Fertility Preservation

Jani R. Jensen, MD; Dean E. Morbeck, PhD; and Charles C. Coddington III, MD

Of the estimated 1.5 million men and women who were diagnosed as having cancer in 2010, approximately 10% are younger than 45 years. For these individuals, cancer treatment can be lifesaving but can permanently affect reproductive capacity. The American Society of Clinical Oncology has recommended that oncologists discuss the possibility of infertility with reproductive-age cancer patients and offer referral for fertility preservation consultation and therapy. Fertility preservation is an emerging field that offers treatment aimed at protecting future reproductive ability for individuals with cancer or other serious illnesses. Although fertility preservation strategies vary by patient age and sex, many allow patients to store gametes or reproductive tissues for potential future use to create offspring. As an emerging discipline, many questions remain about the role of fertility preservation. We performed a MEDLINE search from 1950 to June 2010 using the following MeSH terms: *amenorrhea; antineoplastic agents; ovarian failure; premature; infertility, female; fertility preservation; infertility, male; adolescent and cancer; child and cancer; cryopreservation;* and *reproductive technologies, assisted*. Studies considered for inclusion included those written in English and published before June 2010.

Mayo Clin Proc. 2011;86(1):45-49

An estimated 1.5 million men and women will be diagnosed as having cancer in 2010; of this group, approximately 10% are younger than 45 years, and 1% are younger than 20 years.[1] The most frequently diagnosed cancers in US adults aged 20 to 44 years are breast, lymphoma, skin (excluding basal and squamous types), and leukemia.[1] Although modern treatment regimens have improved the overall 5-year relative survival rate to nearly 80% for individuals younger than 50 years, cancer therapy can result in infertility or premature gonadal failure, thus creating a significant quality-of-life issue for young survivors.[1]

Fertility preservation is an emerging field that encompasses a variety of fertility therapies for patients anticipating medical treatment that could affect future reproductive outcomes. Although most frequently associated with cancer treatment, fertility preservation has also been used for medical conditions like lupus, glomerulonephritis, and myelodysplasia, as well as in adolescent females with conditions known to be associated with premature ovarian failure, such as Turner mosaicism.

From the Division of Reproductive Endocrinology and Infertility, Mayo Clinic, Rochester, MN.

This article is freely available on publication, because the authors have chosen the immmediate access option.

Individual reprints of this article are not available. Address correspondence to Jani R. Jensen, MD, Division of Reproductive Endocrinology and Infertility, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (jensen.jani@mayo.edu).

Concern for future fertility is high among individuals newly diagnosed as having cancer. Approximately three-quarters of men and women younger than 35 years who are childless at the time of cancer diagnosis desire children in the future.[2] Among adolescent females with malignancies, 81% of them and 93% of parents were interested in fertility preservation, even if options were described as experimental.[3] In 2006, the American Society of Clinical Oncology published guidelines recommending that oncologists discuss the possibility of infertility with reproductive-age cancer patients and offer referral for fertility preservation consultation and therapy.[4] Despite these measures, referral patterns are still inconsistent in many centers, even large multidisciplinary ones, and many reproductive-age patients still start treatment without discussion of or opportunity for fertility preservation. Nearly half (45%) of oncologists surveyed at one large university medical center reported never referring patients to a reproductive endocrinologist for fertility consultation.[5]

For editorial comment, see page 6

Fertility preservation counseling should emphasize key clinical messages, including the potential effect of cancer treatment on future fertility, options available to patients plus the time and effort required to complete the treatment, discussion of parenthood after cancer, and provision of patient-education resources. In some cases, patients may also be encouraged to obtain legal assistance to draft documents that specify disposition of stored gametes, embryos, and tissue in the event of death.

We performed a MEDLINE search from 1950 to June 2010 using the following MeSH terms: *amenorrhea*; *antineoplastic agents*; *ovarian failure*; *premature*; *infertility, female*; *fertility preservation*; *infertility, male*; *adolescent and cancer*; *child and cancer*; *cryopreservation;* and *reproductive technologies, assisted*. Studies considered for inclusion included those written in English and published before June 2010.

KEY MESSAGE NUMBER 1

Potential Effect of Cancer Treatment on Future Fertility

Cancer therapy can result in subfertility or sterility due to gonad removal or permanent damage to germ cells from adjuvant therapy. In males, spermatogenesis and steroidogenesis within the testes are postpubertal events. Prepuber-

TABLE. **Current Fertility Preservation Strategies**

Patient population	Mature technologies	Experimental technologies	Time required	Procedures required
Prepubescent males	None	Testicular tissue cryopreservation	Minimal (<1 d)	Surgical removal of testicular tissue
Prepubescent females	None	Ovarian tissue cryopreservation	Minimal (<1 d)	Surgical removal of ovarian tissue
Prepubescent or adult females	Oophoropexy		Minimal (<1 d)	Surgical movement of the ovaries outside of planned radiation field
Adult males	Sperm cryopreservation	Testicular tissue cryopreservation	Sperm cryopreservation: up to 3 collections, each 48 h apart Tissue cryopreservation: minimal (<1 d)	Collection via masturbation Surgical removal of testicular tissue
Adult females	Embryo cryopreservation	Oocyte cryopreservation Ovarian tissue cryopreservation Ovarian suppression	Embryo/oocyte cryopreservation: 2-3 wk Tissue cryopreservation: minimal (<1 d) None; agents can be administered immediately	Ovarian stimulation; egg retrieval Surgical removal of ovarian tissue

tal testes contain primordial germ cells that are susceptible to toxicity but do not contain mature spermatocytes. Loss of all primordial germ cells at this stage can result in permanent azoospermia. Under normal conditions, post-pubertal males produce 100 to 200 million sperm per day, and mitotic division of germ cells maintains a persistent source of new spermatocyte production, allowing sperm production to continue well into advanced age.[6] In contrast, germ cells within the human ovary undergo rapid mitotic multiplication in utero, peaking at 6 to 7 million oogonia at approximately 5 months' gestation.[7,8] Oogonia then enter their first meiotic division and are transformed into oocytes. After the midgestational peak, there is significant apoptotic loss of germ cells, resulting in only 1 to 2 million total oocytes present at birth.[9] Germ cell content continues to decrease throughout the female life span, ultimately resulting in complete oocyte depletion during menopause. It is generally accepted that, once all oocytes are lost, no mechanism or opportunity exists to generate new oocytes.[10]

Risks of adjuvant therapy depend on age of the patient at treatment, as well as dose, site, and type of treatment given. Additionally, although chemotherapy and radiation treatment potentially impart individual risks, a combination of both may be additive. With chemotherapy regimens, alkylating agents such as cyclophosphamide seem to present the greatest risk of ovarian failure, likely because they are non–cell-cycle specific and can damage even "resting" oocytes and their support cells in the ovary. The odds ratio for inducing complete ovarian failure with cyclophosphamide exposure is 3.98 compared to that in unexposed patients.[11] Older women appear more susceptible to permanent ovarian damage: the incidence of amenorrhea after chemotherapy in women exposed to cyclophosphamide, methotrexate, and 5-fluorouracil was 61% in women younger than 40 years and 95% in those older than 40 years.[12] Likewise, studies of posttreatment sperm production from young adult males who survived Hodgkin disease show that both the agent(s) used and the cumulative dose are important variables that affect future fertility. Adolescent and young adult males treated with 6 cycles of chemotherapy, including agents such as procarbazine, vincristine, and nitrogen mustard (an alkylating agent), had a greater than 90% risk of infertility, largely due to azoospermia.[13,14] An alternative regimen of adriamycin, bleomycin, vinblastine, and dacarbazine—none of which are alkylating agents—was associated with a 33% incidence of azoospermia.[15]

With radiation therapy, the median lethal dose (LD_{50}) for permanent oocyte loss is less than 2 Gy,[16] whereas sperm production may be harmed by radiation doses of 1.2 Gy or greater.[17,18] As with chemotherapy exposure, younger patients may be more resilient than older patients; the mean effective sterilizing dose (dose of fractionated radiotherapy [Gy] at which premature ovarian failure occurs immediately after treatment in 97.5% of patients) decreases with increasing age at treatment.[19] Whereas an effective sterilizing dose at birth is 20.3 Gy, at 10 years, it is 18.4 Gy; at 20 years, 16.5 Gy; and at 30 years, 14.3 Gy. Site of radiotherapy is another key variable. Total body, abdominal, pelvic, or spinal radiation increases the risk of gonadal failure, although scattered irradiation can affect the gonads even when outside of the field.[20]

KEY MESSAGE NUMBER 2

Fertility Preservation Options

Fertility preservation options vary by age and sex (Table). For prepubescent males, gonad shielding can be used during radiotherapy but only with selected fields. Cryopreservation of testicular tissue is offered in some centers but is still considered experimental; potential future uses include

in vitro maturation of spermatogonia into spermatocytes or germ-cell transplant into native testicular tissue. Patients and their parents must be counseled that this technology is still being developed, and potential use of specimens is unlikely for several more years. For postpubertal males, sperm cryopreservation after masturbation is a well-established and effective method of fertility preservation. Depending on treatment timing and specimen quality, multiple collections may be obtained. Ideally, we recommend 3 collections with an interval of 48 hours in between collections to allow sperm to reaccumulate. Sperm should be collected before initiation of therapy because sperm DNA integrity and quality may be compromised thereafter. Specimens can be stored for years, even decades, and still yield viable sperm after thawing.

In premenarchal females, ovarian tissue cryopreservation is currently available but is considered experimental because of difficulties in recovering and using immature oocytes. This technique involves surgical removal of all or a portion of one or both ovaries, followed by dissection of the ovarian cortex into thin strips containing immature follicles. Tissue strips are then cryopreserved by slow freezing or vitrification. In most cases, surgery can be performed as a laparoscopic outpatient procedure, but the risks of surgical complications and general anesthesia must be discussed with the patient and her parents. Potential future uses of the tissue include autotransplant into the pelvis or a heterotopic site with natural ovulation or administration of exogenous gonadotropins to stimulate follicular development, followed by harvesting of oocytes for in vitro fertilization. Caution and clinical judgment must be used when discerning whether to return native tissue to the patient because of the possibility of reintroduction of malignant cells. Another technique currently under development is in vitro maturation of follicles obtained from ovarian cortex. Both culture of whole ovarian tissue strips and isolated follicle culture have been studied.[21] In a murine model, isolated follicle culture using a 3-dimensional alginate matrix has yielded mature oocytes capable of fertilization and delivery of healthy mouse pups.[22] Although promising, these techniques must still be considered experimental for humans and await validation in clinical trials.

For certain malignancies in which radiation alone without chemotherapy is anticipated, the ovaries can be surgically transposed outside of the planned radiation field. If oophoropexy is performed before radiation, ovarian function is maintained in most young women.[23,24] If abdominal surgery is planned for tumor removal, oophoropexy can be concomitantly performed; alternatively, it may be performed as a separate, usually laparoscopic, procedure. There are routine surgical risks, as well as possible unique complications, such as fallopian tube infarction, ovarian cyst formation, chronic pain, or migration of the ovaries back to their native position in the pelvis.[25]

Postpubertal females can undergo gonadotropin stimulation of the ovaries, followed by oocyte or embryo cryopreservation. This process relies on in vitro fertilization technology, which has been available for more than 30 years and accounts for millions of conceptions and births worldwide. In ovarian stimulation, gonadotropins are administered for approximately 8 to 12 days. During this time, follicle development is monitored via serial serum estradiol levels and ultrasound measurements of follicle size. When mature, oocytes are removed from the ovaries by transvaginal ultrasound-guided aspiration of follicles. Although light anesthesia is required, recovery is rapid, and cancer treatment can often be initiated the next day.

Once outside the body, oocytes can be combined with sperm to create embryos or cryopreserved in an unfertilized state. Embryo cryopreservation is the most mature technology available for fertility preservation and is the most effective strategy to date. Human embryos can survive the freezing and thawing process up to 95% of the time, and cumulative pregnancy rates can be greater than 60% if multiple embryos are available.[26] Single women may elect to create embryos using donor sperm, but this approach may not be ethically acceptable to all.

Oocyte cryopreservation is a newer technique that attempts to address the aforementioned limitations. Early success with oocyte cryopreservation was followed by nearly 2 decades of failure attributable to difficulties, including intracellular ice-crystal formation, artificial activation of the mitotic spindle, and osmotic swelling.[27] Recent technological advances have now improved oocyte cryopreservation such that oocytes can survive the freezing or vitrification process approximately 50% to 60% of the time, with fertilization rates of 60% to 70% with use of intracytoplasmic sperm injection.[28,29] Clinical pregnancy and live birth rates are lower than those observed with unfrozen oocytes, but preliminary outcomes are encouraging. More than 900 infants have now been born from cryopreserved oocytes with no apparent increase in congenital anomalies compared with those in naturally conceived infants.[30] This technology will likely continue to advance and become more prominent in the future, but some centers currently consider oocyte cryopreservation to be experimental. Thus, when feasible, most women considering oocyte vs embryo cryopreservation are counseled toward embryo creation, even if it requires the use of donor sperm purchased from a commercial sperm bank.

One theoretical concern for women with hormone-responsive cancers, such as breast cancer, is that supraphysiologic hormone levels arising from conventional ovarian stimulation with gonadotropins may increase the risk of

recurrence. Some investigators have responded to this with protocols that combine traditional ovarian stimulation with estrogen-lowering agents, such as aromatase inhibitors, in an attempt to mitigate high estrogen levels.[31] Aromatase inhibitors such as letrozole are a class of pharmacological agents that block the peripheral conversion of testosterone to estradiol. Ovarian stimulation combining follicle-stimulating hormone with the aromatase inhibitor letrozole resulted in significantly lower peak estradiol levels and a nearly 50% reduction in gonadotropin requirement compared with age-matched controls (cancer-free) undergoing in vitro fertilization.[32] Azim et al[33] prospectively compared 79 women with breast cancer who underwent ovarian stimulation plus letrozole with 136 women with breast cancer who did not undergo ovarian stimulation before cancer treatment. The groups were similar in age and stage of disease at diagnosis, as well as in risks of calculated relapse and mortality. After a median follow-up of 23 months for women in the ovarian stimulation group and 33 months for controls, no differences were noted in recurrence or survival. The authors concluded that ovarian stimulation with gonadotropins and letrozole is unlikely to cause significantly increased risk of recurrence, although they acknowledged that longer term follow-up is needed.

For women who do not have sufficient time or who elect not to undergo ovarian stimulation, medical suppression of ovarian function may be an option. Gonadotropin-releasing hormone (GnRH) agonists may directly suppress primordial follicles and thus spare them during cancer treatment; however, some critics have argued that it is unclear whether primordial follicles contain follicle-stimulating hormone and GnRH receptors.[34,35] Some small studies have shown that GnRH agonist administration before and during chemotherapy resulted in ongoing menses in a high percentage of women, particularly those younger than 40 years.[36-38] A recent prospective randomized study of concurrent GnRH agonist use during chemotherapy in premenopausal women with breast cancer showed that nearly 90% of GnRH agonist–treated women resumed menses and that 69% resumed spontaneous ovulation after treatment, compared with 33.3% resumption of menses and 25.6% spontaneous ovulation in women who received chemotherapy only.[39] However, the return of menses does not necessarily equate with fertility potential because oocyte quality may be poor.

KEY MESSAGE NUMBER 3

Pregnancy After Cancer Therapy

Cancer survivors often desire, yet fear, pregnancy after cancer therapy, particularly that for hormone-responsive malignancies like breast cancer. Multiple studies have shown that pregnancy after breast cancer treatment does not appear to adversely affect recurrence or survival.[40-42] In particular, a large population-based study examined more than 10,000 women with primary breast cancer who were younger than 45 years at the time of diagnosis; only 371 had a full-term delivery after cancer treatment.[43] A multivariate analysis including age at diagnosis, stage of disease, and pregnancy history before diagnosis showed that women who had a full-term pregnancy after cancer diagnosis had a reduced risk of dying (0.73; 95% confidence interval, 0.54-0.99) compared with other women with breast cancer. The authors concluded that no evidence exists to suggest that pregnancy after breast cancer had a negative influence on prognosis.

The optimal time to attempt conception after completion of cancer treatment is unknown. Many experts recommend waiting at least 2 years after therapy is concluded because it is speculated that, beyond this window, the greatest risk of recurrence has passed. For women receiving hormone therapy such as tamoxifen, a 5-year delay is often recommended to allow them to complete standard duration hormonal therapy. This lengthy period may be problematic for some women because of reproductive aging and declining fertility.

A final concern of many cancer patients is whether offspring exposed to cytotoxic agents have an increased risk of birth defects. Several large studies that included more than 4000 offspring of cancer survivors showed no statistically significant increase in childhood malignancies or genetic malformations.[44]

KEY MESSAGE NUMBER 4

An Emerging Discipline

Patients must be counseled that fertility preservation is an emerging field, and as such, many unanswered questions remain.

- Are there long-term risks to fertility preservation strategies? Follow-up data are currently limited, but available evidence suggests that outcomes and survival are not exacerbated for patients who undergo fertility preservation.
- Are some patients too ill to consider fertility preservation? If so, who decides?
- What is ethically responsible fertility preservation for minors with cancer? At what age should fertility preservation be discussed?
- Who should pay? Currently, insurance coverage is limited; thus, many cancer patients have to pay out-of-pocket costs associated with fertility preservation.

CONCLUSION

Although the diagnosis of cancer can be overwhelming, most reproductive-age patients are aware of potential loss of fertility with cancer treatment. As such, health care pro-

fessionals need to be informed about fertility preservation to properly counsel and refer patients for fertility preservation therapy. Rapid referral of patients to a reproductive endocrinologist is essential because some fertility preservation strategies require 2 to 3 weeks to complete. Many technical, logistic, and ethical questions surround fertility preservation, and more will emerge as this field continues to develop.

REFERENCES

1. Altekruse S, Kosary C, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2007. Bethesda, MD: National Cancer Institute. Based on November 2009 SEER data submission, posted to the SEER web site; 2010. Updated June 30, 2010. http://seer.cancer.gov/csr/1975_2007/index.html. Accessed October 7, 2010.

2. Schover LR, Rybicki LA, Martin BA, Bringelsen KA. Having children after cancer: a pilot survey of survivors' attitudes and experiences. *Cancer*. 1999;86(4):697-709.

3. Burns KC, Boudreau C, Panepinto JA. Attitudes regarding fertility preservation in female adolescent cancer patients. *J Pediatr Hematol Oncol*. 2006;28(6):350-354.

4. 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(18):2917-2931.

5. Forman EJ, Anders CK, Behera MA. Pilot survey of oncologists regarding treatment-related infertility and fertility preservation in female cancer patients. *J Reprod Med*. 2009;54(4):203-207.

6. Vogel F, Rathenberg R. Spontaneous mutation in man. *Adv Hum Genet*. 1975;5:223-318.

7. Baker TG. A quantitative and cytological study of germ cells in human ovaries. *Proc R Soc Lond B Biol Sci*. 1963;158(972):417-433.

8. Gondos B, Bhiraleus P, Hobel CJ. Ultrastructural observations on germ cells in human fetal ovaries. *Am J Obstet Gynecol*. 1971;110(5):644-652.

9. Himelstein-Braw R, Byskov AG, Peters H, Faber M. Follicular atresia in the infant human ovary. *J Reprod Fertil*. 1976;46(1):55-59.

10. Tilly JL, Niikura Y, Rueda BR. The current status of evidence for and against postnatal oogenesis in mammals: a case of ovarian optimism versus pessimism? *Biol Reprod*. 2009;80(1):2-12.

11. Meirow D. Ovarian injury and modern options to preserve fertility in female cancer patients treated with high dose radio-chemotherapy for hemato-oncological neoplasias and other cancers. *Leuk Lymphoma*. 1999;33(1-2):65-76.

12. Goldhirsch A, Gelber RD, Castiglione M; International Breast Cancer Study Group. The magnitude of endocrine effects of adjuvant chemotherapy for premenopausal breast cancer patients. *Ann Oncol*. 1990;1(3):183-188.

13. da Cunha MF, Meistrich ML, Fuller LM, et al. Recovery of spermatogenesis after treatment for Hodgkin's disease: limiting dose of MOPP chemotherapy. *J Clin Oncol*. 1984;2(6):571-577.

14. Heikens J, Behrendt H, Adriaanse R, Berghout A. Irreversible gonadal damage in male survivors of pediatric Hodgkin's disease. *Cancer*. 1996;78(9):2020-2024.

15. Waring AB, Wallace WH. Subfertility following treatment for childhood cancer. *Hosp Med*. 2000;61(8):550-557.

16. Wallace WH, Thomson AB, Kelsey TW. The radiosensitivity of the human oocyte. *Hum Reprod*. 2003;18(1):117-121.

17. Howell S, Shalet S. Gonadal damage from chemotherapy and radiotherapy. *Endocrinol Metab Clin North Am*. 1998;27(4):927-943.

18. Speiser B, Rubin P, Casarett G. Aspermia following lower truncal irradiation in Hodgkin's disease. *Cancer*. 1973;32(3):692-698.

19. Wallace WH, Thomson AB, Saran F, Kelsey TW. Predicting age of ovarian failure after radiation to a field that includes the ovaries. *Int J Radiat Oncol Biol Phys*. 2005;62(3):738-744.

20. Sonmezer M, Oktay K. Fertility preservation in female patients. *Hum Reprod Update*. 2004;10(3):251-266.

21. Abir R, Nitke S, Ben-Haroush A, Fisch B. In vitro maturation of human primordial ovarian follicles: clinical significance, progress in mammals, and methods for growth evaluation. *Histol Histopathol*. 2006;21(8):887-898.

22. Xu M, Kreeger PK, Shea LD, Woodruff TK. Tissue-engineered follicles produce live, fertile offspring. *Tissue Eng*. 2006;12(10):2739-2746.

23. Cowles RA, Gewanter RM, Kandel JJ. Ovarian repositioning in pediatric cancer patients: flexible techniques accommodate pelvic radiation fields. *Pediatr Blood Cancer*. 2007;49(3):339-341.

24. Thibaud E, Ramirez M, Brauner R, et al. Preservation of ovarian function by ovarian transposition performed before pelvic irradiation during childhood. *J Pediatr*. 1992;121(6):880-884.

25. Meirow D, Nugent D. The effects of radiotherapy and chemotherapy on female reproduction. *Hum Reprod Update*. 2001;7(6):535-543.

26. Seli E, Tangir J. Fertility preservation options for female patients with malignancies. *Curr Opin Obstet Gynecol*. 2005;17(3):299-308.

27. Chen C. Pregnancy after human oocyte cryopreservation. *Lancet*. 1986;1(8486):884-886.

28. Fabbri R, Porcu E, Marsella T, Rocchetta G, Venturoli S, Flamigni C. Human oocyte cryopreservation: new perspectives regarding oocyte survival. *Hum Reprod*. 2001;16(3):411-416.

29. Oktay K, Cil AP, Bang H. Efficiency of oocyte cryopreservation: a meta-analysis. *Fertil Steril*. 2006;86(1):70-80.

30. Noyes N, Porcu E, Borini A. Over 900 oocyte cryopreservation babies born with no apparent increase in congenital anomalies. *Reprod Biomed Online*. 2009;18(6):769-776.

31. 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(16):3858-3859.

32. Oktay K, Hourvitz A, Sahin G, et al. Letrozole reduces estrogen and gonadotropin exposure in women with breast cancer undergoing ovarian stimulation before chemotherapy. *J Clin Endocrinol Metab*. 2006;91(10):3885-3890.

33. 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.

34. Blumenfeld Z. How to preserve fertility in young women exposed to chemotherapy? The role of GnRH agonist cotreatment in addition to cryopreservation of embrya, oocytes, or ovaries. *Oncologist*. 2007;12(9):1044-1054.

35. Oktay K, Sonmezer M, Oktem O, Fox K, Emons G, Bang H. Absence of conclusive evidence for the safety and efficacy of gonadotropin-releasing hormone analogue treatment in protecting against chemotherapy-induced gonadal injury. *Oncologist*. 2007;12(9):1055-1066.

36. Del Mastro L, Catzeddu T, Boni L, et al. Prevention of chemotherapy-induced menopause by temporary ovarian suppression with goserelin in young, early breast cancer patients. *Ann Oncol*. 2006;17(1):74-78.

37. Fox KR, Scialla J, Moore H. Preventing chemotherapy-related amenorrhea using leuprolide during adjuvant chemotherapy for early-stage breast cancer [abstract 50]. *Proc Am Soc Clin Oncol*. 2003;22:13.

38. Urruticoechea A, Arnedos M, Walsh G, Dowsett M, Smith IE. Ovarian protection with goserelin during adjuvant chemotherapy for pre-menopausal women with early breast cancer (EBC). *Breast Cancer Res Treat*. 2008;110(3):411-416.

39. Badawy A, Elnashar A, El-Ashry M, Shahat M. Gonadotropin-releasing hormone agonists for prevention of chemotherapy-induced ovarian damage: prospective randomized study. *Fertil Steril*. 2009;91(3):694-697.

40. 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(3):465-469.

41. Sankila R, Heinavaara S, Hakulinen T. Survival of breast cancer patients after subsequent term pregnancy: "healthy mother effect." *Am J Obstet Gynecol*. 1994;170(3):818-823.

42. von Schoultz E, Johansson H, Wilking N, Rutqvist LE. Influence of prior and subsequent pregnancy on breast cancer prognosis. *J Clin Oncol*. 1995;13(2):430-434.

43. 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.

44. Hawkins MM. Pregnancy outcome and offspring after childhood cancer [editorial]. *BMJ*. 1994;309(6961):1034.