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Can ovarian suppression with gonadotropin-releasing hormone analogs (GnRHa) preserve fertility in cancer patients?

In a meta-analysis of 12 randomized controlled trials (RCTs) including those presented at major meetings, Lambertini et al. concluded that gonadotropin-releasing hormone analogs (GnRHa) co-treatment during chemotherapy reduces premature ovarian failure (POF) and increases pregnancy rate without impacting disease-free-survival (DFS) in women with breast cancer [1]. As fertility specialists and oncologists, we have several concerns with this interpretation.

Lack of information on hormonal and chemotherapy treatments in some studies and heterogeneity of treatments in remainder of the selected studies challenge interpretation. As noted, menstruation is a highly unreliable surrogate for ovarian reserve and women experiencing POF more frequently present with irregular menstruation than amenorrhea. Tamoxifen treatment can affect menstrual regularity, further confounding the interpretation of menses resumption. Because none of the studies were blinded or placebo controlled, those who received GnRHa may be more likely to interpret any bleeding as normal menstruation. The definition of 1-year amenorrhea applies to natural menopause; whereas POF is determined by follicle stimulating hormone (FSH) levels of >40 mIU/ml. The only study using this criterion did not find GnRHa to be protective in lymphoma patients [2]. The small number of pregnancies and lack of comparison of the fertility rates among those who are attempting makes any conclusions regarding fertility preservation (FP) refutable with this approach. Analysis of the data based on the quality of evidence by categorization of the studies with quantified ovarian reserve markers and defined POF criteria does not support any benefit from GnRHa [3].

The current meta-analysis limited itself to breast cancer citing the possibility of ovarian function being affected by hematological cancers. While compromised wellbeing may affect late follicle development, it does not influence primordial follicle reserve, and there is no biological rationale to assume that cytotoxic agents should differentially affect the ovaries of hematological cancer patients. A recent meta-analysis which included all RCTs regardless of the cancer diagnosis did not find benefit for GnRHa based on resumption of periods at the longest follow-up, FSH, anti-müllerian hormone or antral follicle counts [4]. GnRHa treatment has already proved ineffective for FP in men, despite the highly hormone-dependent nature of spermatogenesis. Given the lack of biological plausibility and a proven mechanism of effect due to absence of FSH receptors on primordial follicles, and significant heterogeneity of the criteria and quality among the available studies, women should be primarily counseled on the availability of proven FP options such as oocyte, embryo and ovarian tissue cryopreservation.

Finally, none of the studies were adequately powered to determine the impact of short-term GnRHa during chemotherapy on DFS. Even if we assume a small benefit on menstruation from GnRHa, NSAABBP-B30 trial suggested that prolonged amenorrhea results in improved breast cancer specific outcomes among estrogen receptor (ER)+ women. Large randomized studies showed that prolonged, not short-term, ovarian suppression/ablation improves DFS for young women with high-risk ER+ disease [5]. This would also mean further compounding from age-related decline in fertility or ovarian ablation, and underscores the importance of FP before initiating chemotherapy. Given the foregoing, we conclude that ovarian suppression should remain as an unproven method of FP.

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disclosure

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