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Impact of breast cancer treatment on fertility

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Introduction

Approximately 25% of breast cancers occur in premenopausal women, and 15% occur in women younger than 45 years of age [1]. Because the average age of first pregnancy is rising, the percentage of women diagnosed with breast cancer that are of childbearing age or pregnant is also increasing. In addition, the possibility of a woman willing to become pregnant after breast cancer treatment is also rising.

There are no studies showing that later pregnancy has a negative effect on the survival of patients who have been diagnosed and treated for breast cancer. A recent review concluded that there was no adverse effect, and perhaps even a slight protective effect, on survival by childbearing after breast cancer treatment [2]. The superior survival seen in this and other controlled studies may merely reflect a bias towards the selection of healthy patients, but it is also consistent with a potential antitumor effect of pregnancy [2].

The increased survival and decreased mortality of breast cancer patients is partly due to the use of screening programs that allow an earlier diagnosis, and the improvement of treatments, including chemotherapy and hormone therapy [3]. Most cancer therapies have a substantial morbidity on reproductive function, not only because they increase the risk of early menopause, but also because they are associated with a decreased ovarian reserve and a loss of fertility. The impact of infertility on the quality of life of the patient who survives breast cancer explains the increase in the demand for fertility preservation techniques [3].

Chemotherapy-induced amenorrhea (CIA)

The effects of chemotherapy are reversible in most organs, but not in ovarian tissue. In a significant number of premenopausal women, the administration of adjuvant chemotherapy induces a state of amenorrhea, in many cases irreversible depending on the extent of tissue damage and prior ovarian reserve, which has important short- and

long-term implications [4] (Table 1). Chemotherapy causes a progressive dose-related depletion of ovarian follicles and granulosa cells that translates into oligo-amenorrhea and subsequent premature ovarian failure, ultimately leading to what is known as CIA. [5]. From an endocrine point of view, a decrease in estrogen levels with elevated follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels occurs (i.e. hypergonadotropic hypogonadism).

While there is significant variability in the definition of CIA, some retrospective and prospective studies have reviewed the factors involved in its onset and the degree of reversibility [6-10]. The exact incidence of CIA is difficult to establish because many factors can contribute to it, but the type of chemotherapy, cumulative dose and the patient's age are the main factors that determine the occurrence of CIA. Following chemotherapy, older women have a higher incidence of complete ovarian failure and permanent infertility compared with younger women [3, 11], and it is estimated that the physiological age of the ovaries in a cancer survivor may be 10 years older than the actual chronological age [12].

Therefore, regardless of the beneficial effects that hormonal changes can have as part of the adjuvant endocrine strategy, CIA is an adverse event to take into account for the selection of the best adjuvant treatment.

The abolition of menstruation due to the use of alkylating agents is probably the most reviewed subject in the scientific literature. For patients in whom drugs such as melphalan or cyclophosphamide are used, reported CIA rates range from 25 to 95% respectively [13]. These rates were lower in younger patients and higher when the number of cycles or dosage was increased [9].

Chemotherapeutic agents can be grouped into three risk groups according to their potential to cause ovarian damage [14]:

1. High Risk: Cyclophosphamide, melphalan, busulfan, chlorambucil, procarbazine and nitrogen mustard are alkylating agents that are associated with an

increased risk of ovarian failure, with an overall response of 3.98 compared to unexposed women [15].

2. Moderate Risk: Cisplatin causes ovarian failure with an overall response of 1.77. Doxorubicin and paclitaxel also fall into this group.
3. Low risk or no risk: Methotrexate, 5-fluorouracil, bleomycin and actinomycin D, and vinca alkaloids cause ovarian failure with an overall response of about 1.

Regarding specific group data, there are conflicting results regarding the ability of anthracyclines to increase the rate of CIA when these are used in combination with alkylating agents. Thus, in the MA.5 study comparing cyclophosphamide, methotrexate, and fluorouracil (CMF) versus cyclophosphamide, epirubicin, and fluorouracil (CEF), there were higher rates of amenorrhea in women who received anthracyclines (76% vs 64%; $p=0.03$), although higher doses of alkylating agents were received in the CMF arm [16]. By contrast, in a trial comparing four cycles of doxorubicin and cyclophosphamide (AC) versus six cycles of CMF, the highest percentage of CIA (>12 months) occurred in the CMF arm (34% vs 69%) [17]. Age was the most important predictor of CIA in all these studies. For women older than 40 years treated with anthracyclines, CIA rate was 95%, compared with 30% in women younger than 40 years.

Other studies have analyzed how the dose and duration of anthracyclines impact on ovarian suppression. The Cancer and Leukemia Group B study (CALGB 8541), which compared three doses of adriamycin (30, 40 and 60 mg/m²), found no differences in rates of CIA [18]. In the French Adjuvant Study Group 01 trial (FASG), three different doses of epirubicin were compared with different numbers of cycles. A relationship between CIA and the cumulative dose of anthracyclines was found [19]. Again, the results are contradictory when the relationship with dose density is studied, especially when maintaining the same cumulative dose of anthracyclines.

Taxanes are another group of drugs that have been analyzed for this toxicity. For sequential schedules, CIA rates are very similar in patients older than 40 years (85%). However, there are differences in younger women. A study that compared the same number of cycles of fluorouracil, doxorubicin and cyclophosphamide (FAC) with docetaxel, doxorubicin and cyclophosphamide (TAC) showed that the percentage of amenorrheic patients was higher in the arm that received docetaxel (62% vs 52%; $p=0.007$) [20]. Table 2 shows a summary of studies which have evaluated the incidence of CIA according to different chemotherapy schedules.

The relationship between tamoxifen and amenorrhea is well established, although tamoxifen monotherapy carries a low risk of CIA, which largely depends on the patient's age [21]. The possible mechanism could be an increase in serum estrogen levels and a blockade of the hypothalamic-ovarian axis.

Studies to identify women with diminished ovarian reserve could include measurement of follicle-stimulating hormone, inhibin B or anti-Müllerian hormone levels, or a transvaginal ultrasound to determine the number of antral follicles. Serum anti-Müllerian hormone may be a promising marker of ovarian reserve in women after breast cancer treatment because its level decreases with age and in younger patients who survive cancer; other possibilities include measurement of inhibin B levels and antral follicle count [12].

Strategies to preserve fertility

Young women diagnosed with breast cancer need to be advised by a multidisciplinary team on the impact of treatment on subsequent fertility before starting any treatment, and should be provided with access to specialized units that help them to preserve their fertility.

The choice of the method of preserving fertility depends on the patient's age, her desire to become pregnant, the type of chemotherapeutic treatment to be administered, the

time available before chemotherapy commences, the amount of time pregnancy must be delayed after treatment, and the potential for the cancer to metastasize to the ovary [3, 22].

Embryo and oocyte cryopreservation

Embryo cryopreservation is currently the only clinically tested procedure. Nevertheless, this approach has several limitations because a partner or a sperm donor is required, and ovarian stimulation is necessary, which may delay the start of chemotherapy by 2-6 weeks, a situation which may not always be advisable. Overriding all these considerations, however, are the ethical and legal problems associated with embryo cryopreservation [3, 23].

Oocyte cryopreservation is an emerging option for preserving fertility in women without partners who do not wish to use donor semen. This procedure also requires ovarian stimulation. The rapid freezing technique of vitrification has presented a breakthrough in oocyte cryopreservation. This technique is fast, safe, effective and less costly. Given the high survival rates, together with the high fertilization rates and better results in terms of healthy births, vitrification is the method of choice for oocyte cryopreservation [24]. The advantages of oocyte cryopreservation are that it requires minimal invasion, oocytes can be preserved for an unlimited time and there is no need for a sperm sample. On the other hand, this method does not maintain hormonal function and is applicable only during childbearing years.

Both embryo and oocyte cryopreservation require ovarian stimulation, but in the case of hormone-dependent breast cancer, the increased estrogen levels produced by ovarian stimulants could contribute to the proliferation of tumor cells and hence should be avoided. To minimize exposure to estrogens, two strategies have been suggested: an unstimulated/natural cycle, and the use of chemoprotective agents with low-dose protocol of *in vitro* fertilization. The efficacy of natural cycle techniques is hampered by

high rates of a premature rise in LH levels and premature ovulation [25]. Tamoxifen and aromatase inhibitors appear to be the best candidates for ovarian stimulation because of both their effectiveness in preventing breast cancer recurrence and their ability to induce ovulation [3, 26].

Ovarian cryopreservation

This technique allows the storage of a large number of primordial follicles for long periods of time before subsequent reimplantation of the preserved ovarian material. It has potential advantages over embryo and oocyte cryopreservation as it can be carried out at any time, does not require ovarian stimulation and does not delay the start of chemotherapy. It is indicated in patients with breast cancer in whom treatment must be started immediately and who therefore cannot undergo ovarian stimulation, as well as in girls and in women for whom sperm donation is unacceptable [27].

Compared to whole ovary cryopreservation, ovarian cortical slice cryopreservation is the preferred technique. It is advisable to analyze samples to confirm the presence of follicles and the absence of metastases. There are several strategies to bring about maturation of oocytes after treatment for cancer such as autotransplantation (orthotopic or heterotopic), xenotransplantation and maturation *in vitro* [28]. To date, five studies of children born after reimplantation of cryopreserved ovarian tissue have been reported. The number of reimplantations performed by all groups was relatively low due to the amount of time between implantation and the age at which the dissection procedure originally took place [29].

The biggest problem of this technique is that revascularization of the transplanted tissue occurs after several days with consequent ischemia that may induce partial fibrosis and loss of primordial follicles. Another problem that should be considered with autotransplantation of ovarian tissue in women with cancer is the possibility of

transmitting microscopic metastatic disease. Advantages of this technique are the recovery of hormonal function and the possibility of pregnancy.

Use of gonadotropin-releasing hormone- analogues (GnRH-a)

During treatment with chemotherapy, the use of GnRH-a as the only method to preserve fertility is highly controversial. There are several proposed mechanisms of action to explain the protective action of GnRH-a, including suppression of FSH secretion and decrease in uterine and ovarian blood flow, with a subsequent decrease in the number of primordial follicles exposed to chemotherapy [30].

There are a limited number of studies supporting the use of GnRH-a to prevent ovarian failure in humans, which have been criticized for the lack of randomization, control groups and follow-up periods [31]. Moreover, GnRH-a causes a prepubertal hormonal situation in adult women, but prepubescent girls who receive high doses of chemotherapy continue to suffer from ovarian failure. Another reason not to recommend the use of GnRH-a is because it causes tumor cells to stop in G0 phase of the cell cycle, making them less sensitive to chemotherapy [32]. Definitive evidence of the role of GnRH-a in preserving ovarian function is under evaluation in phase III trials [31, 33]. We believe that GnRH-a should not be offered as the sole method of fertility preservation until the efficacy in protecting ovarian function is fully demonstrated [22].

Conclusions

Most cancer therapies used have substantial morbidity on later reproductive capacity, not only increasing the risk of early menopause but also decreasing ovarian reserve and loss of fertility. CIA is an important adverse event to take into account in young women when selecting the best adjuvant endocrine strategy. According to the Ethics Committee of the American Society for Reproductive Medicine, physicians should

inform cancer patients about their reproductive future and options to preserve fertility prior to treatment.

The only clinically established method for fertility preservation is embryo cryopreservation. Experimental procedures such as oocyte and ovarian tissue cryopreservation and GnRH-a should only be offered as part of a clinical trial protocol.

CIA is a highly complex adverse event that requires close attention, especially with the advent of new chemotherapeutic agents.

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Table 1. Side effects of amenorrhea.

Side effects of amenorrhea
Osteoporosis
Arthralgia
Increased cardiovascular morbidity
Hot Flushes
Genitourinary dysfunctions
Sexual dysfunctions
Sterility
Insomnia
Anxiety
Depression

Table 2. Incidence of chemotherapy-induced amenorrhea according to different chemotherapy schedules.

Author	Treatment regimen	Nº Cycles	Age	% of Amenorrhea
Castiglione [34]	CMF	6	>40	90
			≤40	50
Bonadonna [35]	CMF	12	>40	96
			≤40	40
Roche [36]	CEF	6	>40	76
			≤40	38
Berliere [37]	CEF100 x 6	6	>40	72
	vs		≤40	10
	CEF100 x 3 → T100 x 3	3	>40	71
			≤40	20
Martin [20]	FAC vs	6		52
	TAC	6		62
Tham [38]	AC	4	>40	81
	vs		≤40	44
	AC → (D or P)	8	>40	85
			≤40	61
	Anthracyclines			76
Perez-Fidalgo [39]	vs			
	Anthracyclines + Taxanes			83

AC: doxorubicin and cyclophosphamide; CEF: cyclophosphamide, epirubicin, and fluorouracil; CMF: cyclophosphamide, methotrexate, and fluorouracil; P: paclitaxel; T: docetaxel; FAC: 5-fluorouracil, doxorubicin and cyclophosphamide; TAC: docetaxel, doxorubicin and cyclophosphamide.