



Fertility preservation for women with breast cancer: Current trends and best time-points to attempt pregnancy

Kenny A. Rodriguez-Wallberg MD, PhD, Associate Professor
Head of the Fertility Preservation Program, Reproductive Medicine
Karolinska University Hospital
University Lecturer in Reproductive Oncology, Department of
Oncology-Pathology Karolinska Institutet, Stockholm, Sweden

Fertility preservation has gained increased acceptance, and many reproductive medicine centers have established programs for this service. A recent report, which collected data from all Nordic university hospitals that had initiated programs for fertility preservation (N = 14), found that breast cancer is the most common diagnosis among women who underwent procedures aimed at fertility preservation in Scandinavian countries (1). This Nordic survey also collected data over a twenty-year period that revealed that ovarian tissue cryopreservation has been a preferred method for fertility preservation in women with breast cancer, especially if the women presented with hormonally sensitive tumors. However, data on current fertility preservation trends have indicated that whenever a patient's clinical condition is permissive, oocyte or embryo cryopreservation after hormonal stimulation are the preferred preservation methods. An important argument for the use of these methods was that oocyte cryopreservation is an established clinical option for fertility preservation and that reproductive medicine specialists are familiar with the procedures (1).

Nevertheless, the safety of fertility preservation procedures that involve hormonal stimulation in women with a breast cancer has been a constant concern. Epidemiological and experimental data have indicated that estrogen plays a central role in the initiation and promotion of breast tumorigenesis. For these reasons, the high estradiol levels that result from conventional ovulation stimulation with gonadotropins have been regarded as unsafe for breast cancer patients, especially because the patients have not yet completed their breast cancer treatment when they undergo fertility preservation.

Two approaches that aim to reduce the impact of estrogen on breast tissue during ovarian stimulation with gonadotropins are potentially safer for women with breast cancer. Both approaches utilize drugs that are currently used for the endocrine adjuvant treatment of breast cancer, such as tamoxifen and aromatase inhibitors.

The use of tamoxifen in stimulation cycles for fertility preservation

Tamoxifen is a selective estrogen receptor modulator with demonstrated antiestrogenic actions on breast tissue, and these actions inhibit the growth of breast tumors through the competitive antagonism of estrogen at its receptor site (2). The addition of tamoxifen to either a long gonadotropin-releasing hormone (GnRH) agonist protocol or a GnRH antagonist protocol have been proposed, and both methods have demonstrated efficacy that is comparable to that of conventional gonadotropin stimulation protocols without tamoxifen (3). Irrespective of the induced elevated estradiol levels during

gonadotropin stimulation, tamoxifen prevents the binding of estrogen in breast tissue and blocks subsequent DNA transcription at receptor sites.

Tamoxifen also has the property of recruiting and stimulating ovarian follicles until their final maturation because of its nonsteroidal triphenylethylene structure, which is related to that of clomiphene. Thus, tamoxifen has also been used alone for the induction of ovulation or in combination with gonadotropins for the fertility preservation of women with breast cancer. Studies with tamoxifen have demonstrated that its use for ovulation induction does not adversely affect oocyte or embryo development (4).

The use of aromatase inhibitors in stimulation cycles for fertility preservation

Anastrozole and letrozole, the current third-generation aromatase inhibitors used for the endocrine adjuvant treatment of estrogen-sensitive breast cancer in postmenopausal women, have also been used for ovulation induction in young women. Due to these inhibitors' competitive binding at the enzyme receptor site, which is a process that highly inhibits the aromatase system, the drugs induce an increase in pituitary gonadotropin production as response to estrogenic negative feedback. Available data have indicated that the use of aromatase inhibitors in fertility treatments is safe, and no negative effects have been reported in children born after ovarian induction using letrozole (5).

The addition of aromatase inhibitors alongside gonadotropins has been proposed to increase the safety of hormonal stimulation for fertility preservation in women with breast cancer. In particular, the use of letrozole in this setting has been reported within a GnRH antagonist protocol, and the efficacy of treatments aiming at fertility preservation has been reported as similar to that of conventional ovarian stimulation for in vitro fertilization (IVF), while decreasing gonadotropin requirements, which appears to be cost-effective. Thus this protocol has been named as COST-LESS (Controlled Ovarian Stimulation with Letrozole Supplementation) (6). Estradiol levels during these treatments are consistently lower than the levels found in standard stimulation with gonadotropins for IVF, and the levels of estrogens may be further reduced by triggering oocyte maturation with GnRH agonists (7).

When would be the best time-point to attempt pregnancy after breast cancer?

Several studies indicate that fertility preservation in oncologic patients is effective, and reported pregnancy rates and clinical outcomes have been satisfactory (8,9). However, only a minor proportion of patients that have performed fertility preservation procedures have returned to attempt pregnancy after being cured of their diseases. In most cases, the reasons for patients' non-return are unknown (10). A most plausible reason is that, after the curing of cancer, women must be sufficiently healthy to attempt pregnancy.

Observational studies and two recent meta-analyses have indicated that pregnancy occurring after the diagnosis of breast cancer is associated with a reduced risk of death (11-13). The data, based on case-control and cohort studies, also indicate that the protective effect of pregnancy becomes less pronounced in studies that have accounted

for the “healthy mother effect” (14). The “healthy mother effect” is a selection bias where women with favorable outcomes following diagnosis, i.e., “healthier” women, are most likely to conceive. Regarding breast cancer, some studies have controlled for this bias by matching cases and controls for variables such as nodal status, ER status, disease-free interval, and treatment in the cohorts.

In our program for fertility preservation at Karolinska University Hospital in Stockholm, as well as most Nordic programs for fertility preservation, the largest female patient group is composed of women with a diagnosis of breast cancer (1). However, the disease is heterogeneous, and the risk of relapse will differ among patients. Therefore, the recommended observation time after treatment required to determine the best timepoint to attempt pregnancy is not identical for all women. For the specific patient, it should be individualized. Given the high cure rates of breast cancer today, these discussions are becoming more frequent. At our center, the discussions currently require medical experts from several fields, which has resulted in a multidisciplinary group in reproductive oncology, within the oncology healthcare services.

Our experience indicates that women seem to be more vulnerable than men when facing the risk for treatment-induced infertility, as reported recently by a qualitative study (15). However, patients that have performed fertility preservation can move forward more easily and focus on their cancer treatment, which suggests that compliance with the recommended follow-up period before attempting pregnancy should be improved in these patient groups. However, patients who have not performed fertility preservation would be more anxious that their remaining fertility would be further reduced over time. They may have difficulties in accepting the planned follow-up time and the recommendation to wait to attempt pregnancy. Having oocytes, embryos, or ovarian tissue cryopreserved provides a chance to build a family in the future, but it also gives respite to patients who can more easily complete their recommended adjuvant therapies, when indicated. Thereafter, depending on the individual risk, family-building attempts can be planned when the women are healthy again.

References

- 1- Rodriguez-Wallberg KA, Tanbo T, Tinkanen H, Thurin-Kjellberg A, Nedstrand E, Kitlinski ML, Macklon KT, Ernst E, Fedder J, Tiitinen A, Morin-Papunen L, Einarsson S, Jokimaa V, Hippeläinen M, Lood M, Gudmundsson J, Olofsson JI, Andersen CY. Ovarian tissue cryopreservation and transplantation among alternatives for fertility preservation in the Nordic countries - compilation of 20 years of multicenter experience. *Acta Obstet Gynecol Scand.* 2016 Sep;95(9):1015-26.
- 2- Early Breast Cancer Trialists' Collaborative Group. Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy. 133 randomised trials involving 31 000 recurrences and 24 000 deaths among 75 000 women. *Lancet* 1992; 339: 71–85.
- 3- Meirou D, Raanani H, Maman E, Paluch-Shimon S, Shapira M, Cohen Y, Kuchuk I, Hourvitz A, Levron J, Mozer-Mendel M, Brengauz M, Biderman H, Manela D, Catane R, Dor J, Orvieto R, Kaufman B. Tamoxifen co-administration during controlled ovarian hyperstimulation for in vitro fertilization in breast cancer patients increases the safety of fertility-preservation treatment strategies. *Fertil Steril.* 2014 Aug;102(2):488-495.

- 4- Fisk NM, Templeton AA, Papadopoulos GC, Matlin SA, Wu ZY. Lack of effect of high-dose antioestrogen on the maturation and in-vitro fertilization of human oocytes. *Hum Reprod.* 1989 Jul;4(5):584-7.
- 5- Ata B, Tulandi T. Reassurance of safety of letrozole and suggested approaches in controlled ovarian hyperstimulation. *Fertil Steril.* 2009 Jul;92(1):e6.
- 6- Oktay K, Buyuk E, Libertella N, Akar M, Rosenwaks Z. Fertility preservation in breast cancer patients: a prospective controlled comparison of ovarian stimulation with tamoxifen and letrozole for embryo cryopreservation. *J Clin Oncol.* 2005 Jul 1;23(19):4347-53.
- 7- Oktay K, Türkçüoğlu I, Rodriguez-Wallberg KA. GnRH agonist trigger for women with breast cancer undergoing fertility preservation by aromatase inhibitor/FSH stimulation. *Reprod Biomed Online* 2010 Jun;20(6):783-8.
- 8- Robertson AD, Missmer SA, Ginsburg ES. Embryo yield after in vitro fertilization in women undergoing embryo banking for fertility preservation before chemotherapy. *Fertil Steril.* 2011 Feb;95(2):588-91.
- 9- Cardozo ER, Thomson AP, Karmon AE, Dickinson KA, Wright DL, Sabatini ME. Ovarian stimulation and in-vitro fertilization outcomes of cancer patients undergoing fertility preservation compared to age matched controls: a 17-year experience. *J Assist Reprod Genet.* 2015 Apr;32(4):587-96.
- 10- Alvarez RM, Ramanathan P. Fertility preservation in female oncology patients: the influence of the type of cancer on ovarian stimulation response. *Hum Reprod.* 2016 Jul 1. pii: dew158. [Epub ahead of print]
- 11- Kroman N, Jensen MB, Wohlfahrt J, Ejlersen B; Danish Breast Cancer Cooperative Group. Pregnancy after treatment of breast cancer--a population-based study on behalf of Danish Breast Cancer Cooperative Group. *Acta Oncol.* 2008;47(4):545-9.
- 12- Azim HA Jr, Santoro L, Pavlidis N, Gelber S, Kroman N, Azim H, Peccatori FA. Safety of pregnancy following breast cancer diagnosis: a meta-analysis of 14 studies. *Eur J Cancer.* 2011 Jan;47(1):74-83.
- 13- Hartman EK, Eslick GD. The prognosis of women diagnosed with breast cancer before, during and after pregnancy: a meta-analysis. *Breast Cancer Res Treat.* 2016 Nov;160(2):347-360.
- 14- Sankila R, Heinävaara S, Hakulinen T. Survival of breast cancer patients after subsequent term pregnancy: "healthy mother effect". *Am J Obstet Gynecol.* 1994 Mar;170(3):818-23
- 15- Armuand GM, Wettergren L, Rodriguez-Wallberg KA, Lampic C. Women more vulnerable than men when facing risk for treatment-induced infertility: a qualitative study of young adults newly diagnosed with cancer. *Acta Oncol.* 2015 Feb;54(2):243-52.