Addressing fertility issues in patients with breast cancer

Many breast cancer therapies affect a woman's chances of having a child in the future. A growing body of literature is beginning to throw some light on the impact of different treatment options. How can doctors help their patients to make the right choices?

The number of oocytes declines with age, falling rapidly after a woman reaches around 35 years old. It is at this age that the risk of breast cancer in premenopausal women starts to rise. This can make it very difficult when we see younger women who present with breast cancer, knowing that their number of oocytes is declining and cancer treatment is likely, at the very least, to delay the possibility of becoming pregnant for many years.

Doctors need to understand the medical issues so that they can include considerations of fertility when discussing treatment options. These issues include the risk of chemotherapy-related amenorrhoea, premature menopause, and infertility associated with different regimens, as well as options for fertility preservation, both as standard care and in clinical trials, and the question of safety of pregnancy after breast cancer.

Chemo-related amenorrhoea

The risk of amenorrhoea – no menstrual period – is related to age at diagnosis of breast cancer, as well as treatment received, with the risk increasing dramatically in women in

European School of Oncology
e-grandround

ESO presents weekly e-grandrounds which offer participants the opportunity to discuss, with leading experts, a range of cutting-edge issues, from controversial areas and the latest scientific developments to challenging clinical cases. One of these is selected for publication in each issue of *Cancer World*.

In this issue, Ann Partridge, assistant professor in medicine at the Dana-Farber Cancer Institute, Harvard Medical School, Boston, reviews fertility issues in women with breast cancer. She looks at the risk of amenorrhoea, premature menopause and infertility in young women treated for breast cancer, and reviews the options for preserving fertility. Fedro Peccatori, of the European Institute of Oncology in Milan, raises further issues during a question and answer session. The presentation is summarised here by Susan Mayor.

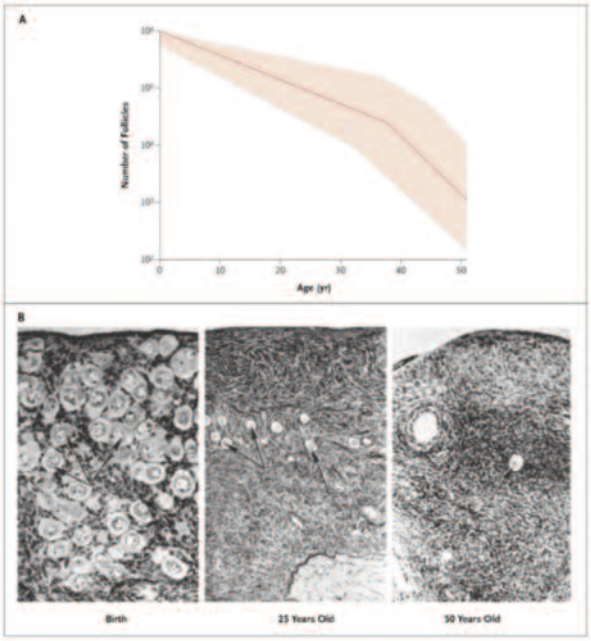
The recorded version of this and other e-grandrounds, together with 15 minutes of discussion, is available at www.e-eso.net/home.do

their mid-30s who receive chemotherapy (Goodwin et al. *JCO* 1999).

Chemotherapy-related amenorrhoea can be permanent, so that a woman loses her menses forever after treatment, or temporary, meaning that menses may resume. Importantly, chemotherapy-related amenorrhoea is not an imperfect surrogate for menopause or for infertility. Women not having periods can be fertile and become pregnant, and women who are having periods can be infertile, especially as they age.

Accurate assessment of ovarian function in breast cancer survivors has important implications for family planning for these women, as well as for contraception in women who want to avoid future pregnancies. It has implications for breast cancer treatment (together with other survivorship concerns including bone health, cognitive function and cardiac function), when we think about trying to incorporate aromatase inhibitors for women with hormone-sensitive disease, and cannot necessarily know whether or not they are going to remain postmenopausal once they have experienced treatment-related amenorrhoea.

NATURAL DECLINE OF OOCYTES WITH AGE



The risk of premenopausal breast cancer starts to rise at just the age when a woman's oocytes begin declining more rapidly

Sources: Top: MJ Faddy et al. Accelerated disappearance of ovarian follicles in mid-life: implications for forecasting menopause. *Hum Reprod* (1992) 7:1342–1346 by permission of Oxford University Press
Bottom: Reprinted from *Menopause*, GF Erickson, chap 2: Ovarian Anatomy and Physiology, 19 (2000), with permission from Elsevier

The risk of chemotherapy-related amenorrhoea with common breast cancer regimens, based on published data that includes rates of amenorrhoea, increases with age. It also increases with more intensive chemotherapy, in particular increased use of alkylating agents. Available data suggest that CMF (cyclophosphamide, methotrexate and fluorouracil) is one of the most gonadotoxic regimens, causing more infertility and chemotherapy-related amenorrhoea. TAC (taxotere, adriamycin and cyclophosphamide) is more gonadotoxic than FAC (fluorouracil, adriamycin and cyclophosphamide), and CMF appears to be a little less gonadotoxic than CEF (cyclophosphamide, epirubicin and fluorouracil) in the short term, but at 12-month follow-up in one publication they were equivalent. However, whether or not a particular regimen is likely to cause amenorrhoea varies with the time at which the risk of amenorrhoea was measured in any given study. All of these studies suffer from the fact that the data are very heterogeneous, with different lengths of follow-up, different groups of women, with different age groups, and different treatment regimens.

Some studies have revealed that the risk of the taxanes added to AC (cyclophosphamide and doxorubicin) may be greater than AC alone. However, this is being called into question, as previous data have suffered from lumping the taxanes docetaxel and paclitaxel together. Recent data suggest that the risk of chemotherapy-related amenorrhoea is greater with docetaxel than with paclitaxel, and that the addition of paclitaxel to AC does not significantly increase the risk of amenorrhoea in follow-up.

Effects of newer agents and regimens

Our group performed a study of the effects on the risk of chemotherapy-related amenorrhoea of newer treatments, including paclitaxel, dose-dense regimens (administered every two weeks rather than every three weeks) and trastuzumab, in addition to standard chemotherapy. The study included 451 women from our database who were premenopausal at diagnosis (mean age 42 years, range 22–55 years) and had received, at a minimum, adjuvant AC chemotherapy.

Mean follow-up was for 34 months and women were required to have at least six months' follow-up after finishing chemotherapy.

The results showed that the effects of paclitaxel, dose density and trastuzumab on chemotherapy-related amenorrhoea did not appear to be substantial. The odds ratios for each of these options were above one, but the confidence intervals crossed one, so adding a taxane to chemotherapy with AC, giving treatment every two weeks, and adding trastuzumab, did not significantly add to the risk of amenorrhoea

(Abusief, *Cancer*, in press). Not surprisingly, as in many other studies, taking tamoxifen and age at diagnosis were significantly associated with an increased risk of chemotherapy-related amenorrhoea at follow-up.

There are many issues that remain for women who are concerned about fertility or about whether or not they will become postmenopausal after treatment, including:

- Will a woman be less fertile after chemotherapy because of toxic effects to the ovaries, even if she continues to menstruate?
- Will a woman go through menopause earlier than she otherwise might have, even if she remains premenopausal in the years immediately following her cytotoxic chemotherapy?

Our group also looked at ovarian reserve in 20 women who remained premenopausal after chemotherapy for early-stage breast cancer, compared with 20 controls matched by age and gravidity. We measured ovarian reserve on days 2–4 of a menstrual cycle, including by antral follicle count (using transvaginal ultrasound) and by serum measures of anti-mullerian hormone, follicle-stimulating hormone (FSH), inhibin B and oestradiol. Cancer survivors appeared to have diminished measures of ovarian reserve compared to controls, with significantly lower antral follicle count measures, anti-mullerian hormone, FSH and inhibin B. Only oestradiol did not appear to differ between the two groups (Partridge et al. *Fert Ster* 2009). These findings provide important preliminary data for future studies looking prospectively not only at measures of ovarian reserve but also at fertility outcomes.

Our group, in conjunction with the International Breast Cancer Study Group (IBCSG), has also looked at the age of menopause among women who remain premenopausal following cytotoxic chemotherapy for early breast cancer. We used long-term data from two large IBCSG studies in which women were all premenopausal at diagnosis, and we included the women (*n*=767) who reported menses in the 12- to 24-month period after diagnosis. The majority (*n*=540) had only received either one perioperative treatment with CMF or no chemotherapy, and only a minority (*n*=227) had received standard chemotherapy (CMF for six or seven cycles). CMF is very gonadotoxic, and so the majority of women became amenorrhoeic for at least the period of time we were considering.

Women who received six or seven cycles of CMF-based chemotherapy before the age of 40 had a median age of menopause of 41 years, even though they remained premenopausal immediately after their chemotherapy. Women receiving only one cycle or none had a later menopause, with a median age of 44 years, although this is still earlier than the average of about 51 years. There is clearly some selection in survivorship bias. It is also not clear whether these data apply to women treated with more modern regimens, such as anthracycline- and taxane-based regimens. However, it is important information for when we counsel patients: they might go through menopause earlier than otherwise, and we need to consider this in terms of family planning and future health risks.

Adjuvant endocrine therapy for breast cancer – tamoxifen, ovarian suppression or an aromatase inhibitor – does not appear to cause permanent infertility or amenorrhoea. However, it usually entails years of treatment when pregnancy is contraindicated, and aging during that time compromises fertility.

Counselling on fertility issues

The American Society of Clinical Oncology (ASCO) has developed recommendations for fertility preservation in people treated for cancer (www.asco.org). These start by recommending assessment of the risk of infertility and communication with the patient. If we do not discuss

RISK OF CHEMOTHERAPY-RELATED AMENORRHOEA

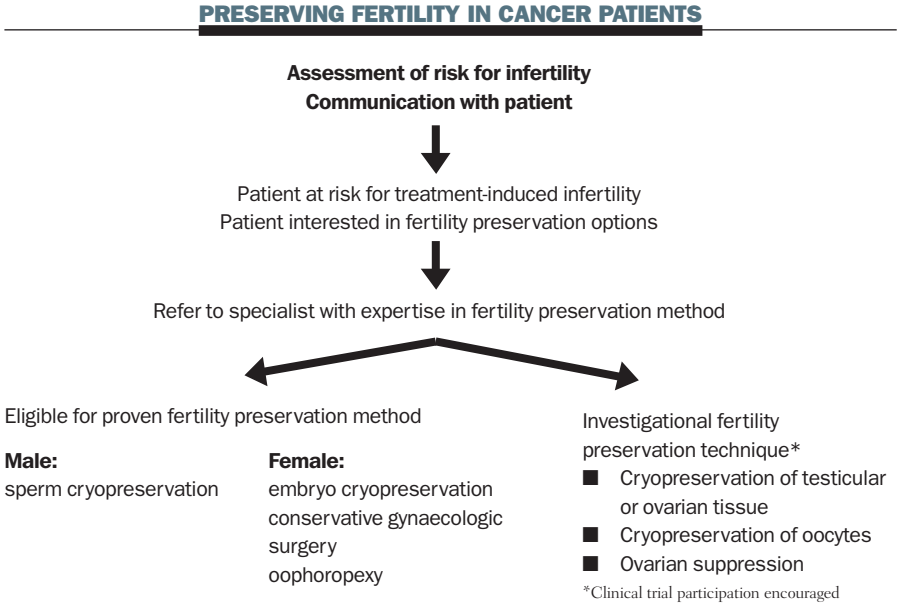
% women with amenorrhoea

Treatment	Age <30	Age 30-40	Age>40
None	~0	<5	20-25
AC x 4	--	13	57-63
CMF x 6	19	31-38	76-96
CAF/CEF x 6	23-47		80-89
TAC x 6	51		
AC x 4, T x 4	38 (15% age <40)		

Some chemotherapy regimens are associated with a much higher risk of amenorrhoea than others

AC – cyclophosphamide and doxorubicin; CMF – cyclophosphamide, methotrexate and fluorouracil; CAF – cyclophosphamide, doxorubicin, and fluorouracil; CEF – cyclophosphamide, epirubicin and fluorouracil; TAC – taxotere, adriamycin and cyclophosphamide

Source: Goodwin et al. *JCO* 1999; Burstein et al. *NEJM* 2000, Nabholtz et al. ASCO 2002, Parulekar et al. *JCO* 2005, Fornier et al. *Cancer* 2005, Petrek et al. *JCO* 2006



The American Society of Clinical Oncology has published step-by-step recommendations on preserving fertility in patients treated for cancer – both men and women

Source: Lee et al. ASCO Recommendations on Fertility Preservation in Cancer Patients. *JCO* 24:2917. Reprinted with permission. © 2008 American Society of Clinical Oncology. All rights reserved

with patients their risk of infertility, and whether they feel they may want to have a biologic child in the future, then we cannot help them fully to manage their expectations or to be referred appropriately.

When counselling women with early breast cancer, we need to weigh up the need for systemic therapy, as it is this that will affect their fertility. We may be overtreating many women with breast cancer in order to help the few. Risk reduction with any given therapy sometimes amounts only to a couple of percentage points. If a woman highly values her fertility and ability to become pregnant in future, and the risk of her cancer is relatively low, so the incremental benefit of chemotherapy is also low, she might reasonably forego chemotherapy in order to protect her fertility. This is something that needs proper discussion with patients, and we need to be very honest with patients and ourselves about the absolute benefits for any given individual, based on her tumour and risk.

Options for preserving fertility

Treatment options for preserving fertility in women with breast cancer include: ovarian suppression with LHRH agonists during treatment, cryopreservation of either ovarian tissue or oocytes and cryopreservation of embryos. However, none of these potential solutions are perfect.

Results from phase II studies of LHRH analogues during chemotherapy indicate that many women retain their menses. One phase II study using goserelin during adjuvant chemotherapy for early breast cancer before polychemotherapy, with or without bone marrow transplant, found that 67% of women resumed menses and had premenopausal hormone levels after a median follow-up of 75 months. All of those under 40 resumed menses, including five women who had undergone bone marrow transplant or high-dose stem cell transplant (Recchia et al. *Cancer* 2006). There were three pregnancies during follow-up, which is a fairly small number, although this was not long-term follow-up and many women are counselled against becoming pregnant for some time, or are on endocrine therapy during which pregnancy is not recommended.

Based on phase II data such as these, we have found that high rates of resump-

Thinking ahead. Ensuring fertility issues are discussed before embarking on a course of treatment could make a huge difference to the patient's future life

D. HURST / ALAMY

tion of menses can be obtained in women on LHRH agonists and successful pregnancies have occurred, but randomised controlled data are lacking. Uncontrolled studies have been flawed, because the patient populations tend to have a younger age profile, simply because it will be younger women who are more concerned about their future fertility, because they have not completed their child bearing.

One of the first randomised trials was presented at last year's ASCO annual meeting, but has yet to be published. The small trial used a GnRH agonist (triptorelin) during chemotherapy. It included 49 women (median age 39 years), with 12 months follow-up for 42 of the patients and 18 months follow-up for 34 of the patients. The median time to resumption of menses was six months in the LHRH treated group and 4.7 months in the control arm (Ismail-Khan et al. ASCO 2008). The vast majority of women in both groups resumed their menses and there was no difference between controls and those treated with triptorelin. This is considered a negative study, but the finding that the vast majority of women resumed their menses is unusual, and more work needs to be done.

There are other ongoing studies, including the POEMS (Prevention Of Early Menopause Study) being run by the South Western Oncology Group (SWOG). This study is much larger, randomising more than 400 women to chemotherapy with ovarian suppression with goserelin or standard chemotherapy. It is having some trouble with accrual, because some people use LHRH agonists outside a trial and some use other methods, but this is a very important question for young breast cancer survivors, and I am hopeful that we will be able to more definitively answer the question: does LHRH agonist therapy during chemotherapy help preserve menses in the future?

Cryopreservation of ovarian tissue or eggs

Cryopreservation requires a surgical procedure to remove ovaries or a piece of the ovary, and simply doing this could increase the risk of infertility in low-risk situations. It also has the potential for reintroducing malignant cells when it is reimplanted, so scientists are working on trying to make sure that cells are clean and that there is no evidence of cancer cells hiding in the ovarian tissue. This is considered highly experimental. While reproductive endocrinologists around the world are working to perfect this technique – and there have been a number of babies born to date – it is something that should only be done on institutional review board or ethics review board controlled trials.

Cryopreservation of eggs or ovarian tissue requires time and stimulation before treatment. There have been technical difficulties with the freeze/thaw process for the cryopreservation of the eggs. It is getting better, and reproductive endocrinology colleagues tell me that more babies are being conceived after thawing a cryopreserved oocyte, but it should still be considered experimental and I advise

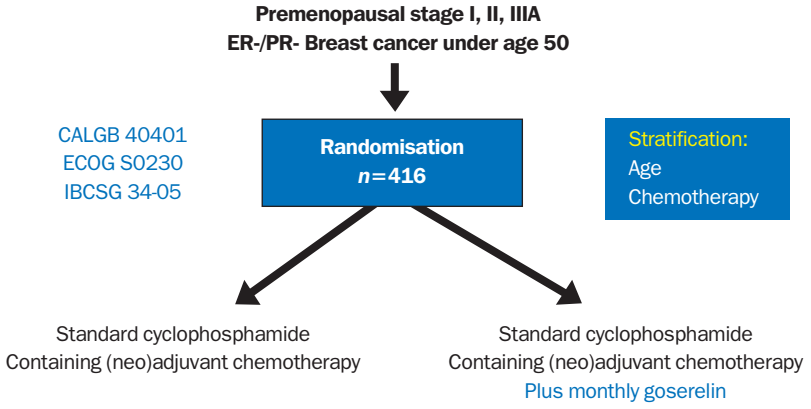
patients to go to a research centre.

Cryopreservation of embryos is available in the US as a standard procedure. It achieves pregnancy rates of 20%–30% per transfer of two to three embryos, on average. However, it requires time for a woman to undergo ovarian stimulation and harvesting of oocytes for fertilisation, and it also requires a partner or sperm, as well as money. It is generally not covered by insurance, because the woman is not yet infertile. Ovarian stimulation in a patient who may have micrometastases raises concerns about stimulating the growth of hidden metastatic disease, particularly in patients with hormone-sensitive tumours, where we might be increasing the rate of recurrence.

Kutluk Oktay, who runs a centre in New York for fertility preservation in women with breast cancer, has compared cycle characteristics and embryo yield with three different ways of stimulating ovaries: tamoxifen stimulation, tamoxifen FSH stimulation and letrozole stimulation. The greatest embryo yield came from a letrozole stimulation protocol and the peak oestradiol levels in this study were much lower than with tamoxifen or tamoxifen FSH (Oktay et al. *JCO* 2005). These are provocative and exciting data, which may mitigate the potential risk of elevated levels of oestradiol that we worry about.

www.fertilehope.org is a web resource for cancer patients and survivors whose medical treatments present the risk of infertility. Patients can read up about the issues, find out about ongoing clinical trials and use interactive tools for calculating their risk and exploring their options

THE POEMS STUDY



The ongoing Prevention Of Early Menopause Study (POEMS) is exploring whether LHRH agonist therapy during chemotherapy can help preserve menses in the future

PREGNANCY AFTER BREAST CANCER

If we are going to preserve fertility in our young patients, how safe is a pregnancy after breast cancer? Recent large studies evaluating the safety of pregnancy after breast cancer give reassuring results, showing that women who become pregnant after breast cancer are no more likely to have a breast cancer recurrence or to die of breast cancer than women who do not. However, these are not randomised controlled trials, and the women who go on to have a pregnancy after breast cancer may be very different from those who do not. The 'healthy mother bias' means that women who are less likely to have a recurrence are more likely to be healthier or to be counselled that it is safe to have a pregnancy after breast cancer. More work is needed to clarify this.

The conventional wisdom for women who have had breast cancer and who want to get pregnant is to wait at least two to three years to get through the early risk of recurrence, and to complete endocrine therapy, if this is given, which usually lasts for at least

five years. However, it is important to let patients know that there are no data to suggest that having a pregnancy after breast cancer worsens survival.

Patient preferences are critical

It is important to address fertility issues up front when you are caring for younger women with breast cancer, and to include fertility concerns in the risk/benefit analysis of treatment. Refer to a fertility specialist early for assistance in implementing fertility preservation procedures or with counselling. Women becoming pregnant after breast cancer, particularly if they have received chemotherapy, should be offered high-risk obstetrics management, as we have little data on their risk of complications during pregnancy.

Fertility issues in breast cancer survivors pose complex and difficult challenges. Limited data are available, and so patient preferences are critical. We should help to manage patients' expectations and help them to deal with the realities, and, unfortunately, sometimes the changes in their lives because of breast cancer.

Q&A

Fedro Peccatori (FP) from the European Institute of Oncology, Milan, hosted a question and answer session with Ann Partridge (AP).

FP: How many of your patients younger than 40 years ask for referral to an ART (assisted reproductive technology) specialist? There are a lot of issues for patients to think about at the time of diagnosis, so some patients may not think about this, or even want to be sent to the ART specialist.

AP: My experience is a little bit skewed, because I run a programme for young women with breast cancer and we highlight at the beginning that fertility may be a concern. In my experience, women newly diagnosed with breast cancer, particularly young women, are overwhelmed and are dealing with all of the issues related to therapy. This means that fertility issues are not always addressed adequately. This is why we have created a programme to address it earlier and make sure that we are not forgetting to address something that might significantly hamper a woman's future quality of life.

I have a lot of people come to me specifically for their fertility issues, but outside of that we probably send only about 5%–10% of younger patients to the fertility specialist. We discuss it with all women, and it is an issue for about 40%–50% of them, which fits with other studies. Ultimately, only about 10% go to a reproductive endocrinologist and follow through on preservation techniques. When push comes to shove, most patients want to focus on treating their cancer. However, it is important that we pay attention to this important survivorship issue. Lyndsey Norbak, from the advocacy group Fertile Hope (www.fertilehope.org) found that, when she was diagnosed with cancer, the hope that fertility preservation provided her was a huge impetus for her to get well.

FP: My experience is quite similar. I try to address fertility issues with all patients. Some of these patients, particularly the very young patients, or those treated with chemotherapy with lower gonadotoxicity, prefer to go through chemotherapy or even hormone treatment and not address the ART issue immediately. Others choose to go through fertility preservation procedures. It is very important to address these issues and then leave the decision to each patient, or each couple.

FP: How well aware are US physicians about the safety of pregnancy after breast cancer? Available data show there is no harm in having babies after breast cancer, yet only 3%–10% of women attempt pregnancy. I see patients referred from elsewhere, and many have been told by their doctors that pregnancy is harmful, and some have even undergone a termination.

AP: I see women all the time who have been told they cannot have a pregnancy, and it has nothing to do with their fertility, but their doctor's concern that it will increase their risk of the cancer recurring. The data, even though they are imperfect, suggest that pregnancy does not cause harm, and that women who become pregnant may actually do a little better. It is important that doctors keep up-to-date and pass this information on to their patients.

FP: There has been misleading information about breastfeeding after breast cancer, because there is a lack of data about breastfeeding after a mastectomy or breast-conserving surgery. We know that even if the breast has been conserved, a breast that has been irradiated has a lower output of milk, but on the other hand, we know that you can breast feed from one breast only. Do you have a network of breastfeeding specialists to refer patients to for lactation consultation after breast cancer?

AP: We do have lactation specialists, but none focus particularly on helping breast cancer survivors. I think that women can, and do, breast feed after breast cancer, and it is certainly feasible, but there are a lot of myths and concerns. As long as a woman is not on tamoxifen, and has had a certain washout period after tamoxifen or chemotherapy, there is no evidence that breastfeeding would hurt the baby.