Burning Questions in the Oncofertility Counseling of Young Breast Cancer Patients

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ABSTRACT: The improved prognosis of breast cancer patients makes survivorship issues an area of crucial importance. In this regard, an increased attention is needed toward the development of potential anticancer treatment-related long-term side-effects, including gonadal failure and infertility in young women. Therefore, fertility preservation and family planning are crucial issues to be addressed in all young women of reproductive age with newly diagnosed cancer. Despite a growing availability of data on the efficacy and safety of fertility preservation options and the fact that conceiving after prior history of breast cancer has become more accepted over time, there are still several gray zones in this field so that many physicians remain uncomfortable to deal with these topics. The purpose of this review is to answer some of the most controversial questions frequently asked by patients during their oncofertility counseling, in order to provide a detailed and up-to-date overview on the evidence available in this field to physicians involved in the care of young women with breast cancer.

KEYWORDS: Breast cancer, young patients, fertility preservation, pregnancy, *BRCA*

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Introduction

Breast cancer is the most frequent malignancy arising in young women, representing 7% of the total number of cases of breast malignancies diagnosed every year in Western countries.[1,2] A significantly higher proportion of triple-negative and HER2-positive tumors are diagnosed in young women as compared with older patients.[3] On the other hand, young women are less likely to develop luminal A-like tumors compared with other age groups.[4] Most of the available data suggest a detrimental prognostic relevance of young age (defined as 40 years and younger) at diagnosis,[4] particularly in the case of luminal-like disease.[5] Therefore, young patients are often candidates to be managed with aggressive multimodality treatments that include also chemotherapy for many of them.[3]

Chemotherapy regimens with cyclophosphamide, anthracyclines, and/or taxanes are the most widely used, also in young patients.[6,7] Among their potential adverse events, the risk of gonadotoxicity is of major concern for young women due to the possible development of gonadal failure and infertility.[8-10] The gonadotoxicity of cyclophosphamide and anthracycline-based chemotherapy is well recognized.[11] More recently, the potential further negative gonadotoxic effect of adding a taxane to cyclophosphamide- and anthracycline-based chemotherapy has been reported.[12-15]

The improved prognosis for breast cancer patients makes survivorship issues an area of crucial importance with an increased attention needed toward the development of potential anticancer treatment-related long-term side-effects, including gonadal failure and infertility in young patients.[16] Therefore, fertility preservation and family planning are crucial issues to be addressed in all young women of reproductive age with a newly diagnosed cancer.[17,18] Nowadays, fertility care should follow a multidisciplinary team-based approach, with a strict interaction needed between medical oncologists, surgeons, and fertility specialists.[19,20]

Available strategies for ovarian function and/or fertility preservation in young breast cancer patients before chemotherapy administration include ovarian suppression with gonadotropin-releasing hormone agonists (GnRHa) during cytotoxic therapy, oocyte and embryo cryopreservation as well as cryopreservation of ovarian tissue.[17,18] Despite a growing availability of data on the efficacy and safety of fertility preservation options and the fact that conceiving after prior history of breast cancer has become more accepted over time, there are still

several gray zones in this field so that many physicians remain uncomfortable to deal with these issues.[21,22]

The purpose of this review is to answer some of the most controversial questions frequently asked by patients during their oncofertility counseling, in order to provide a detailed and up-to-date overview on the evidence available in this field to physicians involved in the care of young women with breast cancer.

Burning Questions During the Oncofertility Counseling of Young Breast Cancer Patients

When estimating the risk of gonadotoxicity induced by anticancer treatments, what is the impact of carrying a germline BRCA mutation?

Gonadotoxicity induced by anticancer treatments is one of the potential adverse effects that premenopausal women with breast cancer may face.[8-10] As demonstrated in several histological studies in human ovaries, chemotherapy agents can cause loss of primordial follicles by damaging DNA structure.[23] The activation of the ataxia-teleangiectasia mutation-mediated DNA double-stranded breaks repair pathway has a crucial role in solving these damages. However, in the case of insufficient ability to repair the DNA, the damage could lead to the apoptosis of the cell. Chemotherapy can also have other indirect effects including a damage in stromal cells and vascular architecture.[23] Type of chemotherapy agent, its dose, and the woman's age and ovarian reserve at the time of treatment are the crucial factors impacting on the severity of treatment-induced ovarian damage and risk of infertility.[24] Hereditary breast cancers related to germline deleterious mutations in *BRCA1* or *BRCA2* genes are the most common in young women.[25,26] Preliminary evidence suggests a role of these genes also in the reproductive potential and fertility of women.[27] Preclinical studies have shown a possible association between *BRCA* mutations and an accelerated involution of the ovarian follicular reserve leading to diminished ovarian reserve, an increased risk of aneuploidies and ultimately an earlier menopause.[28,29] Several studies have also addressed the potential effect of carrying a *BRCA* mutation on the baseline ovarian reserve and response to controlled ovarian stimulation (COS) in young breast cancer patients.[30-33] Conflicting results have been reported, with some studies suggesting a potential negative effect of carrying a *BRCA* mutation.[30,31]

These findings together with the important role of BRCA in repairing DNA damage have raised concerns related to a possible higher risk of treatment-induced gonadotoxicity in breast cancer patients carrying a *BRCA* mutation as compared with those without mutations.[27] However, the available but limited evidence on this regard does not suggest a higher likelihood of gonadotoxicity with the use of anticancer therapies in *BRCA*-mutated breast cancer patients.

The study by Valentini et al[34] analyzed the impact of chemotherapy in 1954 *BRCA*-mutated patients. Among the 1426 patients who received chemotherapy, 35.6% developed long-term amenorrhea (defined as no menses for more than 2 years). On the contrary, out of 528 patients who did not receive chemotherapy, only 5.3% experienced long-term amenorrhea. As secondary analysis, the authors compared the rate of amenorrhea in *BRCA*-mutated patients with that of 100 *BRCA*-negative patients who underwent systemic therapy: no significant difference was observed between the two groups (35.6% vs 49%; $P = .18$). A higher risk of amenorrhea was shown for *BRCA2*-mutated than for *BRCA1*-mutated patients (46.8 vs 32.7%; $P < .001$).[34]

More recently, another study compared treatment-induced gonadotoxicity in breast cancer patients with or without *BRCA* mutations by assessing anti-Müllerian hormone (AMH) levels before and after treatment. Among 148 early breast cancer patients receiving chemotherapy, 35 carried a germline mutation. Similar AMH levels at baseline (1.94 vs 1.66 µg/L, $P = .53$), 1 year (0.09 vs 0.06 µg/L, $P = .39$) and 3 years (0.25 vs 0.16 µg/L, $P = .43$) after diagnosis were observed between breast cancer patients with and without *BRCA* mutations.[14]

Taken together, the available albeit limited evidence does not suggest an increased risk of treatment-induced gonadotoxicity in young patients with breast cancer carrying a *BRCA* mutation (Table 1). However, a potential negative impact of *BRCA* mutations on women's reproductive potential even before starting anticancer therapies cannot be excluded. Importantly, new treatment options are currently being used for the management of *BRCA*-mutated breast cancer patients (eg, platinum salts),[35] and others are in late stage of clinical development also in the early setting (eg, PARP inhibitors).[36] Their potential added burden on the reproductive potential and fertility outcomes of these patients should be urgently investigated.[37]

Is it safe to perform COS for oocyte/embryo cryopreservation in patients who are candidates to neoadjuvant systemic therapy?

Oocyte/embryo cryopreservation is the first option to be discussed with young breast cancer patients to receive chemotherapy and wishing to preserve their fertility.[17,18,38] This technique can be proposed whenever there is enough time available, as 10 to 15 days of COS are needed to allow oocyte collection.[17,18,38,39]

Several recent retrospective and prospective studies have shown the feasibility of oocyte/embryo cryopreservation also in cancer patients.[40] Nevertheless, considering that breast cancer is a hormonally driven form of tumor, the safety of COS has been questioned due to the transient and high increase in estradiol levels.[41] Three studies that addressed specifically the safety of COS for oocyte/embryo cryopreservation in breast cancer patients did not show any signal for a potential detrimental prognostic effect. [42-44] Notably, to mitigate the potential detrimental effect of high estradiol levels during COS, specific protocols including the use of an aromatase inhibitor (or tamoxifen) have been developed and are preferred in breast cancer patients.[45-48]

Table 1. Main evidence on the gonadotoxicity induced by anticancer treatments in *BRCA*-mutated breast cancer patients.

AUTHOR AND YEAR	TYPE OF STUDY	NUMBER OF PATIENTS	STUDY OUTCOMES	MAIN RESULTS
Valentini et al[34]	Observational study	1526 (1426 *BRCA*-mutated 100 *BRCA*-nonmutated)	– Chemotherapy-induced amenorrhea, (%)	25.6% *BRCA*-mutated 49.0% *BRCA*-nonmutated (P = .18)
Lambertini et al (2019)[14]	Retrospective biomarker analysis	148 (35 *BRCA*-mutated 113 *BRCA*-nonmutated)	– AMH levels at baseline, 1 year, 3 years	*BRCA*-mutated vs *BRCA*-nonmutated Baseline: 1.94 vs 1.66 (P = .53), 1 year: 0.09 vs 0.06 (P = .39) 3 years: 0.25 vs 0.16 (P = .43)

Abbreviation: AMH, anti-Müllerian hormone.

Despite COS for oocyte/embryo cryopreservation is an established technique for fertility preservation, it remains debated (and not allowed in some countries) to perform this strategy in women who are candidates to neoadjuvant chemotherapy. Neoadjuvant chemotherapy is nowadays one of the preferred treatment modalities for patients with early breast cancer thanks to the possibility to improve chances of breast conserving surgery but also to assess in vivo tumor response with the possibility to adapt the subsequent adjuvant treatment.[49] In terms of access to oocyte/embryo cryopreservation, the most important difference between the two settings is that adjuvant treatment can rely on more time to perform COS because diagnosis is followed by surgery, postsurgical recovery, and then chemotherapy.[50] In the neoadjuvant setting, on the contrary, chemotherapy follows immediately cancer diagnosis creating an apparent time pressure to complete COS for oocyte/embryo cryopreservation. In addition, the presence of the tumor still in place represents another important concern. For these reasons, the increased popularity of neoadjuvant chemotherapy needs a focus on how to most efficiently and safely complete oncofertility counseling, subsequent COS and oocyte retrieval while minimizing risks and cancer treatment delays.

In 2017, *Letourneau* and colleagues performed a cross-sectional study including 87 patients referred to oncofertility counseling, of whom 58 (67%) decided to undergo COS prior to neoadjuvant anticancer treatment and 29 (33%) did not.[51] Overall, the average time from cancer diagnosis to chemotherapy start was similar between the group that underwent COS and those who did not (38.1 ± 11.3 vs 39.4 ± 18.5 days, P = .672).[51]

In a more recent retrospective study, the same authors evaluated the potential prognostic impact of fertility preservation with oocyte/embryo cryopreservation.[52] This study included 329 patients, with 207 (63%) in the fertility preservation group and 122 (37%) who did not pursue fertility preservation. Over a median follow-up of 43 months, the rates of disease-free survival were similar between the two groups (hazard ratio [HR], 0.7; 95% confidence interval [CI], 0.3-1.7). Also in the subgroup of patients who underwent neoadjuvant chemotherapy, disease-free survival was similar between the two groups (HR, 1.4; 95% CI, 0.2-9.1).[52]

Another cross-sectional study of breast cancer patients undergoing COS for fertility preservation before neoadjuvant chemotherapy included 40 women with hormone-receptor positive breast cancer.[53] COS with letrozole and tamoxifen was used in this protocol. Mean number of collected oocytes was 11.78 ± 9.12 and mean number of vitrified oocytes was 9.72 ± 7.36. This study did not report safety data. Long-term follow-up is needed to determine the safety of this COS protocol in patients with hormone-receptor positive breast cancer candidates to neoadjuvant chemotherapy.[53]

In a retrospective analysis conducted within the neoadjuvant I-SPY 2 trial, the impact of fertility preservation with COS for oocyte/embryo cryopreservation on time to start of neoadjuvant systemic therapy was assessed.[54] A total of 82 patients in the screened population were under 43 years and received neoadjuvant chemotherapy. Patients who decided to undergo COS were 34 and those who did not (control group) were 48. No significant difference in the time to initiation of neoadjuvant chemotherapy was observed. The mean times from diagnosis to initiation of neoadjuvant chemotherapy was 39.8 days vs 40.9 days (P = .75), and the median time was 41.5 days vs 35.5 days (P = .50) in the COS vs control group, respectively. In the analysis of time to recurrence or death, the 5-year progression-free survival was 79.2% in the COS group and 82.4% in control groups, with no significant difference between groups. Cryopreservation data were available for all 34 women who underwent oocyte harvesting, of whom 16 patients cryopreserved oocytes and 20 patients cryopreserved embryos. At a median follow-up of 74 months, 6 of the 34 patients who underwent COS and cryopreservation have returned to use their cryopreserved embryos. The average time between the completion of neoadjuvant therapy and first embryo transfer in these 6 patients was 32.8 months (range: 11.9-47.0 months). In this study, COS for oocyte/embryo cryopreservation did not delay the start of the neoadjuvant therapy as compared with controls.[54] It is interesting to notice that even in the neoadjuvant setting, where patients generally have larger, more aggressive disease and there is perceived urgency to start the treatment, it still takes 5 to 6 weeks on average to initiate chemotherapy, similar to what is reported in the adjuvant setting. Reasons for this fact are likely multifactorial, but at least in part related to the time for referring to oncology specialists, extensive diagnostic work-up especially within clinical trials. This required time represents for

Table 2. Main evidence on the safety to perform controlled ovarian stimulation for oocyte/embryo cryopreservation in breast cancer patients who are candidates to neoadjuvant systemic therapy.

AUTHOR AND YEAR	TYPE OF STUDY	NUMBER OF PATIENTS	STUDY OUTCOMES	MAIN RESULTS
Letourneau et al[51]	Cross-sectional study	87 (58 COS vs 29 no COS)	– Time (days) from cancer diagnosis to neoadjuvant chemotherapy start	Time (days) from cancer diagnosis to neoadjuvant chemotherapy start: – COS: 38.1 ± 11.3 – No COS: 39.4 ± 18.5 (P = .672)
Letourneau et al[52]	Retrospective study	329 (207 fertility preservation vs 122 no fertility preservation)	– Disease-free survival between groups – Disease-free survival in patients undergoing neoadjuvant treatment	Disease-free survival (%) after 43 months in: – Fertility preservation group: 93% – No fertility preservation group: 94% (HR, 0.7; 95% CI, 0.3-1.7) Disease-free survival (%) after 43 months in: – Neoadjuvant chemotherapy group: 41% – No neoadjuvant chemotherapy group: 48% (HR, 1.4; 95% CI, 0.2-9.1; P = .32)
Cavagna et al[53]	Cross-sectional study	40	– Collected oocyte before neoadjuvant therapy	Collected oocytes: – Mean 11.78 ± 9.12 (range: 1-38) – Median 9.72 ± 7.36 (range: 0-34)
Chien et al[54]	Retrospective study	82 (34 COS vs 48 no COS)	– Time between COS and initiation of neoadjuvant therapy – Recurrence or death	Time (days) from diagnosis to initiation of neoadjuvant CT (COS vs no COS): – M: 39.8 vs 40.9 days (P = .75) – Median: 41.5 vs 35.5 days (P = .50) Median time (months) to recurrence or death (COS vs no COS): – 62.96 vs 67.04 (P = .984)
Kim et al[42]	Prospective non-randomized study	120 (106 COS before surgery vs 14 after surgery)	– Cancer recurrence – (subgroup analysis based on timing of COS before vs after surgery)	Cancer recurrence: – Presurgery: 1 (7%) – Postsurgery: 5 (4%) (P = .47)

Abbreviations: CI, confidence interval; COS, controlled ovarian stimulation; CT, chemotherapy; HR, hazard ratio.

patients a window of opportunity to pursue at least one round of COS.

In the study by Kim et al,[42] out of 120 breast cancer patients who underwent oocyte/embryo cryopreservation, 14 underwent COS before surgery and 106 after. There was one recurrence (7%) in the presurgery group, and 5 (4%) in the postsurgery group (P = .47). The relapse-free survival rates were not statistically significantly different between pre- and postsurgery groups (P = .44). Despite the use of COS in the neoadjuvant setting did not appear to compromise outcomes, caution is needed to interpret these results considering the small sample size of the presurgery group.[42]

Taken together, limited data are available to support the safety of performing COS before starting neoadjuvant chemotherapy (Table 2). However, there is no clear evidence to suggest that COS for oocyte/embryo cryopreservation before neoadjuvant chemotherapy causes a significant delay in treatment initiation nor a detrimental prognostic effect. Therefore, use of COS before neoadjuvant chemotherapy should not be contraindicated per se, but the risks and benefits of this strategy needs to be balanced with tumor stage and biological features of the tumors. For women who cannot delay the start of neoadjuvant chemotherapy, ovarian tissue cryopreservation (without the need for COS) is to be preferred.

Who are the best candidates for ovarian tissue cryopreservation?

Ovarian tissue cryopreservation is a surgical fertility preservation technique with the potential to temporary restore ovarian endocrine function. It is no longer considered an experimental technique in many countries nowadays.[55,56] It consists of the surgical removal of pieces of ovarian cortex from both gonads or the entire ovary.[57] The surgical approach of this technique is usually performed by laparoscopy before the administration of systemic anticancer treatments. Ovarian tissue transplantation occurs after exposure to chemotherapy, and it is usually performed in an orthotopic site (ie, the remaining ovary or within the peritoneal cavity). This strategy does not delay anticancer treatment as no COS is needed and the surgery can be scheduled soon after the oncofertility counseling. There are two important safety issues to be considered in this procedure: first, there is a potential risk

(particularly in the case of aggressive hematological diseases) of reintroducing metastatic cancer cells at the time of transplantation[58]; second, this is not the optimal strategy for patients with hereditary cancer syndromes caused by pathogenic mutations in genes predisposing to ovarian cancer (eg, *BRCA*).[31]

Gellert et al[59] published a review in 2018 reporting data from 21 different countries comprising a total of 360 ovarian tissue cryopreservation and transplantation procedures made in 318 women, of whom 65 (24.6%) were affected by breast cancer. Out of 237 cases with available information on endocrine function, 225 (95%) restored gonadal function. A total of 170 cases wished to restore fertility; overall, 131 pregnancies were obtained in 95 patients, counting both biochemical and clinical pregnancies. This resulted in 87 live births in 69 women, and a total of 93 children born. The 40 children in whom data were available showed similar birth weight and similar gestational age as children born from normal pregnancies. Only one child has been reported to have a chromosomal anomaly. Specific data for the breast cancer subgroup are not reported in this study. However, the overall pregnancy rate was 40.6%. The age of the patients who succeeded in having a live birth or ongoing pregnancy (26.4 years, range: 9-38 years) was significantly younger compared with that in patients who failed to conceive despite their wish for a pregnancy (29.6 years, range: 14-39; $P = .0019$).[59]

When looking specifically at the breast cancer field, a recent systematic review has included obstetric and oncological outcomes of 16 patients with breast malignancies who underwent ovarian tissue cryopreservation.[60] The average age of breast cancer patients was 34.3 years (range: 30-39) at the time of cryopreservation. Among them, 12 patients successfully achieved at least one pregnancy. A total of 14 pregnancies were described of which the majority (n = 10) were spontaneous and 4 were achieved via in vitro fertilization. These pregnancies (including twin pregnancies) resulted in the birth of 11 healthy children, 1 spontaneous miscarriage, and 1 voluntary interruption of pregnancy.

In terms of safety, in a series of 272 studies evaluating the cancer risk of reimplanting cryopreserved ovarian tissue in women with breast cancer, only one local recurrence was described approximately 1 year after transplantation of the preserved ovarian tissue.[61] Moreover, after analyzing ovarian samples for the potential presence of metastatic involvement, no cancer cells were found in any of these cases.[60]

The success of ovarian tissue cryopreservation and transplantation in comparison with oocyte/embryo cryopreservation has been indirectly analyzed by Diaz-Garcia et al[62] in a prospective observational cohort study. The primary outcome of this study was live birth rate defined as the number of births of live infants beyond viability (>24 weeks). Secondary outcomes included pregnancy rates diagnosed by serum human chorionic gonadotropin (hCG) determination and clinical pregnancy rates. A total of 2045 patients were evaluated for fertility preservation and, among them, 1024 patients underwent oocyte vitrification and 800 ovarian tissue cryopreservation. The most prevalent disease was breast cancer. Specifically, patients with breast cancer who underwent oocyte vitrification were 618 (60.3% of the total), while those who underwent cryopreservation were 431 (53.9% of the total). Of these patients with breast cancer, those who returned to use vitrified oocytes or cryopreserved ovarian tissue were 38 and 31, respectively. The pregnancy rate of breast cancer patients who underwent oocyte vitrification was 34.2% leading to a live birth rate of 28.9%; for those who performed ovarian tissue cryopreservation, the pregnancy and live birth rates were 16.1% and 6.4%, respectively. The time interval between the first visit and the end date of the fertility preservation procedure was shorter in the ovarian tissue cryopreservation group (24.0 ± 6.2 days vs 4.5 ± 4.1 days; $P < .001$).[62]

To address the best candidates for the use of ovarian tissue cryopreservation, some important points must be certainly taken into account (Table 3). First of all, it should be remembered that this technique is still considered experimental in several countries and therefore should not be recommended as the first choice but only in selected patients, specifically those not suitable for oocyte/embryo cryopreservation. In this context, ovarian tissue cryopreservation should be considered also for breast cancer patients whenever COS is contraindicated (eg, in the case of urgent need to start chemotherapy). Second, the age of the patient and her ovarian reserve are crucial parameters for the success of this procedure. Thus, performing ovarian tissue cryopreservation beyond 36 years does not seem appropriate, especially since the decreased follicular reserve at this age compromises graft quality and the subsequent chances of success. Third, safety considerations should be taken into account before referring patients to ovarian tissue cryopreservation. Ovarian tissue cryopreservation is contraindicated in patients with metastatic disease or very high risk of relapse and ovarian involvement. Moreover, the risk of transplanting cryopreserved ovarian tissue in patients harboring deleterious *BRCA1* and *BRCA2* mutations should be carefully discussed. Although this does not apply to patients with breast cancer, ovarian tissue cryopreservation should be considered the only technique that can be used in patients at prepubertal age.[63]

Can ovarian suppression with GnRHa during chemotherapy be used in place of cryopreservation strategies?

Among the different strategies in young women with breast cancer, it should be highlighted that cryopreservation strategies and particularly oocyte/embryo cryopreservation are those specifically developed as fertility preservation approaches. Use of ovarian suppression with GnRHa during chemotherapy has not been developed as an option to preserve fertility but as an approach for reducing the risk of gonadal damage during chemotherapy.[64] Indeed, pregnancy desire was not an inclusion criterion in any of the trials that assessed the efficacy and safety of this strategy; premenopausal status and not age less than 40 years was needed to be eligible for randomization in these studies.[64]

Table 3. Main evidence to define the best candidates for ovarian tissue cryopreservation among breast cancer patients.

AUTHOR AND YEAR	TYPE OF STUDY	NUMBER OF PATIENTS	STUDY OUTCOMES	MAIN RESULTS
Gellert et al[59]	Systematic review	318 (65 breast cancer patients)	– Restored endocrine function – Pregnancy (on 170 patients who wished to restore fertility) – Births (number)	Endocrine function: – Restored: 225 (95%) – Not restored: 12 (5%) Pregnancy: – 131 pregnancies Births (69 patients): – 93 children born (87 live births)
Fleury et al[60]	Systematic review	16	– Pregnancy (number) – Births (number) – Breast cancer local recurrence (on 272 breast cancer patients)	Pregnancy: – 14 Births: – 11 Breast cancer local recurrence: – 1/272 (0.4%)
Diaz-Garcia et al[62]	Prospective observational cohort study	1049 (618 oocyte vitrification vs 431 ovarian tissue cryopreservation)	– Pregnancy (oocyte vitrification vs ovarian tissue cryopreservation) – Births (oocyte vitrification vs ovarian tissue cryopreservation) – First visit to end of fertility preservation (days)	Pregnancy: – 13 (34.2%) vs 5 (16.1%) Births: – 11 (28.9%) vs 2 (6.4%) First visit to end of fertility preservation: – 24.0 ± 6.2 days (oocyte vitrification) – 4.5 ± 4.1 days (ovarian tissue cryopreservation) ($P < .001$)

The indication to ovarian suppression with GnRHa during chemotherapy has been highly debated for many years.[65-71] One of the main reasons for this controversy is represented by the lack of proper data demonstrating the mechanism behind the protective effect of this strategy.[72-75] Nevertheless, clinical data for patients with breast cancer have recently solved the controversy and this option is now considered a standard strategy for ovarian function preservation in this setting.[16,18,76-78] However, this is not an alternative to cryopreservation options as a strategy for fertility preservation considering the more limited evidence regarding the number of pregnancies obtained by patients who received this strategy.

A large meta-analysis including 12 randomized trials and a total of 1231 premenopausal women with newly diagnosed breast cancer showed that adding GnRHa to chemotherapy alone was effective in reducing the risk of chemotherapy-induced premature ovarian insufficiency (OR, 0.36; 95% CI, 0.23-0.57; $P < .001$).[79] Only 5 trials reported posttreatment pregnancies: a total of 33 among 359 women treated with chemotherapy plus GnRHa became pregnant following treatment completion compared with 19 among 347 patients who received cytotoxic treatment alone (OR, 1.83; 95% CI, 1.02-3.28; $P = .041$).[79] More recently, a meta-analysis based on individual patient data has supported these prior results.[80] Five randomized trials were included for a total of 873 premenopausal patients,[81–85] of whom 436 were assigned to the GnRHa group while 437 to the control group that received chemotherapy alone. The incidence of premature ovarian insufficiency was 14.1% in the GnRHa group and 30.9% in the control group (OR, 0.38; 95% CI, 0.26-0.57; $P < .001$).[80] In the GnRHa group, 37 patients achieved a posttreatment pregnancy compared with 20 in the control group (incidence rate ratio [IRR], 1.83; 95% CI, 1.06-3.15; $P = .030$).[80] Despite the results in posttreatment pregnancies were statistically significant in both meta-analyses favoring the GnRHa group, numbers remain small to support an effect of this strategy in terms of fertility preservation potential.

Despite the latest evidence appears to suggest a potential role for ovarian suppression with GnRHa during chemotherapy not only in preserving gonadal function but also fertility, data on posttreatment pregnancies remain limited (Table 4). Therefore, it should not be considered strictly a fertility-preserving procedure such as cryopreservation options. Hence, ovarian suppression with GnRHa during chemotherapy can be proposed to all premenopausal patients who are concerned about the risk of developing early menopause and are interested in preserving ovarian function (irrespectively of their age and desire for future pregnancies). This is also a relevant issue for many premenopausal breast cancer patients without pregnancy desire.[86] On the contrary, for patients interested in fertility preservation, oocyte/embryo cryopreservation should be always proposed as the first option leaving ovarian suppression with GnRHa during chemotherapy as an additional strategy following oocyte pick up.

Is it safe to interrupt endocrine therapy with the aim to have a pregnancy and is there a preferred timing for attempting to conceive following anticancer therapy completion?

Adjuvant endocrine therapy for 5 to 10 years is standard treatment for all patients with luminal-like breast cancer.[78,87,88] For

Table 4. Main evidence on the role of ovarian suppression with GnRHa during chemotherapy in breast cancer patients.

AUTHOR AND YEAR	TYPE OF STUDY	NUMBER OF PATIENTS	STUDY OUTCOMES	MAIN RESULTS
Lambertini et al (2015)[79]	Meta-analysis of 12 RCT	1231	– POI rate – Posttreatment pregnancies (5 studies included this endpoint)	– POI rate (GnRHa + CT vs CT alone) 18.5% vs 33.5% OR, 0.36; 95% CI, 0.23-0.57; $P < .001$ – Posttreatment pregnancies (GnRHa + CT vs CT alone) 33 vs 19 OR, 1.83; 95% CI, 1.02-3.28; $P = .041$
Lambertini et al (2018)[80]	Meta-analysis Based on IPD of 5 RCT	873 (436 GnRH + CT vs 437 CT alone)	– POI rate – Posttreatment pregnancies	– POI incidence (GnRHa + CT vs CT alone) 14.1% vs 30.9% OR, 0.38; 95% CI, 0.26-0.57; $P < .001$ – Posttreatment pregnancies (GnRHa + CT vs CT alone) 37 vs 20 IRR, 1.83; 95% CI, 1.06-3.15; $P = .030$

Abbreviations: CI, confidence interval; CT, chemotherapy; GnRHa, gonadotropin-releasing hormone agonists; IPD, individual patient data; IRR, incidence rate ratio; OR, odds ratio; POI, premature ovarian insufficiency; RCT, randomized controlled trial.

premenopausal women, tamoxifen alone or added to ovarian function suppression as well as the combination of ovarian function suppression and an aromatase inhibitor are the currently available endocrine treatment options.[88,89] The indication to these different options should be based on the individual risk of recurrence and patients' tolerance.[90]

Considering the teratogen potential of the endocrine therapy, namely tamoxifen, having a pregnancy during treatment is contraindicated.[91,92] Of additional interest, it should be recognized that, being luminal-like breast cancer the most hormonally driven form of tumors, physicians and patients remain concerned about the potential detrimental survival effect of posttreatment pregnancies in this setting.[21,93,94] Despite maternity desire is expressed by a significant proportion of young women with a newly diagnosed cancer, survivors of breast malignancies have very low rates of conception as compared with patients affected by other tumors,[95,96] particularly those with luminal-like tumors.[97]

A growing amount of evidence has proven that pregnancy following adequate treatment and follow-up for breast cancer can be considered safe.[98–102] One of these studies was specifically designed and powered to investigate the safety of pregnancy in patients with luminal-like breast cancer.[100] This study compared the outcomes of 333 women with pregnancy following breast cancer (of whom 194 had estrogen receptor-positive disease) to 874 nonpregnant patients with similar characteristics (of whom 492 had estrogen receptor-positive disease). The primary endpoint was specifically disease-free survival between estrogen receptor-positive breast cancer patients with or without subsequent pregnancy. No differences in disease-free survival (HR, 0.94; 95% CI, 0.70-1.26; $P = .68$) nor in overall survival (HR, 0.84; 95% CI, 0.60-1.18; $P = .32$) were observed between the pregnant and nonpregnant cohorts in the estrogen receptor-positive groups. The potential impact of time to pregnancy on patients' outcome was also explored in the overall study population: adjusting by tumor characteristics and treatment received, no difference in terms of disease-free survival was observed between the group of patients who became pregnant after 2 or more years from breast cancer diagnosis and the group who became pregnant within 2 years from diagnosis (HR, 1.10; 95% CI, 0.70-1.75; $P = .67$). Moreover, in an exploratory subgroup analysis, no difference in disease-free survival was observed in the estrogen receptor-positive cohort with subsequent pregnancy between the group that received less than 5 years of endocrine therapy and the group that received more than 5 years of endocrine therapy (HR, 0.98; 95% CI, 0.31-3.10; $P = .98$).[100] Nevertheless, these are subgroup analyses of a retrospective study and should be considered with caution and not as the evidence to suggest the safety of interrupting endocrine therapy for having a pregnancy.[103]

Therefore, to date, there is no evidence to support the safety of a temporary interruption of endocrine therapy before the standard 5 years for trying to have a pregnancy. Currently, a large international prospective study investigating this important issue has recently completed accrual.[104] In the POSITIVE trial, young women (⩽42 years) who have completed 18 to 30 months of endocrine therapy and who desire to become pregnant were enrolled. Interruption of endocrine therapy was allowed for up to 2 years (comprehensive of wash-out, conception, delivery, and breastfeeding). Following this period of time, the treatment had to be resumed to complete the recommended 5 to 10 years of adjuvant therapy.[104] Although some recommendations suggest the possibility to propose a temporary interruption of the endocrine therapy to patients willing to conceive before 5 years of endocrine therapy,[77,78] women should be clearly informed about the lack of proper safety data on this regard. Therefore, while waiting for the results of the POSITIVE trial, patients should be counseled about the safety of pregnancy also in the case of luminal-like breast cancers but upon endocrine treatment completion (Table 5).

Table 5. Main evidence on the timing for attempting to conceive following anticancer therapy completion among breast cancer patients.

AUTHOR AND YEAR	TYPE OF STUDY	NUMBER OF PATIENTS	STUDY OUTCOMES	MAIN RESULTS
Lambertini et al (2018)[100]	Multicenter case-control study	333 BC patients with a subsequent pregnancy (194 ER+) vs 874 BC patients without subsequent pregnancy (492 ER+)	– DFS and OS in ER+ – DFS in patients with subsequent pregnancy >2 y after BC diagnosis vs <2 y after BC diagnosis – DFS in ER+ patients <5 y of ET vs patients >5 y of ET	– DFS in ER+ (pregnancy vs no pregnancy): HR, 0.94; 95% CI, 0.70-1.26; P=.68 – OS in ER+ (pregnancy vs no pregnancy): HR, 0.84; 95% CI, 0.60-1.18; P=.32 – DFS (>2 y vs <2 y): HR, 1.10; 95% CI, 0.70-1.75; P=.67 – DFS (<5 y vs >5 y): HR, 0.98; 95% CI, 0.31–3.10; P=.98
Ives et al[105]	Retrospective case-control study	123 BC patients with a subsequent pregnancy vs 2416 BC patients without a subsequent pregnancy	– OS in patients conceiving >6 months from completion of anticancer treatment vs nonpregnant group – OS in patients conceiving <6 months from completion of anticancer treatment vs nonpregnant group	– OS (>6 months vs nonpregnant group): HR, 0.45; 95% CI, 0.16-1.28; P=.135 – OS (<6 months vs nonpregnant group): HR, 2.20; 95% CI, 0.14-35.42; P=.579
Kranick et al[106]	Retrospective case-control study	107 BC patients with a subsequent pregnancy vs 344 BC patients without a subsequent pregnancy	– DFS and OS in patients who conceived <12 months after completion of anticancer treatments vs nonpregnant group	– DFS (<12 months vs nonpregnant): HR, 1.4; 95% CI, 0.8-2.7 OS (<12 months vs nonpregnant): HR, 1.5; 95% CI, 0.7-3.6
Hartnett et al[107]	Retrospective cohort study	4203 cancer patients (754 BC patients)	– Preterm birth and low birth weight rates between patients who conceived <12 months and control group (healthy women with pregnancy) – Preterm birth and infant born small for gestational age rates between BC patients who conceived from 12 to 24 months after treatment and control group (healthy women with pregnancy)	– Preterm birth rate (<12 months vs control, any tumor): HR, 1.9; 95% CI, 1.3-2.7 – Low birth weight rate (<12 months vs control, any tumor): HR, 2.0; 95% CI, 1.4-3.0 – Preterm birth rate (<12 months vs control, BC only): HR, 2.4; 95% CI, 1.4-4.0 – Low birth weight rate (<12 months vs control, BC only): HR, 3.3; 95% CI, 1.9-5.8 – Preterm birth rate (12-24 months vs control, BC only): RR, 0.9; 95% CI, 0.4-2.0 – SGA rate (12-24 months vs control, BC only): RR, 0.8; 95% CI, 0.3-1.8

Abbreviations: BC, breast cancer; CI, confidence interval; DFS, disease-free survival; ER, estrogen receptors; ET, endocrine therapy; HR, hazard ratio; OS, overall survival; RR, risk ratio; SGA, small for gestational age.

Another important issue regarding pregnancy following breast cancer diagnosis and treatment is the optimal timing for attempting to conceive after the completion of anticancer therapies. Ives et al[105] investigated this issue in a large retrospective case-control study that compared 123 women with history of breast cancer who become subsequently pregnant to 2416 breast cancer patients without subsequent pregnancies. Although not statistically significant, having a subsequent pregnancy was associated with improved overall survival in women who waited at least 6 months to conceive after treatment (HR, 0.45; 95% CI, 0.16-1.28; P=.135). On the other hand, when the conception occurred within 6 months from the termination of anticancer treatment, it was associated with a detrimental prognostic survival effect (HR, 2.20; 95% CI, 0.14-35.42; P=.579).[105]

Similar results were reported in 2010 by Kranick et al,[106] who demonstrated a higher risk for both recurrence and death in patients who conceived within 12 months after completion

Table 6. Answers to 5 burning questions in the oncofertility counseling of young breast cancer patients.

QUESTIONS	SUMMARY
When estimating the risk of gonadotoxicity induced by anticancer treatments, what is the impact of carrying a germline *BRCA* mutation?	Carrying a germline *BRCA* mutation does not appear to increase the risk of treatment-induced gonadotoxicity in young breast cancer patients. However, a potential negative impact of *BRCA* mutations on women's reproductive potential even before starting anticancer therapies cannot be excluded. The gonadotoxicity of currently available treatments in these patients (eg, platinum salts and PARP inhibitors) should be urgently investigated.
Is it safe to perform controlled ovarian stimulation (COS) for oocyte/embryo cryopreservation in patients who are candidates to neoadjuvant systemic therapy?	The available albeit limited data suggests the safety of performing COS before starting neoadjuvant chemotherapy. There is no clear evidence to support that COS for oocyte/embryo cryopreservation before neoadjuvant chemotherapy causes a significant delay in treatment initiation nor a detrimental prognostic effect. COS before neoadjuvant chemotherapy should not be contraindicated per se but the risks and benefits of this strategy needs to be balanced with tumor stage and biological features.
Who are the best candidates for ovarian tissue cryopreservation (OTC)?	Taken that this technique is still considered experimental in several countries and should not be recommended as a first choice, the best candidates for OTC are women <36 years with high risk of developing premature ovarian insufficiency and contraindications to oocyte/embryo cryopreservation including those with no time to wait 2-3 weeks before starting anticancer treatments.
Can ovarian suppression with GnRHa during chemotherapy be used in place of cryopreservation strategies?	Latest evidence supports the role of ovarian suppression with GnRHa during chemotherapy as a standard strategy for preserving gonadal function. However, it should not be considered strictly a fertility-preserving procedure. Hence, in patients interested in fertility preservation, oocyte/embryo cryopreservation remains the first option to be proposed using ovarian suppression with GnRHa during chemotherapy following cryopreservation options.
Is it safe to interrupt endocrine therapy with the aim to have a pregnancy and is there a preferred timing for attempting to conceive following anticancer therapy completion?	No proper evidence exists to counsel women on the safety of an early temporary interruption of endocrine therapy to conceive; the POSITIVE trial will provide an answer on this regard. There is no optimal cut-off to plan a pregnancy following breast cancer diagnosis and treatment. Conception should be postponed at least 12 months following the end of chemotherapy (due to a potential detrimental prognostic effect and higher risk of pregnancy complications for early conceptions). A wash-out period of 3 and 7 months should be considered following exposure to endocrine therapy and anti-HER2 biologic agents, respectively.

Abbreviations: COS, controlled ovarian stimulation; GnRHa, gonadotropin-releasing hormone agonists; OTC, ovarian tissue cryopreservation; PARP, poly(ADP-ribose) polymerase.

of oncological therapies (HR, 1.4; 95% CI, 0.8-2.7 and HR, 1.5; 95% CI, 0.7-3.6, respectively). An additional important concern for early pregnancies following anticancer therapies is the potential adverse effects in terms of pregnancy outcomes. In 2018, Hartnett et al[107] investigated this issue retrospectively in a cohort of 4203 patients affected by different tumors, 754 of whom affected by breast cancer. It was observed a higher risk in preterm birth (RR, 1.9; 95% CI, 1.3-2.7) and low birth weight (RR, 2.0; 95% CI, 1.4-3.0) in the group of patients who conceived less than 12 months after chemotherapy completion. Similar results were observed among breast cancer survivors for both preterm birth (RR, 2.4; 95% CI, 1.4-4.0) and low birth weight (RR, 3.3; 95% CI, 1.9-5.8).[107] On the contrary, breast cancer patients who conceived between 12 to 24 months after treatment did not have higher risks of preterm birth (RR, 0.9; 95% CI, 0.4-2.0) or infants born small for gestational age (RR, 0.8; 95% CI, 0.3-1.8) than matched women without cancer.[107]

Taken together (Table 5), these studies suggest that despite there is no optimal cut-off to plan a pregnancy following breast cancer diagnosis, attempts to conceptions should be postponed at least 12 months following chemotherapy completion. A wash-out period of 3 and 7 months should be also considered following exposure to endocrine therapy and anti-HER2 biologic agents, respectively. Nevertheless, a case by case discussion should be done on this regard taking into account patient's age, tumor biology, and individual risk of recurrence.

Conclusions

Thanks to the increase in survival rates also for young breast cancer patients, one of the areas of growing importance and development in recent years is the management of issues related to preservation of fertility and the possibility to have a family following treatment completion.

Managing these issues remains not always optimal due to both inadequate expertise of treating physicians and disparities in access to fertility care services making the availability of services related to oncofertility counseling extremely heterogeneous worldwide.[108] Providing financial coverage for fertility preservation represents an important commitment to reduce health disparities by providing broaden access to all patients.[109]

It is now clear that more than 50% of patients who will undergo cytotoxic treatments are concerned about the possible future effects of cytotoxic treatments and it is the role of healthcare providers to give the right answers to these needs.[110,111]

In this work, we provided an updated overview of the evidence available around 5 controversial questions in the oncofertility field. A summary of the main messages from each of these questions is reported in Table 6. As highlighted in this work, the

evidence on these issues is often based on few small and mostly retrospective studies. Therefore, this work also voices for the need to further develop additional research efforts in the oncofertility field for trying to solve the still remaining controversies.

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All authors contributed to literature search, data interpretation and manuscript writing.

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