Fertility after breast cancer and strategies to help women achieve pregnancy
Michelle Peate,¹ Lesley Stafford,² Martha Hickey¹

1. Obstetrics and Gynaecology, Royal Women’s Hospital, University of Melbourne, Victoria, Australia.
2. Centre for Women’s Mental Health, The Royal Women’s Hospital, Melbourne, Victoria, Australia.

Email: michelle.peate@unimelb.edu.au

Abstract
Around a quarter of breast cancer patients are premenopausal at diagnosis. As cancer treatment can increase premature menopause, fertility and pregnancy after breast cancer are important issues for many women. This review summarises the literature on fertility after breast cancer and strategies to help women achieve pregnancy – specifically, the risk of infertility, fertility measurement after cancer, the impact of future pregnancy on prognosis, birth outcome, contraception, the psychosocial impact of infertility and pregnancy and assisted reproduction after breast cancer. Pregnancy rates after breast cancer are low. Nonetheless, it is important that women are made aware of the potential impact on their fertility and given information regarding their options for fertility preservation before treatment and about their options after treatment to achieve a pregnancy. Decisions to conceive are challenging as women are weighing up their desire for children against fears of recurrence and potential inability to detect future cancers. Providing evidence-based information and psychosocial support to breast cancer survivors who wish to conceive is an important clinical issue in need of greater attention.

Approximately 25% of breast cancer patients are premenopausal at diagnosis.¹ Combined with the social trend of later childbearing,² there are growing numbers of women diagnosed with breast cancer before they have started or completed their families. Survival rates from early breast cancer are high but effective treatments commonly impair ovarian function and reduce fertility.³,⁴

Clinical practice guidelines recommend discussion of the impact of cancer treatment on fertility and fertility preservation options prior to commencing gonadotoxic treatment.⁵,⁶ Although there is no guarantee of future parenthood, cryopreservation of embryos or oocytes gives women additional options for achieving a pregnancy if they become infertile. Ovarian tissue cryopreservation, although still considered experimental, may also be an option particularly if delays in treatment are not feasible. Ideally, fertility preservation should occur prior to commencing gonadotoxic therapy.⁵ In practice, when women are faced with a new cancer diagnosis, decisions relating to fertility presentation may seem overwhelming and often, these decisions are delayed until after adjuvant treatment.

Risk of infertility and predicting fertility after breast cancer treatment

Understanding the impact of breast cancer treatments on fertility is made more complex by the range of outcome measures used and the variation in baseline ovarian function in study participants. Post-chemotherapy amenorrhea has been widely used as a marker of ovarian function, but definitions of amenorrhea have varied between studies and age-groupings are inconsistent.⁷

It is well recognised, however, that the most commonly used adjuvant chemotherapy regimens are gonadotoxic and adversely affect fertility by reducing the primordial follicle pool.⁸ The classic cyclophosphamide-containing regimens are associated with rates of amenorrhea ranging from 8%-98%.³,⁹,¹⁰ Taxane-containing regimens are associated with amenorrhea in 15-85% of cases.¹¹,¹² The limited data on women under 35 show extremely low rates of chemotherapy-induced amenorrhea, 0-10% in most studies,¹³ this circumstance becoming pronounced (and likely permanent) in patients over 40 years of age.¹⁴ Those who remain amenorrheaic for one year are likely to remain so
Although modern chemotherapies appear to be less toxic than older therapies, with many young women remaining pre-menopausal following treatment, they may still have varying degrees of ovarian dysfunction. It has also been suggested that the risk of ovarian failure after chemotherapy may be underestimated because of the use of amenorrhea as a proxy for fertility. 

Radiotherapy and endocrine treatment do not appear to reduce long-term fertility. With proper radiation technique and use of radiation shields there should be no adverse impact on fertility and birth outcomes. The impact of endocrine treatment is less clear. Although by definition endocrine treatment causes amenorrhea, most patients regain their menses after completion of therapy. The relative contribution of tamoxifen to treatment-induced amenorrhea is debated since most young patients have also received adjuvant chemotherapy. Some studies show an increased incidence with the addition of tamoxifen, others report no impact, with tamoxifen having apparently less effect on amenorrhea in younger women. Women need to consider that their ovarian reserve will naturally decrease when on endocrine treatment (5-10 years).

Measuring fertility after breast cancer

Measuring fertility after cancer treatment is challenging and should reflect both the quantity and quality of gametes. Many published studies have used menstruation as a marker of ovulation, but it is not a reliable surrogate for this.

Indirect markers of fertility include age, endocrine markers such as follicle stimulating hormone (FSH), luteinising hormone, estradiol, inhibin B (InB), antimullerian hormone (AMH), and other measurements such as antral follicle count (AFC) and ovarian volume (ultrasound). Most information about these markers comes from the in vitro fertilisation context (i.e. women who are undergoing ovarian stimulation and/or have a history of infertility) and may not be directly applicable to spontaneous conception.

Growing information about the role of these indicators in the cancer population suggest that cytotoxic chemotherapy results in consistent measurable changes including lower AMH, AFC, InB, and higher FSH and an increase in amenorrhea. Of these, AMH may be the most objective and consistently accurate as AMH reflects follicle numbers at early stages of development and does not vary substantially during the menstrual cycle. However, it is still uncertain whether AMH reliably predicts ovarian recovery after chemotherapy. Limitations of AMH include wide variations within age groups, lack of standardisation of assays and the possibility that women with breast cancer may have a lower AMH prior to chemotherapy compared to healthy age-matched controls. Generally, none of these markers can reliably predict pregnancy or menopause.

In summary, current measures of fertility after cancer treatment have limitations. A combination of clinical information and measures of circulating AMH, AFC, FSH and InB will provide some insight into future reproductive potential and likely need for assisted reproductive intervention.

Prevalence of pregnancy after breast cancer

Few women become pregnant and give birth to a live infant after breast cancer. In Australia, a population-based descriptive study using the Western Australian data linkage system reported that only 4.8% of women with breast cancer (out of 2539) under the age of 45 had at least one subsequent pregnancy. International studies report pregnancy rates of 4%-15%. This low pregnancy rate is surprising considering the importance of fertility reported by women with breast cancer. Factors contributing to this low rate may include treatment-induced infertility, fear of recurrence, poor understanding of the risks, insufficient counselling, and patient preference.

Impact of future pregnancy on prognosis

Pregnancy is associated with high circulating concentrations of sex steroids and this observation has led to concerns about the safety of pregnancy following hormone-sensitive breast cancer. Existing evidence is reassuring that pregnancy after breast cancer does not increase morbidity or mortality, potentially due to a ‘healthy mother effect’ and may even confer a survival benefit. The mechanisms underlying this apparent survival benefit are not known, although they have been linked...
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with potential immunological changes associated with pregnancy. Overall, although the mechanisms are not fully understood, the clinical outcomes following pregnancy after breast cancer appear reassuring. However, in clinical practice, oncologists commonly advise against pregnancy for at least two to three years following diagnosis when the risk of recurrence is highest. However current best evidence suggests that a 6-12 month delay after diagnosis may be sufficient. Others have reported that because younger women have significantly lower survival rates and higher local and distant relapse rates than older women, those under 33 years of age might be better advised to delay pregnancy for at least three years, to reduce the risk of recurrence. These same authors advise that patients with lymph node involvement should consider deferring pregnancy for at least five years after treatment and those with distant metastases should not consider conception at all because of treatment intensity and poor prognosis. Ultimately, the decision as to when to attempt conception needs to take into account the evidence, its limitations and other factors like residual fertility and age at eventual conception.

Impact of a breast cancer diagnosis on future offspring

There are concerns about the impact of cancer treatment on future offspring. These include concerns that treatment may cause genetic abnormalities (e.g. germ-line mutation, chromosomal aberrations), which could result in birth defects and/or cancer in offspring. Existing evidence is limited but seems largely reassuring that birth abnormalities are not increased, although the induced abortion rate is high at 20-44% and the spontaneous miscarriage rate has been reported at up to 28%. Obstetric complications may also be increased after breast cancer, including caesarean section, very preterm birth (<32 weeks) and low birth weight (<1500g) in breast cancer survivors (compared to healthy controls). Overall, it has been advised that women wait at least six months, if not 12 months, to minimise potential risk.

Contraception

Some women may opt not to have children after cancer treatment. They may have completed their families, fear the impact of a pregnancy on recurrence, fear a limited lifespan, or may be following a clinical recommendation to avoid pregnancy. Contraception is, therefore, likely to be necessary, but hormonal contraception (e.g. the contraceptive pill or implants) is contraindicated in hormone-receptive positive women. Therefore, it is recommended that women use non-hormonal forms of contraception such as barrier methods (e.g. condoms, diaphragms, intrauterine contraceptive devices), or male or female sterilisation.

Psychosocial impact of infertility and pregnancy

Concerns around quality of life, menstrual changes, potential infertility, desire for children, pregnancy, breastfeeding, contraception and support from partners and family may impact on decisions to have a child following breast cancer.

Over 50% of young women are concerned about future fertility and a major proportion (76%) wish to consider pregnancy following cancer treatment. Concerns about infertility appear to be greater in women who have yet to complete their families, those who have experienced prior difficulty in conceiving, and those younger than 40 years. Unpartnered women report an additional concern of having to wait until they find a partner with whom they want to have a child before learning about their infertility. Dealing with infertility has been associated with significant psychological distress, with levels of depression double that of the normal population and reduced quality of life in areas of emotional wellbeing, sexuality and relationships. When this occurs in the context of cancer, the patient, partner and family may experience great distress and even if the patient is not planning to have children, the threat of infertility may result in anger and a sense of loss. Concerns about potential infertility and the inability to conceive in the future often result in psychological morbidity and worse physical wellbeing. Infertility may also impact a woman’s role identity. Clearly, issues related to fertility are very important in the short and long-term and should not be dismissed or trivialised.

Pregnancy-related issues have been identified as the second highest concern among women who had not yet completed their families. A nested case-control study investigating physical and mental health correlates of pregnancy found that mental health was marginally better in women who had a child after breast cancer. The main motivation for pursuing parenthood after cancer appears to be
that it gives women a sense of feeling normal by reclaiming their lives and achieving goals that they set prior to diagnosis. More time since diagnosis appears to result in fewer pregnancy-related concerns. Although not specifically a reason to avoid pregnancy, de-motivators include fears and concerns about the impact of pregnancy on recurrence, whether pregnancy and breastfeeding impacts on the detection of breast cancer, and feelings that it would be selfish to have a child when lifespan is potentially compromised. Other reasons given for decisions to avoid pregnancy include age or relationship status (29%) and clinician recommendation (19%).

Contraception is also a key concern among women with breast cancer. Failed contraception has been linked to anxiety and fear of recurrence. Concerns about how to best avoid pregnancy have been reported, with hormonal contraception considered unsafe and male sterilisation thought undesirable.

When planning treatment for women with breast cancer, consideration needs to be given to the psychological implications of potential infertility, and fears associated with the impact of pregnancy on prognosis and recurrence. There are concerns that the desire for a child may impact on adherence to endocrine therapy. American Society of Clinical Oncology recommends early discussions about fertility preservation and the management of psychosocial late effects of treatments. It has been suggested that fertility and pregnancy should be part of a survivorship care plan.

Given the motivators and reasons for avoiding pregnancy, it is important that women are well informed about the risks and are well supported in the decision-making process. BRCA mutation carriers may be concerned about transmission to their offspring and so this may influence decisions regarding pregnancy. Several studies have identified unmet information needs about fertility, pregnancy and breastfeeding in this group. To address these needs, decision aids regarding fertility preservation prior to cancer treatment have been developed and found to be effective. However, there are no such tools for pregnancy after breast cancer.

Assisted reproduction after breast cancer treatment

Timing is a key challenge when considering pregnancy after breast cancer. Although the research suggests that women can safely pursue a pregnancy 12 months following cancer, many women with hormone receptor-positive breast cancer are advised to receive endocrine therapy for 5-10 years during which time they are advised to avoid pregnancy. The impact of a temporary treatment interruption to allow conception is currently being investigated. In the absence of data, women who wish to pause cancer treatment should only do so after seeking medical advice from both their oncologist and reproductive specialist.

Options to, and success in, achieving a pregnancy through assisted reproductive technologies will depend on a number of factors including access to preserved gametes. Ideally gametes should be preserved prior to chemotherapy. If this is not possible, it may be possible to pause endocrine therapy to try and achieve pregnancy or to preserve gametes for future conception. Infertility is defined as a 12-month period of unprotected intercourse that does not result in a pregnancy, after which it is recommended that women seek assistance.

Alternatively, women who have preserved oocytes, embryos or tissues can thaw and use these. Embryos can be transferred and oocytes fertilised and transferred into a prepared uterus. There are limited data on live birth rates from frozen embryos or oocytes following cancer. Live birth rates per frozen embryo transfer is approximately 44.1% in women <35 years and 35.8% in women aged 35-39 years, with rates up to 75% reported. Similar live birth per transfer rates of 50-55% in women <36 years and 18-37% in women >34 years have been reported. The use of exogenous sex steroids is avoided after hormone-positive breast cancers. Ovarian tissue cryopreservation is considered ‘experimental’, with only around 60 live births worldwide reported. Although this procedure holds promise, there may be concerns about re-seeding the cancer. Should these options be unsuccessful or unfeasible, it may be worth considering using donor eggs or embryos. Donor eggs or embryos may also be a good option for women who are concerned about transmission of BRCA genes. The chance of success from these options is largely dependent on the age of the oocytes, with younger oocytes more likely to result in a successful live birth.

Alternative options for becoming a parent include surrogacy, adoption or foster care; however, these are not without challenges and can be difficult for cancer survivors to access.
Conclusion

Pregnancy after breast cancer is an important issue for many women. Pregnancy rates after breast cancer are relatively low. Nonetheless, it is important that women are made aware of the potential impact on their fertility and given information regarding their options for fertility preservation before treatment as well as about achieving a pregnancy after treatment. Decisions to conceive are challenging as women are weighing up their desire for children against fears of recurrence and potential inability to detect future cancers. Providing evidence-based information and psychosocial support to breast cancer survivors who wish to conceive is an important clinical issue in need of greater attention.

References:


