Review

Cancer and fertility preservation: fertility preservation in breast cancer patients

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Abstract

Aggressive chemotherapy has improved the life expectancy for reproductive-age women with breast cancer, but it often causes infertility or premature ovarian failure due to destruction of the ovarian reserve. Many questions concerning fertility preservation in breast cancer patients remain unanswered – for example, whether fertility preservation methods interfere with chemotherapy, and whether subsequent pregnancy has negative effects on the prognosis. Fertility preservation is a critical factor in decision-making for younger breast cancer patients, however, and clinicians should address this. The present article reviews the incidence of chemotherapy-induced amenorrhea, and discusses fertility-preservation options and the prognosis for patients who become pregnant after breast cancer.

Introduction

Breast cancer is the most common malignancy in women of reproductive age, and about 13% of all breast cancer diagnoses are made in women younger than age 45 years [1]. In Germany, the average age of primiparas is 29.8 years [2], which means that many breast cancer patients have not completed their family planning and wish to have children after the diagnosis of breast cancer. The majority of women diagnosed with early-stage breast cancer today have an excellent long-term prognosis, but many of them will undergo a temporary or permanent cessation of menses. Although premature ovarian insufficiency can improve the breast cancer prognosis for women with hormone-positive breast cancer, these women have to face subsequent infertility and many psychological problems [3].

In the present review, we discuss the effect of the most up-to-date chemotherapy regimens for breast cancer on fertility, and we analyze the options for fertility preservation, as well as the various *in vitro* fertilization (IVF) protocols that can be applied in this specific patient group. Finally, a review of the available studies on the effect of a subsequent pregnancy on the outcome in breast cancer survivors is conducted.

Effect of chemotherapy for breast cancer on fertility

This section discusses the effect on fertility of chemotherapy for breast cancer (Table 1) [4–13]. The risk of chemotherapy-related amenorrhea depends on the patient's age, on the specific chemotherapeutic agents used, and on the total dose administered. Older women have a higher incidence of complete ovarian failure and permanent infertility in comparison with younger women [14]. This higher incidence can be explained by younger women's larger primordial follicle reserve, which declines with age.

With regard to the chemotherapy regimen, according to Meirow, alkylating agents (for example, cyclophosphamide) involve the greatest risk for inducing ovarian failure among all chemotherapeutic agents (odds ratio 3.98 in comparison with unexposed patients) [15]. The higher the cumulative dose of cyclophosphamide, the higher the observed incidence of menopause. Goldhirsch and colleagues reported that, with the classic cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) regimen, the incidence of amenorrhea was 61% in patients aged <40 years and was 95% in patients aged >40 years [4].

The classic fluorouracil, epirubicin, and cyclophosphamide regimen (intravenous administration on day 1 of all drugs for

CI = confidence interval; CMF = cyclophosphamide, methotrexate, and 5-fluorouracil; FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; IVF = *in vitro* fertilization.

Table 1

Incidence of amenorrhea induced by the most commonly used chemotherapy regimens in breast cancer

Reference	Year	Patients (*n*)	Chemotherapy regimen	Duration of treatment (months)	Follow-up to definite amenorrhea (months)	Rate of amenorrhea	
						Percentage	Age (years)
Goldhirsch and colleagues [4]	1990	541	CMF	1	9	14/34	<40/>40
		387		6		33/81	<40/>40
Bines and colleagues [5]	1996	3,628	CMF	3 to 24	12	40/76	<40/>40
Levine and colleagues [6]	1998	359	CMF	6	NA	42.6	
		132	FEC	6			
Goodwin and colleagues [7]	1999	83	CMF	6	12	55.6	
		25	FEC	6		64.6	
Nabholtz and colleagues [8]	2002	745	ACD	6	33	51.4	
		746	FAC	6			
Fornier and colleagues [9]	2005	84	AC-T/D	6	12	13	
		82	AC-T/D + tamoxifen			17	
Martin and colleagues [10]	2005	420	ACD	6	NA	61.7	
		403	FAC			52.4	
Venturini and colleagues [11]	2005	503	FEC	4	120	64	
Petrek and colleagues [12]	2006	120	AC	4	36	53	
		168	ACT	6		42	
		83	CMF	8		82	
		38	FAC	6		NA	
		34	FACT	6		NA	
		19	ACD	6		45	
Tham and colleagues [13]	2007	75	AC	4	12	44/81	<40/>40
		116	AC + T/D	4 + 3		61/85	<40/>40
Total		8,681					

AC, adriamycin (doxorubicin), and cyclophosphamide; ACD, adriamycin (doxurubicin), cyclophosphamide and docetaxel; AC-T/D, adriamycin (doxorubicin), cyclophosphamide and taxol (paclitaxel)/docetaxel; CMF, cyclophosphamide, methotrexate, and 5-fluorouracil; FAC, 5-fluorouracil, adriamycin (doxorubicin), and cyclophosphamide; FACT, 5-fluorouracil, adriamycin (doxorubicin), cyclophosphamide and taxol (paclitaxel); FEC, 5-fluorouracil, epirubicin, and cyclophosphamide; NA, not available.

six cycles, cyclophosphamide 600 mg/m^2, epirubicin 60 mg/m^2, fluorouracil 600 mg/m^2) induces menopause in 60% of patients [11].

The National Cancer Institute of Canada adjuvant trial comparing CMF with the fluorouracil, epirubicin, and cyclophosphamide regimen indicated that the incidence of amenorrhea was slightly higher in the fluorouracil, epirubicin, and cyclophosphamide arm (51%) in comparison with the CMF arm (42.6%) [6]. This arm was a dose-intensified fluorouracil, epirubicin, and cyclophosphamide regimen (cyclophosphamide 75 mg/m^2 orally on days 1 to 14, epirubicin 60 mg/m^2 intravenously on days 1 and 8, and fluorouracil 500 mg/m^2 intravenously on days 1 and 8), given for six cycles.

Most anthracycline-based regimens are associated with a lower incidence of amenorrhea, most probably due to the lower cumulative cyclophosphamide dosages used in comparison with the classic CMF regimen. The doxorubicin and cyclophosphamide regimen (adriamycin (doxorubicin), and cyclophosphamide) has been reported by Bines and colleagues to result in amenorrhea at a rate of 34% [5].

With regard to the taxanes, a study including 191 patients showed that older age and the addition of taxane to adriamycin and cyclophosphamide increased the risk of chemotherapy-induced amenorrhea, and that the amenorrhea was more likely to be irreversible for women over 40 years old [13]. Younger women often resume menstruation even after

6 months of amenorrhea, and the addition of a taxane does not play a role [13]. Some other studies have evaluated the impact of the addition of paclitaxel or docetaxel [9,10,12,16–18]. These limited data suggest that, when age is controlled for, adding a taxane to adriamycin and cyclophosphamide-type chemotherapy has little if any effect on the subsequent risk of chemotherapy-related amenorrhea. Taxanes inhibit the function of the mitotic spindle and appear to have an even lower likelihood of resulting in persistent ovarian dysfunction [19].

With regard to trastuzumab, a preliminary study evaluating the risks of the most up-to-date treatment modalities found that the addition of trastuzumab did not have a detrimental affect on fertility [18].

Another recent prospective cohort survey study evaluated 595 women aged 25 to 40 years who were treated for early breast cancer with different chemotherapy regimens [12]. The study found that menstrual cycles were more likely to persist among women treated with regimens that contained less total cyclophosphamide, such as adriamycin and cyclophosphamide, or taxol (paclitaxel), adriamycin, and cyclophosphamide, or docetaxel, adriamycin, and cyclophosphamide. While women who were on CMF treatment were more likely than those on adriamycin and cyclophosphamide, those on docetaxel, adriamycin, and cyclophosphamide, or those on taxol, adriamycin, and cyclophosphamide to bleed during the first month following chemotherapy (approximately 50% versus 20%; odds ratio, 2.9; 95% confidence interval (CI), 1.7 to 5), the likelihood of menses 1 year later was lower in the CMF group (odds ratio, 0.37; 95% CI, 0.37 to 0.67). The study also revealed that tamoxifen accounted for a modest but significant decrease (15%) in menstrual cycling at 1 year and 2 years, regardless of the chemotherapy program. Premenopausal women generally continue to menstruate while receiving tamoxifen, although menses can become irregular. The effect on the ovary is assumed to be reversible and temporary [12].

Fertility preservation strategies

The most effective approach to date is embryo cryopreservation. The human embryo is very resistant to damage caused by cryopreservation. The post-thaw survival rate of embryos is in the range of 35% to 90%, while implantation rates are between 8% and 30%; if multiple embryos are available for cryopreservation, cumulative pregnancy rates can be more than 60% [20]. Delivery rates per embryo transfer using cryopreserved embryos are reported to be in the range of 18% to 20% [20]. This approach, however, requires IVF and a participating male partner. If many mature oocytes are retrieved, there is an opportunity to carry out several attempts at embryo transfer from a single cycle. This option may not be acceptable for prepubertal adolescent girls [21].

Cryopreservation of mature oocytes after gonadotropin stimulation

Oocyte banking is more problematic than cryopreservation of sperms or embryos. The first obstacle is the sensitivity of oocytes to chilling, probably because of the sensitivity of the spindle apparatus and the higher lipid content of the cells. Cooling and exposure to cryoprotecting agents affect the cytoskeleton and may aggravate the already high incidence of aneuploidy in human oocytes [22]. Exposure to cryoprotecting agents also causes hardening of the zona pellucida, so that all oocyte cryopreservation protocols involve intracytoplasmic sperm injection as a precaution. Fertilization has to be carried out about 3 to 5 hours after thawing while the oocyte remains fertile.

Further disadvantages of this method are that cancer patients may not have more than one opportunity for oocyte harvesting before undergoing potentially sterilizing treatment, since a cycle of controlled stimulation requires several weeks, and there is normally a delay of a few months before treatment cycles. The success of the method is also dependent on the total number of eggs harvested (<10 oocytes means very low chances of pregnancy).

With the introduction of intracytoplasmic sperm injection and the publication of reassuring data [23], however, efforts to cryopreserve oocytes have resumed in recent years – with conventional slow cooling–rapid thawing protocols, and later with vitrification. More than 4,300 oocytes have been cryopreserved and more than 80 children have been born to date, mostly with the conventional slow cooling method. The overall live birth rate per cryopreserved oocyte is about 2%, which is much lower than that with IVF using fresh oocytes [24].

These data were confirmed by a recent meta-analysis by Oktay and colleagues, who found that the live birth rate per injected oocyte was approximately 2% with the most commonly used slow-freezing technique. Pregnancy rates were one-third to one-quarter of the success rates seen with unfrozen oocytes [25].

A further alternative, which is still at an experimental stage, is the cryopreservation of immature oocytes (with or without *in vitro* maturation). This method is currently still associated with a relatively low pregnancy rate, as well as a high rate of miscarriages [26].

Several small studies have evaluated the utility of gonadotropin-releasing hormone receptor (GnRH) analogue treatment to preserve ovarian function during cytotoxic therapy, including among women with breast cancer (Table 2) [27–30]. This research has suggested that receiving GnRH analogue throughout treatment may increase a woman's likelihood of remaining premenopausal after chemotherapy, although there has been intensive debate concerning the existence of follicle-stimulating hormone (FSH) receptors in

Table 2

Published studies of ovarian suppression with gonadotropin-releasing hormone agonists

Reference	Year	Patients (*n*)	Chemotherapy regimen	Pregnancies (%)	Births (%)	Menses 1 year after therapy (%)	Menses at the end of follow-up (%)	Study type	Outcome
Fox and colleagues [27]	2003	24	AC, AC-T, FAC, AT-CMF	21	8	96	75	Prospective, single-arm	Ovarian function preservation
Del Mastro and colleagues [28]	2006	29	100% FEC	–	–	94	92	Prospective, single-arm	Ovarian function preservation
Recchia and colleagues [29]	2002	100	26% CMF, 11% FEC, 54% CMF + epirubicin, 9% HCST	3	2	100		Retrospective, single-arm	Ovarian function preservation
Urruticoechea and colleagues [30]	2007	50	78% FEC, 14% AC, 8% AC-T/D	16	16	86	90	Prospective, single-arm	Ovarian function preservation
Total		203							

AC, adriamycin (doxorubicin), and cyclophosphamide; AC-T, adriamycin (doxorubicin), cyclophosphamide and taxol (paclitaxel); AC-T/D, adriamycin (doxorubicin), cyclophosphamide and taxol (paclitaxel)/docetaxel; AT-CMF, adriamycin (doxorubicin), taxol (paclitaxel), cyclophosphamide, methotrexate, and 5-fluorouracil; CMF, cyclophosphamide, methotrexate, and 5-fluorouracil; FAC, 5-fluorouracil, adriamycin (doxorubicin), and cyclophosphamide; FEC, 5-fluorouracil, epirubicin, and cyclophosphamide; HCST, high dose chemotherapy and autologous peripheral blood progenitor cell transplantation.

primordial follicles and GnRH analogue receptors in the human ovary [31,32].

GnRH analogue treatment appeared to reduce the incidence of amenorrhea in a population of relatively older reproductive-age women, but the reproductive outcome was poor. Twenty-three of the 24 women resumed menstruation after receiving a GnRH analogue along with chemotherapy, and went on to attempt to conceive. Six pregnancies occurred in five patients; three pregnancies resulted in miscarriage, one pregnancy was terminated because of Down's syndrome, one pregnancy was ongoing, and one woman delivered [27].

A retrospective evaluation by Recchia and colleagues included 100 consecutive premenopausal women (median age 43 years) with high-risk early breast carcinoma who received a GnRH analogue for ovarian protection during adjuvant chemotherapy [29]. After a median follow-up of 75 months, normal menses were resumed by all patients under the age of 40 years and by 56% of patients older than 40 years. Three pregnancies were observed, which resulted in two normal deliveries and one voluntary abortion. The projected recurrence-free survival rates at 5 years and at 10 years were 84% and 76%, respectively, and the projected overall survival rates at 5 and 10 years were 96% and 91%, respectively [29].

In a single-center, prospective, single-arm, phase II study in 29 premenopausal women (median age 38 years) with early breast carcinoma who received GnRH analogue for ovarian protection during adjuvant chemotherapy, after a median follow-up of 72 months, normal menses were resumed in 94% (16/17) of patients under the age of 40 years and by 42% (5/12) of patients older than 40 years [28].

In a very recent prospective, single-arm study by Urruticoechea and colleagues including 50 women who received combination anthracycline-containing chemotherapy regimens with a mean cumulative cyclophosphamide dose of 3.9 g/m^2 and concurrent goserelin administration, amenorrhea occurred in all but one patient. Forty-five patients (90%) recovered menstruation during the first year of follow-up, with a mean time to recovery of 5 months. Ten of the women attempted to become pregnant, resulting in eight pregnancies in seven patients [30].

The available studies are limited, however, by their small sample sizes, by the lack of a randomized control group, and by the lack of definitive information regarding actual fertility outcomes. Randomized controlled trials are currently underway internationally to evaluate this strategy in women with cancer.

The Southwestern Oncology Group is running an ongoing randomized evaluation among women with hormone receptor-negative Stage I–IIIA breast cancer who are either receiving or not receiving goserelin during treatment. In the United Kingdom, the Ovarian Protection for Premenopausal Women having Chemotherapy for Breast Cancer (OPTION) trial is similar, but is also including women with hormone receptor-positive disease. The potential benefit of ovarian suppression in addition to tamoxifen for women with hormone receptor-

positive breast cancer is currently under active investigation in the Suppression of Ovarian Function Trial. Other prospective randomized trials – such as the Zoladex Rescue of Ovarian Function study in Germany, the Italian multicenter study for breast cancer patients, the German Hodgkin Lymphoma Group multicenter study, the UK lymphoma multicenter study, the Spanish lymphoma multicenter study, and the Prevention of Gonadal Toxicity and Preservation of Gonadal Function and Fertility in Young Women with Systemic Lupus Erythematosus Treated by Cyclophosphamide (PREGO) study – can be expected to provide definitive evidence of the role of GnRH analogue in ovarian function preservation [32].

In a recent, very interesting, review by Oktay and colleagues [32], the possible hazards of GnRH analogue treatment for fertility preservation purposes have been sufficiently described. GnRH analogues are not only expensive and cause severe menopausal symptoms, but in addition the direct effects of GnRH agonists on human cancer cells are not adequately understood. A variety of human cancers, including those of the breast, the ovary, and the endometrium, express GnRH receptors. These receptors mediate several effects, such as inhibition of proliferation, induction of cell-cycle arrest, and inhibition of apoptosis induced, for example, by cytotoxic drugs [33]. The possibility therefore cannot be excluded that GnRH agonist therapy concomitant with cytotoxic chemotherapy might reduce the efficacy of chemotherapy for breast cancer. There are data from randomized studies, however, as well as the results of the Early Breast Cancer Trialists' Collaborative Group meta-analysis and the results of the LHRH-agonists in Early Breast Cancer Overview group, that have not shown a different outcome in patients who received ovarian suppression concurrent with the chemotherapy in comparison with patients treated with chemotherapy alone [34-36].

At a more practical level, up to 97% of patients suffer from hypoestrogenic symptoms when using a GnRH analogue along with chemotherapy [28]. Furthermore, when the analogue is used for >4 months, patients may experience bone loss, which may not be reversible with longer periods of use [37].

The American Society of Clinical Oncology has pointed out that there is at present insufficient evidence regarding the safety and effectiveness of GnRH analogues and other methods of ovarian suppression on female fertility preservation. The Society recommends that women who are interested in ovarian suppression for this purpose should be encouraged to participate in clinical trials [38].

At present, cryopreservation of ovarian tissue appears a very promising method of providing the cancer patient with a realistic chance of fertility preservation – a prospect that is also extremely important for psychological reasons [39].

The cryopreservation of ovarian cortical strips has recently emerged as an easy, fast, and inexpensive technique, and has already yielded the first two livebirths [40,41]. The idea of cryopreserving ovarian tissue is based on the finding that the ovarian cortex harbors primordial follicles that are more resistant to cryoinjury than mature oocytes, because the oocytes they contain have a relatively inactive metabolism and lack a metaphase spindle, zona pellucida, and cortical granules [42]. The clinical indications are almost identical with those for the oocyte, but there are fewer logistical restrictions and there is a greater fertility potential, because of the far larger number of oocytes preserved. Ovarian tissue cryopreservation may be the only acceptable method for any prepubertal or premenarchal female patients receiving chemotherapy or pelvic radiotherapy [43]. Follicular viability after cryopreservation and thawing has been demonstrated in several studies [44-48].

The risks of ovarian tissue cryopreservation include reimplantation of the primary tumor, malignant transformation, and risks related to the invasiveness of the procedure. Limiting factors with this method are that it remains in experimental status, the availability of the procedure in only a few selected centers, and the limited life of the ovarian grafts. Questions in the field of ovarian tissue cryopreservation that are still unanswered include the optimal site for retransplantation, the size of the ovarian grafts, and the effect of gonadotropin stimulation [39].

In vitro fertilization after breast cancer

An increase in estradiol during controlled ovarian hyperstimulation may not be safe in women diagnosed with estrogen-sensitive breast cancer who are seeking fertility preservation. It has been clearly shown that estrogen stimulates breast cancer cell growth, even at low concentrations [49,50].

The embryo yield with natural-cycle IVF (without hormone stimulation), however, is very low [51]. In such cases, alternative stimulation regimens can be used – for example, tamoxifen [52] or aromatase inhibitors [53] – although these regimens are less effective without added gonadotropins. Although these medications should not be used during pregnancy, studies with tamoxifen and letrozole have demonstrated that their short-term use for ovulation induction does not adversely affect oocyte and embryo development. Moreover, no detrimental effects on fetal development have been demonstrated. In any case, clomiphene, a compound related to tamoxifen, has been safely used for ovulation induction for almost four decades [54].

In a study by Oktay and colleagues, tamoxifen 40–60 mg was started on day 2 or day 3 of the cycle and was administered daily for 5–12 weeks. The control group consisted of patients with an unstimulated IVF cycle. The tamoxifen group had a significantly higher number of mature oocytes, higher peak

estradiol, and a higher number of embryos (mean of 1.6 embryos versus 0.6 embryos) than the natural-cycle group [52].

Third-generation aromatase inhibitors (letrozole, anastrozole, and exemestane) entered clinical practice initially as first-line and second-line agents for the treatment of breast cancer [55,56]. The use of aromatase inhibitors for ovulation induction was first reported in 2001; letrozole was reported to provide superior results to clomiphene and was associated with 50% lower estradiol levels [57]. Many groups are currently testing the feasibility of ovarian stimulation with aromatase inhibitors in patients with breast cancer and in patients with endometrial cancer. The patient is stimulated with gonadotropins, and an aromatase inhibitor is simultaneously introduced to reduce serum estradiol levels. Oocyte development is unaffected. A luteinizing hormone-releasing hormone antagonist is also used to prevent a premature luteinizing hormone surge [58].

Oktay and colleagues compared the combination of tamoxifen or letrozole with FSH for stimulation in women with breast cancer, with very promising results [51]. Letrozole–FSH and tamoxifen-alone stimulation were associated with significantly lower peak estradiol levels than tamoxifen–FSH stimulation. The combined letrozole–FSH protocol resulted in peak estradiol levels close to those seen in unstimulated cycles, and breast cancer recurrence rates were not increased compared with controls [59]. The same group also reported the first pregnancy from cryopreserved embryos generated after tamoxifen stimulation [51], and reported that breast cancer patients who underwent ovarian stimulation with anastrozole had a significantly higher exposure to estradiol than those who were stimulated with letrozole [60].

Nevertheless, Partridge and Winer have listed a series of questions that remain unanswered [61]. How does even brief exposure to high estrogen levels through tamoxifen or FSH–letrozole stimulation affect the risk of breast cancer recurrence? Does brief exposure to tamoxifen or letrozole before treatment compromise the effect of chemotherapy? Finally, do these substances have any influence on the quality of the oocytes harvested?

Pregnancy after breast cancer

Pregnancy after breast cancer is another area of investigation (Table 3) [62-72]. The incidence of live births after breast cancer is very small. Among women <45 years of age at diagnosis, only 3% have full-term pregnancy [70]; and among women <35 years at diagnosis, 8% give birth to a liveborn infant [71]. There has been concern that continued menstrual cycling or pregnancy after breast cancer may worsen the prognosis, since breast cancer is often hormone sensitive.

In a Finnish study among 2,548 women <40 years old diagnosed with carcinoma of the breast during 1967 to 1989, there were 91 eligible patients with subsequent deliveries (≥10 months after the diagnosis) – for whom 471 control individuals were matched for stage, age, and year of breast cancer diagnosis. The controls had a 4.8-fold (95% CI, 2.2 to 10.3) risk of death in comparison with those who were delivered after the diagnosis of breast cancer. This result was interpreted as a healthy mother effect (that is, only women who feel healthy give birth and those who are affected by the disease do not). Nevertheless, six of eight deaths among the 91 patients who did give birth were related to breast cancer [64].

A very interesting study investigated the prognostic influence of pregnancies 5 years before ($n = 173$) and 5 years after ($n = 50$) breast cancer diagnosis in 2,119 women younger than 50 years of age with a primary operable breast cancer [65]. Women who had undergone a pregnancy before diagnosis had slightly larger tumors than the control group. The women did not differ, however, with respect to nodal status or estrogen receptor status. There was no evidence that women who had undergone a pregnancy during the 5-year period preceding the diagnosis of breast cancer had a poorer prognosis in comparison with women who had not been pregnant in the same period. Similarly, there was no evidence that women who became pregnant after the diagnosis of breast cancer had a poorer prognosis. In fact, the relative hazard for women who became pregnant after a diagnosis of breast cancer in comparison with women without a subsequent pregnancy was 0.48 ($P = 0.14$), suggesting a possibly reduced risk of distant dissemination [65].

Müller and colleagues retrospectively compared 438 patients who became pregnant after a diagnosis of breast cancer, on the one hand, with 2,775 control patients without pregnancies, on the other. They found that women who had births at least 10 months after the cancer diagnosis had a significantly lower mortality risk [70].

A Danish study examined 173 women, from a total population of 5,725 women with primary breast cancer, who became pregnant after treatment. Women who had a full-term pregnancy after breast cancer treatment had a nonsignificantly reduced risk of death (relative risk 0.55; 95% CI, 0.28 to 1.06) in comparison with women who did not have a full-term pregnancy. Neither miscarriages nor induced abortions after breast cancer treatment influenced the prognosis [67].

Partridge and Ruddy postulate that there might even be a beneficial biological effect of the high hormonal levels of pregnancy, since high-dose estrogen and progestins have been conventionally used as a treatment modality for breast cancer [73].

A Japanese research group demonstrated an antitumor effect in an animal model, possibly due to signaling via the insulin growth factor pathway [74]. In the same animal model, it was found that early age at full-term pregnancy or short-term hormone treatment mimicking pregnancy may suppress the

Table 3

Effect of a subsequent pregnancy on outcome in breast cancer survivors

Reference	Year	Patients (*n*)	Controls (*n*)	Relative risk (95% confidence interval) of recurrence or death/ % recurrence	Outcome
Ariel and Kempner [62]	1989	47		30% recurrence	No adverse effect on survival
Sutton and colleagues [63]	1990	23	204	28% recurrence, 3 deaths	No adverse effect on survival
Sankila and colleagues [64]	1994	91	471	0.20 (0.10 to 0.50)	No adverse effect on survival
von Schoultz and colleagues [65]	1995	50	2,119	0.48 (0.18 to 1.29)	No adverse effect on survival
Malamos and colleagues [66]	1996	21	222	14.3% recurrence	No adverse effect on survival
Kroman and colleagues [67]	1997	173	5,514	0.55 (0.28 to 1.06)	Decreased risk in pregnant women
Velentgas and colleagues [68]	1999	3	265	0.80 (0.30 to 2.30)	No adverse effect on survival
Gelber and colleagues [69]	2001	94	94	0.44 (0.21 to 0.46)	Decreased risk in pregnant women
Müller and colleagues [70]	2003	438	2,775	0.54 (0.41 to 0.71)	Decreased risk in pregnant women
Blakely and colleagues [71]	2004	47	323	0.70 (0.25 to 1.95)	No adverse effect on survival
Ives and colleagues [72]	2007	123	2,416	0.59 (0.37 to 0.95)	Decreased risk in pregnant women
Total		1,110	14,164		

risk of breast cancer. The age of hormone exposure is a crucial factor, however, because hormone exposure mimicking pregnancy in aged individuals may exert effects that are the opposite of those exerted in younger individuals [75].

The optimal timing of a subsequent pregnancy after breast cancer is unclear and depends on the patient's prognosis, age, and personal situation. Meirow and Schiff postulated that patients who recover from ovarian failure after high-dose chemotherapy or radiotherapy treatments should not delay childbearing for too many years. These patients should try to conceive after a disease-free interval of a few years, but not <6 to 12 months after the treatment, due to the possible toxic effects of the therapy on growing oocytes [76]. A delay of 2 to 3 years after the cancer treatment is conventionally recommended, so that the period associated with the greatest risk of recurrence has passed before a pregnancy. In patients with hormone-positive cancers, tamoxifen and GnRH analogues do not cause permanent amenorrhea, but this treatment can last up to 5 years, during which a pregnancy is contraindicated [7].

In summary, an analysis of a number of studies in a population of over 15,000 women, including more than 1,100 breast cancer patients, demonstrates that there are at present no conclusive data to suggest any deleterious effects, such as an increased risk for relapse, due to subsequent pregnancy in women with a history of breast cancer. A limiting factor in this analysis is that none of the studies concerned was randomized and controlled. Performing a randomized trial on this specific issue is not possible, however, since no woman can be denied the right to become pregnant. Notwithstanding all the above, two studies published in the *New England Journal of Medicine* [77,78] have reported that good observational studies can give results similar to those of randomized controlled trials [31].

It is therefore our firm belief that fertility preservation options should be discussed with these patients.

Prognostic factor of amenorrhea

Chemotherapy-induced amenorrhea may be reversible; however, the vast majority of women who remain amenorrheic 1 year after treatment do not regain ovarian function. Less than 11% of women over 40 years old and only 12% to 15% of younger women experience a return of menses after 1 year of amenorrhea [7].

Ovarian estrogens play an important role in the oncogenesis and development of breast cancer. The positive effect of ovarian hormone suppression in the preventive situation, the adjuvant situation, and also the palliative situation has been adequately proven. There is no doubt that, particularly in very young patients, chemotherapy acts at least partially via chemotherapy-induced amenorrhea [79-82].

The fact that both ovarian suppression and chemotherapy produce an improvement in the disease-free survival for premenopausal women poses the question of whether this effect is mediated at least partly by the same biochemical pathways – a hypothesis that may be supported by the following four points [83].

First, cytotoxic chemotherapy will induce amenorrhea in a proportion of premenopausal women, ranging from about 15% to close on 100%, depending on age. The younger the woman, the greater the resistance to the castrating effect of cytotoxic drugs [5].

Second, the endocrinological profile of a woman exposed to cytotoxic chemotherapy is similar to that of a castrate woman. In other words, estradiol levels fall and gonadotropin levels rise [84,85].

Third, there is now extensive literature illustrating the fact that the induction of amenorrhea by adjuvant cytotoxic chemotherapy or endocrine therapy is in itself a prognostic factor. Those women who develop permanent amenorrhea fare better than those whose menstrual periods return during or after the completion of the course of treatment. This association is seen most clearly amongst women whose tumors express the estrogen/progesterone receptors [86-88]. A meta-analysis on the influence of chemotherapy-induced amenorrhea on the prognosis has demonstrated a significant advantage of survival for amenorrheic patients in 15 of 23 studies included [89]. Similarly, a meta-analysis of randomized studies including 3,307 patients confirmed a significant difference in the overall survival (15% reduction, $P = 0.04$) with GnRH therapy after chemotherapy [90]. Altogether, the available data allow the conclusion that chemotherapy-induced amenorrhea or amenorrhea after GnRH therapy following chemotherapy improves the prognosis.

Finally, there have been trials that have attempted to carry out a direct comparison of endocrine therapy and chemotherapy in premenopausal women. In a recent meta-analysis, data from 11,906 premenopausal women with early breast cancer who were randomly assigned to treatments in 16 trials were examined. When used as the only systemic adjuvant treatment, luteinizing hormone-releasing hormone agonists did not significantly reduce the recurrence rate (28.4% relative reduction; 95% CI consistent with a 50.5% reduction to a 3.5% increase; $P = 0.08$) or the rate of death after recurrence (17.8%; 95% CI consistent with a 52.8% reduction to a 42.9% increase; $P = 0.49$) with hormone-receptor-positive cancers. The addition of luteinizing hormone-releasing hormone agonists to tamoxifen or chemotherapy, or to both, reduced the recurrence rate by 12.7% (95% CI, 2.4 to 21.9; $P = 0.02$) and reduced the rate of death after recurrence by 15.1% (95% CI, 1.8 to 26.7; $P = 0.03$). Luteinizing hormone-releasing hormone agonists showed similar efficacy to chemotherapy (recurrence, 3.9% increase; 95% CI consistent with a 7.7% reduction to 17.0% increase; and death after recurrence, 6.7%; 95% CI consistent with a reduction, 20.7% reduction to 9.6% increase; neither significant). No trials have assessed a luteinizing hormone-releasing hormone agonist versus chemotherapy with tamoxifen in both arms. Luteinizing hormone-releasing hormone agonists were ineffective in hormone receptor-negative tumors [34].

Conclusion

Young female breast cancer patients are still being poorly counseled with regard to the negative impact of the treatment on their fertility and on their options for fertility preservation. Although there have been a few studies that show a positive effect of GnRH analogues on fertility preservation, there is insufficient evidence to establish the use of GnRH analogues as a first-line therapy. There are currently a few ongoing prospective randomized studies on the topic, but their long-awaited results will probably not yet be published for several years. In the meantime, the use of GnRH analogues in breast cancer patients should be offered in the context of clinical trials after adequate counseling of the patients with regard to the possible influence of this treatment on the effectiveness of chemotherapy. Other methods of preserving fertility, such as ovarian tissue cryopreservation, *in vitro* maturation, and IVF after ovulation induction with aromatase inhibitors, should also be discussed with the patient. Pregnancy after breast cancer treatment does not appear to limit the prognosis.

The present review has focused both on the effects of cancer treatments on fertility and on the various assisted-reproduction innovations that are available to provide the breast cancer patient with the option of future pregnancies. We are currently passing through a period of uncertainty and change with regard to the role of ovarian suppression and other fertility preservation measures in the management of early breast cancer, but developments in the near future promise to be very exciting.

Competing interests

The authors declare that they have no competing interests.

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