Commentary: Ovarian Function Does Not Equal Fertility Does Not Equal Babies

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In the debate about preserving fertility for patients treated with chemotherapy, more is known about inducing gonadal toxicity than is known about avoiding gonadal toxicity. Controversy over how best to advise patients facing a medical decision will commonly occur when inadequate data are available on which to base a sound opinion. The debate becomes passionate when emotionally charged issues such as cancer and fertility preservation are involved, as evidenced by the two reviews in this issue of The Oncologist [1, 2].

Premature ovarian failure is the most common significant long-term toxicity of chemotherapy in premenopausal women. While chemotherapy-induced ovarian ablation is potentially beneficial for some individuals, such as those with hormone receptor–positive breast cancer, it is an unwanted side effect for others. Adverse consequences of premature menopause include hot flashes, mood changes, genitourinary dysfunction, osteoporosis, and infertility.

The choices of chemotherapy drug, dose, duration, and schedule are important risk factors for gonadal failure. Alkylating agents are well known to result in ovarian failure, but anthracyclines and taxanes contribute as well [3, 4]. The age of the patient at exposure to the drug also affects ovarian function outcome. The younger the patient and the lower the dose of exposure, the greater the potential for preserving ovarian function. It is important to note, however, that preservation of ovarian function does not equal fertility, which in turn may not result in live births. Potential interventions to preserve ovarian function and/or fertility have not yet been subjected to rigorous scientific assessment. For patients strongly desiring preservation of fertility or ovarian function, the debate centers on whether it is appropriate to offer gonadotropin-releasing hormone (GnRH) analogue coadministration with curative-intent chemotherapy outside of a clinical trial.

Based on biologic plausibility and clinical data from single-arm or suboptimally controlled studies, Blumenfeld [1] supports the potential for cotreatment with a GnRH analogue and chemotherapy to reduce the gonadal toxicity of chemotherapy. On the other hand, Oktay et al. [2] point out the failure of these studies to demonstrate superior fertility with GnRH analogue coadministration. Furthermore, Oktay et al. [2] discuss mechanisms whereby GnRH analogue cotreatment might be not only ineffective, but also potentially detrimental to ovarian function. Both papers support participation in ongoing randomized clinical trials assessing this method for ovarian function preservation.

Oktay et al. [2] offer three requirements “for a new medical treatment to be proven effective.” The authors then provide a rationale to support their view that GnRH analogues do not meet these criteria. Certainly, there are no prospective, randomized, controlled trials showing consistent preservation of ovarian function during and after chemotherapy exposure (point 2). Oktay et al. [2] question the plausibility of GnRH analogues to have the desired effect of protecting the ovaries from cytotoxic agents. In the presentation of their detailed analysis it becomes clear that most, if not all, studies of GnRH analogue coadministration with chemo-
therapy to date have lacked appropriate endocrine assessments of ovarian function and detailed menstrual histories. These flaws, in addition to other design issues (sample size, endpoint variability, lack of appropriate controls, varied treatment regimens, and the broad age range of participants), make interpretation and application of the study results impractical.

Whether the “potential risks of treatment exceed the potential benefits” is potentially testable in a clinical trial. But risks must be precisely defined and relevant potential benefits accrued to study participants and those they represent must be established. If the desired benefit is pregnancy, studies must include this as an endpoint. In terms of risks to intervention, Oktay et al. [2] cite safety concerns as a major reason for discouraging GnRH analogue administration for ovarian protection. It must be pointed out, however, that any of the invasive assisted-reproduction techniques also carry potential safety concerns, particularly in women with hormone-sensitive cancers. Although ovarian stimulation for oocyte collection performed with an aromatase inhibitor plus gonadotropin treatment results in estradiol levels that are lower than those observed with standard in vitro fertilization (IVF) techniques, these levels remain quite high and supraphysiologic [5]. It is understood, however, that some patients will choose to expose themselves to some degree of risk, whether known or theoretical, for the possibility of gain even if benefit cannot be guaranteed.

Blumenfeld [1] argues for the safety and efficacy of GnRH analogue coadministration for preservation of ovarian function and cites 33 patients who have conceived “spontaneously” 46 times. He also proposes five potential explanations for the beneficial effects of GnRH analogue coadministration for minimizing gonadal toxicity of chemotherapy. Explanation I does not appear to be testable in a clinical trial setting. Testing for utero-ovarian perfusion (explanation II) also seems to be a feverous endpoint for clinical trial testing. Similarly, explanations III–V do not seem like endpoints for human subject research. The explanations, however, do offer theoretical grounds for the study of GnRH analogue use for the purpose of fertility preservation.

While both papers provide compelling arguments as to why GnRH analogue cotreatment with chemotherapy may or may not preserve fertility and/or ovarian function, it is the clinical results observed that best support or refute the efficacy of the intervention. In general, the reported studies suggest that rates of preservation of menstrual function are high among female patients cotreated with a GnRH analogue and chemotherapy, while the more limited findings addressing pregnancy outcomes remain disappointing. While theoretical concerns of risk persist, to date, there are no compelling clinical data to support a harmful effect of GnRH analogue cotreatment with chemotherapy on either cancer outcome or pregnancy outcome.

The authors find common ground in accepting IVF with embryo cryopreservation as an important technique for fertility preservation. Both agree that egg and ovarian cryopreservation are not established and are experimental. In addition, both agree that well-designed, statistically valid, randomized, controlled trials are essential to answer the question of preservation of ovarian function during chemotherapy with GnRH analogue coadministration.

Women of childbearing age receiving care for cancer need to be advised of ovarian toxicity from chemotherapy. Discussion regarding their hopes and desires for future pregnancy must be directly discussed and the options for fertility preservation—both clinically proven and investigational—should be made clear to them prior to beginning a treatment program. Oncologists need to refer female patients desiring fertility preservation to a reproductive endocrinologist in as timely a manner as possible. These recommendations are supported by fertility preservation guidelines recently published by the American Society of Clinical Oncology [6]. As a practical matter, some women may decline assisted-reproduction options because of concerns over the potential delay in initiating systemic therapy, concerns over the unknown effects of hormonal stimulation on their cancer, unwillingness to undergo the invasive procedures required, or the lack of a partner for embryo cryopreservation. Because the larger, prospective, randomized trials addressing safety and efficacy of GnRH analogue coadministration have not yet been completed, we are forced to individualize recommendations based on limited data and patient priorities.

Studies of the use of GnRH analogues for ovarian preservation are important and meaningful for women and treating physicians. Further information is needed about the most effective and useful ways to profile ovarian function and fertility before, during, and after cancer therapy. Long-term data on pregnancy and outcomes would further support clinical decision making in this area of the unknown. We strongly encourage participation in prospective, randomized, controlled clinical trials evaluating the ability of GnRH analogue coadministration with chemotherapy to prevent premature ovarian failure. Success in the prevention of chemotherapy-induced ovarian failure will not only improve prospects for future fertility but should prevent other adverse effects of premature menopause, such as bone density loss, sexual dysfunction, and vasomotor symptoms.
REFERENCES


