Reproduction after breast cancer

Stefanos Zervoudis, MD, PhD, Gynaecologist and Breast Surgeon^{a,b,c,1}, George Iatrakis, MD, PhD, Gynaecologist-Obstetrician^{c,d,*1}, Iordanis Navrozoglou, MD, PhD, Gynaecologist-Obstetrician^{c,e}

^{a} University of Medicine and Pharmacy, C. Davila, Bucharest, Romania
^{b} Breast Department of Lito Hospital, Athens, Greece
^{c} MANOSMED: Mastology Association of the Northern and Southern Mediterranean-Mobile University of Mastology, Ioannina, Greece
^{d} Technological Educational Institution of Athens, Greece
^{e} Department of Obstetrics & Gynaecology, University of Ioannina, Greece

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Breast cancer is the most frequently occurring cancer in women of developed countries, and as a result of new developments in breast cancer treatment, more women are cured after being diagnosed with this disease. It is important that fertility preservation strategies are addressed before chemotherapy, because chemotherapy may induce premature ovarian failure (depending on the woman’s age, the drugs used, the dosage and duration of treatment). Among possible solutions are embryos or oocytes cryopreservation, ovarian tissue cryopreservation–freezing with a subsequent orthotopic and heterotopic autotransplantation, whole ovary cryopreservation, ovarian suppression with gonadotropin-releasing hormone (GnRH) analogues, which inhibit ovarian follicular depletion induced by chemotherapeutic agents and in vitro fertilisation (IVF) after ovulation induction with aromatase inhibitors or tamoxifen.

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Breast cancer and future fertility

Cancer is the leading cause of death among women of reproductive age. Over time, great strides are being made in the care of cancer sufferers. The longevity and quality of life of patients with cancer continues to improve and the term cure is being used more commonly. In a similar manner, there is...
also much reason for optimism regarding the future fertility options for female (and male) patients with cancer.¹

Breast cancer is the most frequently occurring cancer in women of developed countries.² A total of 12% of breast cancer occurs in women aged 20–34 years.³ As a result of new developments in breast cancer treatment, more women are cured or remain in long-term remission after being diagnosed with the disease. Although young women constitute a minority of breast cancer patients, these women commonly have more distinct concerns and issues compared with older women, including queries regarding fertility and pregnancy.

Nowadays, more cancer patients want to have children after the diagnosis of such a disease. Taking into account that the mean age at first pregnancy continues to rise worldwide, the question of pregnancy after breast cancer is thus raised more frequently. Similarly, survival from breast cancer has significantly improved, and the potential late effects of treatment and the impact on quality of life and fertility have become increasingly important.

**Chemotherapy for breast cancer and impact on reproduction**

Some studies have already reviewed the possibility and risks of giving birth among women with breast cancer previously treated by chemotherapy.⁴ Reproductive medicine specialists and gynaecologists commonly see these young women either shortly after initial diagnosis or following adjuvant therapy and should be aware of current management of breast cancer, the prognosis of patients with early stage breast cancer and how adjuvant systemic treatments may impact reproductive function.³ It must be emphasised that the majority of women, younger than 35 years of age experience only temporary amenorrhoea due to chemotherapy and can maintain fertility. On the other hand, in premenopausal women with breast cancer, it was shown that cytotoxic chemotherapy is beneficial because it causes premature menopause. Evidence appears to support the hypothesis of a dual mechanism of action of chemotherapy in this patient population: direct cytotoxicity and ovarian suppression resulting from chemotherapy-induced ovarian failure. There is ample preclinical and clinical evidence to support a direct cytotoxic mechanism of action. The evidence supporting the gonadotoxic mechanism of action of chemotherapy is indirect but biologically compelling. Chemotherapy, particularly with alkylators such as cyclophosphamide, can cause ovarian fibrosis with a concomitant loss of function. Furthermore, amenorrhoea and premature menopause are well-known side effects of adjuvant chemotherapy for breast cancer. The onset of ovarian failure and amenorrhoea is accompanied by increased follicle stimulating hormone (FSH) and decreased inhibin B, anti-Mullerian hormone (AMH) and oestradiol. Amenorrhoea occurs after a median of two cycles of chemotherapy (range: 1–6 cycles). In women aged less than 35 years, amenorrhoea is induced in less than 10% of the cases. In the rest of the patients, median resumption time of menstruations is 3.5 months (range: 1–10 months). In women aged >40 years, most chemotherapeutic regimens induce premature ovarian failure or premature menopause.

The rates of chemotherapy-induced amenorrhoea are shown in Table 1.

Nevertheless, it seems that chemotherapy-induced ovarian failure would confer benefit, particularly in patients with hormone receptor-positive disease.⁵ On the other hand, target therapies, such as

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>Percentage (%) of permanent or temporary amenorrhoea</th>
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<tbody>
<tr>
<td>Doxorubicin/Adriamycin-Cyclophosphamide</td>
<td>&gt;30</td>
</tr>
<tr>
<td>Cyclophosphamide-Methotrexate-Fluorouracil</td>
<td>&lt; 35 years: &gt; 10</td>
</tr>
<tr>
<td></td>
<td>&gt; 35 years: &gt; 65</td>
</tr>
<tr>
<td>Cyclophosphamide-Epirubicin-Fluorouracil</td>
<td>&gt; 50</td>
</tr>
<tr>
<td>Doxorubicin/Adriamycin</td>
<td>&gt; 55</td>
</tr>
<tr>
<td>Fluorouracil-Doxorubicin/Adriamycin-Cyclophosphamide</td>
<td>&gt; 30</td>
</tr>
<tr>
<td>Docetaxel/Taxol-Doxorubicin/Adriamycin- Cyclophosphamide</td>
<td>&gt; 50</td>
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</table>
trastuzumab (Herceptin), lapatinib (Tykerb) and bevacizumab (Avastin), used as anti-neoangiogenetic agents have no impact on fertility.

It is important that fertility preservation strategies are addressed before chemotherapy, because chemotherapy regimens (including paclitaxel (Taxol), cyclophosphamide, methotrexate, epirubicin, fluorouracil and adriamycin) may induce premature ovarian failure (depending on the woman’s age, the drugs used, the dosage and duration of treatment).

Interventions to retain fertility

A number of interventions are available, which may increase the likelihood of future successful pregnancy, and the relative safety of these interventions is well established in most cases. Among possible solutions are embryos* or oocytes cryopreservation; ovarian tissue cryopreservation–freezing6,7, with or without vitrification,** with a subsequent orthotopic and heterotopic auto-transplantation8; ovarian suppression with gonadotropin-releasing hormone (GnRH) analogues,*** which inhibit ovarian follicular depletion induced by chemotherapeutic agents9 and IVF after ovulation induction with aromatase inhibitors.10 Natural cycle IVF was recommended to avoid hyperoestrogeny.

* Embryos are implanted once treatment has been completed.
** A technique that provides the benefits of cryopreservation without damage due to ice crystal formation; the method usually requires the addition of cryoprotectants prior to cooling.
*** GnRH analogues block ovulation, induce transitory amenorrhoea and protect ovary stock when associated to chemotherapy.

The problem of rapid graft exhaustion has led to focus on whole ovary cryopreservation, which has proved successful experimentally.11

The delay between cancer treatment and pregnancy should be discussed, depending on the initial stage of the disease.12 Equally important could be the histologic type, grade, axillary lymph nodes involvement and co-existence of emboli to the lymphatic vessels and surgical margins (in case of conservative surgery). In general, a delay of 2 years between the end of the treatment of breast cancer and the beginning of a pregnancy is mandatory in early breast cancer patients.

Today, young women undergoing chemotherapy for breast cancer can maintain their fertility and get pregnant. Furthermore, previous chemotherapy does not present any additional risks for the children’s mental or physical health.4

Pregnancy after breast cancer and survival

A pregnancy after breast cancer treatment results in high concentration of plasma oestrogen, and this may contribute to breast cancer recurrence. It has been assumed that the hormonal and immunosuppressant alterations of pregnancy may have deleterious effects. In addition, it was found that pregnancy is a risk factor of the development of breast cancer among carriers of BRCA1 and BRCA2 genetic mutations.13 Some authors reported a worse outcome for women with early subsequent pregnancy but others have refused this, showing no worse outcome with subsequent pregnancy, even in young women. Indeed, it was shown that a subsequent childbearing in young women with breast carcinoma is unlikely to increase their risk of mortality.14

In general, for those patients who conceive following breast cancer, there is no good evidence that pregnancy is detrimental to survival.15 In fact, medical literature has not demonstrated a higher proportion of distant metastasis in women who have given birth after breast cancer compared with controls (those without a subsequent pregnancy after breast cancer).16 It was shown that subsequent pregnancy in women who have been treated for breast cancer does not confer a prognosis worse than that in patients who did not get pregnant17, and overall survival in patients treated for breast cancer who subsequently become pregnant compares favourably with controls.18,19

Some studies showed that women, who have a subsequent pregnancy, have equivalent or, possibly, better survival matched for stage. In fact, population-based studies showed that a subsequent
pregnancy results in an improvement of survival, with favourable relative risks of 0.2 (range: 0.1–0.5)\textsuperscript{20} to 0.8 (range: 0.3–2.3).\textsuperscript{19,21} In the study of Sankila et al.,\textsuperscript{20} women diagnosed with carcinoma of the breast and subsequent deliveries (>10 months after the diagnosis) were compared with controls that were matched for stage, age and year of breast cancer diagnosis (who have survived at least the interval between the diagnosis and the delivery of their matched counterparts). It was shown that the controls had an almost fivefold (95% confidence interval: 2.2–10.3) risk of death compared with those who were delivered after the diagnosis of breast cancer. Although this suggests that subsequent pregnancy may provide a survival benefit, there may be observational bias involved. It is concluded that there is a healthy mother effect (i.e., that only women who feel healthy give birth and those who are affected by the disease do not). Similarly, data from Velentgas et al.\textsuperscript{21} do not suggest that pregnancy after a diagnosis of breast carcinoma has an adverse effect on survival.

However, it is difficult to draw definite conclusions from available studies because of the relatively small number of patients reported and the associated selection bias. In general, the effect of subsequent pregnancy on patients who have had breast cancer with regard to local recurrence, distant metastasis and survival remains debatable, due to sampling and methodological limitations.

The patient should be involved in the various steps of the process, after being properly informed. The patient must similarly be informed that the pregnancy outcome may as well be impaired by the history of cancer, leading to an increased likelihood of preterm birth and low-birth-weight rates.

Theoretically, pregnancy after breast cancer may implicate a potentially higher risk of cancer recurrence, but the available literature provides reassuring data. Many researchers believe that there is no increased risk for relapse if a breast cancer patient becomes pregnant. However, the timing of pregnancy has not yet been fixed.

**How long to wait before getting pregnant?**

For women with early stages of breast cancer, some authors recommend waiting from at least 6 months up to 2 years after the end of treatment before trying to become pregnant, because most of the recurrences of cancer occur during this period of time. Similarly, because recurrence is most likely in the first 2 years, most investigators recommend delaying conception for 2–3 years after treatment, although these recommendations are mainly arbitrary. Similarly, the risk of discontinuing tamoxifen prematurely should be carefully evaluated and tamoxifen (or anti-aromatases such as letrozole) stimulation appeared to resultin a higher number of embryos and a safe method of IVF and fertility preservation in breast-cancer patients.\textsuperscript{22–24} Nevertheless, tamoxifen should not be used during pregnancy due to possible negative effects on embryos, and a pregnancy test should be done before starting tamoxifen. A non-hormonal contraception (condoms, diaphragm and IUCD) is recommended until 2 months after the end of tamoxifen treatment even in the lack of regular menstruation. It must be emphasised that although tamoxifen causes hot flashes, it does not induce menopause.

However, a recent study does not support the current medical advice given to premenopausal women with a diagnosis of breast cancer to wait 2 years before attempting to conceive. The previous study supports the fact that this recommendation may be valid for women who are receiving treatment or have systemic disease at diagnosis, but for women with localised disease, early conception 6 months after completing their treatment, is unlikely to reduce survival.\textsuperscript{25}

The classical view was that young women with positive hormonal receptors treated for breast cancer by surgery, radiotherapy (on the breast in cases of conservative surgery and or on the subclavicular area in case of involved axillary nodes) and tamoxifen could become pregnant 5 years after completion of therapy. On the contrary, young women with negative hormonal receptors treated for breast cancer by surgery, radiotherapy and chemotherapy could become pregnant much earlier after completion of the therapy.\textsuperscript{4}

Although chemotherapy has been shown to result in increased miscarriage frequency, children born to mothers who have received chemotherapy are not at a higher risk for congenital defects compared with the general population. In ideal cases, laboratory testing during pregnancy must be negative and, after an uneventful course, patients could give birth to healthy children. In addition, breastfeeding does not seem to worsen prognosis.
Conclusion

It seems that, following treatment for breast cancer, pregnancy should be possible for most young women. Long-term survival of the mother with breast cancer is today a reality, and modern therapy avoids orphan children. However, several problems must be taken into account in future plans. Probable depression following the diagnosis of the disease, psychological problems after the change of the body’s image (mastectomy) and during the difficult period of chemotherapy (alopecia, gastrointestinal disorders, fatigue), lack of interest for sex and divorce decisions are common problems in these cases. Physicians should encourage young patients with treated breast cancer to try a new start: that is the challenge of life.

Practice points

- Fertility preservation strategies are addressed before chemotherapy
- Among possible solutions are:
  - embryos or oocytes cryopreservation
  - ovarian tissue cryopreservation–freezing with subsequent orthotopic and heterotopic autotransplantation
  - whole ovary cryopreservation
  - ovarian suppression with GnRH analogues
  - IVF after ovulation induction with aromatase inhibitors or tamoxifen

Research agenda

Chemotherapy with less impairment of fertility
Ideal interval between breast cancer therapy and next pregnancy
The healthy mother effect must be further evaluated
Breastfeeding in the next pregnancy offers further benefits

References