Reproductive Health Issues in Women With Cancer

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According to the American Cancer Society, approximately 679,000 women are newly diagnosed with cancer in the United States annually, and approximately 10% of these cancers occur in women of reproductive age, with 1 per 1,000 in pregnant women.[1–3] To achieve the primary objective of cancer treatment—survival—reproductive health issues including fertility conservation, contraception, and pregnancy are often overlooked. However, these challenging issues are critical to providing a complete continuum of care for women with cancer.

Although a growing body of literature addresses the issue of fertility preservation for reproductive-aged women with cancer, very little pertains to the other facets of reproductive health. In this article, we describe six cases that illustrate some of the challenges of caring for reproductive-aged cancer patients who become pregnant, desire child bearing, or desire effective contraception.

Case Studies

Case 1

A 42-year-old woman who had experienced six previous pregnancies and had six living children, noticed a mass on her right breast. Core biopsy showed ductal carcinoma in situ with microinvasion. Magnetic resonance imaging revealed multicentric disease with suspicious adenopathy on the right side. A right modified radical mastectomy was performed, and the pathology report showed infiltrating ductal carcinoma with metastatic carcinoma of one lymph node. The treatment plan was radiation followed by chemotherapy. On pretreatment work-up, the patient tested negative for pregnancy. She received five courses of doxorubicin/cyclophosphamide (AC) and a single dose of docetaxel. She complained of nausea and vomiting during chemotherapy treatment. After the fifth course, she felt fetal movements and was found to be pregnant. Ultrasound examination revealed a 22-week-old fetus with several abnormalities including left occipital encephalocele containing cerebellum, club foot, and microcephaly. After discussing the findings and extremely poor fetal prognosis, the patient opted to terminate the pregnancy, which was performed via medical induction without any complications. On delivery, the fetus was noted to have a peculiar facies, hairline extending to eyebrows, low-set ears, depressed nasal tip, short neck, webbing, and microcephaly. Chromosomal analysis demonstrated an aberrant chromosome 9, inversion versus unbalanced translocation.

Case 2

A 27-year-old woman with one prior pregnancy and one living child presented with significant weight loss and an enlarging neck mass. The patient was diagnosed with stage IV nodular sclerosing Hodgkin's lymphoma after biopsy. She later stated that no discussion regarding contraception was made at the time of diagnosis, and she became pregnant 1 month after the diagnosis. The patient was counseled on options regarding the pregnancy and the treatment. She had concerns that chemotherapy may reduce her future childbearing potential. She opted to continue the pregnancy and to start chemotherapy in the second trimester. The patient received six cycles of ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine). A healthy baby was delivered at term with no complications or anomalies. No known cancer progression occurred during the pregnancy.

Case 3

A 25-year-old in her first pregnancy presented at 11 weeks of gestation with a left supraclavicular neck mass. The biopsy of the mass and subsequent work-up revealed stage IV adenocarcinoma of the colon. After counseling on pregnancy options, she opted to terminate the pregnancy at 16 weeks and underwent sigmoid colectomy and adjuvant chemotherapy with fluorouracil, oxaliplatin, and leucovorin.

Case 4

A 39-year-old woman with one prior pregnancy and one living child presented with a painful left breast and was diagnosed with stage IIIB inflammatory breast carcinoma. During her work-up, she tested positive for pregnancy, and a 7-week pregnancy was confirmed by ultrasound. Rather than waiting to start chemotherapy in the second trimester, the patient opted to terminate the pregnancy and start treatment immediately.

Case 5

A 32-year-old woman with five previous pregnancies and five living children presented with a right breast mass and was diagnosed with stage IIB (estrogen/progesterone receptor [ER/PR]–negative) infiltrating ductal carcinoma. She underwent a right partial mastectomy. At the time of diagnosis, the patient was found to be 9 weeks pregnant by ultrasound. At that time, she opted to terminate the pregnancy and began four cycles of adjuvant AC. The patient was lost to follow-up for 7 months before completing chemotherapy. When she represented, the medical oncologist planned to commence radiotherapy. On preradiation work-

up, she was found to be pregnant again, this time confirmed at 16 weeks by ultrasound. The patient opted to continue her pregnancy and resume cancer treatment after delivery. The high-risk obstetrics service provided follow-up, and the patient delivered at 34 weeks by Cesarean section indicated because of a previous classical Cesarean section in active labor. The patient consented to tubal ligation at the time of delivery. Two months after delivery, she developed liver and bone metastasis and began receiving weekly doses of paclitaxel. The patient died 2 months later as a result of pneumonia and acute respiratory distress syndrome.

Case 6

A 34-year-old nulliparous woman was diagnosed with stage IIB infiltrating ductal carcinoma of left breast (ER/PR–positive) for which a partial mastectomy and sentinel lymph node biopsy were performed. Her *BRCA1* and HER-2/*neu* status were negative. Considering her age and nulliparous status, the possibility of ovarian suppression was discussed. Subsequently, she received four cycles of AC and four doses of docetaxel followed by radiotherapy. Later, she began receiving tamoxifen along with a progesterone-medicated intrauterine device (IUD) to suppress tamoxifen-induced endometrial changes as well as for its benefits as a contraceptive.

Examining the Experiences

With the growing number of cancer survivors and increased survival rates, quality-of-life issues, including reproductive health, are in the forefront. Reproductive health issues are not limited to fertility preservation, but also include sexuality, prevention, and treatment for unintended pregnancy; preconception counseling; and optimization of desired pregnancy. Each of these six cases demonstrates one of these components. Our main focus in the remainder of this article is:

- undiagnosed pregnancy in cancer patient;
- concomitant pregnancy and cancer; and
- pregnancy after cancer treatment.

Undiagnosed and Concomitant Pregnancy

We cannot overstate the importance of evaluating women for pregnancy during cancer treatment. The absence of menstrual cycles due to cancer treatment does not necessarily indicate the lack of ovarian function.[4] Amenorrhea, nausea, and vomiting are common adverse effects of radiation or chemotherapy as well as of early pregnancy. The pregnancy in our first patient went undiagnosed for months during the course of chemotherapy. Because the pregnancy test results were negative before treatment started, one can assume either that the patient had an extremely early pregnancy at the time of the first chemotherapy dose or that she became pregnant during treatment. Although it is difficult to determine the etiology of fetal anomalies in this case, chemotherapy is a possible and even probable cause for the developmental anomalies.

Essentially, there are no data that document how frequent pregnancy tests need to be performed during cancer treatment. In our clinical setting, pregnancy tests are routinely performed before surgery or radiation treatment; we have also adopted a policy of performing a pregnancy test before administration of each chemotherapeutic dose.

The majority of chemotherapeutic agents belong to US Food and Drug Administration pregnancy category D.[5] Presently, the recommendation is that chemotherapy be avoided during the first trimester, but is generally reported to be safe in the second and third trimesters. Chemotherapy administered in the first trimester during the early fetal development was associated with congenital abnormalities in nine of 11 infants according to a 2004 review.[2] In contrast, it is relatively safe in the second trimester.[6] Combination chemotherapy with fluorouracil, doxorubicin, and cyclophosphamide is generally safe in the second and third trimesters for treatment of breast cancer. Similarly, ABVD has been reported to be safe for the treatment of Hodgkin's lymphoma in pregnancy.[2]

Surgery generally is not contraindicated in early-stage cancer or in early pregnancy, except in certain gynecologic cancers. Similarly, the use of radiotherapy to treat cancer in pregnancy is not absolutely contraindicated, but an appropriate thickness of lead shielding should be used to reduce fetal and ovarian dose.[7] Radiation in early pregnancy is found to have an all-or-none effect for the termination of an early pregnancy.[8]

Pregnancy After Cancer

Regardless of age and extent of disease, concerns about fertility are present for the majority of premenopausal women with cancer.[9] The extent of damage to a patient's ovarian function depends on the agent administered, the doses received, and patient age at time of treatment. Even though survival is prolonged by adjuvant chemotherapy, it is known to cause premature ovarian failure.[10] Some women continue to have regular menstrual cycles during and after chemotherapy. However, they may develop diminished fertility or iatrogenic menopause.[11] The incidence of temporary or definitive chemotherapy-induced amenorrhea ranges from 22% to 61% in women under 40 years of age and from 61% to 97% in those over 40.[4]

Davis stresses that pediatric cancers as well as cancers during adulthood can have a significant impact on fertility. "Leukemia and lymphoma tend to be more childhood cancers, and in women who survive to adulthood there are reproductive issues in terms of lower fertility," she says. "Sometimes patients think they're infertile, but then they get pregnant, which is a surprise. The drugs have long ago worn off, but the effects of the treatment are still present, such as strain on their heart. [Patients need to] think about what they were exposed to as kids—what they were treated with." Patients who have or have had cancer must be vigilant to ensure that their birth control really is under control, Davis

says. "They may assume that they're infertile, but they can't take chances."

Of all the treatment modalities, chemotherapy, particularly with alkylating agents and radiation in the doses of 5 to 20 Gy, has the most damaging effect on the maternal gonads, whereas platinum compounds produce a similar but less intense result.[7] Cytotoxically induced changes are irreversible in the ovary because the number of germ cells is limited and fixed since fetal life and cannot be regenerated. In tissues with rapidly dividing cells, these changes are reversible.[12] Cell cycle–specific drugs such as methotrexate, fluorouracil, etoposide, and doxorubicin have a milder effect on gonads.[13] Although chemotherapy causes ovarian damage, there seems to be no risk of toxicity to future offspring of women treated with these agents before pregnancy.[14]

In addition to gonad-preserving chemotherapeutic treatment regimens, well-established methods of fertility preservation are gonadal shielding during radiation therapy, oophoropexy, and embryo cryopreservation. Other techniques include oocytes cryopreservation, ovarian cryopreservation, and ovarian suppression with gonadotropin-releasing hormone (GnRH) analogs, but are investigational.[15] The use of GnRH analog cotreatment for prolonging survival and increasing disease-free interval is being researched in women of reproductive age receiving chemotherapy. To determine the role of ovarian suppression in adjuvant treatment of endocrine-responsive breast cancer in premenopausal women, the International Breast Cancer Study Group has initiated randomized clinical trials. Two of such ongoing trials are Tamoxifen and Exemestane Trial and Suppression of Ovarian Function Trial.[16]

Even though no overwhelming evidence of benefits for the use of GnRH analogs has been published, experimental studies in Rhesus monkeys have shown a protective effect from cyclophosphamide-induced gonadal damage.[17] The role of GnRH agonists in temporarily suppressing the pituitary gonadal axis and thereby protecting the gonads from chemotherapy-induced damage has also been studied in humans. In a prospective clinical study of 44 lymphoma patients, more than 96% of women who received the cotreatment resumed spontaneous menstruation and ovulation in 6 months, whereas in the control group, only 42% had normal ovarian function, with the remaining 58% developing premature ovarian failure.[10] These preliminary studies demonstrated a protective effect, but larger prospective double-blind, randomized studies are needed for confirmation.

Key Issues

If a woman decides to pursue or continue a pregnancy, optimal preconception counseling and cancer treatment with the fewest possible fetotoxic effects should be offered, and optimal gestational age for delivery must be determined after consulting with an obstetrician. No evidence shows that termination of pregnancy changes the outcome of any type of cancer except in molar pregnancy, and the prognosis is similar in both pregnant and nonpregnant women with breast cancer.[18]

Even if a patient's childbearing process or potential is not complete, some women may decide to terminate the pregnancy for their own health benefit or because of concerns for risk of fetal anomalies, as in cases 3 and 4. Under such circumstances, access to pregnancy termination options should always be available and, in women with advanced cancers, treatment should not be delayed.[19]

Reproductive health assessments should be performed periodically throughout the course of treatment; women's reproductive health choices may change during treatment. This was seen in case 5, where the patient treated the two pregnancies during her cancer course differently.

Contraceptive counseling should be tailored to the needs of the patient. If childbearing is complete, long-term or permanent contraception such as an IUD, tubal ligation, or partner vasectomy may be suggested. For women who desire reversible contraception, providers should recommend natural, barrier, intrauterine, or hormonal methods depending on the type of cancer.

Presently, the medical literature is unclear regarding restricting the use of estrogen-based contraceptives in women with cancer due to a theoretic combined risk of thromboembolic events resulting from underlying cancer and exogenous estrogen. The American College of Obstetricians and Gynecologists 2006 practice bulletin *The Use of Hormonal Contraception in Women With Co-Existing Medical Conditions* does not address the issue of cancer and contraceptive use.[20] However, assumptions based on the guidelines from National Guidelines Clearinghouse would suggest restricting contraception to nonhormonal or progestin-only methods.[21] Furthermore, estrogen- and progesterone-based contraceptives are not recommended in breast and in some gynecologic cancers. Breast cancer patients receiving tamoxifen have been shown to be an exception. The levonorgestrel intrauterine system may provide both contraceptive and endometrial protective benefits for women taking tamoxifen for breast cancer; however, these findings are controversial.[22]

Future Pregnancy

At present, the American Society for Reproductive Medicine recommends delaying pregnancy in breast cancer patients until after cancer treatment is completed because of concerns over the effect of treatment on the fetus.[23] Patients who regain ovarian function after treatment should delay pregnancy for at least 6 to 12 months because of possible toxicity of treatment on growing oocytes[7]; the genetic damage

suffered by the developing oocytes when exposed to treatment seems to be repaired within 6 months. However, the optimal timing of conception after cancer treatment is uncertain because every individual case of cancer is biologically unique.

Recommendations

On the basis of the cases described herein, recent literature, and current comments on reproductive health issues in women with cancer, we recommend the following:

(1) A reproductive health assessment should be performed on all young women who are diagnosed with cancer to understand reproductive health goals of each patient.

(2) Inquiry regarding future childbearing must be performed to optimize fertility preservation, treatment options, preconception counseling, and pregnancy outcomes.

(3) Appropriate contraceptive counseling should be provided to all women of reproductive age who are undergoing cancer treatment.

(4) A pregnancy test should be administered to rule out pregnancy before each course of chemo- or radiotherapy, and thereafter at each subsequent visit before delivering additional therapy.

(5) Consultation with an obstetrician, and possibly a geneticist or radiation oncologist, or medical oncologist is reasonable when and if a post-therapy pregnancy is desired to optimize fetal outcome.

Ultimately, a multidisciplinary approach involving a cancer care team with physicians, nurses, and ancillary staff should address the patient's wishes and attempt to understand her reproductive goals.

Critical Care Issues for Pregnant Patients With Cancer

Among the most important factors in treating cancer in women who are pregnant is aligning the priorities of the patient, the obstetrician, and the oncologist. For a woman who wishes to continue her pregnancy to term, the ideal situation is one in which there is a collaborative agreement to optimize both the fetal and maternal condition to the greatest extent possible.

Whether and how long to wait to initiate treatment are typically the central areas of debate in treating cancer during pregnancy, and determining whose health should come first in decision making is a particularly sensitive challenge. Whereas the patient and obstetrician may consider the health of the developing child as an equal priority, the oncologist may be more concerned with the immediate health of the mother.

"For obstetricians, the pregnant woman with cancer is clearly always an incredible challenge because we are essentially dealing with disease in one patient and worried about the impact of treatment in another patient," says Lee Shulman, MD, a professor of reproductive genetics in the Department of Obstetrics and Gynecology at the Northwestern University Feinberg School of Medicine in Chicago, Illinois. "For example, how you treat detected cervical cancer at 9 weeks of gestation differs from how you treat it at 29 weeks."

Says Lee Shulman, MD, of Northwestern University, "The good news is that this is not a common occurrence. We're dealing in obstetrics with a primarily healthy population of women." However, as Shulman points out, the increasing age at which women become pregnant is likely to correlate with an increase in age-related risks, "not just cases of cancer but also other diseases like heart disease."

When faced with cancer during pregnancy, "It's not just the context of the disease, but the genetational age at which it's diagnosed," Shulman says. "What complicates the issue is the temporal nature," says Shulman. "Do we wait for the fetus to reach viability before we initiate treatment? Do we initiate treatment regardless of its impact on the fetus? In one sense, we are dealing with two patients, but in this case the patients are not equal. Clearly, the mother in this case has precedence. The oncologist will initiate treatment even if it is potentially detrimental to the fetus because withholding it may be fatal for the mother."

In Shulman's experience, he sees patients with cancer primarily to discuss the implications of treatment for the fetus from the perspective of a geneticist and prenatal diagnostician. "Many of these women have elected to initiate timely treatment and are interested in the potential impact on the fetus," he says. The decision is based on the prognosis with initiating treatment versus the prognosis without initiating treatment, Shulman says. "Management of these patients does not lend itself to easy answers."

Because cancer seldom affects the fetus directly, delaying treatment to allow fetal development without potential ill effects from chemotherapy or radiotherapy does not typically expose the child to the disease. Rare cases of malignant melanoma have been seen to metastasize to the placenta and fetus[24]; however, this is uncommon. The more pertinent concern is an adverse effect on the health of the mother that could indirectly cause damage to the fetus.

Discussions of treatment for cancer during pregnancy exist in the literature, but much remains unknown. One thing that is certain is that chemotherapy is less detrimental to fetal development the later it occurs during gestation. However, for particularly aggressive cancers, waiting until the second or third trimester to begin treatment may not be an option. With the support of her oncologist and obstetrician, a patient

may have to choose between maximizing the health of the fetus and saving her own life.

Anne Davis, MD, MPH, FACOG, who is an assistant professor of clinical obstetrics and gynecology at Columbia Presbyterian Medical Center in New York, New York, and codirector of Columbia's Fellowship in Family Planning, agrees that cancer treatment during pregnancy is a balancing act. "There is occasionally the case that a woman who's pregnant is diagnosed with cervical cancer at the same time she finds out she's pregnant, when she goes in for prenatal care," Davis says. Cancers in younger women are less common than in older women, but if a patient neglects preventive gynecologic care, this could be an unpleasant surprise. "It's really rare, but you have to assess risks and benefits for [the mother]. Cancer that is super early, you could wait and treat after the pregnancy is over, [but if it is] at an advanced stage and really aggressive, you have to treat it right away. Then think of the best way to terminate the pregnancy."

She says, "Sometimes if it's early in the pregnancy, it's an easier decision. In the second trimester, it becomes more complicated for the woman and also the treatment for the cancer gets more complex." Davis emphasized the importance of good contraception. "People who have cancer are advised not to become pregnant, and should try nonhormonal methods like an IUD."

In cases where sparing the fetus from exposure to cancer treatments severely compromises the mother's chances of survival, Davis recommends that abortion may be the best option. "Counseling about pregnancy during cancer is a very difficult subject," she says. Obstetricians are dealing primarily with women in their teens to 40s, and concomitant cancer and pregnancy is uncommon in that age group. However, the situation still arises, and physicians must be prepared to help their patients make educated, balanced decisions and to support the patients' choice.

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References

1. Surveillance Epidemiology and End Results (SEER) Cancer Statistics Review: 1975–2003. http://seer.cancer.gov/csr/1975_2003/results_merged/topic_age_dist.pdf

2. Cardonick E, Lacobucci A: Use of chemotherapy during human pregnancy. Lancet Oncol 5:283-291, 2004

3. American Cancer Society: Cancer Facts & Figures 2006. http://www.cancer.org/downloads/STT/CAFF2006PWSecured.pdf

4. Mastro LD, Catzeddu T, Venturini M: Infertility and pregnancy after breast cancer: Current knowledge and future perspectives. Cancer Treat Rev 32:417-422, 2006

5. Current categories for drug use in cancer. FDA Consumer Magazine 35, May-June 2001. http://www.fda.gov/fdac/features/2001/301_preg.html#categories

6. Hahn KM, Johnson PH, Gordon N, et al: Treatment of pregnant breast cancer patients and outcomes of children exposed to chemotherapy in utero. Cancer 107:1219-1226, 2006

7. Meirow D, Nugent D: The effects of radiotherapy and chemotherapy on female reproduction. Hum Reprod Update 7:535-543, 2001

8. Lishner M: Cancer in pregnancy. Ann Oncol 14:iii31-iii36, 2003 (suppl 3)

9. Partridge AH, Gelber S, Peppercorn J, et al: Web-based survey of fertility issues in young women with breast cancer. J Clin Oncol 22:4174-4183, 2004

10. Blumenfeld Z, Avivi I, Ritter M, et al: Preservation of fertility and ovarian function and minimizing chemotherapy induced gonadotoxicity in young women. J Soc Gynecol Investig 6:229-239, 1999

11. Byrne J, Fears TR, Gail MH, et al: Early menopause in long term survivors of cancer during adolescence. Am J Obstet Gynecol 166:788-793, 1992

12. Ataya K, Moghissi K: Chemotherapy induced premature ovarian failure: Medications and prevention. Steroids 54:607-626, 1989

13. Abdallah Rony T, Muasher Suheil J: Surviving cancer, saving fertility-the promise of cryopreservation. Sexuality, Reproduction and Menopause 4:7-12, 2006

14. Simon B, Lee SJ, Partridge AH, et al: Preserving fertility after cancer. CA Cancer J Clin 55:211-228, 2005

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

16. Francis P, Fleming G, Nasi ML, et al: International Breast Cancer Study Group (IBCSG), Breast International Group (BIG), and North American Breast Intergroup: Tailored treatment investigations for premenopausal women with endocrine responsive (ER+ and/or PR+) breast cancer–The SOFT, TEXT, and PERCHE Trials. Breast 12:S44 (suppl; abstr P104)

17. Ataya K, Rao LV, Laurence E, et al: Luteinizing hormone releasing hormone agonist inhibits cyclophosphamide induced ovarian follicular depletion in Rhesus monkeys. Biol Reprod 52:365-372, 1995

18. Barthelmes L, Davidson LA, Gaffney C, et al: Pregnancy and breast cancer. BMJ 330:1375-1378, 2005

19. Kelly HL, Collichio FA, Dees EC: Concomitant pregnancy and breast cancer-options for systemic therapy. Breast Disease 23:95-101, 2005

20. ACOG Practice Bulletin No. 73: Use of hormonal contraception in women with coexisting medical conditions. Obstet Gynecol 107:1453-1472, 2006

21. Royal College of Obstetricians and Gynecologists, Medical Specialty Society: Venous thromboembolism and hormonal contraception. NGC:004481, www.guideline.gov

22. Gardner FJE, Konje JC, Abrams KR, et al: Endometrial protection from tamoxifen stimulated changes by a levonorgestrel releasing intrauterine system: A randomized controlled trial. Lancet 356:1711-1717, 2000

23. Fertility preservation and reproduction in cancer patients: Ethics committee report—American Society for Reproductive Medicine. Fertil Steril 83:1622-1628, 2005

24. Pregnancy and cancer. People Living With Cancer. http://www.plwc.org/portal/site/PLWC/menuitem.034b98abc65a8f566343cc10ee37a01d/?vgnextoid=89a7ea97a56d9010VgnVCM100000f2730ad1RCRD#