should be considered.[62] Finally, medical factors that may influence the feasibility of fertility preservation, such as severity of the gonadotoxic chemotherapy, time available before commencing chemotherapy, and available expertise and facilities, should also be explained to the patient. A sample decision algorithm for deciding about the suitability of fertility preservation options in both emerging and routine clinical practice is shown in the Figure.

Another common patient concern is cancer recurrence or disease progression due to future pregnancy. This fear may cause patients to delay or abandon future pregnancies. A meta-analysis showed that women who become pregnant following breast cancer treatment have an improved prognosis, reflected by significantly increased overall survival compared with those who did not become pregnant (pooled hazard ratio=0.63, 95% CI=0.51-0.79).[63] The meta-analysis also revealed a non-significant increase in disease-free survival for pregnant women.[63] The meta-analysis findings, however, may be due to a selection bias termed the "healthy mother" effect, where healthier women are more likely to conceive than those who have relapsed hence skewing the true effect.[64] Nonetheless a subsequent multicentre case-control study has supported the conclusion of the meta-analysis regarding pregnancy safety following breast cancer treatment.[65] At 7.2 years after pregnancy, no difference in disease-free survival was observed between pregnant and nonpregnant patients.[65] Although there was no

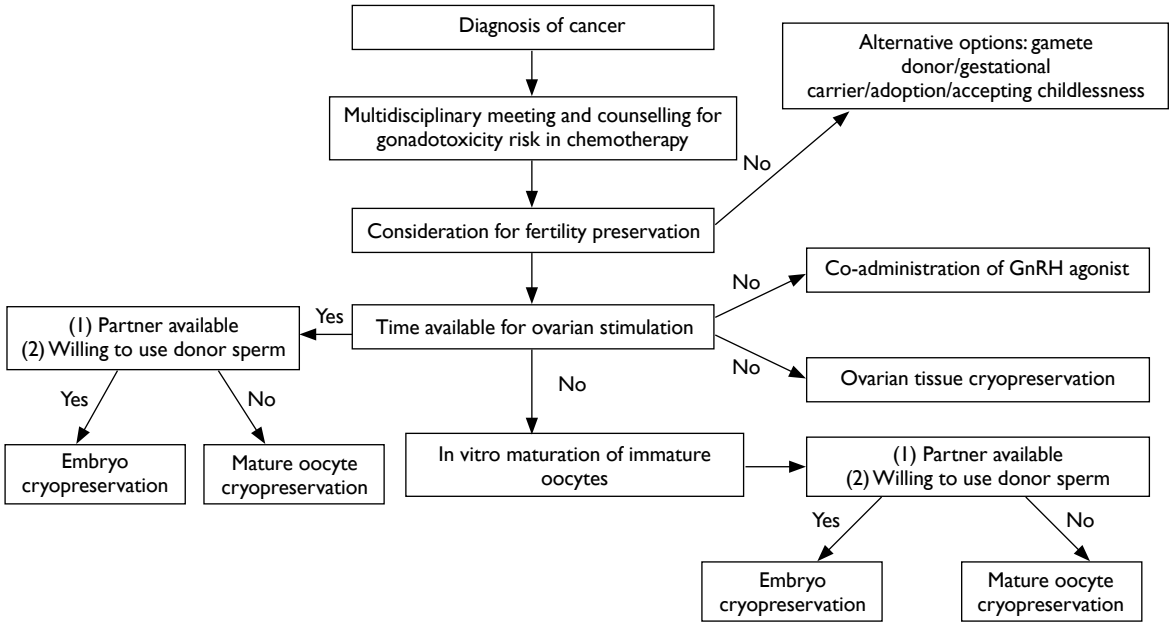


FIG. Sample decision algorithm for deciding suitable fertility preservation options
Abbreviation: GnRH = gonadotropin-releasing hormone

difference in overall survival for oestrogen receptor–positive pregnant patients, there was an increased overall survival for oestrogen receptor–negative patients.[65] Therefore, pregnancy is being considered safe following previous breast cancer diagnosis and maybe associated with an improved prognosis for oestrogen receptor–negative patients.

All of the patient's fears and concerns regarding fertility preservation should be discussed with a dedicated oncofertility unit. This allows for informed discussion between patient and healthcare practitioner, which can help to allay patients' fears. Such communication can be facilitated via printouts, brochures, and decision aids, which can help to avoid miscommunication and allow patients to be fully informed of their potential choices in fertility preservation. Research has shown that a dedicated oncofertility unit can improve the frequency and thoroughness of fertility preservation discussions.[66] This research is particularly relevant, as oncofertility units allow focus on young cancer patients, including those with breast cancer, who will benefit the most from fertility preservation options.

## Conclusions

Fertility preservation is still a major issue for premenopausal patients with breast cancer. Several treatment modalities can now be considered and combined.[67] A potential fertility preservation protocol for premenopausal patients with breast cancer could involve an initial oocyte and ovarian tissue harvest and subsequent cryopreservation of oocytes, embryos, and ovarian tissue. Gonadotropin-releasing hormone agonist can be co-administrated alongside chemotherapy to minimise POF.

This review aimed to summarise and evaluate the current clinical status of fertility preservation techniques available to premenopausal patients with breast cancer, thereby raising awareness of fertility preservation techniques among oncologists, fertility specialists, surgeons, nurses, and psychologists who care for premenopausal patients with breast cancer. Hopefully, a multidisciplinary and holistic approach to fertility preservation treatments for premenopausal patients with breast cancer will be possible in East Asia.

### Author contributions

Concept or design: SSY Wang.
Acquisition of data: SSY Wang.
Analysis or interpretation of data: All authors.
Drafting of the manuscript: All authors.
Critical revision of the manuscript for important intellectual content: All authors.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

### Conflicts of interest

As editors of the journal, H Loong and JPW Chung were not involved in the peer review process. Other authors have no conflicts of interest to declare.

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