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Utility of Gonadotropin-Releasing Hormone Agonists for Fertility Preservation: Lack of Biologic Basis and the Need to Prioritize Proven Methods

TO THE EDITOR:

We read the meta-analysis by Lambertini et al[1] and the accompanying editorial.[2] We have concerns about the methodology and the interpretation of the data.

The meta-analysis was limited to five randomized trials of women with breast cancer, which make up less than 50% of all randomized controlled trials, so the analysis disproportionately represents those trials with positive results. Moreover, the restriction of this meta-analysis to breast cancer does not have biologic basis, because similar chemotherapeutics are also used in hematologic malignancies.[3-5] Given that the randomized studies in hematologic cancers have been negative, their exclusion creates a selection bias. Studies in hematologic cancers are easier to interpret, because no adjuvant endocrine therapy that affects ovarian function, such as tamoxifen, is used.

Furthermore, anti-Müllerian hormone (AMH) is the most reliable serum marker of ovarian reserve, and levels do not largely fluctuate during menstrual cycle. Randomized controlled trials that used AMH did not find benefit of a gonadotropin-releasing hormone agonist (GnRHa) in ovarian preservation. These trials were the OPTION (Ovarian Protection Trial In Premenopausal Breast Cancer Patients) trial, which was included in the current meta-analysis, and several other trials that were excluded from the current meta-analysis.[4,5]

Another shortcoming of this meta-analysis is that each included study had its own definition of ovarian insufficiency, and the meta-analysis did not standardize the diagnosis criteria. For example, in the OPTION trial, researchers[1] used a single follicle-stimulating hormone (FSH) value of greater than 25 mUI/mL, but accepted criteria for premature ovarian insufficiency is FSH levels greater than 30 to 40 mIU/mL on two separate occasions. Furthermore, the serum estradiol and FSH levels are cycle-day dependent, and they were randomly measured in studies that were included in the meta-analysis.

The meta-analysis analyzed true individual patient data for amenorrhea and showed similar incidences in the GnRHa and the control groups at 1 year. The data robustly represented 87.1% of all patients, in contrast to the 2-year time point, when the representation was less than 50%. Because it takes approximately 4 to 6 months for surviving primordial follicles to grow and produce hormones that result in menstruation, any benefit from GnRHa would be reflected in the 6- to 12-month menstruation assessment. Therefore, there is no biologic rationale for using 2-year amenorrhea rates to assess the effectiveness of GnRHa in preservation of ovarian reserve.

Post-treatment pregnancy information was available for 83.2% patients in the meta-analysis. However, the pregnancy intent was known in one trial, in which the fertility preservation was a preplanned secondary end point. Because the trials were not blinded or placebo controlled, treatment assignment could have influenced the desire to attempt pregnancy. In fact, there was a trend for higher intent in the study by Moore et al[6]; when analysis was controlled for this trend, no statistical difference in pregnancy rates between the GnRHa and control groups was found. The current meta-analysis did not adjust fertility rates for pregnancy intent, duration and number of attempts, or use of assisted reproductive technology procedures. Moreover, the fact that there were no pregnancies in women older than 40 years of age, when chemotherapy would have had the most important impact on ovarian reserve, raises additional doubts about the effectiveness of GnRHa in preservation of fertility.

Also, the biologic rationale for fertility preservation by GnRHa is lacking, because primordial follicles, which make up the ovarian reserve, are hormonally insensitive (Fig 1).[7] We previously showed that gonadotoxic chemotherapy destroys ovarian germ cells by inducing severe DNA damage in both mouse and human ovary.[8] In a follow-up study, we showed that GnRHa coadministration did not prevent chemotherapy-induced primordial follicle DNA damage and apoptotic death.[9] Furthermore, it is often impossible to achieve full ovarian suppression within the short time before the initiation of chemotherapy.[10] Additional data support the lack of plausibility: although male germ cells are similarly affected by gonadotoxic chemotherapeutics, GnRH suppression has been ineffective in male fertility preservation.[10]

Some researchers hypothesize that GnRHa may still antagonize the ovarian cytotoxicity of chemotherapeutics through unknown mechanisms. If this were true, GnRHa would likely reduce the overall effectiveness of chemotherapy. The current meta-analysis presented solid data that the concurrent GnRHa treatment does not impair survival, which we also interpret as additional evidence for its ineffectiveness against cytotoxicity in germ cells. Others may argue that, if there is no harm, one can use a GnRHa just in

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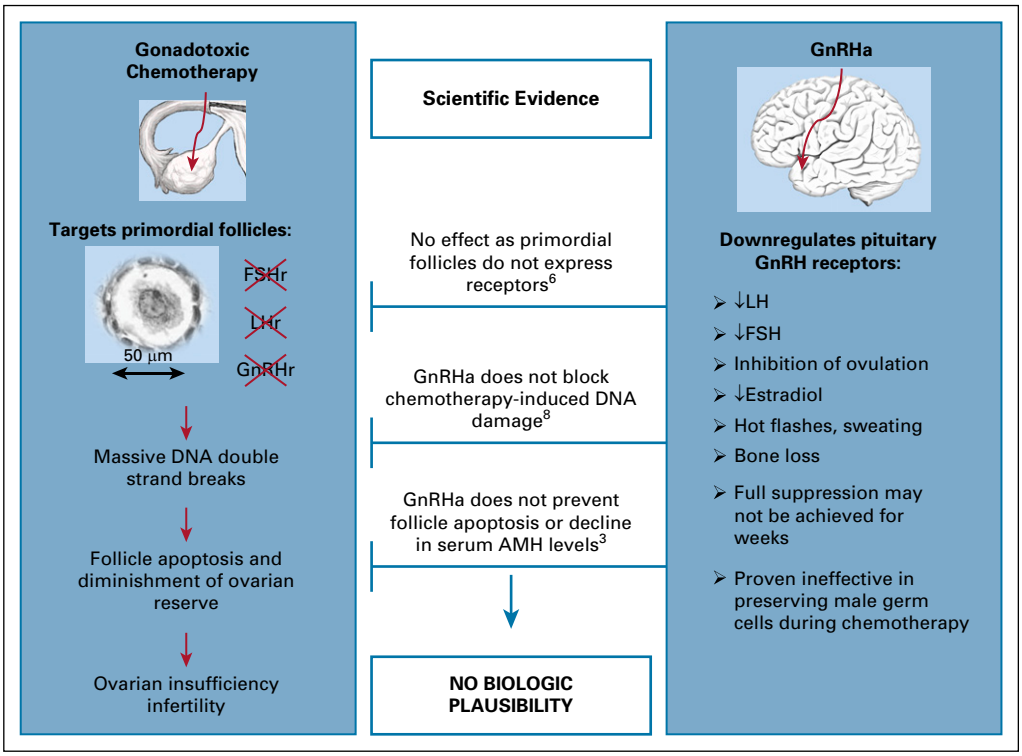

FIG 1. Lack of biologic plausibility. Gonadotoxic chemotherapy reduces ovarian reserve, which is made up of resting and hormone-insensitive primordial follicles, by induction of DNA double-strand breaks and apoptotic death in oocytes.[7] The gonadotropin-releasing hormone (GnRH) agonist (GnRHa) reduces pituitary GnRH production; as a result, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) release from the pituitary, which in turn stops late-stage follicle development. Because primordial follicles do not have FSH, LH, or GnRH receptors (FSHr, LHr, or GnRHr, respectively), GnRHa cannot have a direct influence on ovarian reserve.[6] Laboratory and clinical studies also show that GnRHa coadministration does not prevent DNA damage, apoptosis, or ovarian reserve reduction, as determined by serum anti-Müllerian hormone (AMH) levels, induced by gonadotoxic chemotherapy.[3,4] Similarly, GnRHa suppression has been proven to be clinically ineffective in the preservation of testicular function against chemotherapy-induced damage.

case. Such an approach is not justified when effective options are widely available. GnRHa preparations not only are costly but also result in adverse effects that impair quality of life, as this meta-analysis showed, as well as irreversible bone loss with long-term use.

On the basis of the foregoing assessment, the ASCO expert panel did not recommend ovarian suppression for fertility preservation in its recent update of the Fertility Preservation Guidelines. The panel emphasized the importance of prioritizing proven methods, such as the embryo, oocyte, or ovarian tissue freezing.[11]

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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