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Should Oncologists Routinely Discuss Fertility Preservation With Cancer Patients of Childbearing Age?

In June 2006, the American Society of Clinical Oncology published guidelines to improve the clinical practices of oncologists when they address fertility preservation in and counseling of cancer patients.[1] An expert panel agreed that any oncologist who sees fertile patients who are considering cancer therapy should address potential treatment-induced infertility before starting therapy. The panel reviewed extensive fertility preservation literature from 1987 to 2005 and realized the paucity of large and/or randomized studies. As such, the proposed guidelines were derived predominantly from cohort studies, case series, small nonrandomized clinical trials, and case reports. The methods proven most efficacious to preserve fertility were sperm cryopreservation in males and embryo cryopreservation in females. The panel did not attempt to review and quantify risks to fertility from various cancers and specific treatments. The consensus was that oncologists should discuss infertility as a potential risk of therapy. Additionally, oncologists should answer basic questions about whether fertility preservation options decrease the chance of successful cancer treatment, increase the risk of maternal or perinatal complications, or compromise the health of offspring. Furthermore, oncologists should refer appropriate patients to reproductive specialists and practitioners of psychosocial care.[1]

Despite these guidelines that were designed to increase awareness and influence clinical practice, several national surveys have shown that oncologists are still not discussing treatment-associated fertility risks with patients and are not referring patients to reproductive specialists. In a national survey published in 2009, Quinn et al[2] reported that only 47% of health care professionals routinely referred their cancer patients of childbearing age to a reproductive endocrinologist. In another survey of academic medical centers, 95% of oncologists reported that they routinely discuss the effect that treatment may have on patients' fertility, but only 39% routinely referred patients to a specialist in reproductive medicine.[3] Regarding sperm conservation, 91% of oncologists agreed it should be offered to eligible men, but only 10% reported actually offering it.[4]

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Against this background, the article by Jensen et al[5] in this issue of *Mayo Clinic Proceedings* provides an excellent review of contemporary fertility preservation strategies and associated issues for individuals with cancer or other serious illnesses. The article focuses on 4 key messages.

The Potential Effect of Cancer Treatment on Future Fertility

Although the consensus is that cancer therapy can result in infertility, research data are insufficient to identify the risk of each agent and/or regimen because of the complexity of variables involved. The effects of chemotherapy and radiation therapy on fertility depend on the individual drug(s) and/or size and location of the radiation field, overall dose, dose intensity, method of administration, disease, age, sex, and pretreatment fertility of the patient. Most of the available literature that quantifies infertility risks reports rates of azoospermia and amenorrhea, although these are only surrogate measures of infertility. In addition, infertility risk data for patients undergoing newer chemotherapy regimens and receiving targeted biologic agents are scant.[1]

Fertility Preservation Options

Since 2006, new fertility preservation options have been introduced for both males and females, as outlined by Jensen et al. However, in females, the most proven method, embryo cryopreservation, requires a 2- to 6-week delay of chemotherapy, depending on the timing of the patient's

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menstruation cycle. Women who require chemotherapy more urgently have the option of medical suppression of ovarian function to mitigate the effect of chemotherapy. However, this option is less well proven and at best merely increases the probability of resuming menses after therapy, which does not equate with fertility potential.[6] Of theoretical concern (but potentially important) is the relapse of hormonally sensitive tumors after subsequent ovarian stimulation. Azim et al[7] prospectively studied 79 women using letrozole for ovarian stimulation. Although they found no increased risk of tumor recurrence, it is doubtful that their study provided sufficient power to confidently counsel patients.

Pregnancy After Cancer Therapy

There is concern that pregnancy increases the risk of recurrent hormonally responsive tumors like breast cancer. The best available data are from large retrospective epidemiological studies conducted in Scandinavia that identified no increased risk of breast cancer recurrence.[8-10] Unfortunately, no properly designed prospective studies exist to support this notion.

Fertility Preservation as an Emerging Discipline

Currently, there are many unresolved issues related to fertility preservation in oncology patients. Cancer survivors face risks of relapse and secondary malignancies. In this context, the risks of fertility preservation strategies are largely unknown. Some patients inherently have a higher risk of relapse by virtue of their age alone, and this in turn affects their long-term mortality. A retrospective study that evaluated more than 200,000 women in a SEER (Surveillance Epidemiology and End Results) database of patients diagnosed as having breast cancer between 1988 and 2003 showed that women younger than 40 years were 39% more likely to die than were older patients.[11]

Optimal counseling for patients with a high risk of cancer recurrence and mortality is unclear. Is it ethical to recommend fertility preservation with such knowledge on overall prognosis? Is it ethical to recommend semen cryopreservation in male patients who are receiving palliative care and who desire offspring? Another issue that complicates decision making is that adoption agencies may discriminate against cancer survivors.[12] Additionally, there is uncertainty about who should pay for fertility preservation. Although most of the techniques are not covered by insurance, financial support may be available from agencies such as the "Sharing Hope" program (www.fertilehope.org).

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1. Lee SJ, Schover LR, Partridge AH, et al. American Society of Clinical Oncology Recommendations on Fertility Preservation in Cancer Patients [published correction appears in *J Clin Oncol*. 2006;20;24(36):5790]. *J Clin Oncol*. 2006;24(18):2917-2931.

2. Quinn GP, Vadaparampil ST, Lee JH, et al. Physician referral for fertility preservation in oncology patients: a national study of practice behaviors. *J Clin Oncol*. 2009;27(35):5952-5957.

3. Forman EJ, Anders CK, Behera MA. A nationwide survey of oncologists regarding treatment-related infertility and fertility preservation in female cancer patients. *Fertil Steril*. 2010;94(5):1652-1656.

4. Schover LR, Brey K, Lichtin A, Lipshultz LI, Jeha S. Oncologists' attitudes and practices regarding banking sperm before cancer treatment. *J Clin Oncol*. 2002;20(7):1890-1897.

5. Jensen JR, Morbeck DE, Coddington CC III. Fertility preservation. *Mayo Clin Proc*. 2011;86(1):45-49.

6. Ben-Aharon I, Gafter-Gvili A, Leibovici L, Stemmer SM. Pharmacological interventions for fertility preservation during chemotherapy: a systematic review and meta-analysis. *Breast Cancer Res Treat*. 2010;122(3):803-811.

7. Azim AA, Costantini-Ferrando M, Oktay K. Safety of fertility preservation by ovarian stimulation with letrozole and gonadotropins in patients with breast cancer: a prospective controlled study. *J Clin Oncol*. 2008;26(16):2630-2635.

8. Hemminki K, Försti A, Sundquist J, Ji J. Risk of familial breast cancer is not increased after pregnancy. *Breast Cancer Res Treat*. 2007;108(3):417-420.

9. Kroman N, Jensen MB, Wohlfahrt J, Ejlertsen B. Pregnancy after treatment of breast cancer: a population-based study on behalf of Danish Breast Cancer Cooperative Group. *Acta Oncol*. 2008;47(4):545-549.

10. Kroman N, Jensen MB, Melbye M, Wohlfahrt J, Mouridsen HT. Should women be advised against pregnancy after breast-cancer treatment? *Lancet*. 1997;350(9074):319-322.

11. Anders CK, Johnson R, Litton J, Phillips M, Bleyer A. Breast cancer before age 40 years. *Semin Oncol*. 2009;36(3):237-249.

12. Rosen A. Third-party reproduction and adoption in cancer patients. *J Natl Cancer Inst Monogr*. 2005;(34):91-93.