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FERTILITY AND PREGNANCY AFTER TREATMENT OF BREAST CANCER

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ABSTRACT

Nowadays, with an increasing number of women surviving breast cancer, fertility and the desire for pregnancy they have become critically important factors to evaluate in the risk / benefit analysis that is carried out when planning a cancer therapy plan. The purpose of this article was to update the latest news regarding two issues complementary: the influence of treatment for breast cancer on subsequent pregnancies; the effects of a subsequent pregnancy the diagnosis of breast cancer on the main pathology. By reviewing the international literature we first highlighted the effects of adjuvant chemotherapy, endocrine therapy and radiotherapy on fertility and we subsequently verified how pregnancy is not only safe but also protective for those women who have been diagnosed with breast cancer. Most breast cancer recurrences occur in the first two years after diagnosis, for this reason it is It is recommended that a woman postpone her pregnancy for at least two years after a diagnosis of breast cancer.

Keywords: breast cancer; fertility; pregnancy.

INTRODUCTION

Nowadays, with an increasing number of women who survive breast cancer, fertility and pregnancy have become critically important factors that cannot be ignored in that context of risk / benefit analysis that takes place when planning a cancer therapy plan. Also the desire for scientifically updated information and the patients' doubts regarding the possibility and clinical opportunity to start a pregnancy after facing breast cancer, they represent two key points in the management of this new patient-patient counseling. Recent studies by the Office for National Statistics show that the average age of women engaged in their first pregnancy gradually increased from 26.2 years in 1972 to 29.1 years in 2000 (1); this data suggests that there is a large class of patients with breast cancer and premenopausal age who may still become pregnant in the following decades of life. Only 6.5% of all breast cancers are diagnosed in women under the age of 40 and 21.8% in those under the age of 50 (2). It therefore seems essential to have a valid scientific data base to rely on in providing information about the potential risks related to a pregnancy after a breast cancer diagnosis**.**

This article wants to deepen and revisit this topic by moving along two complementary directions:

- the influence of breast cancer treatment on subsequent pregnancies;
- the effects of a pregnancy following the diagnosis of breast cancer on the main disease.

Sector literature on pregnancy in breast cancer survivors is limited to case-control studies and, in most cases, survival is the main measure.

INFLUENCE OF BREAST CANCER TREATMENT ON SUBSEQUENT PREGNANCES

A. EFFECTS OF ADJUVANT CHEMOTHERAPY ON FERTILITY

Female germ cells proliferate during fetal life by stopping at the oocyte stage. At birth there are about 1,000,000 oocytes, which further decrease to about 300,000 at puberty. There is also a progressive loss of oocytes during each menstrual cycle, which means that less than 1,000 oocytes remain until the menopause period (which in Italy is estimated to be 50 years old). During the menstrual cycle, the production of estrogen determines the stimulation of the theca and granulosa cells by the luteising hormone (LH) and the follicle stimulating hormone (FSH), whose outcome is represented by the peak of LH and the consequent ovulation. All this is necessary to allow the complete progression of mature follicles.

Chemotherapy involves depletion of mature follicles due to induced damage to pre-granulosa cells or a direct effect on oocytes. If the maturing follicles are destroyed, oligomenorrhea results (irregular menstrual cycles, reduced and with a greater chronological interval between them) and, if the number of primordial follicles falls below a valoresoglia, it would result in an irreversible exhaustion of ovarian function (i.e. menopause).

Menopause is defined as an amenorrhea dating back more than twelve months associated with an FSH level greater than 30 mIU / ml. For women under the age of 50, two years of amenorrhea are needed to define menopause.

Cytotoxic chemotherapy can lead to amenorrhea - due to direct ovarian damage - both simultaneously with the period of administration of the therapy, with an immediate and irreversible menopause, and subsequently, a few years after chemotherapy, when amenorrhea occurs. This means that even for those women in whom there is a resumption of menstruation, their menopausal age will necessarily be anticipated if compared to that in the absence of chemotherapy. In this regard, it is important to underline that any persistence of menstrual cycles after chemotherapy does not necessarily mean having retained one's fertility: that is, menstruation can only represent a poor fertility surrogate since the cycles can be anovulatory.

The consequences of menopause will include the typical symptomatic set represented by hot flashes, sudden changes in mood, weight gain and, in the longer term, a reduction in bone mineral density as a consequence of the reduced estrogenic levels.

The risk of oligomenorrhea, or menopause, resulting from chemotherapy is related to the age at which the woman receives the treatment as well as to the age at which her physiological menopause would be expected in the absence of chemotherapy, and is also connected to the type of drug cytotoxic chosen, at its dose and duration of treatment (3, 4). It is now established that alkylating agents are the most inducing amenorrhea among the cytotoxic drugs, while this risk is slightly reduced with anthracyclines or antimetabolites (4, 5). For example, at the age of 40 the risk of menopause related to a type of chemotherapy scheme CMF (cyclophosphamide / methotrexate / 5-fluorouracil) is approximately 78%, compared with the 38% risk associated with an FEC treatment (5 fluorouracil / epirubicin / cyclophosphamide) in which, in fact, the total dose of alkylating agent (in this case cyclophosphamide) is lower (5, 6). The risk of menopause is lower for regimens short-lived chemotherapies when compared to longer-lasting ones; for example, with four cycles of doxorubicin and cyclophosphamide the risk is estimated at 10-15%, while it rises to approximately 40% with six cycles of a scheme similarly based on anthracyclines such as FEC (6).

For some women, the evaluation of their ovarian reserve before treatment may prove fundamental to support decisions regarding adjuvant chemotherapy and for the analysis of the pros and cons of any method that can subsequently be considered in the context of fertility protection. For these reasons, an ultrasound measurement of ovarian volumes is important to ensure a good assessment of ovarian function.

B. ENDOCRINE THERAPY: TAMOXIFEN AND GNRH

For women with steroid hormone receptor positive breast cancer, tamoxifen treatment for five years is usually recommended. Although tamoxifen itself has a slight impact on innate fertility and as much as it really started as a fertility drug, natural fertility for all women begins to decline after the age of 36 due to the progressive loss of oocytes and therefore, after five years of treatment with tamoxifen - possibly administered in combination with chemotherapy, which per se reduces ovarian reserve - the chances of getting pregnant are relatively low, unless the woman is really young (under 30 years of age) at the time of diagnosis and has considerable initial ovarian reserve. Gonadotropin releasing hormone (GnRH) analogues such as goserelin and buserelin are sometimes used in adjuvant systemic treatments and in combination with tamoxifen to ensure suppression of ovarian function in women with steroid hormone receptor positive breast cancer (ER and / or PR). There is, at the moment, no convincing evidence that use
of GnRH analogues guarantees an additional benefit in terms of reducing the risk of recurrence and mortality beyond chemotherapy and tamoxifen in those women who have already needed chemo treatment by virtue of the tumor prognostic factors identified during the surgical time. However, for some patients at low risk of recurrence, an analogue of GnRH, associated with tamoxifen, may represent an adjuvant treatment option instead of chemotherapy.

Following this approach, the GnRH analogue should be administered for at least two or three years during which the woman may experience some symptoms of menopause; tamoxifen should be continued for the standard duration of treatment, i.e. five years.

TIMING AND CONCLUSIONS

In the past, it was not in the least advisable for a woman with breast cancer to engage in pregnancy or to proceed with an ovarian stimulation aimed at the collection of oocytes for in vitro fertilization.

The percentage of women who become pregnant after receiving breast cancer diagnosis is estimated at between 3 and 8% (13), among these there is also an increased risk of spontaneous abortion defined as 25% (14 , 15). Nowadays, for women who survive the tumor and who become pregnant, yescompare with an ever-increasing objectivity that shows how gestational status does not negatively interfere with survival. However, it is recommended that a woman postpone her pregnancy for at least two years after a diagnosis of breast cancer (16).

It is also advisable that a multidisciplinary team, equipped with a specialist in pathophysiology of the reproduction, take care of these women who face the diagnosis of breast cancer before they have the opportunity to generate children or women who have survived the disease who want a pregnancy, so that they do not live and face such physical and emotional stress alone.

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