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Commentary

Temporary Ovarian Suppression With Gonadotropin-Releasing Hormone Agonist During Chemotherapy for Fertility Preservation: Toward the End of the Debate?

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Disclosures of potential conflicts of interest may be found at the end of this article.

In this issue of ***The Oncologist***, Blumenfeld et al. present encouraging data on the efficacy of temporary ovarian suppression with gonadotropin-releasing hormone agonist (GnRHa) during chemotherapy as a strategy to preserve not only ovarian function but also fertility in young patients with different types of diseases undergoing cytotoxic therapy [1]. In this retrospective cohort study, the fertility outcomes (i.e., cyclic ovarian function recovery and pregnancies after chemotherapy) of 286 patients who received GnRHa during cytotoxic therapy were compared with those of 188 women who underwent chemotherapy alone [1]. Among evaluable patients, more patients in the GnRHa group resumed cyclic ovarian function after chemotherapy than patients receiving chemotherapy alone (87% vs 49%; odds ratio [OR]: 6.87; $p = .0001$) [1]. A total of 85 patients (69.7%) conceived in the GnRHa group compared with 28 (42.4%) in the control group ($p = .0003$), resulting in 124 and 40 newborns ($p < .01$), respectively [1]. Spontaneous pregnancies occurred in 80 women (65.6%) in the GnRHa group and 25 (37.9%) in the control group (OR: 3.12; $p = .0004$) [1].

Premature ovarian failure (POF) and subsequent infertility are possible consequences of chemotherapy and are associated with substantial psychosocial impact in young cancer patients. In recent years, because of improvement in the prognosis of cancer survivors, fertility issues have received increasing attention [2].

As recommended by major international guidelines and as early as possible, physicians should discuss the potential negative impact of anticancer treatments on fertility with all young patients who are at risk of infertility and interested in having children after cancer and help with informed fertility preservation decisions [3, 4]. In female cancer patients, cryopreservation of embryos or oocytes are standard strategies for fertility preservations, whereas other options (e.g., ovarian tissue cryopreservation and temporary ovarian suppression with GnRHa during chemotherapy) are considered experimental techniques [3, 4].

Pharmacological protection of the ovaries with GnRHa during chemotherapy is an attractive option to preserve gonadal function and fertility with the advantage of causing no delay in the initiation of anticancer therapies and the wide availability of such compounds [5]. Nevertheless, despite extensive research efforts in this field consisting of several randomized trials and meta-analyses, there is still active debate in the literature on the efficacy of this strategy [6]. In particular, the lack of data on pregnancy rates with the use of this strategy has been considered an important limitation, and the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) do not recommend the use of GnRHa-induced temporary ovarian suppression during chemotherapy as a reliable strategy to preserve fertility in young patients undergoing cytotoxic therapy [3, 4]. However, more than 2 years have passed since the publication of the ASCO and ESMO clinical practice guidelines on fertility preservation in cancer patients, and new data in this field have become available.

Temporary ovarian suppression with GnRHa during chemotherapy has been studied as a strategy to preserve ovarian function rather than as an option for fertility preservation [7]; however, the recovery of cyclic ovarian function after chemotherapy does not always imply fertility restoration. A growing amount of evidence suggests the possible utility of this technique to preserve fertility, particularly in patients with breast cancer.

In a prospective observational study conducted at the Royal Marsden Hospital Breast Unit in London (U.K.), of 125 consecutive breast cancer patients undergoing concurrent GnRHa and chemotherapy, 104 (84%) recovered menstruation [8]. Among the 57 patients (46%) who were interested in getting pregnant, 42 (74%) attempted pregnancy, and 30 of those patients (71% of those who attempted pregnancy) achieved pregnancy [8]. At the time of the analysis, a total of 42 pregnancies with 30 healthy deliveries were described [8].

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In the past year, two large randomized trials evaluating the efficacy of temporary ovarian suppression with GnRHa during chemotherapy in breast cancer patients have reported promising data on fertility outcomes [9, 10]. The POEMS-SWOG S0230 study enrolled only women with endocrine-insensitive breast cancer [9], whereas the majority of patients in the PROMISE-GIM6 study had hormone receptor-positive disease and received adjuvant endocrine therapy for at least 5 years after the end of chemotherapy [10, 11]. Both trials showed a statistically significant reduction in the incidence of treatment-related POF (i.e., the primary endpoint of the studies) in patients receiving GnRHa, with a 72% reduced risk at 1 year after the end of chemotherapy in the PROMISE-GIM6 trial (OR: 0.28; $p < .001$) [11] and a 70% reduced risk at 2 years after the end of cytotoxic therapy in the POEMS-SWOG S0230 study (OR: 0.30; $p = .04$) [9]. Moreover, both trials reported more patients achieving pregnancy among those receiving concurrent GnRHa and chemotherapy compared with women receiving chemotherapy alone: 8 versus 3, respectively, in the PROMISE-GIM6 trial (hazard ratio [HR]: 2.56; $p = .142$) [10] and 22 versus 12, respectively, in the POEMS-SWOG S0230 study (OR: 2.45; $p = .03$) [9].

A recent meta-analysis assessing the role of temporary ovarian suppression with GnRHa during chemotherapy in preserving ovarian function and fertility of breast cancer patients confirmed the efficacy of the procedure on both endpoints [12]. The use of GnRHa was associated with a significant reduced risk of POF (OR: 0.36; $p < .001$) and a significantly increased number of patients achieving pregnancy (33 vs. 19 women; OR: 1.83; $p = .041$) [12].

More limited data are available on patients with lymphoma; however, in the German Hodgkin Study Group HD14 study, concurrent use of GnRHa and chemotherapy was associated with a significant increased probability of becoming pregnant in patients with Hodgkin lymphoma (OR: 12.87; $p = .001$) [13].

The study by Blumenfeld et al., including mainly patients with lymphoma, confirmed the potential efficacy of GnRHa during chemotherapy in preserving not only ovarian function (OR for preserving cyclic ovarian function: 6.87; $p = .0001$) but also fertility (OR for spontaneously conceiving: 3.12; $p = .0004$) [1].

A very interesting finding from the studies described is the high pregnancy rate reported. In the study by Wong et al., of 42 patients who tried to become pregnant, 30 (71%) achieved pregnancy [8]. In the chemotherapy plus GnRHa arm of the POEMS-SWOG S0230 study, 25 patients declared attempting pregnancy, and 22 (88%) achieved pregnancy [9]. In the study by Blumenfeld et al., 69.7% of patients conceived after chemotherapy [1]. These findings confirm the importance of maintaining fertility of young cancer patients who are candidates to receive gonadotoxic therapies. Approximately 50% of cancer patients desire pregnancy at the time of cancer diagnosis [14]; however, female cancer survivors have lower fecundity rates than the general population [15]. Maximum efforts to refer patients to fertility specialists should be made by treating physicians to give women the chance of undergoing available fertility-preserving procedures before the initiation of systemic anticancer treatments.

The results of Blumenfeld et al. add new insight into the potential role of GnRHa as a fertility-preserving strategy; however, these encouraging results should be considered with caution because of some study limitations. Being a retrospective cohort study, it was prone to bias and confounding by definition. Moreover, more patients enrolled in the GnRHa cohort than in the chemotherapy-alone group were diagnosed with Hodgkin lymphoma (48.4% vs. 31.8%); these women are generally young and treated with doxorubicin/bleomycin/vinblastine/dacarbazine (ABVD regimen) chemotherapy, a regimen with low sterilizing potential [16]. In this situation, the risk of treatment-related infertility is not very high, and the majority of these women might have achieved subsequent pregnancy regardless of any fertility-preserving option used.

In conclusion, the findings of the study by Blumenfeld et al. are consistent with recent data suggesting the efficacy of GnRHa-induced temporary ovarian suppression during chemotherapy in preserving fertility. To date, in addition to standard techniques for fertility preservation in cancer patients (i.e., cryopreservation of embryos and oocytes) [3, 4], temporary ovarian suppression with GnRHa during chemotherapy might be considered a reliable strategy not only to preserve ovarian function but also to increase the likelihood of becoming pregnant after the end of cytotoxic therapy.

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References

1. Blumenfeld Z, Zur H, Dann EJ. Gonadotropin releasing hormone agonist cotreatment during chemotherapy may increase pregnancy rate in survivors. ***The Oncologist*** 2015;20:1283–1289.

2. De Vos M, Smitz J, Woodruff TK. Fertility preservation in women with cancer. Lancet 2014; 384:1302–1310.

3. Loren AW, Mangu PB, Beck LN et al. Fertility preservation for patients with cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 2013;31:2500–2510.

4. Peccatori FA, Azim HA Jr, Orecchia R et al. Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013;24(suppl 6): vi160–vi170.

5. Lambertini M, Ginsburg ES, Partridge AH. Update on fertility preservation in young women undergoing breast cancer and ovarian cancer therapy. Curr Opin Obstet Gynecol 2015;27:98–107.

6. Lambertini M, Poggio F, Levaggi A et al. Protecting ovaries during chemotherapy through gonad suppression: A systematic review and meta-analysis. Obstet Gynecol 2015;126:901.

7. Tomasi-Cont N, Lambertini M, Hulsbosch S et al. Strategies for fertility preservation in young

early breast cancer patients. Breast 2014;23: 503–510.

8. Wong M, O'Neill S, Walsh G et al. Goserelin with chemotherapy to preserve ovarian function in premenopausal women with early breast cancer: Menstruation and pregnancy outcomes. Ann Oncol 2013; 24:133–138.

9. Moore HCF, Unger JM, Phillips K-A et al. Goserelin for ovarian protection during breast-cancer adjuvant chemotherapy. N Engl J Med 2015;372:923–932.

10. Lambertini M, Boni L, Michelotti A et al. Long-term outcome results of the phase III PROMISE-GIM6 study evaluating the role of LHRH analog (LHRHa) during chemotherapy (CT) as a strategy to reduce ovarian failure in early breast cancer (BC) patients. J Clin Oncol 2014;32:105a.

11. 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; 306:269–276.

12. Lambertini M, Ceppi M, Poggio F et al. Ovarian suppression using luteinizing hormone-releasing hormone agonists during chemotherapy to preserve ovarian function and fertility of breast cancer patients: A meta-analysis of randomized studies. Ann Oncol 2015 [Epub ahead of print].

13. Behringer K, Thielen I, Mueller H et al. Fertility and gonadal function in female survivors after treatment of early unfavorable Hodgkin lymphoma (HL) within the German Hodgkin Study Group HD14 trial. Ann Oncol 2012;23: 1818–1825.

14. Letourneau JM, Ebbel EE, Katz PP et al. Pretreatment fertility counseling and fertility preservation improve quality of life in reproductive age women with cancer. Cancer 2012;118: 1710–1717.

15. Stensheim H, Cvancarova M, Møller B et al. Pregnancy after adolescent and adult cancer: A population-based matched cohort study. Int J Cancer 2011;129:1225–1236.

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

EDITOR'S NOTE: See the related article, "Gonadotropin-Releasing Hormone Agonist Cotreatment During Chemotherapy May Increase Pregnancy Rate in Survivors," on page 1283 of this issue.

For Further Reading:
Jeong-Yeol Park, Joo-Hyun Nam. Progestins in the Fertility-Sparing Treatment and Retreatment of Patients With Primary and Recurrent Endometrial Cancer. ***The Oncologist*** 2015;20:270-278.

Implications for Practice:
In young women with endometrial cancer, the cure rate is very high. Therefore, the efficacy of treatment should not be limited to the oncologic outcomes. The quality-of-life issue is as important as oncologic outcomes in these patients. Fertility preservation is one of the most important quality-of-life issues. Based on the results of numerous studies, fertility-sparing progestin therapy can be safely performed in endometrioid adenocarcinoma confined to the endometrium. It also can be reasonably recommended to selected women with more advanced disease and recurrent disease. However, careful follow-up is important because of the high rate of recurrence.