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Fertility Preservation and Reproductive Health in Patients Undergoing Hematopoietic Stem Cell Transplantation

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To the Editor:

The very interesting article by Murphy et al [1], “A Practical Guide to Gynecologic and Reproductive Health in Women Undergoing Hematopoietic Stem Cell Transplantation,” was recently published in this journal. Reproductive and gynecologic health in young patients with cancer is a major emerging problem from a quality of life standpoint, certainly meriting (today more than ever) greater clinical attention, considering that more and more patients with cancer recover completely with modern therapeutic strategies. Although this review is essentially dedicated to young women undergoing hematopoietic stem cell transplantation (HSCT), this problem currently affects a very large number of women suffering from solid and hematologic malignancies. And certainly it must be acknowledged that in this context too little has been done in the past, even recently, by independent researchers. Most of the published studies concern young patients affected by mammary and gynecologic malignancies, whereas those affected by hematologic tumors have been studied mostly under a purely epidemiologic and nonclinical profile.

In our opinion, the review of Murphy et al addresses some critical considerations to better understand the different aspects of gynecologic and reproductive care in these young patients. Very appropriately, the authors highlight the role and importance of the multidisciplinary consultation between hematologist-oncologists and gynecologists aimed at preserving fertility and reproductive health in patients undergoing HSCT. This type of multidisciplinary consultation is now

widely used, especially in cases of breast cancer, so that in disease management groups and breast units, a gynecologist is almost always available. This is much less common in cases of other solid tumors and hematologic cancers, however. In this regard, the American Society of Clinical Oncology (ASCO) deserves much credit for publishing complete and updated guidelines aimed at preserving fertility in patients with cancer [2]. According to Murphy et al, the best methods to evaluate ovarian reserve after chemotherapy or total body radiation are dynamic follicle-stimulating hormone (FSH) and estradiol levels, amenorrhea, antral follicle count, and anti-Müllerian hormone (AMH) levels, a menstrual cycle-independent marker of ovarian reserve and premature ovarian failure (POF). The predictive value of AMH is increased when it is associated with other clinical and laboratory markers and when AMH blood levels are regularly analyzed over time. However, it was recently demonstrated that in childhood cancer, FSH level identified POF in the later stages, confirming the utility of dosing AMH for the assessment of diminished ovarian reserve in adolescent and young adult survivors of childhood cancer [3]. Unfortunately, in that study, a considerable number of patients (nearly 20%) had low AMH and normal FSH, suggesting a reduced diagnostic value of AMH in early phases of POF. Not by chance do the authors state that a level <1.5 ng/mL is predictive of low ovarian reserve, even though it is not an absolute indicator of reduced fertility in the general population. In this context, it is useful to observe that use of recombinant AMH in association with chemotherapy might represent a promising option for fertility preservation in patients with cancer [4].

As Murphy et al report, it is now very clear that the preservation of fertility and reproductive health is an important aspect of quality of life in cancer patients. In young patients with hematologic and solid tumors, there are many strategies to guarantee the possibility of preserving their reproductive capacity and becoming mothers [5,6]. Unfortunately, not all the most attractive strategies of fertility preservation are available everywhere. This factor deserves some consideration, especially today when, in association with many established methods (eg, oocyte collection and cryopreservation, embryo cryopreservation, ovarian tissue transplantation), they look out on the horizon new futuristic approaches that should be

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considered and offered to patients desiring offspring (eg, uterus transplantation and beyond).

The possibility of maintaining reproductive capacity in such patients is also a duty not only medical but also social, as today there is no scientific evidence to show a greater risk in cancer patients of having a worse prognosis than healthy women in case of pregnancies that arose after the diagnosis of a tumor. Moreover, Murphy et al's opinion about the opportunity to suggest that patients avoid pregnancy for at least 2 years after HSCT, due to the hypothetical risk of recurrence, is not acceptable since they do not have certain data about. The authors make no mention of the possibility of preserving the ovarian function in young women suffering from cancer by using gonadotropin-releasing hormone agonists (GnRHa) in association with chemotherapy. In our opinion, this possibility, mainly explored and tested in breast cancer patients, can be used in any other type of cancer treated with chemotherapy. It is an effective and safe therapeutic strategy, so much so that ASCO considers it a worthy strategy to include in oncologic guidelines [2]. The ASCO consensus paper follows other papers that over the years have highlighted the role of protective therapy with GnRHa aimed at preserving ovarian function in patients undergoing chemotherapy for cancer [7,8]. Even though there are conflicting opinions about the use of GnRHa and other ovarian suppression strategies in clinical practice to preserve fertility, the ASCO expert panel stated that GnRHa may be used in cancer patients to reduce chemotherapy-induced ovarian failure. However, the experts suggest that gonadal suppression with GnRHa, if necessary, should be always be associated with other fertility conservation strategies.

In conclusion, currently there is great interest by clinicians (oncologists, gynecologists, radiotherapists, hematologists, and others) and scientific societies in the risk of treatment-related infertility and fertility preservation strategies. Current guidelines suggest increasing the use of assisted reproductive techniques to maintain fertility and reproductive health in young female patients with cancer. In this context, the use of GnRHa is a new therapeutic strategy that clinicians and patients should consider for ovarian protection during

chemotherapy in patients with solid tumors and hematologic malignancies, with or without HSCT [9].

There is no doubt that the best strategy for the preservation of fertility in patients with solid and hematologic malignancies is to provide a multidisciplinary team in all the onco-hematologic referral centers, consisting of a gynecologist, onco-hematologist, reproduction physician, andrologist, and radiotherapist, who jointly decide the best diagnostic and therapeutic personalized strategy for these women to guarantee their preservation of fertility and reproductive capacity.

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