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Review

Strategies for fertility preservation in young early breast cancer patients

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ABSTRACT

Diagnosis of breast cancer in young women poses a threat to fertility. Due to a recent trend of delaying pregnancy, an increasing number of breast cancer patients in reproductive age wish to bear children. Health care providers have the responsibility to know how to manage fertility issues in cancer survivors. Oncofertility counseling is of great importance to many young women diagnosed with cancer and should be managed in a multi-disciplinary background. Most of young breast cancer patients are candidate to receive chemotherapy, which could lead to premature ovarian failure. A baseline evaluation of ovarian reserve may help in considering the different fertility preservation options. The choice of the suitable strategy depends also on age, type of chemotherapy, partner status and patients' motivation. Various options are available, some established such as embryo and oocyte cryopreservation, some still experimental such as ovarian tissue cryopreservation and ovarian suppression with GnRHa during chemotherapy. An early referral to a reproductive specialist should be offered to patients at risk of infertility who are interested in fertility preservation.

Introduction

About 12% of breast cancers are diagnosed in women younger than 44 years of age [1]. Tumors that occur in young women seem to be more aggressive than the one arising in older patients [2], with higher rate of nodal disease, triple negative immunohistochemical profile and need of systemic treatments [3,4]. Adjuvant chemotherapy and endocrine treatments have improved both disease-free survival (DFS) and overall survival (OS) in young breast cancer patients [5], but may cause acute and chronic side effects, including ovarian function loss. Chemotherapy related-infertility and early menopause cause psychological distress and negative impacts on global health of young breast cancer survivors [6]. Moreover, due to the fact that women decide to have children at a later stage of life, they can be childless or may want to enlarge their family at the time of breast cancer diagnosis [7].

Health care providers should be knowledgeable about guidelines on fertility preservation in cancer patients [8–10]. They have the responsibility to raise awareness on potential fertility problems related to cancer and anticancer treatments and should be able to deal with these issues. Every young patient who is candidate to chemotherapy should receive information about ovarian damage due to cancer treatments. In fact, irrespective of the occurrence of transient amenorrhea following anticancer therapies, young cancer patients are at risk of losing fertility nonetheless, due to a depletion of the ovarian reserve [11,12]. If patients show interest about future procreation, physicians should reassure them that pregnancy after breast cancer is possible, and that a previous diagnosis of breast cancer does not increase the obstetrical or oncological risk. Fertility preservation options should be illustrated, highlighting success rates, costs, as well as the risks inherent to the procedures and their ethical implications [13].

The purpose of this paper is to review the literature on fertility issues in young breast cancer patients and to focus on the key points of appropriate counseling, including evaluation of ovarian reserve, discussion about chemotherapy-induced gonadotoxicity and the impact of a subsequent pregnancy on breast cancer

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prognosis, as well as a description of all the available options to preserve fertility.

Ovarian reserve and prediction of ovarian damage due to anticancer treatments

The ovaries have a reserve of primordial follicles, progressively depleting during reproductive life [14]. These follicles cannot regenerate. Some antineoplastic agents increase the rate of follicle loss, inducing premature ovarian failure (POF). POF leads to infertility and early menopause, and is associated with hot flashes, sexual dysfunction, mood disturbances and an increased risk of osteoporosis.

The assessment of ovarian reserve is best performed through antral follicle count, follicle-stimulating hormone (FSH), estradiol and anti-Mullerian hormone (AMH) [15,16]. Among these, AMH levels seem to be the most reliable and promising marker of remaining fertility after chemotherapy [17]. AMH is produced by the granulosa cells of small antral follicles: its levels are proportional to primordial follicle count and seem a good estimate of ovarian reserve. They are also used to predict ovarian response to a hormonal stimulation and *in vitro* fertilization (IVF) treatment [18]. Nevertheless, future researches are needed to better define the clinical role of AMH in patients with early breast cancer, particularly its role in predicting treatment-induced infertility.

Ovarian reserve should guide fertility counseling, as it may influence the impact of chemotherapy on further reproduction and the success of fertility preservation techniques [13]. Amenorrhea is often used as a synonym of ovarian damage, but it is a rather inaccurate marker of fertility. Women may have regular menses after chemotherapy but may be subfertile, and vice versa.

Unfortunately, data on molecular markers of ovarian damage are limited and further studies are needed in order to investigate their role as predictors of chemotherapy-induced gonadotoxicity.

Chemotherapy-induced gonadotoxicity

Antineoplastic drugs are known to have different gonadotoxicity. The rate of chemotherapy related infertility is variable and depends on several factors: class, dose, dose-intensity of the drug used, method of administration (oral vs intravenous), age of the patient, disease, history of previous treatment for infertility and comorbidities (Table 1) [8].

High risk of ovarian failure is associated with alkylating agents like cyclophosphamide. Anthracyclines alone and anthracyclines in association with taxanes have an intermediate risk, whereas methotrexate and 5-fluorouracil demonstrate low risk of ovarian damage [19,20].

Chemotherapy-induced ovarian toxicity has been attributed to two major mechanisms: direct induction of oocyte apoptosis and indirect effect via stromal damage.

Morphological observations demonstrate a reduction in primordial follicle stockpiles and vascular damage with infarcts related to hyalinization of ovarian cortical vessels, intimal fibrosis and thickening of the muscular layer [21,22]. Furthermore, subcapsular cortical fibrosis has also been described with reduced ovarian weight and macroscopic signs of atrophy after chemotherapy [22].

A recent *in vivo* study analyzed the effect of cyclophosphamide administration on the ovaries of mice [23]. Physiologically dormant primordial follicles represent the ovarian reserve: once activated, they initiate unidirectional and irreversible growth until ovulation or atresia. In normal ovaries there is a balance between activation and inhibition factors that maintain most of the primordial follicles in a dormant state. It was observed that cyclophosphamide disturbs this equilibrium, inducing an increase in follicle activation. Hence, growing and proliferating follicles become susceptible to cyclophosphamide-induced apoptosis. Continuous recruitment of primordial follicles into activation, growth and apoptosis cause ovarian reservoir burnout [23].

Table 1
Risk of permanent amenorrhea in breast cancer patients treated with anticancer therapies [modified from the original [8]].

Degree of risk	Type of anticancer treatment
High risk (>80%)	- CMF, CEF, CAF, TAC × 6 cycles in women ≥40 years.
Intermediate risk	- CMF, CEF, CAF, TAC × 6 cycles in women age 30–39; -AC × 4 cycles in women ≥40 years; - AC or EC × 4 → T.
Lower risk (<20%)	- CMF, CEF, CAF, TAC × 6 cycles in women ≤30 years; - AC × 4 cycles in women ≤40 years.
Very low or no risk	- Methotreaxte; - Fluorouracil; - Tamoxifen; - GnRHa in women ≥40 years;
Unknown risk	- Monoclonal antibodies (trastuzumab).

Abbreviations: CMF, cyclophosphamide/methotrexate/fluorouracil; CEF, cyclophosphamide/epirubicin/fluorouracil; CAF, cyclophosphamide/doxorubicin/fluorouracil; TAC, docetaxel/doxorubicin/cyclophosphamide; AC, doxorubicin/cyclophosphamide; EC, epirubicin/cyclophosphamide; T, taxane; GnRHa, gonadotropin releasing hormone analogues.

Influence of pregnancy on breast cancer prognosis

Historically, based on purely theoretical assumptions, pregnancy after breast cancer was not recommended due to the fear of a potential negative impact on patients' prognosis. Recent clinical data do not confirm such hypothesis and all the available evidences suggest that spontaneous pregnancy after breast cancer does not affect prognosis.

Case–control and population-based studies have been conducted to evaluate survival in women who become pregnant after breast cancer. The hormonal changes during pregnancy are complex and do not seem to have a negative impact on breast cancer prognosis [24].

A meta-analysis of fourteen studies reported a significant improvement in OS with a 41% reduced risk of death (pooled relative risk [PRR]: 0.59; Confidence Interval [CI]: 0.50–0.70) in women who became pregnant after breast cancer compared with those who did not get pregnant after cancer [25]. Some authors introduced the concept of the "healthy mother effect" [26]: a possible explanation of this improved outcome could be the selection bias of healthier women. To investigate this confounding factor, a subgroup analysis was performed in the previously cited meta-analysis, restricting the field to non-relapsing patients. Pregnant women maintained a non-statistically significant trend toward better survival [25].

Recently, a multicenter retrospective cohort study with the aim to better clarify the impact of pregnancy on DFS in breast cancer patients according to estrogen receptor status was published [27]. No difference in DFS was observed between pregnant and non-pregnant patients in the estrogen-receptor-positive group (the primary end point of the study: hazard ratio [HR]: 0.91; 95% CI: 0.67–1.24) or in the estrogen receptor negative cohort (HR: 0.75; 95% CI: 0.51–1.08). However the pregnant group showed a better OS with a 28% reduced risk of death (HR: 0.72; 95% CI: 0.54–0.97) without an interaction with the estrogen receptor status [27].

Hence, it is reasonable to state that pregnancy after breast cancer could be considered safe even for patients with a history of endocrine-sensitive breast cancer, and that women should not be discouraged in completing their family plan.

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It is not clear yet how much time should elapse between the end of anticancer treatments and conception. Experts recommend avoiding pregnancy within 2 years after breast cancer diagnosis, to avoid early relapse [28] but no biological rationale or supporting evidence exists to define a "gold standard time" for women to become subsequently pregnant [29]. Recently, the Breast International Group and North American Breast Cancer Group (BIG-NABCG) have planned a study on this issue [30]. This is a prospective trial directed to young patients with endocrine-sensitive breast cancer who wish to become pregnant and who are free of disease after 18–30 months of adjuvant hormonal therapy. The main objectives of this trial are to evaluate the feasibility and the impact of a temporary treatment interruption to allow conception, focusing both on pregnancy outcome (abortion, miscarriage, ectopic stillbirth, live birth rates), birth (preterm birth, low birth weight, birth defects rates) and breast cancer outcomes (DFS and OS) [30]. So far, the timing for women to become subsequently pregnant should be "personalized" taking into account the age of patients, their risk of relapse, the previous treatments received and the need for adjuvant endocrine therapy [31,32].

Strategies for fertility preservation in breast cancer patients

There are four main available options, standard and experimental, for fertility preservation in breast cancer patients (Table 2): oocytes and embryo cryopreservation, ovarian tissue cryopreservation and the ovarian suppression with gonadotropin releasing hormone analogues (GnRHa).

Oocytes and embryos cryopreservation

Cryopreservation of embryos and oocytes are considered standard strategies and are the recommended fertility preservation options for breast cancer patients [33]. Embryo cryopreservation has been the only established procedure for fertility preservation for many years, but since January 2013, cryopreservation of oocytes is no longer considered experimental [34]. The main advantages of oocytes cryopreservation over embryo cryopreservation are the applicability even in patients without a partner and in countries where embryo cryopreservation is prohibited. Not all breast cancer patients are good candidates for these two techniques. They requires a delay in chemotherapy initiation by 2–6 weeks (standard ovarian stimulation lasting about 9–15 days) and can only be proposed to patients under the age of 38–40 years with a good ovarian reserve.

There are still some concerns about the possible impact of the ovarian stimulation required for the collection of oocytes on breast cancer prognosis. With the aim to reduce the potential risk of short-term exposure to high estrogen levels, alternative approaches using concomitant administration of letrozole or tamoxifen have been proposed (controlled ovarian stimulation) [35–37]. During controlled ovarian stimulation, estrogen levels remain similar to those of spontaneous cycles and oocyte and embryo collection was comparable to that obtained after standard ovarian stimulation. A few years ago, Azim et al. carried out a prospective non-randomized controlled study, to determine whether ovarian stimulation with the concurrent administration of letrozole and gonadotropins before chemotherapy could affect breast cancer recurrence and prognosis [38]. Out of the 215 breast cancer patients evaluated before adjuvant chemotherapy, 79 underwent embryo or oocyte cryopreservation: the remained 136 patients underwent no procedures for fertility preservation and served as control population. At a median follow-up of 23.4 months after the end of the chemotherapy (range: 7.5–63.6 months), the HR for recurrence was 0.56 (95% CI: 0.17–1.9) and the survival of patients who underwent controlled ovarian stimulation for IVF procedures was not compromised compared with the control ($P = 0.36$) [38]. However long-term follow-up and future research are needed to confirm these promising results.

Few data are available on pregnancies occurring after embryo or oocyte cryopreservation: therefore, to estimate the potential pregnancy rate of these strategies, it is necessary to consider data derived from the age-matched infertile population [39,40]. As reported by the US database for assisted reproductive technology in 2011, the pregnancy rate is approximately 27% after embryo cryopreservation, with a higher percentage for women under 35 years [41]. Good results are also obtained from oocyte cryopreservation, thanks to ultra-rapid freezing (vitrification) which has decreased the oocyte damage rate compared to the traditional freezing process [40]. With the slow freezing procedure, a recent publication showed a pregnancy rate per transfer of 22.8% [42]; oocytes vitrification seems to be a more efficient and reliable approach with a pregnancy rate per transfer of 29.4% [43].

In the attempt to avoid the delayed start of chemotherapy, two emerging strategies are being developed: cryopreservation of immature oocyte and oocytes matured *in vitro*. With these techniques, oocytes collection can be obtained without hormonal stimulation or with a short stimulation lasting 3–5 days. Immature oocytes can be cryopreserved after *in vitro* maturation or cryopreserved at the immature stage and then matured *in vitro* after thawing. These techniques should still be considered experimental as they guarantee lower effectiveness than the standard strategy with the cryopreservation of mature MII oocytes; no data are available to estimate the potential pregnancy rate with these techniques [44,45].

Table 2
Main characteristics of the available options for fertility preservation in breast cancer patients.

Type of strategy	Definition	Experimental or standard strategy	Ovarian stimulation required	Delay in the initiation of cancer therapy	Surgery required	Preservation of ovarian function	Available in all centers
Oocyte cryopreservation	Harvesting and freezing of unfertilized eggs	Standard	Yes	Yes	Yes	No	No
Embryo cryopreservation	Harvesting eggs, *in vitro* fertilization, and freezing of embryos	Standard	Yes	Yes	Yes	No	No
Ovarian tissue cryopreservation	Freezing of ovarian tissue and re-implantation after cancer treatment	Experimental	No	No	Yes	Yes[a]	No
Ovarian suppression with GnRHa	Use of hormonal therapies to protect ovarian tissue during chemotherapy.	Experimental	No	No	No	Yes[a]	Yes

Abbreviation: GnRHa, gonadotropin releasing hormone analogues.
[a] No data are available about the long-term recovery of ovarian function.

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Ovarian tissue cryopreservation

Up to now, freezing and transplantation of ovarian tissue should be still considered experimental [9]. Worldwide, around 30 live births have been reported after transplantation of cryopreserved ovarian tissue [46,47], but no data are available so far to estimate the potential pregnancy rate of this strategy. This procedure has also the potential of restoring normal FSH and estrogen levels, thus reducing the detrimental effects of POF. Restoration of ovarian function after re-implantation is expected in 3–6 months [48]. Nonetheless, controversy about this procedure still remains [49,50].

A minimum of two operations is required, with a cost of around 572–636 US dollars for each operation. Ovarian tissue could be stored as a whole ovary, fragments of ovarian cortex or isolated follicles. When the tissue is re-implanted, there is a potential hypoxia-induced loss of primordial follicles and a risk of re-introducing malignant cells [51–53]. The technique does not require a delay in the initiation of anticancer treatments; furthermore, it is the only possibility of cryopreservation for pre-menarchal patients as it requires no hormone stimulation, which is necessary for both embryo or oocyte freezing [53–55]. Studies are being conducted on better freezing–thawing methods, better revascularization techniques of the transplanted tissue, optimal grafting sites and reliable methods to detect residual disease in grafts [50,53].

Ovarian suppression with GnRHa

The GnRH is a hypothalamic neuropeptide, which controls pituitary secretion of FSH and luteinizing hormone (LH). The wavering of these hormones regulates two ovarian functions: steroidogenesis and gametogenesis. Synthetic GnRHa is a decapeptide derived from the native hormone, with a higher affinity to pituitary receptors and a prolonged bioavailability. GnRH agonists initially have a flare up effect, stimulating the release of FSH and LH and chronic administration results in a down-regulation of GnRH receptors and a long-term desensitization of gonadotropins decreasing FSH secretion and thus suppressing ovarian function.

The reasoning behind the use of GnRHa to reduce the gonadal toxicity of chemotherapy is the observation that chemotherapy mostly affects tissues with a rapid cellular turnover; a state of induced gonadal inhibition during exposure to cytotoxic drugs may protect the ovaries [56]. The inhibitory effect of GnRHa on ovarian function, has been hypothesized to reduce chemotherapy toxicity on the gonads [57].

Preclinical data in animal models (rats and rhesus monkeys) confirmed the potential protective effect of GnRHa against the gonadotoxicity of chemotherapy [58–60].

The potential protective effect of GnRHa for the prevention of chemotherapy-induced POF in breast cancer patients has been investigated in several observational and phase II studies. A large majority (70%–100%) of women with breast cancer treated with GnRHa during chemotherapy did not experience POF [61–64].

Six phase III studies investigating the efficacy of such strategy to preserve ovarian function in breast cancer patients candidates for chemotherapy have been recently published (Table 3) [65–70]. In these studies, breast cancer patients were randomly assigned to receive adjuvant and/or neo-adjuvant chemotherapy in combination with GnRHa or chemotherapy alone. These studies reported conflicting results. Major limitations of these studies are: heterogeneous target population, differences in the selection of patients enrolled in the studies, different patients' age at the study entry, differences in chemotherapy regimens used, different duration of follow-up, and differences in the end points identified to assess treatment efficacy (Table 3).

The results of these studies have recently been analyzed in several meta-analysis, demonstrating the fact that there is still active debate on the potential effectiveness of this strategy (Table 4) [71–76].

Two meta-analysis were specifically designed to assess the efficacy of GnRHa administration to prevent chemotherapy-induced POF in breast cancer patients [74,75]. The meta-analysis by Yang et al. included five randomized clinical trials for a total number of 528 patients: significantly fewer patients in the GnRHa group experienced post-treatment POF (risk ratio [RR]: 0.40; 95% CI: 0.21–0.75). However, similar rates of resumed menses (RR: 1.31; 95% CI: 0.93–1.85) and spontaneous pregnancy (RR: 0.96; 95% CI: 0.20–4.56) were shown in both groups [75]. The meta-analysis by Wang and colleagues included seven randomized studies with a total of 677 participants: compared with adjuvant chemotherapy alone, the number of breast cancer women with resumption of spontaneous menstruation was statistically bigger in the GnRHa co-treatment group (odds ratio [OR]: 2.83; 95% CI: 1.52–5.25) [74]. Overall, the available meta-analysis showed a uniform benefit of the administration of GnRHa in the prevention of chemotherapy-induced POF. Nevertheless, it should be noted that this technique has been developed as a strategy for hormonal ovarian function

Table 3
Main characteristics of the phase III studies evaluating the efficacy of GnRHa for the prevention of chemotherapy-induced ovarian failure in breast cancer patients.

Authors and year of publication	Number of patients included	Median age (years) GnRHa + CT arm vs CT alone arm	Treatment arms	Definition of POF in the studies	Timing of end point assessment in the studies
Badawy et al., 2009 [65]	78	30 vs 29.2	FAC + goserelin vs FAC	No resumption of spontaneous ovulation	8 months after the end of CT
Del Mastro et al., 2011 [66]	281	39 vs 39	CT + triptorelin vs CT	No resumption of menstrual activity and postmenopausal levels of FSH and E2	12 months after the end of CT
Gerber et al., 2011 [67]	60	35 vs 38.5	CT + goserelin vs CT	No reappearance of two consecutive menstrual periods within 21–35 days	6 months after the last administration of GnRHa
Munster et al., 2012 [68]	47	39 vs 38	CT + triptorelin vs CT	No maintenance of menses and no resumption of menses	24 months after the end of CT
Sverrisdottir et al., 2009 [69]	94	45 vs 45	CMF + Tamoxifen + goserelin vs CMF + Tamoxifen	Absence of menses	36 months after the end of CT
Elgindy et al., 2013 [70]	93	Not reported	CT + triptorelin + GnRH antagonist vs CT	No resumption of menstruation	12 months after the end of CT

Abbreviations: GnRHa, gonadotropin releasing hormone analogues; CT, chemotherapy; POF, premature ovarian failure; FAC, fluorouracil, doxorubicin and cyclophosphamide; CMF, cyclophosphamide, methotrexate, fluorouracil; FSH, follicle-stimulating hormone; E2, estradiol.

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Table 4
Available meta-analyses that evaluated the role of GnRHa in the prevention of chemotherapy-induced POF which included the available trials in breast cancer patients.

Authors and year of publication	Number of patients included	Type of disease	Total number of studies included in the meta-analysis	Main results of the meta-analysis
Kim et al., 2010 [71]	124	Breast cancer, HL and NHL	11[a]	Concerning only randomized studies, no statistically significant difference between GnRHa group and control group was showed: OR = 5.76 (95% CI: 0.47–71.03). Including non-randomized trials, it was showed increased odds of maintaining ovarian function in GnRHa group (OR = 10.57; 95% CI: 5.22–21.39).
Bedaiwy et al., 2009 [72]	340	Breast cancer, HL and ovarian cancer	6	A statistically significant difference in the rates of spontaneous resumption of menses in favor of the use of GnRHa was showed (OR = 3.46; 95% CI: 1.13–10.57).
Chen et al., 2011 [73]	157	Breast cancer and HL	4	The administration of GnRHa showed a protective effect on menstruation resumption after chemotherapy (OR = 1.90; 95% CI: 1.33–2.70).
Wang et al., 2013 [74]	677	Breast cancer	7	The number of patients with resumption of spontaneous menstruation was statistically greater in the GnRHa group (OR = 2.83; 95% CI: 1.52–5.25).
Yang et al., 2013 [75]	528	Breast cancer	5	The POF rate in the GnRHa group was 60% lower than in the control group (OR = 0.40; 95% CI: 0.21–0.75). In contrast, both treatment groups experienced similar rates of resumed menses (OR = 1.31; 95% CI: 0.93–1.85).
Del Mastro et al., 2014 [76]	765	Breast cancer, HL, NHL and ovarian cancer	9	The pooled OR estimate indicated a highly significant reduction in the risk of POF (OR = 0.43; 95% CI: 0.22–0.84; $p = 0.013$) in patients receiving GnRHa.

Abbreviations: GnRHa, gonadotropin releasing hormone analogues; POF, premature ovarian failure; HL, Hodgkin's lymphoma; NHL, non Hodgkin's lymphoma; OR, odds ratio; CI, confidence interval.
[a] Authors included 8 non-randomized studies.

preservation more than as a technique for fertility preservation; moreover, so far, no data are available on the efficacy of GnRHa administration in terms of long-term ovarian function and of pregnancy rates. For these reasons, the recently published guidelines of the American Society of Clinical Oncology (ASCO) consider this strategy still experimental [9] and also the guidelines of the European Society for Medical Oncology (ESMO) do not recommend this strategy for fertility preservation [10].

Discussion

In vitro fertilization and embryo cryopreservation are considered standard techniques for fertility preservation in women who have a partner and the few data available about pregnancy rate are encouraging [9] (Table 5). Cryopreservation of unfertilized oocytes is an alternative standard method, especially for women without a partner [9] (Table 5). Both of these techniques require a good ovarian reserve and hormonal stimulation for follicle recruitment and growth. Ovarian stimulation and oocyte collection take 2–5 weeks, resulting in a delay in the start of the chemotherapy. Only patients who do not necessitate a prompt start of systemic treatment are candidate to these procedures [9]. Freezing and *in vitro* maturation of immature oocytes take less time but have lower effectiveness than mature oocytes cryopreservation. Women should be referred to a reproductive specialist shortly after surgery to minimize the time loss.

For women who cannot delay the beginning of chemotherapy, ovarian tissue cryopreservation may be considered. This is a promising but still experimental procedure, which may save fertility and steroidogenic function (Table 5). However concerns exist about the potential risk of an inadvertent transfer of malignant cells with the ovary. For this reason, an accurate histological analysis of ovarian biopsies before re-implantation is mandatory [9].

Ovarian suppression through GnRHa administered before the start of chemotherapy and during the entire period of cytotoxic treatment has shown conflicting results, as previously discussed. The potential preservation of the overall ovarian function, the accessibility in every cancer center and the fact that this method does not require an invasive procedure are considered advantageous. Furthermore, it could be combined with other fertility preservation strategies with an expected improvement of fertility outcome [77]. On the other hand, few data are available on the long-term efficacy and ASCO and ESMO guidelines still consider this strategy experimental [9,10] (Table 5).

Again, in a pharmacological setting, a recent study investigated the mechanisms responsible for cyclophosphamide-induced gonadotoxicity and the role of an immunomodulator, called AS101, as an ovarian protective agent [23]. Preliminary results look encouraging and co-administration of AS101 and cyclophosphamide seems to reduce follicle loss, but further confirmation is required.

The reported findings highlight the need of further research: understanding the pathway damage could lead to new preventive strategies aimed to avoid the premature loss of ovarian function.

Although these techniques appear to be potentially valuable methods, many controversies remain about which patient may benefit from these fertility preservation strategies and which approach could be appropriate [51] as not every fertility preservation technique is suitable for every patient. The choice depends on the type of anticancer treatments, the timing of therapies, the patient's age and the partner status [54]. Also the patient's prognosis as well as the pre-existing pregnancies and subfertility conditions at time of diagnosis have to be taken into account.

First, a complete pre-treatment evaluation of the possible ovarian damage, based on the age at the time of exposure and type of cancer therapy, is required [78]. Baseline hormonal profile and AMH level are useful in all pre-menopausal women before starting a systemic treatment, in order to get information about ovarian reserve and to modulate fertility management.

Afterwards, the fact that cancer treatments vary in their likelihood of causing infertility should also be taken into consideration. Type and dose of chemotherapy influence risk of infertility, together with genetic pre-disposition and lifestyle habits.

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Table 5
Summary of current guidelines on the available fertility preservation strategies in breast cancer patients.

Type of strategy	ASCO update 2013 [9]	ESMO 2013 [10]
Embryo cryopreservation	It is an established fertility preservation method. Newer hormonal stimulation regimens with letrozole or tamoxifen may be effective as traditional methods, and their use may be preferred in women with hormone-sensitive cancers. More flexible ovarian stimulation protocols for oocyte collection are now available; stimulation can be initiated with less delay compared with old protocols.	It's the main method to preserve female fertility. The use of gonadotropins and letrozole or tamoxifen for ovarian stimulation is generally recommended for cancer patients: the use of this stimulation in patients with endocrine-receptor-positive breast cancer should be made during a personal discussion with the patient and requires intensive interdisciplinary discussion.
Oocyte cryopreservation	It is no longer considered an experimental strategy. It is an option, particularly for patients who do not have a male partner, do not wish to use donor sperm, or have religious or ethical objections to embryo freezing. It should be performed in centers with the necessary expertise. The same recommendations as for embryo cryopreservation regarding ovarian stimulation protocols can be applied.	It's the main method to preserve female fertility. The same recommendations as for embryo cryopreservation regarding ovarian stimulation protocols can be applied.
Ovarian tissue cryopreservation	It is considered experimental and should be performed only in centers with the necessary expertise. It may be the only method available in children.	It is still considered experimental, but remains a unique option for young girls with cancer.
Ovarian suppression with GnRHa	GnRHa should not be relied upon as a fertility preservation method. Women interested in this method should participate in clinical trials. GnRHa may have other medical benefits such as a reduction of vaginal bleeding when patients have low platelet counts as a result of chemotherapy.	The use of GnRHa should not be regarded as a reliable means of preserving fertility. Data on long-term ovarian function and pregnancy rates in these cohorts are warranted.

Abbreviation: GnRHa, gonadotropin releasing hormone analogues; ASCO, American Society of Clinical Oncology; ESMO, European Society for Medical Oncology.

Generally, up to 0.9% of the female population is confronted with POF [68]. In the case of women treated for cancer, this risk is reported to increase with a factor of 4–27, respectively in the case of teenagers and of women between 21 and 25 years of age [79]. However, this risk is mostly overestimated [51].

Finally, the essential point for a fertility preservation strategy is whether or not patients still want to become pregnant after cancer. Women who are interested in fertility preservation options should know that many possibilities are available and time is crucial as some techniques should be performed before the initiation of chemotherapy. Most of them show preferences for biological offspring and assisted reproductive technology needs to be considered earliest to maximize success rate [8,9].

Conclusions

Oncofertility counseling is of great importance to many young women diagnosed with breast cancer [80]. These cases should be managed in a multi-disciplinary background, involving different health care specialists – oncologists, breast surgeons, gynecologists, reproductive specialists, breast nurses, as well as psychologists – with the aim to ensure an educated team can keep up with the progress of fertility preservation knowledge [81].

A better selection of the candidate patients, based on the estimated risk of POF and the patient's motivation towards future pregnancy, is needed to maximize the benefits of the procedures. A long-term follow-up of the patients' procreative desire and further research with the aim to optimize efficacy and safety of the techniques will lead to a higher success rate. In the meantime, it is our ethical responsibility to suggest the different options for fertility preservation to all patients desiring future childbearing on the one condition that those options do not adversely affect their oncological outcome.

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