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Pregnancy and fertility counseling in breast cancer survivors

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Breast cancer is the commonest malignancy in females, with nearly 1.5 million newly diagnosed cases worldwide each year. In developed countries, it affects up to 1 in 8 women in their lifetime. Whilst breast cancer is relatively uncommon in younger women, with only 15% of cases diagnosed in women less than 45 years, the prevalence of the disease results in large numbers of women of childbearing age being affected. The recent and growing trend in developed countries to delay childbearing is leading to an increase in the number of premenopausal women who have not started or completed their families at the time of diagnosis. Under these circumstances, younger women who are diagnosed with breast cancer have important but complex decisions to make, and these decisions relate not only to treatment but also to how it will affect their fertility, chance of pregnancy and contraceptive choices in the future. Previous research has shown that young women diagnosed with breast cancer want the opportunity to discuss and understand the consequences of the options open to them; however, studies find that fertility issues are not fully discussed or that information is lacking¹⁻³. Even when information is available, women often do not feel adequately supported in making decisions.

Breast cancer treatment exerts a negative impact on fertility for several reasons: first, the toxic effects of chemotherapy on ovarian follicles reduce ovarian function and reserve;

second, once chemotherapy treatment is completed, women are advised to delay attempting conception for 2 years, thus further reducing potential ovarian function; and third, when endocrine therapy is recommended for up to 5 years, ovarian function declines even further⁴. In addition, and most importantly, the knowledge of having a potentially life threatening illness and the associated psychosocial effects of a breast cancer diagnosis may color the decision a couple may make about future children. The negative impact of breast cancer treatment and its associated recommended delays in attempting conception mean that only 7% of premenopausal women remain fertile⁵⁻⁸ and only 3-4% become pregnant following a diagnosis of breast cancer⁹⁻¹¹.

It is important to consider, however, that the reported low proportion of women who become pregnant after a diagnosis of breast cancer could result from under-reporting of pregnancy terminations and missed abortions in this population, as is the case in the general population. According to Barthelmes and Gateley, 14-44% of pregnancies conceived after a diagnosis of breast cancer are terminated¹². These numbers suggest the actual percentage of women who conceive after a diagnosis of breast cancer may be far greater than previously appreciated.

The reasons women may choose to terminate a pregnancy subsequent to a diagnosis of breast cancer include fear that the

breast cancer will recur or that the cancer will affect their child. Many women successfully deliver a healthy child following a diagnosis of breast cancer, but still may fear the effects of the breast cancer on the child and/or the pregnancy on the cancer. Studies to date demonstrate that a subsequent pregnancy is not likely to affect the outcome of the breast cancer, and, equally, a prior diagnosis of breast cancer will not necessarily affect the pregnancy outcome^{9-11,13}. Further prospective studies are needed, however, to explore how pregnancy and fertility affect a diagnosis of breast cancer and how the breast cancer may affect the offspring of women who conceive after diagnosis.

OUTCOMES AND SURVIVAL OF WOMEN WITH PRIOR BREAST CANCER WHO SUBSEQUENTLY CONCEIVE

Pregnancy is not usually recommended in the first 2 years following the treatment of breast cancer, as most early recurrences develop within this time^{14,15}. This recommendation is not made because the pregnancy will affect breast cancer outcome. Rather, it is made to ensure that the woman does not become pregnant and concurrently develop an early recurrence, with its poor prognosis, or become pregnant during active anticancer treatment which can harm the developing fetus. The most favorable time to attempt conception after breast cancer diagnosis is not currently known due to the lack of large, population-based studies; timing is likely to be idiosyncratic to each woman. Factors such as age, disease stage, histological grade, lymph node involvement, hormone receptor status and the type of breast cancer all impact on the type of cancer treatment undertaken, and each treatment has a differing impact on ovarian function. These diverse factors need simultaneous consideration when offering advice to breast cancer survivors on appropriate delays in attempting a subsequent pregnancy. In assessing breast

cancer prognosis, the most important variables include lymph node status, tumor size, tumor grade and hormone receptor status. Various algorithms can be constructed which then give a likely prognosis. One of the most widely used of these is found on the adjuvant online website (www.adjuvantonline.com), although it is recognized that this is less precise in very young women due to the small numbers of these women in clinical studies^{16,17}.

Studies have examined subsequent pregnancies in women previously diagnosed with breast cancer. One recent study of women with localized disease suggests that early conception following the completion of breast cancer management is unlikely to adversely affect survival for women with good prognosis tumors⁹. Moreover, women who conceive after a diagnosis of breast cancer have equivalent or better survival than similar aged women who do not conceive after a diagnosis of breast cancer^{9,13,18-24}. This observation suggests that a subsequent pregnancy may provide a positive survival benefit to women. It is important, however, to interpret these studies with caution due to the bias known as the 'healthy mother' effect. Simply stated, only a select group of women with good prognostic tumors become pregnant after a diagnosis of breast cancer (Figure 1). These studies may therefore be prone to selection bias.

POPULATION BASED STUDY OF WOMEN DIAGNOSED WITH BREAST CANCER WHO SUBSEQUENTLY CONCEIVED

A population based study exploring breast cancer and subsequent pregnancy looked at all women under 45 years of age, diagnosed with breast cancer between 1 January 1982 and 31 December 2000 within Western Australia (WA). This huge state has a population of 2.1 million individuals and recorded 25,000 live births and 7000 abortions per annum in

the study period. Of the 2539 women (15–44 years) with a pathologically confirmed diagnosis of breast cancer, 1421 (56%) had naturally conceived at least one full-term pregnancy prior to their diagnosis of breast cancer, and 123 (5%) had at least one pregnancy following their breast cancer diagnosis (median age 31 years at diagnosis and 35 years at first subsequent pregnancy). The women who had

a subsequent pregnancy were significantly younger at the time of their breast cancer diagnosis compared to other women aged less than 45 years diagnosed with breast cancer, but when they became pregnant were older than other mothers who had a live birth in WA during the same time period.

The types of breast cancers diagnosed within the subsequent pregnancy group, were largely comparable to similar aged women (77% invasive ductal carcinoma, ranging in size from 1 to 90 mm, with half less than 20 mm in diameter). Tumors were reported to be estrogen receptor (ER) positive in 24% of the cases, although 42% had unknown ER status and 64% were lymph node negative.

In this study, as in previous reports, survival was very good, with 85% of women alive at 10-year follow-up, although 37% of women had experienced disease recurrence. Tables 1 and 2 show recurrence-free and overall survival in women who had a subsequent pregnancy after initial breast cancer diagnosis⁹. As seen in the tables, the 5-year overall survival was 91.8% and 10-year overall survival was 78.5%. Recurrence and survival rates were similar whether survival was measured from time of diagnosis or first subsequent pregnancy.

In terms of pregnancy outcomes for the WA study, 175 subsequent pregnancies were confirmed from 123 women previously diagnosed with breast cancer. Over one-third of the



Figure 1 A pregnant woman with mastectomy

Table 1 Recurrence-free survival from breast cancer diagnosis and from date of pregnancy completion (%)

<i>Recurrence-free time</i>	<i>From diagnosis</i>	<i>From subsequent pregnancy</i>
5 years	74.5	62.2
10 years	59.8	57.3

Table 2 Overall survival from breast cancer diagnosis and from date of pregnancy completion (%)

<i>Overall survival</i>	<i>From diagnosis</i>	<i>From subsequent pregnancy</i>
5 years	91.8	87.6
10 years	78.5	84.9

women conceived more than one subsequent pregnancy, with four women experiencing more than three subsequent live births.

The first subsequent pregnancy following a breast cancer diagnosis in these women resulted in a live birth for 66 women (54%). Three women successfully underwent *in vitro* fertilization (IVF) treatment to conceive following their breast cancer diagnosis; they all remained alive and recurrence free at last follow-up. The median time from breast cancer diagnosis to first subsequent pregnancy was 23 months (interquartile range 11–42). There were no stillbirths or ectopic pregnancies. Two births occurred before 36 weeks: a set of twins at 32 weeks following spontaneous rupture of membranes, and a singleton birth by cesarean section at 30 weeks when the mother developed both local and distant metastases. All children were alive and well at last follow-up.

Compared to other women diagnosed with breast cancer when they were less than 45 years of age, women who wait at least 24 months after they have been diagnosed to become pregnant were less likely to die (HR 0.48, 95% CI 0.27–0.83, $p = 0.009$). The likelihood of dying was also reduced for women who waited 6–24 months to become pregnant (HR 0.45, 95% CI 0.16–1.28, $p = 0.135$)⁹; however, this was not a statistically significant finding. Only a few women became pregnant in the 2 years after being diagnosed with breast cancer, but this result suggests that those women who have completed treatment, have good prognosis tumors and are unlikely to have disease recurrence during this time can safely consider pregnancy.

Forty-two (34%) women underwent pregnancy termination. Of the women who terminated their first subsequent pregnancy, ten had at least one subsequent live birth. Three main reasons were given for these terminations: the woman's fear of disease recurrence; the recommendation of the clinician; and the woman having received adjuvant therapy whilst pregnant.

As long as women have completed adjuvant therapy, available evidence suggests that conception within 2 years of a diagnosis of breast cancer does not adversely impact on survival. Consequently, there is no need for some women to wait the full 2 years before attempting conception. However, it is important that this advice be focused on women with good prognosis tumors who are not on adjuvant treatment such as tamoxifen. Available research examining outcomes and survival in those who become pregnant and those who do not shows similar results, but further research will be necessary to corroborate these findings.

FETAL TOXICITY OF BREAST CANCER TREATMENTS

Treatments for early breast cancer in premenopausal women may include local treatments, surgery and radiotherapy, as well as systemic treatments including hormone therapies (tamoxifen, ovarian ablation and ovarian suppression with gonadotropin releasing hormone analogues such as goserelin), chemotherapy and biological agents such as Herceptin. All can be toxic to a developing fetus, particularly in the first trimester of pregnancy. Surgery is fairly safe, although anesthetic consultation concerning risk is required. Radiotherapy is contraindicated during pregnancy²⁵. Tamoxifen has potential fetal toxicity, including Goldenhar's syndrome^{12,26}. Chemotherapy is likely to be teratogenic in the first trimester of pregnancy, resulting in embryo loss in the very early stages of development and potential fetal damage later on; this is possibly related to the agent used²⁷. Data on the use of Herceptin and pregnancy are very limited, but this agent may cause complications, including a decline in the quantity of amniotic fluid^{28–37}. This information is important in counseling a woman who may fall pregnant or consider doing so during her breast cancer treatment (Figure 2).



Figure 2 Fetal ultrasound

CONTRACEPTION AND PREGNANCY DURING BREAST CANCER TREATMENT

Anecdotal evidence suggests a number of reasons to explain why women conceive following a diagnosis of breast cancer. The main reason is quite simple, that is, the desire to have a child, especially in women who may have delayed this decision for some years and, unfortunately, are diagnosed with breast cancer in the interim. However, some women have unplanned pregnancies after breast cancer due to lack of contraceptive advice or failure of a contraceptive method.

Whilst breast cancer is being actively treated, it is important that the woman avoids pregnancy, and personalized instruction regarding the use of adequate mechanical forms of contraception, including condoms or the fitting of a diaphragm, becomes a priority. It is essential that contraceptive advice be offered to all pre- and perimenopausal women following their diagnosis of breast cancer for two reasons: first, mechanical contraception is preferred, as the oral contraceptive pill is associated with a potentially increased risk of recurrence^{38,39}; and, second, the teratogenic effect that chemotherapeutic or hormonal agents and radiotherapy may have on a developing fetus should a woman conceive during these

treatments is real (see above). Moreover, some hormonal agents (including tamoxifen and the aromatase inhibitors) can induce ovulation in premenopausal women¹². It is thus imperative that younger women be informed of this and realize that tamoxifen is not a contraceptive and can, in fact, stimulate multiple ovulations which may result in multiple pregnancy⁴. Whilst a progestin-only contraceptive agent has been used by women following a diagnosis of breast cancer, the evidence concerning harms and benefits of this type of contraception is unclear, and concern over the potential stimulating effects of progestin is present in both epidemiological⁴⁰ and biological⁴¹ literature.

If a woman conceives during active breast cancer treatment, then she should be counseled about the effects that the radio-, chemo- or hormone therapy may have on the fetus. The decision to terminate the pregnancy or not should ultimately be taken by the woman herself, although her partner (if one is present and available) may be consulted; the woman should be supported regardless of her final choice.

FERTILITY AFTER BREAST CANCER DIAGNOSIS

One of the most important issues facing women who have not yet started or completed their families when diagnosed with breast cancer is fertility preservation and/or options for conception after breast cancer treatment is complete. For some women, the opportunity (rather than the reality) to have a child is more important than their own long-term survival. Health professionals need to sensitively assess how individuals feel about preserving their fertility and the importance of maintaining reproductive potential. In the first instance, any woman of reproductive age should be offered referral to a fertility specialist for fertility advice and counseling prior to commencing

treatments such as chemotherapy. Even if they decline the referral, they should be advised of the impact their breast cancer treatment may have on their ability to conceive.

Both cytotoxic and hormone treatments affect fertility⁴²⁻⁴⁴, with 64% of adult females who undergo chemotherapy experiencing some symptoms of ovarian failure^{26,27}. Many women become amenorrheic, particularly those aged over 40 years⁶. In women with ER positive tumors, temporary or permanent ovarian failure may be the aim of treatment; however, the survival gains must be weighed against morbidity and patient concerns⁴⁵. Figure 3 compares the number of menopausal women by age based on treatment with or without chemotherapy. As evident in the graph, the number of women who become menopausal after treatment with chemotherapy is significantly higher across all age groups.

Infertility can be devastating for the woman who desperately wants a child. Interventions undertaken before chemotherapy commences can increase the long-term chances of a woman having a biological child. Fertility

options currently available, such as IVF, are usually only available to women diagnosed with breast cancer who have a male partner and are planning to have children together. The embryos would then be cryopreserved for use later. To undergo IVF, chemotherapy needs to be delayed for at least 4 weeks while the woman receives fertility drugs. The success rate is not very high, with only about 15% of thawed embryos resulting in a live birth⁴⁷. There is also a concern for women with ER positive breast cancer, that the raised estrogen levels caused by IVF may increase the disease progression. This has yet to be clarified in research studies, although recent data suggest fertility treatment does not increase breast cancer risk in otherwise healthy women⁴⁸. Treatments that include ovarian stimulation, however, may delay the start of adjuvant chemotherapy with as yet unknown consequences on the breast cancer outcome. For some women this delay in the commencement of treatment is unacceptable.

Some research findings indicate that it may be useful to preserve a woman's fertility

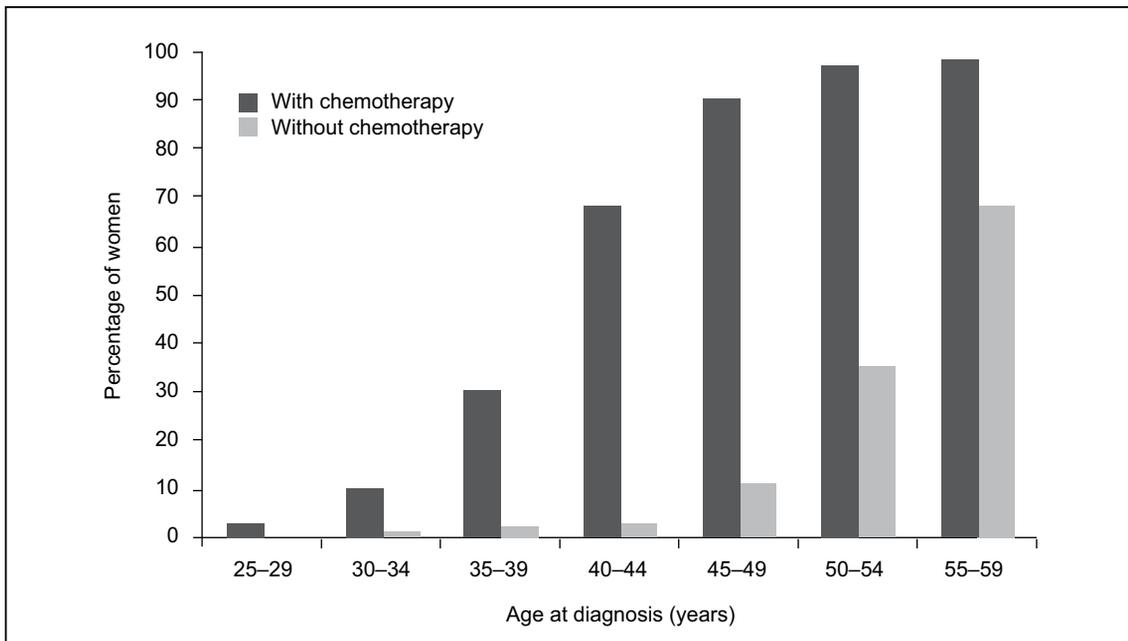


Figure 3 Estimated number of women who become menopausal after chemotherapy depending on their age at diagnosis. Adapted from Goodwin *et al.*, 1999⁴⁶

by suppressing ovarian function for up to 6 months with an agonist whilst the individual is receiving chemotherapy treatment. This would involve reversible chemical sterilization to protect the follicles during therapy using such drugs as goserelin. However, additional research is necessary to explore the safety and viability of goserelin as an ovarian function protector before this can be fully recommended as a fertility option⁴⁷. Currently women are encouraged to enter a clinical trial, if available locally⁴⁹.

For premenopausal women who are single at the time of their diagnosis, fertility preserving options are limited, as many options are still in the early stages of development. Available experimental techniques include undergoing therapy with fertility drugs and the retrieval of mature oocytes for freezing and later use. To date this option has resulted in a very low birth rate, so it would need careful consideration in relation to the women's individual cancer and recommended treatment. Surgically removing a wedge of ovarian tissue is another option where, following cryopreservation, the ovarian tissue can be re-implanted. Use of this option has, however, resulted in only a handful of pregnancies worldwide⁵⁰⁻⁵³. Both techniques are likely to have increased success rates in the future as scientists and clinicians work collaboratively to improve them. Some women may not want to receive any fertility preserving treatment and may wait until after their treatment to find out whether they are able to have children.

Table 3 below shows the known advantages and disadvantages of fertility preserving strategies. As the table shows and was noted earlier, the most effective fertility preserving strategy is IVF and embryo cryopreservation; however, this requires male participation and may not be a viable option for all women. Whilst it may not be possible to preserve fertility for all women, other options for having non-biological children are also available. These include oocyte donation, surrogacy

and adoption. For all women who have had a diagnosis of breast cancer, and have endured and completed a course of treatment which has left them infertile, oocyte donation is a reasonable possibility, which should be discussed prior to and after the completion of breast cancer treatment⁴⁷. In reality, it would be useful to discuss all of the available options with individuals whose fertility is unlikely to be preserved and to refer women to relevant sources who can provide further information and counseling about alternative options.

The chances of a woman being able to conceive after a diagnosis of breast cancer are fraught with numerous difficulties. Fertility preservation strategies are still in their infancy and may delay treatment. This is compounded by reduced ovarian function secondary to adjuvant breast cancer treatments and the advice to delay conception for 2 years following breast cancer diagnosis. A decline in already poor ovarian function for women diagnosed with breast cancer in their late 30s and early 40s makes pregnancy more improbable⁵. This has significant clinical implications when advising younger women diagnosed with breast cancer who have good prognostic tumors and want the opportunity to conceive after treatment. It is imperative that full counseling concerning the ramifications of conceiving and raising a child following treatment for breast cancer be part of the management plan for all young women.

The issue of fertility must be discussed with the premenopausal woman at or shortly after a diagnosis of breast cancer. This discussion should be initiated by the health care provider. A woman newly diagnosed with cancer is likely to be overwhelmed with information and will have many pertinent issues to consider. Many women are consumed with issues concerning treatment and survival, and will not be cognisant or aware of the impact of cancer treatment on their fertility.

In order to make an informed choice about her treatment and fertility, it is important

Table 3 Advantages and disadvantages of fertility preserving strategies

<i>Potential fertility preserving strategies</i>	<i>Advantages</i>	<i>Disadvantages</i>
IVF and embryo cryopreservation	Relatively effective in achieving pregnancy Clinically available	Requires a male partner and embryos legally owned by both partners Likely to increase circulating estrogen levels which may impact on prognosis of ER positive breast cancer May delay chemotherapy In gene mutation, carriers may transmit increased cancer risk to offspring
Ovarian stimulation and oocyte cryopreservation	Does not require a male partner	Very few successful pregnancies Likely to increase circulating estrogen levels which may impact on prognosis of ER positive breast cancer May delay chemotherapy In gene mutation, carriers may transmit increased cancer risk to offspring
Ovarian tissue cryopreservation and xenotransplantation	Does not require a male partner Does not require ovarian stimulation and increased estradiol levels Unlikely to delay chemotherapy	Very few successful pregnancies May reimplant ovarian tissue affected by micrometastases In gene mutation, carriers may transmit increased cancer risk to offspring Surgical procedure
Ovarian suppression with GnRH agonists	Does not require a male partner Simple to administer Unlikely to delay chemotherapy Relatively less invasive	Efficacy in fertility preservation not confirmed Side-effects unknown

ER, estrogen receptor; GnRH, luteinizing hormone releasing hormone; IVF, *in vitro* fertilization. Reproduced with permission from Hickey *et al.*, 2009⁴

that the clinician raises the issue of fertility with women prior to the commencement of treatment. If, after the initial discussion with the primary physician, a woman would like the opportunity to consider pregnancy after completing breast cancer treatment, it is absolutely essential that she be referred to a fertility specialist to discuss her options and undergo any necessary procedures before systemic therapy commences⁵⁴. With more young women being diagnosed at an earlier

disease stage, and improved and targeted breast cancer treatments available worldwide, women are surviving longer. Given the rapid progress in reproductive medicine of the past decade, it is likely that new and advanced fertility techniques will allow women greater opportunity in the future to conceive after a breast cancer diagnosis.

Health professionals should be able to communicate effectively with all women regarding the options available, detailing the

pros and cons of each treatment and supporting the woman's concerns, whatever they may be. Throughout the consultation process, a woman should be allowed every opportunity to make a decision which is right for her. Anecdotal evidence suggests that impartial and honest communication from the health professional may help to lower a woman's distress and improve her psychosocial well-being, allowing her to make an informed decision regarding her treatment, and improving treatment compliance.

This latter area may need some improvement, as many women report that they were not fully informed or made aware of the adverse consequences of breast cancer treatment on fertility prior to commencing treatment^{3,54,55}. A recent study by Thewes *et al.*³ showed that young women wanted information about fertility and the potential side-effects of treatment at the time of their diagnosis and when making treatment decisions, and that they rated this as highly important.

The decision making process for a woman and/or her partner on whether to undergo fertility interventions prior to treatment is complex. Issues to consider include the type of interventions available, how effective the intervention is, potential delays to the cancer management whilst undergoing fertility treatment, possible long-term health risks, cost of the intervention, and ethical and legal considerations⁵⁶. Unfortunately there are large gaps in our knowledge base, particularly concerning long-term effects, and this can make it difficult for women to make a fully informed decision. A fertility decision aid for young women with early breast cancer has been developed (M. Peate, Sydney, personal communication) which may help individuals to make such a decision prior to commencing treatment; this will shortly be available in the published literature, and on the Australian National Breast and Ovarian Cancer Centre website⁵⁷.

MANAGEMENT OF PREGNANCY IN WOMEN WITH A PRIOR DIAGNOSIS OF BREAST CANCER

The obstetric management of a woman who conceives after a breast cancer diagnosis should be the same as for any pregnant woman with a few provisos. Prior to attempting conception the woman should consult her oncologist to ensure that she has no disease recurrence, and any psychological fears should be discussed and addressed. Mothers can breastfeed from the unaffected breast, although this is very unlikely to happen from the affected breast due to the damage caused by radiotherapy. Women who choose to breastfeed may require additional support from midwives or lactation consultants on how to protect their nipple if they are feeding from just one breast.

If disease does recur when the woman has conceived, then the woman should be given all available information on how her cancer can be treated and what measures can be taken to protect her unborn child so that she can make an informed decision about her treatment and her pregnancy. A multidisciplinary approach including the cancer surgeons and physicians, and obstetric health professionals should be used and the pregnancy treated as high risk.

CONCLUSIONS

Women with breast cancer welcome the option to discuss and explore the fertility and pregnancy options available to them prior to commencement of their treatment. In fact, this is essential to promote women's well-being and can increase treatment compliance later on. Effective communication is at the forefront of this approach, and we encourage health professionals working with women diagnosed with breast cancer to approach fertility at the outset of treatment. This is of paramount importance to women and building a positive rapport

surrounding this issue can help and facilitate each individual woman's cancer journey.

It is important to consider future fertility options at the time of breast cancer diagnosis and treatment, as part of the multidisciplinary care of young women with breast cancer.

Women who conceive after a diagnosis of breast cancer find that children bring normalcy back into their lives and allow them to think about something or someone other than their own health⁵⁸.

Women diagnosed with breast cancer who conceive have a similar survival compared with those who do not, when taking into account the likelihood that only those with better outlook tumors will go on to have children. When time to pregnancy was accounted for, an increase in survival was only significant for women who waited at least 24 months to conceive. These results provide evidence for the clinical recommendation that women delay pregnancy for 2 years after a diagnosis of breast cancer but may suggest that women who have a good prognosis need not wait 2 years to become pregnant. While some women will choose not to become pregnant after their breast cancer diagnosis, an increasing number of women are likely to want the option of having children. For women with localized disease, conception following the completion of their breast cancer management is unlikely to adversely affect their survival.

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