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Editorial

EDITORIAL

Gonadotropin-Releasing Hormone (GnRH) Agonists for Fertility Preservation: Is POEMS the Final Verse?

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The detrimental effect of chemotherapy on ovarian function and fertility is widely recognized. All current oncology practice guidelines recommend that oncologists address this issue in female cancer patients of reproductive age and refer interested patients to reproductive specialists as soon as possible after cancer diagnosis. Standard fertility preservation methods including embryo or oocyte cryopreservation are available in most fertility centers with assisted reproductive technologies laboratories. Ideally, cryopreservation of embryos or oocytes should be performed before the start of gonadotoxic cancer treatment. However, with limited insurance coverage in most states for fertility treatments, fertility preservation using assisted reproductive technologies is not a financially viable option for many patients, especially in the face of a new cancer diagnosis. Also, for some cancers such as acute leukemia, a two- to three-week delay in starting life-saving cancer treatment in exchange for fertility preservation and the higher risks associated with oocyte retrieval in the setting of pancytopenia are not acceptable. In addition, preserving embryos or gametes does not protect ovaries from damage by gonadotoxic cancer treatment, and premature ovarian insufficiency/failure or early menopause has adverse effects on subsequent cardiovascular, bone, and mental health. Therefore, much effort has been devoted to finding measures that may preserve both fertility and ovarian function and are financially and medically feasible for all patients. GnRH agonists (GnRHa) have shown promise in this regard.

Most, but not all, of the 10 randomized control trials (RCTs), 12 meta-analyses, and many observational studies conducted to date [summarized in (1)] have demonstrated a protective effect of GnRHa on ovarian reserve, especially in breast cancer patients, using surrogate markers such as menstrual resumption or regularity and random serum follicle-stimulating hormone (FSH) or anti-müllerian hormone levels. Unfortunately, these surrogate markers correlate poorly with fertility or the ability to achieve pregnancy. The ultimate measure for fertility preservation is pregnancy outcome, namely live birth rate in patients who attempt pregnancies. However, because of the small number of reproductive-age women who actively pursue pregnancy after cancer diagnosis and treatment and a lack of long-term follow-up of these women, the data on pregnancy outcomes are quite limited.

In this issue of the Journal, Moore et al. (2) add to our knowledge about whether GnRHa preserves fertility in breast cancer patients during adjuvant chemotherapy through a secondary analysis of the Prevention of Early Menopause Study (POEMS)/SWOG trial focused on self-reported pregnancy rates. This trial randomly assigned and evaluated 218 premenopausal women with stage I-IIIA estrogen and progesterone receptor–negative breast cancer treated with adjuvant cyclophosphamide-containing chemotherapy to receive concurrent goserelin or not. With 5-year follow-up, a higher number of pregnancies was reported in the chemotherapy plus goserelin arm than the chemotherapy only arm (5-year cumulative incidence 23.1%, 95% confidence interval [CI] = 15.3% to 31.9%, and 12.2%, 95% CI = 6.8% to 19.2%, respectively; odds ratio = 2.34; 95% CI = 1.07 to 5.11; $P = .03$). No adverse effect on disease-related outcomes was observed although the study was underpowered for survival outcomes.

Five other randomized trials of GnRHa in breast cancer and one in lymphoma have reported information about numbers of pregnancies (3–8). Ovarian function protection was the most common primary outcome for these trials and observed pregnancies were reported as an incidental finding. The POEMS reported its primary outcome, ovarian failure two years after randomization, in 2015, and GnRHa showed a protective effect. Ovarian failure rate was 8% in the chemotherapy plus goserelin group and 22% in the chemotherapy-alone group with an odds ratio of 0.30 (95% CI = 0.09 to 0.97; two-sided $P = .04$) (9). However, unlike the other trials, POEMS included pregnancy and pregnancy attempts in the study design, and information

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on pregnancy outcomes was collected annually. This is the only trial that has shown a statistically significant improvement in pregnancy rate with GnRHa use during chemotherapy, perhaps in part because of its high number of evaluable patients, preplanned effort, and relatively long follow-up period. Most pregnancies occurred at least two years after start of cancer treatment, so the short follow-up period in some other trials would be insufficient to observe pregnancy outcomes.

Nonetheless, major limitations exist with this report (2), some of which were acknowledged by the authors. The most important limitation is lack of data on pregnancy intent. Pregnancies are more likely to occur in patients who are off birth control and attempt regular or timed intercourse or seek fertility treatments. The actual fertility preservation effect of GnRHa cannot be reliably estimated without knowing how many patients in each group actively pursued pregnancy or at least did not use contraception. It is possible that the patients in the GnRHa group had a higher rate of menstrual resumption and therefore sought to become pregnant. Detailed data on fertility treatments, pregnancy history, and baseline fertility evaluations were not obtained, all of which could markedly affect the observed pregnancy rate. Finally, self-reporting without obstetric confirmation can lead to bias. Because some biochemical pregnancies and early losses may be related to poor oocyte quality or declined fertility, live birth rate rather than pregnancy rate would be a more accurate measure of fertility protection effect.

Several guidelines have endorsed use of GnRHa as a routine fertility preservation method during adjuvant breast cancer treatment. Some have limited its use to estrogen receptor–negative breast cancer (10, 11), whereas others have not (12–14), given the results of the TEXT trial which show excellent breast cancer outcomes with use of chemotherapy plus GnRHa followed by GnRHa plus tamoxifen or aromatase inhibitor in premenopausal hormone receptor–positive breast cancer patients (15). Three current guidelines do not recommend GnRHa as a reliable means to preserve fertility (16–18).

So does the POEMS trial (2) resolve the controversy of the ovarian and fertility preservation effect of GnRHa, or do more verses need to be composed? In our view, ovarian function protection and fertility preservation are two separate but related issues. GnRHa has been shown to exert some protective effect on ovarian function in most studies including the POEMS trial, and therefore should be routinely discussed with premenopausal breast cancer patients for the purpose of decreasing risks of premature ovarian insufficiency after cancer treatment. However, the use of GnRHa as a means for fertility preservation should only be considered as an alternate strategy at this time. Embryo or oocyte cryopreservation before initiation of chemotherapy is still the most reliable strategy to preserve fertility. If this is not feasible because of medical, financial, or religious considerations, GnRHa can be discussed as an approach that may afford imperfect fertility benefits through potential ovarian protection effects in breast cancer patients of any receptor type, but the limitations of our understanding should be carefully communicated. The protective effect of GnRHa on both fertility and ovarian function in women with other types of cancers and cytotoxic therapies warrants further investigation. If future trials are to be undertaken to provide a definitive answer for the fertility preservation effect of GnRHa, a well-designed, adequately powered, randomized trial with long-term follow-up that controls for important confounding factors that can affect pregnancy and reports live birth rates as the primary outcome will be needed.

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References

1. Lambertini M, Del Mastro L, Pescio MC, et al. Cancer and fertility preservation: international recommendations from an expert meeting. *BMC Med*. 2016;14:1.
2. Moore HCF, Unger JM, Phillips K-A, et al. Final analysis of the Prevention of Early Menopause Study (POEMS)/SWOG Intergroup S0230. *J Natl Cancer Inst*. 2018;111(2):210–213.
3. Demeestere I, Brice P, Peccatori FA, et al. No evidence for the benefit of gonadotropin-releasing hormone agonist in preserving ovarian function and fertility in lymphoma survivors treated with chemotherapy: Final long-term report of a prospective randomized trial. *J Clin Oncol*. 2016;34(22):2568–2574.
4. Elgindy EA, El-Haieg DO, Khorshid OM, et al. Gonadatrophin suppression to prevent chemotherapy-induced ovarian damage: a randomized controlled trial. *Obstet Gynecol*. 2013;121(1):78–86.
5. Leonard RCF, Adamson DJA, Bertelli G, et al.; Anglo Celtic Collaborative Oncology G, National Cancer Research Institute T. GnRH agonist for protection against ovarian toxicity during chemotherapy for early breast cancer: yhe Anglo Celtic Group OPTION trial. *Ann Oncol*. 2017;28(8):1811–1816.
6. 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(5):533–538.
7. Gerber B, von Minckwitz G, Stehle H, et al. Effect of luteinizing hormone-releasing hormone agonist on ovarian function after modern adjuvant breast cancer chemotherapy: the GBG 37 ZORO study. *J Clin Oncol*. 2011;29(17):2334–2341.
8. Lambertini M, Boni L, Michelotti A, et al. Ovarian suppression with triptorelin during adjuvant breast cancer chemotherapy and long-term ovarian function, pregnancies, and disease-free survival: a randomized clinical trial. *JAMA*. 2015;314(24):2632–2640.
9. Moore HC, Unger JM, Phillips KA, et al. Goserelin for ovarian protection during breast-cancer adjuvant chemotherapy. *N Engl J Med*. 2015;372(10):923–932.
10. Coates AS, Winer EP, Goldhirsch A, et al. Tailoring therapies—improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. *Ann Oncol*. 2015;26(8):1533–1546.
11. Munoz M, Santaballa A, Segui MA, et al. Clinical guideline of fertility preservation and reproduction in cancer patients (2016). *Clin Transl Oncol*. 2016;18(12):1229–1236.
12. Paluch-Shimon S, Pagani O, Partridge AH, et al. Second international consensus guidelines for breast cancer in young women (BCY2). *Breast*. 2016;26:87–99.
13. Lambertini M, Cinquini M, Moschetti I, et al. Temporary ovarian suppression during chemotherapy to preserve ovarian function and fertility in breast cancer patients: a GRADE approach for evidence evaluation and recommendations by the Italian Association of Medical Oncology. *Eur J Cancer*. 2017;71:25–33.
14. National Comprehensive Cancer Network Guidelines – Breast Cancer. 2017. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed September 7, 2018.
15. Francis PA, Pagani O, Fleming GF, et al. Tailoring adjuvant endocrine therapy for premenopausal breast cancer. *N Engl J Med*. 2018;379(2):122–137.
16. Oktay K, Harvey BE, Partridge AH, et al. Fertility preservation in patients with cancer: ASCO Clinical Practice Guideline update. *J Clin Oncol*. 2018;36(19):1994–2001.
17. 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.
18. National Comprehensive Cancer Network Guidelines – Adolescent and Young Adult (AYA) Oncology. 2017. https://www.nccn.org/professionals/physician_gls/pdf/aya.pdf. Accessed September 7, 2018.