Fertility Preservation in Young Women with Breast Cancer

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Published online: 9 January 2013
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Abstract Approximately 10,000 cases of breast cancer are diagnosed in women younger than 40 years of age each year in the United States. This creates a population of young women with breast cancer who may have not started or completed their family. Given that technology and treatment have improved outcomes for these women, quality of life issues, such as fertility preservation, must be considered. This review examines breast cancer patient and physician attitudes toward fertility preservation, ovarian toxicity of chemotherapeutic agents, fertility preservation options for breast cancer patients, and the safety of subsequent pregnancies for these women.

Keywords Breast cancer · Fertility preservation (FP) · Egg and embryo banking · Young women with breast cancer · GnRH analogues · Cryopreservation techniques · Aromatase · Anti-müllerian hormone (AMH) · Managing breast problems

Introduction

In 2011, an estimated 230,480 new cases of invasive breast cancer were diagnosed, making it the most common cancer in women except for skin cancer. Among these diagnoses, approximately 10,000 of these cases or 5 % were in women who were younger than 40 years of age [1]. In addition, women have been delaying childbearing over the past four

decades. In the United States, the average age of a woman's first birth increased from age 21.4 years in 1970 to 25.2 years in 2009 (National Center for Health Statistics). Because the average age of first-time births is increasing, many young patients diagnosed with breast cancer have not started or completed their family. Fertility planning must quickly be considered soon after diagnosis, because chemotherapy can be toxic to the ovaries. Several issues, therefore, must be discussed quickly regarding patient education of fertility preservation (FP), the effects of chemotherapy on ovarian function, FP techniques, and the subsequent safety of future pregnancy for the mother and fetus.

Patient Attitudes Toward Breast Cancer and FP

The incidence of breast cancer in women younger than age 40 years combined with delayed childbearing necessitates patient education regarding FP. Fertility issues have been shown to influence a patient's choice of breast cancer treatment if her condition permits. Fallowfield et al. showed that 40 % of women younger than age 40 years would elect to use a breast cancer treatment that increased their chances of retaining fertility options [2]. Connell et al. showed that after fear of recurrence and future uncertainty, children and family were the most commonly reported personal concerns of young women with breast cancer [3]. The American Society of Clinical Oncology recommends that fertility concerns should be considered as early as possible during cancer treatment plans [4]. Unfortunately, recent studies have reported that only half of young breast cancer patients are offered counseling regarding FP [5, 6]. Younger women therefore have unmet needs for fertility-related information.

The need for fertility education is more acute given the average cancer patient's unawareness of fertility issues and low pretreatment FP knowledge. Compared with young women with cancer, a typical infertility patient enters into

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treatment after 1 year of unsuccessful pregnancy attempts. During this time, an infertility patient often will obtain a base knowledge of fertility issues and have a grasp of the complex language involved with reproductive anatomy, embryology, and statistics. On the other hand, breast cancer patients seeking information about FP have limited knowledge of fertility issues given their abrupt onset of diagnosis. Balthazar et al. found that cancer patients tended to have low scores on a FP knowledge scale BEFORE their visit with a FP specialist [7]. Peate et al. also showed that knowledge of FP was poor in the group of breast cancer patients that they studied [8]. This decreased knowledge was associated with increased decisional conflict and more distress for these patients.

Improvement of FP options may occur if access to information is improved. Lee et al. evaluated the value of early referral to reproductive endocrinologists in young women with breast cancer [9]. In this study, women who were referred before breast cancer surgery, rather than afterwards, were more likely to have one (or more) egg/embryo banking cycles per patient and shorter time to cycle initiation from initial cancer diagnosis. This study also showed that the presurgical referral group had a shorter delay to adjuvant chemotherapy following surgery compared with the post-surgery referral group (83.9 ± 24.3 days vs. 107.8 ± 42.9 days). This was the first study showing the benefit of early FP referral for patients with cancer.

Physician Attitudes About FP

If early referral shows benefit for the patient, what are the physician barriers to discussing fertility concerns or referring to a reproductive endocrinologist? Factors identified include limited access to fertility specialists, older physicians, and physician's specialty (medical oncologists are more likely to refer than surgical oncologists) [10]. Forman et al. performed a nationwide survey of 249 oncologists to evaluate their knowledge and practice patterns concerning FP [11]. More than 90 % of responders believed that they were "very knowledgeable" or "aware of" FP options, yet only 17 % had experience with the most established FP technique: embryo cryopreservation. Thirty percent of responders stated that they rarely considered a woman's desire for fertility when planning treatment. Optimistically, 75 % of responders expressed a great interest in attending educational seminars about FP, which demonstrates physician willingness to learn more about these issues [11].

Adjuvant Chemotherapy for Breast Cancer

Adjuvant chemotherapy following surgical intervention is a common treatment course for women with breast cancer. Typically, adjuvant chemotherapy is recommended to

women who have at least stage II disease or stage I disease with a tumor >1 cm. Approximately two-thirds of women younger than age 40 years with breast cancer meet these criteria [12]. Certain types of chemotherapy have been shown to be chemotoxic to the ovaries. Although the exact etiology of chemotoxicity is unknown, proposed mechanisms include depletion of mature follicles, depletion of primordial follicles, or induction of ovarian fibrosis [13, 14]. Regardless of etiology, typical regimens of adjuvant chemotherapy can decrease or completely eliminate the fertile capacity of the ovary. Risk factors for decreased fertility secondary to adjuvant chemotherapy include the type and cumulative dose of chemotherapy and the age of the woman at time of treatment [15].

Alkylating agents induce DNA damage by attaching an alkyl group to DNA in cells that divide frequently. A common alkylating agent used in breast cancer treatment protocols is cyclophosphamide. These agents are particularly cytotoxic to ovaries with known effects including fibrosis of the ovaries and depletion of follicles and oocytes [14]. Meiorow examined the ovarian effects of five classes of chemotherapy agents used in female cancer patients, including breast cancer [16]. This study demonstrated that alkylating agents caused the highest rate of ovarian failure (odds ratio (OR)=3.98), followed by platin derivatives (OR=1.77) compared with antibiotics, anti-metabolites, and plant alkaloids. Other studies have shown that in humans, greater age and higher doses are associated with an increased risk of premature ovarian failure [17, 18]. The combination of different chemotherapeutic drugs does create different risks of premature ovarian failure. For example, the risk of menopause for a 40-year-old woman undergoing CMF (cyclophosphamide, methotrexate, 5-fluorouracil) treatment is 78 % compared with a 38 % risk when using an FEC (5-fluorouracil, epirubicin, cyclophosphamide) regimen [19, 20].

Other than ovarian toxicity, another challenge to future fertility in breast cancer patients is the length of cancer treatment, particularly in receptor-positive patients. These women require an additional 5 years of Tamoxifen treatment. Although Tamoxifen can be used as an ovulation induction agent for short amounts of time in women with infertility, long-term Tamoxifen use is not recommended during pregnancy [21]. Therefore, patients would need to either wait 5 years to consider pregnancy or temporarily interrupt their Tamoxifen treatment to attempt conception.

Several studies have assessed the risk of premature ovarian failure in premenopausal women receiving chemotherapy for treatment of breast cancer [22–24]. Previously, assessment of pretreatment and posttreatment ovarian function has been evaluated by serological markers and ultrasonography [25•, 26, 27]; many of these studies have used chemotherapy-related amenorrhea as an indicator of ovarian function. This, however, likely underestimates fertility potential, because some women who continue to have menstrual cycles have low likelihood for conception given poor egg quality/quantity.

To date, initial studies have found that pretreatment serum anti-müllerian hormone (AMH) levels may offer some estimation of ovarian reserve and possible ovarian recovery following chemotherapy [25•, 28]. Anderson et al. performed a prospective, longitudinal study in breast cancer patients that evaluated pretreatment AMH levels as a predictor of ovarian function 5 years after treatment [25•]. They found that higher AMH levels predicted better long-term ovarian function using multivariate logistical analysis (OR=13.0; 95 % confidence interval=2.5–66.7). Other serum markers, such as estradiol, inhibin B, and follicle-stimulating hormone were not predictive. However, the authors used menstruation as an indicator of ovarian function. Further studies assessing AMH as a predictor of fertility potential are needed.

FP Techniques

Women diagnosed with breast cancer who seek FP have unique and complex issues to consider. Issues that these women face include:

- Proper timing of FP treatment with breast cancer treatments
- Treatment options and decisions for those women without partners (banking eggs vs. embryos by using donor sperm)
- Hypothetical concern about cancer recurrence after pregnancy, and
- Fear of potentially passing on the BRCA 1/2 mutation to an offspring.

In addition, concern initially was raised that endocrine manipulations and delaying treatment for fertility may increase the risk of disease progression or recurrence. That fear has not been substantiated in the literature, as discussed below. Regardless of these challenges, FP is possible and may be classified into three main techniques, including ovarian suppression during treatment with GnRH analogues, cryopreservation of embryos, and cryopreservation of oocytes (Table 1). Cryopreservation of ovarian tissue is considered experimental and less than 20 births have been documented to date worldwide from this technique. Each of these techniques provides distinct advantages and disadvantages.

GnRH Analogues

GnRH agonists (such as leuprolide acetate and triptorelin) are medications that temporarily inhibit the reproductive axis, by replicating a prepubertal state. This class of medication is routinely used in conditions, such as leiomyoma or endometriosis management. Several studies have evaluated the use of GnRH agonists during chemotherapy, with the hypothesis that ovaries in a temporary prepubertal state

should be less susceptible to injury by chemotherapeutic agents, although the exact hypothetical mechanism of ovarian protection is unknown [29–32]. Treatment with GnRH agonists ideally begins in the luteal phase of a woman's menstrual cycle, before the start of chemotherapy to avoid the initial brief ovarian stimulation associated with GnRHa use in the follicular phase. Depot injections of GnRHa are continued throughout chemotherapy treatment and for at least 2 weeks following the end of chemotherapy.

However, contradictory findings have questioned the benefit of GnRH agonist as a FP technique. The PROMISE-GIM6 study examined the effect of triptorelin during chemotherapy on the incidence of early menopause in young breast cancer patients [33•]. This study randomized women to chemotherapy alone or chemotherapy plus triptorelin. Twelve months after treatment, the rate of early menopause was 25.9 % in the chemotherapy only group and 8.9 % in the chemotherapy plus triptorelin group. In contrast, Munster et al. were not able to replicate these differences [34]. In this group's study, premenopausal women age 44 years or younger were randomly assigned to receive either triptorelin or no triptorelin during adjuvant chemotherapy. No differences in rates of amenorrhea were found between groups. Again, pregnancy rates were not addressed. Future studies are needed that evaluate fertility after treatment with GnRH agonists.

Cryopreservation of Reproductive Tissue

Currently the most successful forms of FP in breast cancer patients use cryopreservation techniques. This involves the preservation of embryos or oocytes for future use after breast cancer treatment has been completed. Ovarian stimulation is needed for these techniques. This presents several issues, including timing of stimulation, choosing an appropriate stimulation protocol for breast cancer patients, and financial concerns (self-pay FP treatments can cost >\$10,000). Once these issues have been addressed, a woman must then decide between embryo and/or oocyte preservation.

Timing of treatment is an essential issue in FP for women diagnosed with breast cancer. Given the chemotoxicity of most adjuvant chemotherapy to the ovaries, oocyte collection must be performed before any chemotherapy or radiation. Typically in breast cancer treatment regimens, adjuvant chemotherapy is administered at least 4–6 weeks following initial surgical intervention. Given that it takes approximately 2–4 weeks for a woman to undergo ovarian stimulation (depending on where she is in her menstrual cycle), early referral to the fertility specialist is essential to allow time for stimulation in the limited window of opportunity.

Various methods have been studied to develop safe ovarian stimulation methods in breast cancer patients. Because ovarian stimulation results in elevated estrogen levels, there

Table 1 Fertility preservation findings with no FP treatment, GnRH analogues, embryo banking, or egg banking

	No FP treatment	GnRH analogues	Embryo banking	Egg banking
Chance of pregnancy	Depends on age, type of chemotherapy	Data are mixed about ovarian protection	Depends on age and number of embryos. For example: - Age <30: 40 % per embryo transfer cycle - Age >40: <20 % per embryo transfer cycle	Depends on age. For example: - Age <30: similar to embryo rates - Age >30: limited data
Time needed before cancer treatments	Can start cancer treatments immediately	Can start cancer treatments immediately	2–3 weeks	2–3 weeks
Cost	No cost	Often covered by insurance	Sometimes covered by insurance. If not, ~\$5,000+ medications	Sometimes covered by insurance. If not, ~\$4,500+ medications
Other factors	Menstrual cycles≠fertility	“Off-label” use Side effects: hot flashes, vaginal dryness	Most successful method to date.	For women who: - don’t have a male partner and don’t want to use donor sperm - don’t want to create embryos

is a hypothetical concern that this brief supraphysiological elevation in estrogen may be harmful to women with hormone-sensitive cancers, although this harm has not been demonstrated in studies. However, given this hypothetical risk, some providers use strategies to mitigate these high estrogen levels. Natural-IVF cycles that do not use ovarian stimulation techniques are low yield, producing on average 0.6 embryos per patient [35]. Investigators also have attempted using medications during the ovarian stimulation, such as aromatase inhibitors, to try to achieve reasonable egg yield with lower estrogen levels.

Aromatase is an enzyme of the cytochrome P450 family that catalyzes the conversion of androgens into estrogens in tissues like the granulosa cells of ovarian follicles. Aromatase inhibitors thus decrease the amount of circulating estrogen produced. Letrozole, an aromatase inhibitor, has a half-life of 48 hr and has been shown to be a potent suppressor of estradiol. A retrospective analysis of IVF cycles compared women with hormone-sensitive cancer who did or did not use concurrent letrozole and found no difference in the number of mature oocytes, fertilization rate, and number of days stimulated [36]. They also found that letrozole groups had significantly lower peak estradiol levels compared with traditional IVF protocols. Ovarian stimulation with letrozole is therefore usually used in receptor-positive breast cancer patients, because it produces similar numbers of oocytes with decreased levels of estradiol. Azim et al. also found that this appeared to be a safe protocol, with no difference in recurrence rates of breast cancer in women who underwent a letrozole stimulation protocol compared with women who did not undergo IVF before cancer treatments [37].

Following stimulation and oocyte collection, oocytes either may be frozen as is or fertilized and frozen as embryos. Fertilization before cryopreservation (frozen embryos) is a standard treatment used routinely with infertile couples. Embryos are able to withstand the freezing process with high post-thaw survival rates allowing for reasonable pregnancy rates [38]. If multiple embryos are implanted (e.g., 2–4 based on the woman’s age at the time of embryo banking), pregnancy rates are between 20–60 % [38, 39]. Pregnancy rates with IVF are higher in younger patients with 65 % success rate in women younger than age 33 years. Once older than age 43 years, the success rates are very low (<5 % per attempt).

Traditionally, cryopreservation of oocytes is less successful than embryo banking, because oocytes are more susceptible to injury by the cryopreservation process. The human oocyte is one of the largest cells in the human body with a large amount of cytoplasmic water, which can cause ice crystal formation during the freezing process [40]. The preservation process also hardens the zona pellucida. Intracytoplasmic sperm injection therefore must be used for fertilization after thawing, which can be costly. Recent data using a newer technique called vitrification demonstrates more promising success rates using frozen oocytes, especially in young healthy women [41]. Initial reports show similar implantation rates and no differences in aneuploidy rates compared with regular IVF cycles [42]. However, data still lack regarding future pregnancy rates in women older than age 30 years who attempt conception with frozen oocytes.

Additional research has been performed on the cryopreservation of immature oocytes [43–45]. This avoids depolymerization of spindle fibers, because these cells remain in prophase I. However, because of their less mature state,

oocytes must incubate for 24–48 hours to continue through the remaining meiotic phases before fertilization may occur. Initial reports have shown that success rates for this experimental process are similar or less than mature oocyte success rates [44].

Pregnancy Safety

Initially, concern was expressed that pregnancy following breast cancer may cause disease recurrence because of the increase of hormones associated with pregnancy [46]. Recent studies have shown that breast cancer patients are sometimes even counseled against pursuing pregnancy [47]. In one study, 69 % of women with a history of breast cancer were advised by their treating physicians to proceed with abortion rather than proceed with pregnancy [48]. However, a meta-analysis by Valachis et al. showed that pregnancy after breast cancer treatment does not increase the risk of disease recurrence [49•]. In fact, Azim et al. showed a 41 % reduced risk of death in patients who became pregnant after breast cancer treatment [46]. The authors hypothesized that parous women have significantly reduced expression of estrogen receptor alpha, progesterone receptor, and HER2 and a twofold higher ER-beta expression compared with nulliparous subjects. More studies however need to be performed regarding these findings, particularly in women who are BRCA1/2 mutation carriers.

Studies have shown that infant outcomes of these pregnancies for women with prior breast cancer are generally good. Langagergaard et al. examined 216 births of women who previously had breast cancer and found no increased risk of premature birth, low birth weight, stillbirth, or congenital abnormalities [50]. Risk of miscarriage has been found to be elevated in some studies, particularly in the first year following treatment. Velentgas et al. showed 24 % miscarriage rate in breast cancer patient compared with 18 % in the control group [51]. General guidelines recommend waiting at least 6 months following treatment to attempt natural conception.

Conclusions

As technology and treatment options improve for women with breast cancer, quality of life issues, such as FP, are becoming more prominent concerns for these women. Several FP techniques exist with promising results. Referral and education of young breast cancer patients is essential. With the proper timing of treatment and knowledge of FP, future pregnancies are possible for these women.

Disclosures No potential conflicts of interest relevant to this article were reported.

References

Papers of particular interest, published recently, have been highlighted as:

•• Of major importance

1. Cancer statistics available at www.cancer.org. Accessed August 2012.
2. Fallowfield L, McGurk R, Dixon M. Same gain, less pain: potential patient preferences for adjuvant treatment in premenopausal women with early breast cancer. *Eur J Cancer*. 2004;40:2403–10.
3. Connell S, Patterson C, Newman B. Issues and concerns of young Australian women with breast cancer. *Support Care Cancer*. 2006;14:419–26.
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;24:2917–31.
5. Thewes B, Meiser B, Taylor A, et al. Fertility- and menopause-related information needs of younger women with a diagnosis of early breast cancer. *J Clin Oncol*. 2005;23:5155–65.
6. Meneses K, McNees P, Azuero A, Jukkala A. Development of the Fertility and Cancer Project: an Internet approach to help young cancer survivors. *Oncol Nurs Forum*. 2010;37:191–7.
7. Balthazar U, Fritz MA, Mersereau JE. Fertility preservation: a pilot study to assess previsit patient knowledge quantitatively. *Fertil Steril*. 2011;95:1913–6.
8. Peate M, Meiser B, Friedlander M, et al. It's now or never: fertility-related knowledge, decision-making preferences, and treatment intentions in young women with breast cancer—an Australian fertility decision aid collaborative group study. *J Clin Oncol*. 2011;29:1670–7.
9. Lee S, Ozkavukcu S, Heytens E, et al. Value of early referral to fertility preservation in young women with breast cancer. *J Clin Oncol*. 2010;28:4683–6.
10. Quinn GP, Vadaparampil ST, Gwede CK, et al. Discussion of fertility preservation with newly diagnosed patients: oncologists' views. *J Cancer Surviv*. 2007;1:146–55.
11. 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;94:1652–6.
12. Rosenberg R, Levy-Schwartz R. Breast cancer in women younger than 40 years. *Int J Fertil Womens Med*. 2003;48:200–5.
13. Chapman RM. Effect of cytotoxic therapy on sexuality and gonadal function. *Semin Oncol*. 1982;9:84–94.
14. Familiari G, Caggiati A, Nottola SA, et al. Ultrastructure of human ovarian primordial follicles after combination chemotherapy for Hodgkin's disease. *Hum Reprod*. 1993;8:2080–7.
15. Behringer K, Breuer K, Reineke T, et al. Secondary amenorrhea after Hodgkin's lymphoma is influenced by age at treatment, stage of disease, chemotherapy regimen, and the use of oral contraceptives during therapy: a report from the German Hodgkin's Lymphoma Study Group. *J Clin Oncol*. 2005;23:7555–64.
16. Meirrow D. Reproduction post-chemotherapy in young cancer patients. *Mol Cell Endocrinol*. 2000;169:123–31.
17. Meirrow 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;33:65–76.
18. Mok CC, Lanchbury JS, Chan DW, Lau CS. Interleukin-10 promoter polymorphisms in Southern Chinese patients with systemic lupus erythematosus. *Arthritis Rheum*. 1998;41:1090–5.
19. Goodwin PJ, Ennis M, Pritchard KI, et al. Risk of menopause during the first year after breast cancer diagnosis. *J Clin Oncol*. 1999;17:2365–70.

20. Hortobagyi GN, Buzdar AU, Marcus CE, Smith TL. Immediate and long-term toxicity of adjuvant chemotherapy regimens containing doxorubicin in trials at M.D. Anderson Hospital and Tumor Institute. NCI Monogr 1986;105–9.
21. Braems G, Denys H, De Wever O, et al. Use of tamoxifen before and during pregnancy. *Oncologist*. 2011;16:1547–51.
22. Meirow D, Nugent D. The effects of radiotherapy and chemotherapy on female reproduction. *Hum Reprod Update*. 2001;7:535–43.
23. Schmidt KL, Andersen CY, Loft A, et al. Follow-up of ovarian function post-chemotherapy following ovarian cryopreservation and transplantation. *Hum Reprod*. 2005;20:3539–46.
24. Meirow D, Epstein M, Lewis H, et al. Administration of cyclophosphamide at different stages of follicular maturation in mice: effects on reproductive performance and fetal malformations. *Hum Reprod*. 2001;16:632–7.
25. •• Anderson RA, Cameron DA. Pretreatment serum anti-müllerian hormone predicts long-term ovarian function and bone mass after chemotherapy for early breast cancer. *J Clin Endocrinol Metab*. 2011;96:1336–43. *A prospective, longitudinal study that examined the change in anti-müllerian hormone (AMH) and ovarian function prior to and 5 years after chemotherapy in breast cancer patients. This group proposes measurement of AMH at cancer diagnosis predicts long-term ovarian function after chemotherapy.*
26. Anderson RA, Themmen AP, Al-Qahtani A, et al. The effects of chemotherapy and long-term gonadotrophin suppression on the ovarian reserve in premenopausal women with breast cancer. *Hum Reprod*. 2006;21:2583–92.
27. Lie Fong S, Laven JS, Hakvoort-Cammel FG, et al. Assessment of ovarian reserve in adult childhood cancer survivors using anti-Müllerian hormone. *Hum Reprod*. 2009;24:982–90.
28. Anders C, Marcom PK, Peterson B, et al. A pilot study of predictive markers of chemotherapy-related amenorrhea among premenopausal women with early stage breast cancer. *Cancer Invest*. 2008;26:286–95.
29. 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;91:694–7.
30. 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;17:74–8.
31. Recchia F, Saggio G, Amiconi G, et al. Gonadotropin-releasing hormone analogues added to adjuvant chemotherapy protect ovarian function and improve clinical outcomes in young women with early breast carcinoma. *Cancer*. 2006;106:514–23.
32. Urruticoechea A, Arnedos M, Walsh G, et al. Ovarian protection with goserelin during adjuvant chemotherapy for pre-menopausal women with early breast cancer (EBC). *Breast Cancer Res Treat*. 2008;110:411–6.
33. •• Del Mastro L, Boni L, Michelotti A, et al. Effect of the gonadotropin-releasing hormone analogue triptorelin on the occurrence of chemotherapy-induced early menopause in premenopausal women with breast cancer: a randomized trial. *JAMA*. 2011;306:269–76. *A parallel, randomized, open-label, phase 3 superiority trial that examined the effect of temporary ovarian suppression with triptorelin on the incidence of early menopause in young breast cancer patients undergoing chemotherapy treatment. This group found that triptorelin was protective against early menopause compared with a control group.*
34. Munster PN, Moore AP, Ismail-Khan R, et al. Randomized trial using gonadotropin-releasing hormone agonist triptorelin for the preservation of ovarian function during (neo)adjuvant chemotherapy for breast cancer. *J Clin Oncol*. 2012;30:533–8.
35. Oktay K, Buyuk E, Davis O, et al. Fertility preservation in breast cancer patients: IVF and embryo cryopreservation after ovarian stimulation with tamoxifen. *Hum Reprod*. 2003;18:90–5.
36. 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;91:3885–90.
37. 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;26:2630–5.
38. Maltaris T, Seufert R, Fischl F, et al. The effect of cancer treatment on female fertility and strategies for preserving fertility. *Eur J Obstet Gynecol Reprod Biol*. 2007;130:148–55.
39. Seli E, Tangir J. Fertility preservation options for female patients with malignancies. *Curr Opin Obstet Gynecol*. 2005;17:299–308.
40. Borini A, Bianchi V. Cryopreservation of mature and immature oocytes. *Clin Obstet Gynecol*. 2010;53:763–74.
41. Cobo A, Meseguer M, Remohi J, Pellicer A. Use of cryo-banked oocytes in an ovum donation programme: a prospective, randomized, controlled, clinical trial. *Hum Reprod*. 2010;25:2239–46.
42. Forman EJ, Li X, Ferry KM, et al. Oocyte vitrification does not increase the risk of embryonic aneuploidy or diminish the implantation potential of blastocysts created after intracytoplasmic sperm injection: a novel, paired randomized controlled trial using DNA fingerprinting. *Fertil Steril*. 2012;98:644–9.
43. Chian RC, Buckett WM, Tulandi T, Tan SL. Prospective randomized study of human chorionic gonadotrophin priming before immature oocyte retrieval from unstimulated women with polycystic ovarian syndrome. *Hum Reprod*. 2000;15:165–70.
44. Escriba MJ, Grau N, Escribá L, et al. Spontaneous in vitro maturation of oocytes prior to ovarian tissue cryopreservation in natural cycles of oncologic patients. *J Assist Reprod Genet*. 2012.
45. Fernandez-Reyez F, Ducoy Y, Romo S, et al. Viability, maturation and embryo development in vitro of immature porcine and ovine oocytes vitrified in different devices. *Cryobiology*. 2012;64:261–6.
46. Azim Jr HA, Santoro L, Pavlidis N, et al. Safety of pregnancy following breast cancer diagnosis: a meta-analysis of 14 studies. *Eur J Cancer*. 2011;47:74–83.
47. Peccatori FA, Azim Jr HA. Pregnancy in breast cancer survivors: a need for proper counseling. *Breast*. 2009;18:337–8.
48. 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;19:1671–5.
49. •• Valachis A, Tsali L, Pesce LL, et al. Safety of pregnancy after primary breast carcinoma in young women: a meta-analysis to overcome bias of healthy mother effect studies. *Obstet Gynecol Surv*. 2010;65:786–93. *A meta-analysis that examined the effect of pregnancy on overall survival of primary breast cancer patients younger than age 45 years.*
50. Langagergaard V, Gislum M, Skriver MV, et al. Birth outcome in women with breast cancer. *Br J Cancer*. 2006;94:142–6.
51. Velentgas P, Daling JR, Malone KE, et al. Pregnancy after breast carcinoma: outcomes and influence on mortality. *Cancer*. 1999;85:2424–32.