

Pregnancy after breast cancer

Nabiel Alkhouri, MD,¹ Pasquale Patrizio, MD, MBE,² and Jame Abraham, MD¹

¹ Mary Babb Randolph Cancer Center and West Virginia University, Morgantown, WV, and ² Yale University Medical School, New Haven, CT

Every year, about one in four patients diagnosed with breast cancer will be premenopausal. Many of these women still desire pregnancy either to start a family or to extend the family they now have. This article focuses on the risk of breast cancer recurrence and mortality for women who have been successfully treated and want to become pregnant. The news is generally good. Evidence is growing that a subsequent pregnancy will not adversely affect their survival, although it is prudent to wait 2 years after diagnosis, when the risk of recurrence lessens, before trying to conceive. Neither surgery nor radiation therapy has been shown to affect the ability of breast cancer survivors to become pregnant or to have a normal child. The risk of amenorrhea following chemotherapy, however, is relatively high, especially among women over 40, and is dependent on the type of chemotherapy used and the cumulative dose. Several strategies for preserving fertility after breast cancer treatment are discussed, as are the ethical implications.

One in seven women in the United States will have breast cancer in her lifetime. Although the incidence of breast cancer increases with age, about 25% of new cases, amounting to about 45,000 per year, occur in premenopausal women.^{1,2} As a result of increasing awareness and screening, breast cancer is being detected in earlier stages and in younger patients.^{3,4} More women in developed countries have their newborns at a late age due to career goals and educational, social, and economic factors.⁵ There is an increasing breast cancer risk with advanced maternal age at first childbirth.⁶

The emotional distress

Putting all of these issues together, an increasing number of women will face the tragedy of having a breast cancer diagnosis during the time when they are ready to have their first child. Consequently, in addition to having the stress of dealing with this cancer, they will have concerns of how to preserve their ability to bear children. These women will worry about the possible effects of the cancer and its treatment on their future offspring and the effects of future pregnancies on their own survival.

Overall quality of life in young women who survive breast cancer is usually good; however, there is evidence of increased emotional disruption, particularly among the youngest survivors. Factors that may contribute to poorer health perceptions and quality of life include experiencing a menopausal transition as a part of therapy and

feeling more vulnerable after cancer.⁷

Chances of pregnancy after breast cancer

Adjuvant chemotherapy and hormonal therapies for breast cancer may cause amenorrhea.⁸ The

KEY POINTS

One in four women diagnosed with breast cancer is premenopausal.

The risk of amenorrhea after chemotherapy for breast cancer is high.

Accumulating evidence suggests that pregnancy after successful treatment of breast cancer does not increase the risk of recurrence or shorten survival.

There is no clear evidence that cytotoxic chemotherapy, once completed, has any adverse effects on future fetal development or the neonate.

Women should wait 2 years after diagnosis, when the recurrence risk diminishes, before trying to become pregnant.

Several alternatives are available to women who wish to preserve their fertility after treatment.

Manuscript received December 18, 2006; accepted April 30, 2007.

Correspondence to: Jame Abraham, MD, Associate Professor of Medicine, Chief, Section of Hematology/Oncology, West Virginia University, Morgantown, WV 26506-9162; telephone: 304-293-4229; fax: 304-293-2519; e-mail: jabraham@hsc.wvu.edu.

Commun Oncol 2007;4:331-348 © 2007 Elsevier Inc. All rights reserved.

risk of amenorrhea after these treatments increases with increasing patient age.⁹

In fact, age and systemic chemotherapy are the strongest predictors of menopause in women with locoregional disease. They independently contribute to menopause. In a multivariate analysis performed by Goodwin et al,⁹ age, systemic chemotherapy, and hormonal therapy (specifically, tamoxifen) were all shown to contribute significantly to the onset of menopause. The incidence of amenorrhea varies from 49% to 100% in women older than age 40, which is higher than the incidence of 21%–71% in younger women.²

The likelihood of developing amenorrhea after treatment for breast cancer is based also on the specific adjuvant chemotherapy regimen used. The alkylating agent cyclophosphamide, which has been the most intensely studied, has a fourfold increased risk of inducing amenorrhea when compared with other chemotherapeutic agents. Furthermore, the higher the cumulative dose of cyclophosphamide, the higher the observed incidence of menopause. Amenorrhea associated with anthracyclines is less understood, and studies reveal significant variation among them. Bines et al² found that the combination of doxorubicin and cyclophosphamide (AC regimen) results in amenorrhea in 34% of treated women. Different CEF regimens (cyclophosphamide, epirubicin, and 5-fluorouracil) have been shown to induce menopause in 51%–60% of women.¹⁰ This variation might be explained by differences in cumulative doses.

The incidence of amenorrhea associated with the use of taxanes is not clearly established. Fornier and Davis noticed no increase in the rate of amenorrhea after adding taxanes to adjuvant chemotherapy.^{11,12} Yet, Martin et al¹³ reported that the substitution of docetaxel [Taxotere] for 5-fluorouracil, when used in combination with doxorubicin and cyclophosphamide as adjuvant chemotherapy in women with node-positive disease, resulted in a significantly high-

er incidence of amenorrhea (61.7% vs 52.4%; $P = 0.007$).¹³

Neither surgery nor radiation therapy has been shown to affect the ability of breast cancer survivors to become pregnant or to have a normal child, should their menstrual function be preserved or restored.

Effects of pregnancy on recurrence and survival

Historically, women have been discouraged from becoming pregnant after a diagnosis of breast cancer. It was thought that the surge of hormones—particularly estradiol—during the gestation period might adversely affect the risk of recurrence and overall survival.

Several population-based and case-control studies have been done to evaluate the safety of pregnancy after treatment for breast cancer.¹⁴ No study has shown that the pregnancy adversely affected the survival of breast cancer patients, despite the theoretical risk of activation of dormant micrometastases by elevated hormone levels during gestation. In fact, some studies have suggested that a subsequent live birth may confer a survival advantage to these mothers.

In a study of 47 patients conducted between 1974 and 1998 at The University of Texas M. D. Anderson Cancer Center in Houston, pregnancy was not associated with an increased risk of disease recurrence or poorer survival in patients who were previously treated for breast cancer.¹⁵

Gelber et al¹⁶ concluded that subsequent pregnancy after breast cancer does not adversely affect the prognosis of early-stage breast cancer. In this study, 94 patients who had a total of 137 pregnancies after breast cancer diagnosis were compared with 188 patients selected from the International Breast Cancer Study Group (IBCSG) database. The 5-year survival rate, calculated from initial diagnosis of breast cancer, was $92\% \pm 3\%$ (standard error of the mean) among the women who became pregnant, compared with $85\% \pm 3\%$ among

age-matched controls who did not become pregnant. Likewise, the 10-year survival rate was also superior among women who subsequently became pregnant compared with those who did not ($86\% \pm 4\%$ vs $74\% \pm 4\%$).

Three population-based studies showed a decrease in the risk of death in women who became pregnant or delivered a live-born child after being diagnosed and treated for breast cancer. A Swedish study showed a relative risk of death for breast cancer survivors who became pregnant of 0.48 (95% confidence interval [CI], 0.18–1.29) compared with a control group who did not become pregnant.¹⁷ A Danish study on 173 women who became pregnant after breast cancer treatment revealed a relative risk of death of 0.55 (95% CI, 0.28–1.06) in women who had a full-term pregnancy compared with women who did not have a full-term pregnancy.¹⁸ Lastly, a reduction in mortality, with a relative risk of 0.21 (95% CI, 0.10–0.45), was reported in a Finnish study of women who delivered a live-born infant subsequent to a diagnosis of breast cancer. Taken together, these results were interpreted by Sankila et al¹⁹ as a “healthy mother” effect.

A cohort study conducted by Mueller et al²⁰ on 438 women younger than 45 years of age with primary invasive breast carcinoma found that women who subsequently became pregnant and gave birth 10 months or more after diagnosis had a significantly decreased risk of death (relative risk, 0.54; 95% CI, 0.41–0.71) compared with women who did not subsequently become pregnant and gave birth. In contrast, women who were already pregnant at the time of diagnosis had a mortality rate similar to that of women who did not give birth (relative risk, 1.10; 95% CI, 0.80–1.60).

In a Norwegian population-based study, Reed et al²¹ studied 51 patients who became pregnant subsequent to a diagnosis of breast cancer and reported a high overall survival rate in both node-negative and node-positive women; 5-year survival rates were 80% and 73%,

respectively, and 10-year rates were 86% and 76%. This study also confirmed that survival at 5 and 10 years of women with both node-negative and node-positive disease who were already pregnant at the time of diagnosis was significantly reduced ($P < 0.001$) when compared with the survival of women who became pregnant subsequent to their being diagnosed with breast cancer.

Effects of previous breast cancer treatment on the fetus

There is no known adverse clinical outcome on pregnancy subsequent to surgical or radiation treatment for breast cancer, aside from absence or diminished lactation from the treated breast.

In a study done by the Joint Center for Radiation Therapy in Boston, 22 of 23 women who had pregnancies after breast cancer radiation therapy delivered normal, full-term babies.²² The remaining patient delivered a low-birth-weight infant.

Although there is an increased chance of spontaneous abortion after treatment for breast cancer, there is no clear evidence that cytotoxic drugs used in the treatment of breast cancer prior to a pregnancy cause any adverse effects on fetal development or the neonate.²³

Preserving fertility after breast cancer

Many surveys of cancer survivors have identified an increased risk of emotional and psychological distress in those who become infertile because of their treatment.²⁴⁻²⁶ Cancer survivors who are free of disease typically view themselves as healthy enough to be good parents and, in fact, view their experience of illness as one that can enrich their parental role.²⁷ Most such women put a higher value on family closeness after cancer and believe they are less bothered by daily stresses.^{24,25}

There are a number of strategies to preserve future fertility. The choice and success of a particular option depend upon the patient's age, diagnosis, and

treatment; whether she has a partner; the time available; and the potential that cancer has metastasized to her ovaries.²⁸

Embryo cryopreservation

Embryo cryopreservation is routinely used for storing surplus embryos following in vitro fertilization for infertility treatment. This approach typically requires approximately 2 weeks of ovarian stimulation, consisting of follicle-stimulating hormone (FSH) treatment after an injection of human chorionic gonadotropin to trigger oocyte maturation. Thirty-six hours later, the oocytes are retrieved by ultrasound-guided transvaginal aspiration. The oocytes are fertilized in vitro, and the resulting embryos are cryopreserved at either the pronuclear or blastocyst stage.

For women with hormone-sensitive tumors, alternative hormonal stimulation regimens consisting of aromatase inhibitors, such as letrozole (Femara), or tamoxifen have been developed to minimize the risk of exposure to high levels of estrogen.^{29,30} Short-term breast cancer recurrence rates after ovarian stimulation using letrozole or tamoxifen concurrent with FSH administration appear to be comparable to those in nonrandomized controls in these early studies.

Oocyte cryopreservation

Cryopreservation of unfertilized oocytes is another option for fertility preservation, particularly for patients who do not have a partner.

Ovarian stimulation and harvesting requirements are identical to those described for embryo cryopreservation. The overall pregnancy rate with frozen/thawed oocytes is slightly lower than that associated with standard in vitro fertilization procedures using fresh oocytes. Approximately 140 babies have been born with this approach, and efforts to improve the efficiency of oocyte cryopreservation may increase success rates.³¹

Ovarian tissue cryopreservation

Ovarian tissue cryopreservation is

an investigational method of fertility preservation that has the advantage of requiring no ovarian stimulation. Ovarian tissue can be removed laparoscopically and frozen in cryo-vials as cortical strips. At a later date, the ovarian tissue is thawed and reimplanted. Primordial follicles can be cryopreserved with great efficiency,^{32,33} but because of the initial ischemia encountered after ovarian transplantation, one fourth of these follicles might be lost. The benefit of ovarian cryopreservation for women > 40 years of age is highly uncertain because of the scant numbers of primordial follicles remaining in the ovaries.³⁴

Ovarian tissue cryopreservation has been performed in humans for less than a decade, and recently there have been reports of the first few live births following orthotopic ovarian transplantation in cancer patients.^{35,36} One concern with reimplanting ovarian tissue is the potential for reintroduction of cancer cells. In patients without evidence of systemic metastasis to other organs, the likelihood of occult ovarian metastasis appears to be low.

Ovarian cryopreservation and transplantation and oocyte cryopreservation procedures should only be performed in centers with the necessary expertise under institutional review board-approved protocols that include follow-up for recurrent cancer.

Ovarian suppression

Ovarian suppression through the use of a gonadotropin releasing hormone (GnRH) agonist or antagonist treatment during chemotherapy is highly controversial as a method to maintain fertility. There are some concerns of the effect of patient age on the success of such an approach and the possible detrimental effect on the outcome associated with the lack of chemotherapy-induced menopause in hormone receptor-positive patients.¹⁰

At this time, there is insufficient evidence regarding the safety and effectiveness of GnRH analogs and

other means of ovarian suppression for preserving female fertility.³⁷

Ethical questions

From an ethical standpoint, the key reason for pursuing fertility protection is to restore personal autonomy to those women who are unable to conceive. However, since many of these innovative technologies are still experimental, it is difficult to design clinical trials. Among the questions involved are: How to provide a proper informed consent and respect for autonomy? Who to include or exclude in the trials? How to assess the risks? Can the moral principle of beneficence be upheld if oocyte or ovarian tissue cryopreservation poses future risks to any children who might result from this technique?³⁸

Timing pregnancy after breast cancer

Most breast cancer recurrences and/or systemic disease will develop within the first 2 years after diagnosis. Many authorities advise deferring pregnancy until after this period has passed.³⁹ Yet, the time interval has been defined differently in different studies. Although some investigators define it from the diagnosis of breast cancer to the delivery of a live newborn, others have defined it from the time of diagnosis of breast cancer to the diagnosis of pregnancy, excluding miscarriages and abortions.¹⁴

Should women become pregnant after breast cancer?

Although the effect of pregnancy on survivors of breast cancer with regard to local recurrence, distant metastasis, and survival remains debatable, there is increasing evidence from studies using various approaches to reassure young women faced with a breast cancer diagnosis that subsequent pregnancies are unlikely to worsen their survival.

Conclusion

About one in four patients diagnosed yearly with breast cancer will be premenopausal. The number of

women who will have the stress of facing a diagnosis of breast cancer before having their first child is likely to increase. Many questions still need to be answered. For some of them, we are getting insight from clinical studies; for others, we still have no clear answer. In the past, it was not advisable for woman to become pregnant after a breast cancer diagnosis or to have her ovaries stimulated to produce oocytes for in vitro fertilization.

The percentage of women who become pregnant after being diagnosed with breast cancer is low (3%–8%).¹⁰ Among them, there is an increased chance of having a spontaneous abortion (25%).^{15,40} More research is needed in the field of fertility preservation for young women with breast cancer and for survivors who cannot keep their pregnancy to full term.

Currently, for breast cancer survivors who do become pregnant, there is growing evidence that subsequent pregnancies will not adversely affect their survival. We think that there is no convincing evidence that a healthy survivor should refrain from becoming pregnant. However, we suggest that a woman defer her pregnancy for at least 2 years after a diagnosis of breast cancer. Prospective studies to determine the mortality risk of pregnancy after breast cancer are still needed.

Women who face the diagnosis of breast cancer before having the chance to bear children or survivors of breast cancer looking to become pregnant should not face this stress alone. A knowledgeable multidisciplinary team, including a reproductive specialist, should be available to care for them.

References

1. Theriault RL, Sellin RV. Estrogen replacement therapy in younger women with breast cancer. *J Natl Cancer Inst Monogr* 1994;16:149–152.
2. Bines J, Oleske DM, Cobleigh MA. Ovarian function in premenopausal women treated with adjuvant chemotherapy for breast cancer. *J Clin Oncol* 1996;14:1718–1729.
3. Kerlikowske K. Efficacy of screening mammography among women aged 40 to 49

years and 50 to 59 years: comparison of relative and absolute benefit. *Monogr Natl Cancer Inst* 1997;22:79–86.

4. Nystrom L, Rutqvist LE, Wall S, et al. Breast cancer screening with mammography: overview of Swedish randomised trials. *Lancet* 1993;341:973–978.

5. Mathews TJ, Hamilton BE. Mean age of mother, 1970–2000. *Natl Vital Stat Rep* 2002;1–13.

6. Lee SH, Akuete K, Fulton J, Chelmon D, Chung MA, Cady B. An increased risk of breast cancer after delayed first parity. *Am J Surg* 2003;186:409–412.

7. Ganz PA, Greendale GA, Petersen L, Kahn B, Bower J. Breast cancer in younger women: reproductive and late health effects of treatment. *J Clin Oncol* 2003;21:4184–4193.

8. Minton SE, Munster P. Chemotherapy-Induced amenorrhea and fertility in women undergoing adjuvant treatment for breast cancer. *Cancer Control* 2002;9:466–472.

9. Goodwin PJ, Ennis M, Pritchard KI, Trudeau M, Hood N. Risk of menopause during the first year after breast cancer diagnosis. *J Clin Oncol* 1999;17:2365–2370.

10. Del Mastro L, Catzeddu T, Venturini M. Infertility and pregnancy after breast cancer: current knowledge and future perspectives. *Cancer Treatment Rev* 2006;32:417–422.

11. Fornier MN, Modi S, Panageas KS, Norton L, Hudis C. Incidence of chemotherapy-induced, long-term amenorrhea in patients with breast carcinoma age 40 years and younger after adjuvant anthracycline and taxanes. *Cancer* 2005;104:1575–1579.

12. Davis AL, Klitus M, Mintzer DM. Chemotherapy-induced amenorrhea from adjuvant breast cancer treatment: the effect of addition of taxanes. *Clin Breast Cancer* 2005;6:421–424.

13. Martin M, Pienkowski T, Mackey J, et al. Adjuvant docetaxel for node-positive breast cancer. *N Engl J Med* 2005;352:2302–2313.

14. Upponi SS, Ahmad F, Whitaker JS, Purushotham AD. Pregnancy after breast cancer. *Eur J Cancer* 2003;39:736–741.

15. Blakely LJ, Buzdar AU, Lozada JA, et al. Effects of pregnancy after treatment for breast carcinoma on survival and risk of recurrence. *Cancer* 2004;100:465–469.

16. Gelber S, Coates AS, Goldhirsch A, et al. Effect of pregnancy on overall survival after the diagnosis of early-stage breast cancer. *J Clin Oncol* 2001;19:1671–1675.

17. von Schoultz E, Johansson H, Wilking N, Rutqvist LE. Influence of prior and subsequent pregnancy on breast cancer prognosis. *J Clin Oncol* 1995;13:430–434.

18. Kromann N, Jensen MB, Melbye M, Wohlfahrt J, Mouridsen HT. Should women be advised against pregnancy after breast-cancer treatment? *Lancet* 1997;350:319–322.

19. Sankila R, Heinavaara S, Hakulinen T. Survival of breast cancer patients after subsequent term pregnancy: “healthy mother effect.”

continued on page 337

continued from page 334

Am J Obstet Gynecol 1994;170:818-823.

20. Mueller BA, Simon M, Deapen D, Kamini A, Malone KE, Daling JR. Childbearing and survival after breast carcinoma in young women. *Cancer* 2003;98:1131-1140.

21. Reed W, Hannisdal E, Skovlund E, Thoresen S, Lilleng P, Nesland JM. Pregnancy and breast cancer: a population-based study. *Virchows Arch* 2003;443:44-50.

22. Dow KH, Harris JR, Roy C. Pregnancy after breast-conserving surgery and radiation therapy for breast cancer. *J Natl Cancer Inst Monogr* 1994;16:131-137.

23. MacLean AB, Sauven P. Pregnancy and breast cancer. Royal College of Obstetricians and Gynaecologists Guideline No 12; January 2004.

24. Schover LR, Brey K, Lichtin A, Lipshultz LI, Jeha S. Knowledge and experience regarding cancer, infertility, and sperm banking in younger male survivors. *J Clin Oncol* 2002;20:1880-1889.

25. Schover LR, Rybicki LA, Martin BA, Bringelsen KA. Having children after cancer: a pilot survey of survivors' attitudes and experiences. *Cancer* 1999;86:697-709.

26. Carter J, Rowland K, Chi D, et al. Gynecologic cancer treatment and the impact of cancer-related infertility. *Gynecol Oncol* 2005;97:90-95.

27. Leiblum SR, Aviv A, Hamer R. Life after infertility treatment: a long-term investigation of marital and sexual function. *Hum Reprod* 1998;13:3569-3574.

28. Roberts JE, Oktay K. Fertility preservation: a comprehensive approach to the young

woman with cancer. *J Natl Cancer Inst Monogr* 2005;57-59.

29. Oktay K. Further evidence on the safety and success of ovarian stimulation with letrozole and tamoxifen in breast cancer patients undergoing in vitro fertilization to cryopreserve their embryos for fertility preservation. *J Clin Oncol* 2005;23:3858-3859.

30. Oktay K, Buyuk E, Rosenwaks Z. Novel use of an aromatase inhibitor for fertility reservation via embryo cryopreservation in endometrial cancer: a case report. *Fertil Steril* 2003;80:144.

31. Borini A, Sciajno R, Bianchi V, Sereni E, Flamigini C, Cotichio G. Clinical outcome of oocyte cryopreservation after slow cooling with a protocol utilizing a high sucrose concentration. *Hum Reprod* 2006;21:512-517.

32. Meirov D, Fasouliotis SJ, Nugent D, Schenker JG, Gosden RG, Rutherford AJ. A laparoscopic technique for obtaining ovarian cortical biopsy specimens for fertility conservation in patients with cancer. *Fertil Steril* 1997;71:948-951.

33. Poirot C, Vacher-Lavenue MC, Helardot P, Guibert J, Brugieres S, Jouannet P. Human ovarian tissue cryopreservation: indications and feasibility. *Hum Reprod* 2002;17:1447-1452.

34. Oktay K. Evidence for limiting ovarian tissue harvesting for the purpose of transplantation to women younger than 40 years of age. *J Clin Endocrinol Metab* 2002;87:1907-1908.

35. Donnez J, Dolmans MM, Demylle D, et al. Livebirth after orthotopic transplantation of cryopreserved ovarian tissue. *Lancet* 2004;364:1405-1410.

36. Meirov D, Levron J, Eldar-Geva T, et al. Pregnancy after transplantation of cryopre-

served ovarian tissue in a patient with ovarian failure after chemotherapy. *N Engl J Med* 2005;353:318-321.

37. Lee SJ, Schover LR, Partridge AH, et al. American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. *J Clin Oncol* 2006;24:2917-2931.

38. Patrizio P, Butts S, Caplan A. Ovarian tissue preservation and future fertility: emerging technologies and ethical considerations. *J Natl Cancer Inst Monogr* 2005;107-110.

39. Calhoun K, Hansen N. The effect of pregnancy on survival in women with a history of breast cancer. *Breast Dis* 2005-2006;23:81-86.

40. Velentgas P, Daling JR, Malone K E, et al. Pregnancy after breast carcinoma: outcomes and influence on mortality. *Cancer* 1999;85:2424-2432.

ABOUT THE AUTHORS

Affiliations: Dr. Alkhouri is a fellow, Section of Hematology/Oncology, Mary Babb Randolph Cancer Center, West Virginia University, Morgantown, WV; Dr. Patrizio is Professor of Obstetrics and Gynecology and Director of the Yale Fertility Center, Yale University Medical School, New Haven, CT; and Dr. Abraham is Chief, Section of Hematology/Oncology, Associate Professor of Medicine, and Director, Comprehensive Breast Cancer Program, Mary Babb Randolph Cancer Center, West Virginia University, Morgantown, WV.

Conflicts of interest: Drs. Alkhouri and Patrizio have nothing to disclose. Dr. Abraham has received a research grant from Ortho Biotech and AstraZeneca LLC. He has received honoraria from sanofi-aventis Group, Genentech, and AstraZeneca.

Commentary

Fertility and breast cancer: the issues

Richard L. Theriault, DO | The University of Texas M. D. Anderson Cancer Center, Houston, TX

As women delay pregnancy and the fertility rate and incidence of breast cancer in the United States increase with increasing age (Tables 1 and 2),^{1,2} it is not surprising that breast cancer and pregnancy have become important clinical issues.

Breast cancer diagnosed during pregnancy and pregnancy occurring subsequent to successful treatment for primary breast cancer are two clinically challenging issues. Dr. Na-

biel Alkhouri and colleagues discuss a number of topics related to fertility and breast cancer. Among these is loss of fertility due to systemic treatment for primary breast cancer. Infertility may occur as a consequence of chemotherapy as well as ablative endocrine therapy.

Preserving fertility

Alkhouri et al correctly identify that alkylating agents and the cumulative drug dose are the primary che-

motherapy culprits affecting ovarian function. They also note the interaction with patient age. Women under 30 years of age are unlikely to become permanently amenorrheic with currently used adjuvant chemotherapy regimens, whereas women over the age of 40 face a substantial risk.

All premenopausal women need to be asked about fertility issues, their concerns regarding preserving fertility, and the likelihood of subsequent pregnancies. For those wishing to pre-

TABLE 1

Breast cancer in the United States

New cases of breast cancer	180,510*
Deaths from breast cancer	40,910*
Risk of developing breast cancer	
From birth to death	12.67% (1 in 8) [†]
From birth to age 39	0.48% (1 in 210) [†]
From age 40 to 59	3.98% (1 in 25) [†]

* 2007 estimated incidence

[†] 2001–2003 data

Adapted from American Cancer Society¹

TABLE 2

Fertility rates* in the United States

Age of mother, years	1980	1999
15–24	168.1	169.6
25–34	174.8	207.4
35–44	23.7	45.7

* Per 1,000 women; US Census Bureau statistics

Adapted from Minton and Munster²

serve their fertility, the authors correctly identify available strategies. The only technique of proven reliability and in widespread clinical use is embryo cryopreservation. This procedure may require the use of in vitro fertilization techniques and a brief delay in the initiation of adjuvant systemic therapy for women who choose it.

The other strategies discussed, in-

cluding oocyte cryopreservation and ovarian tissue cryopreservation, are considered experimental at this time and have had limited success. There are very few reports in the literature of in vitro fertilization in breast cancer survivors; however, Oktay et al³ have reported successful harvesting of oocytes and subsequent pregnancy.

The use of donor egg and embryo transfer has also been considered for women who desire to become pregnant subsequent to a diagnosis of primary breast cancer.

Pregnancy following treatment

Pregnancy after successful treatment for primary breast cancer raises a number of issues related to risks for the mother and any potential risks for the fetus. A primary issue for the mother is predicting the risk of breast cancer recurrence based on antecedent disease stage, the biologic characteristics of the disease, and previous treatment.

There has been concern regarding the potential for hormonal effects on latent micrometastatic disease, especially for women who have had primary tumors that are estrogen- and progesterone-receptor positive.

An additional concern is the potential initiation of ipsilateral or contralateral new breast cancers and the impact of pregnancy on the mother's overall survival, namely, whether

pregnancy increases her risk of breast cancer recurrence and death.

The data on pregnancy following breast cancer are limited. Retrospective case series, case-control comparative studies, single and multi-institution studies, reports of clinical trials of adjuvant therapy, and population-based registry survival studies using databases have not shown an increase in cancer recurrence or risk of death.

Recent studies, as noted by Alkhouri et al, have shown that pregnancy subsequent to successful treatment for primary treatment of breast cancer does not increase the risk of recurrence or death from breast cancer. In this regard the studies of von Schoultz et al,⁴ Kroman et al,⁵ Gelber et al,⁶ and Mueller et al⁷ are particularly reassuring (Table 3). A recent study by Ives et al⁸ adds to the growing body of data regarding the safety of pregnancy after breast cancer.

The ethical questions

Alkhouri and colleagues ask the question of whether women who have had a primary breast cancer successfully treated *should* become pregnant. The authors note that this issue raises ethical questions and cite autonomy as a foundation for a woman's decision-making in this regard. I would concur that as long as a woman has competence and capacity, pregnancy after successful treatment for primary breast cancer is a personal choice. Physicians have a duty-based obligation to inform, advise, and support women who choose to become pregnant following a diagnosis and successful treatment for primary breast cancer.⁹

As treatment for primary breast cancer improves and more women become long-term survivors, discussion of fertility and means of preserving fertility have become essential components of care for young women with cancer.

References

1. American Cancer Society. Cancer Facts

continued on page 347

TABLE 3

Risk of recurrence or death from breast cancer among women who became pregnant after successful treatment

Author	Study type	Number of pregnancies	Relative risk (CI)
Von Schoultz et al ⁴	Case comparison, clinical trial participants	50	0.42 (0.16–1.12)
Kroman et al ⁵	Multiple registries/comparative	173	NS
Gelber et al ⁶	Case comparison	137	0.41 (0.21–0.96)
Mueller et al ⁷	Cohort population-based cancer registry	438	0.54 (0.41–0.72)
Ives et al ⁸	Population-based registry	62	0.59 (0.37–0.95)

CI = confidence interval; NS = not significant

continued from page 338

& Figures 2007. Atlanta, Ga: American Cancer Society; 2007.

2. Minton SE, Munster PN. Chemotherapy-induced amenorrhea and fertility in women undergoing adjuvant treatment for breast cancer. *Cancer Control* 2002;9:466-472.

3. Oktay K, Buyuk E, Libertella N, Akar M, Rosenwaks Z. Fertility preservation in breast cancer patients: a prospective controlled comparison of ovarian stimulation with tamoxifen and letrozole for embryo cryopreservation. *J Clin Oncol* 2005;23:4347-4353.

4. von Schoultz E, Johansson H, Wilking N, Rutqvist LE. Influence of prior and subsequent pregnancy on breast cancer prognosis. *J Clin Oncol* 1995;13:430-434. 5. Kroman N, Wohlfahrt J, Andersen KW, Mouridsen HT, Westergaard T, Melbye M. Time since childbirth and prognosis in primary breast cancer: population based study. *BMJ* 1997;315:851-855.

6. Gelber S, Coates AS, Goldhirsch A, et al. Effect of pregnancy on overall survival after the diagnosis of early-stage breast cancer. *J Clin Oncol* 2001;19:1671-1675.

7. Mueller BA, Simon MS, Deapen D, Kamini A, Malone KE, Daling JR. Childbearing and survival after breast carcinoma in young

women. *Cancer* 2003;98:1131-1140.

8. Ives A, Saunders C, Bulsara M, Semmens J. Pregnancy after breast cancer: population based study. *BMJ* 2007;334:194-196.

9. Lee SJ, Schover LR, Partridge AH, et al. American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. *J Clin Oncol* 2006;24:2917-2931.

Dr. Theriault is Professor of Medicine, Department of Breast Medical Oncology, University of Texas M. D. Anderson Cancer Center, Houston, TX. He can be reached at rtheriau@mdanderson.org.

From the Editor's Desk

Counseling patients on pregnancy after breast cancer: arming yourself with the facts

Linda D. Bosserman, MD, FACP | Wilshire Oncology Medical Group, Inc., La Verne, CA

She sat across from me in my office and poured her heart out. "I didn't mean to dump all this emotion on you today," she began.* "I know we scheduled this visit to discuss starting tamoxifen after I completed my initial therapy. I know you're really busy with all you do for your cancer patients, but I'm a wreck and need your help and advice.

"I am grateful to be alive more than a year after my advanced breast cancer [was diagnosed], but I find myself overwhelmed with wanting to have another child. I am not done being a mother yet! I want a brother or sister for my 3-year-old daughter. I'm willing to take some risks, but I also want to be realistic and be there for my husband and the daughter I have now. I know my disease might come back, and I might die young no matter what, but we want more children. My husband is so frightened about possibly losing me that he doesn't want me to risk having another pregnancy, not if

it means delaying my use of tamoxifen and possibly increasing the chances of my disease coming back."

I "derailed" another on-time clinic visit for the real reasons we all went into medicine: to bring the best of science and compassion to helping our patients make the best decisions for their health while living out a full life.

I discussed the usual issues with her, that becoming pregnant has not been shown to definitely increase the risk of breast cancer recurrence. I discussed the risk of a recurrence of her tumor even if she goes on tamoxifen now—or doesn't—and becomes pregnant. I tried to describe scenarios to her that she could weigh in her and her husband's decision-making.

I also discussed what I see as the paternalistic advice most often given, to wait 2 years before becoming pregnant. This recommendation is based on the purely medical decision that since the risk of recurrence is greatest in the first 2 years, that patients wait before trying to become pregnant un-

til after 2 years, when the risk lessens. There is no magic in waiting 2 years, but if they choose not to, breast cancer survivors have a higher chance of their tumor recurring during their pregnancy or shortly after giving birth, which would require undergoing treatment while facing the demands of pregnancy or caring for a new infant and possibly other siblings.

Identifying the issues

The issues for patients come down to several decisions that we can help them sort through and for which both partners in the decision can weigh in on. Often, each partner sees things differently, so identifying the issues can help them make the best decision.

Do you and your husband want more children?

Would you want more children whether or not you were likely to be alive to raise them in, say, 1, 2, 3, or 5 or 10 years from now?

Do either of you have the support of family or friends if either of you were to die?

Cancer recurrence is not the only risk. We live every day with the chance, no matter how remote, that a car accident or other disaster could suddenly snuff out the life of a parent.

Do you have to have a biologic child, or is adoption an option?

Any discussion of the option to adopt should include the high costs of adoption, possible barriers due to the parent's age, existing medical conditions (including the patient's breast cancer), out-of-country adoption issues, and so on.

If the breast cancer comes back, do you have the resources or support to continue to raise your children effectively?

If illness or death drains emotional and financial resources from your family, would the addition of another child place an undue burden on your spouse?

In the case of BRCA1/2 positivity or a high-risk family history, would the likelihood of passing on genes that would increase the risk of cancer for your daughter influence your decision to have a pregnancy or to adopt?

As we sorted these issues out, I advised my patient that I would be gathering more data about the risk of breast cancer recurrence to give her better information on which to base her decision. We initially delayed starting hormonal therapy to give her time to think things through with her husband, as tamoxifen would not be used if she were planning to become pregnant or during her pregnancy. We also scheduled a visit for her and her husband with our cancer counselor to to give them time to work through these issues.

They are now researching adoption

options. After our talk, she decided she would not get pregnant, wanted to start tamoxifen and see how she does with it, and continue follow-up every 3 months until she decided whether she might want to try to become pregnant.

We need the best scientific data available

I felt particularly blessed when the accompanying article by Dr. Alkhouri and colleagues was submitted to *Community Oncology* and eagerly encouraged its publication and further commentary by an additional gynecologic expert, which Dr. Richard Theriault was kind enough to submit. I will be sending these articles to my patient to review (she is a well-educated school teacher) and scheduling a follow-up visit to discuss her and her husband's feelings after counseling, a tamoxifen trial, and further education about possible benefits of pregnancy to her cancer prognosis.

Whatever our patients decide, it is important that we arm ourselves with the best scientific data available in a readable format. This is especially true when, as in this case, the results go against the common thinking that hormone-positive breast cancer is more likely to recur with the surges of estrogen during pregnancy. We continue to learn more about hormone resistance in breast cancer. Recent data show that breast cancer cells grown in a hormone-starved environment become exquisitely sensitive to hormonal boluses. I can't help but wonder would we be most helpful to breast cancer patients like the woman described here if we prescribed complete hormonal blockade (using a gonadotropin releasing hormone inhibitor with an aromatase inhibitor or tamoxifen) for 1–2 years and then encourage pregnancy after the washout phase to further decrease the risk of a recurrence?

These issues cry out for a US regis-

try where all such patient data could be reported for long-term analysis. Even better would be widely available, clinically based trials in which patients could opt for various treatment alternatives and their outcomes studied.

Although academically based physicians may refer these patients to reproductive specialists, the reality is that 85% of US women with breast cancer are well treated in their local community by highly trained medical oncologists who manage all aspects of their cancer care and build the kind of therapeutic long-term relationships where these emotional, and very personal, issues can be expertly addressed. Community gynecologists, in fact, most often look to their medical oncology colleagues for information on pregnancy risk after breast cancer. Arming ourselves and our colleagues through tumor boards and personal communications with the kind of information Dr. Alkhouri's article and Dr. Theriault's commentary impart will help increase the tools we have to best care for our patients with our accessible and affordable multimodality medical teams.

Dr. Bosserman is a medical oncologist and president of Wilshire Oncology Medical Group, Inc., La Verne, CA. She can be reached at linda.bosserman@womgi.com.

* The patient described here was diagnosed with stage IIIA breast cancer (T2, N2, M0) just before her 34th birthday. Following a biopsy, laboratory tests revealed that the tumor was both estrogen- and progesterone-receptor positive and HER2/*neu* negative. She reported a positive family history for breast cancer but was *BRCA1/2* negative. To shrink the 3.8-cm tumor prior to surgery, the patient underwent 6 cycles of neoadjuvant docetaxol, doxorubicin, and cyclophosphamide chemotherapy with bevacizumab (Avastin) on a UCLA/TORI (University of California, Los Angeles/Translational Oncology Research International) Network trial, with a further 8 treatments of bevacizumab after bilateral mastectomy and during subsequent radiation therapy to the right chest wall, nodes, and supraclavicular region.