Oncofertility: preserve and protect your eggs, but what about the uterus?

As treatments for cancer become increasingly sophisticated, many fortunate women find that when the question of survival fades, the focus begins to shift to the sequelae of the disease and its treatments. Before initiating chemotherapy, more and more patients will have had consultations with reproductive endocrinologists to discuss techniques for "fertility preservation." In fact, the counseling focuses on oocyte or embryo cryopreservation, procedures that may or may not actually allow them to preserve their fertility. During the race to retrieve oocytes and begin chemotherapy, discussions about the uterus are largely left untouched.

The effects of chemotherapy on the ovaries have long been an important focus of research efforts as many chemotherapeutic agents, particularly alkylating agents, are known to be gonadotoxic. The ovary lends itself relatively easily to study and intervention: its function can be assessed through noninvasive methods such as serum hormonal measurements and ultrasound imaging, and its major output can be safeguarded through oocyte cryopreservation before chemotherapy. The uterus has not been similarly explored because its function is harder to measure, and the effects of chemotherapy may not be as apparent. This issue's article by Garg et al. (1) sheds light on some of the unanswered questions surrounding the impact of chemotherapy on the uterus. In this retrospective pilot study of 12 women approximately 2.5 years after alkylating agent chemotherapy for Hodgkin lymphoma, the investigators found that chemotherapy, fortunately, does not appear to have a long-term impact on endometrial thickness or histology compared with endometrium of age-matched controls. The investigators acknowledge the limitation that all women studied received multiagent therapy (doxorubicin hydrochloride, bleomycin sulfate, vinblastine sulfate, and dacarbazine), such that any potential findings could not be specifically attributed to any one agent. Although studies, such as this one, add to our growing knowledge base, much remains to be uncovered. Significant progress has been made toward understanding the impact of chemotherapy on the ovaries and fertility preservation through oocyte/embryo cryopreservation. It is time to think about the uterus.

Although Garg et al. (1) provide reassuring morphologic data, the studies to date assessing live birth as an outcome after chemotherapy have conflicting results and are fraught with the limitations inherent to retrospective studies (2). Cancer treatments vary and can include combinations of chemotherapy and radiation, and it is often the case that results are pooled from different combinations of chemotherapeutic agents. In these retrospective studies, it can also be difficult to tease out the differential effect of treatment on the ovaries and the uterus. Well-designed basic studies aimed at understanding the cellular and molecular mechanisms of damage to the uterus, if any, are therefore vitally important. If we become armed with reliable mechanistic data, therapeutics developed to target those mechanisms may decrease the risk of infertility or maternal and fetal complications once pregnancy is achieved.

Furthermore, any conversation about the uterus must recognize the unique complexity of this organ which undergoes tremendous growth and remodeling during pregnancy and contains multiple different tissues and cell types. At a tissue level, the effects of chemotherapy may differ between the endometrium and the myometrium. The endometrium is a more accessible tissue that can be studied with endometrial biopsies, as done by Garg et al (1). The myometrium is not as easily accessed for the purposes of scientific study; however, the effects of chemotherapy on the myometrium must be assessed because it plays a crucial role in the health and maintenance of pregnancy and parturition. Studies of both tissues ideally need to parse out the effects of chemotherapy on the different cell types. For example, it cannot be assumed that the stromal, epithelial, vascular, and immune components of the endometrium will respond similarly to chemotherapy. In addition to differentiated cell types, more than a decade of data increasingly support the existence of stem cell populations in both the endometrium and myometrium, which are at least in part responsible for the regeneration and remodeling of these remarkable tissues on a cyclic basis (endometrium) and during pregnancy (3). Although true adult tissue stem cells spend much of their lifespan in the G0 (noncycling) phase, any effects of chemotherapy on these uterine cell populations remain unknown and ripe for future inquiry.

Beyond the academic questions surrounding the effects of chemotherapy on the uterus, practical questions arise as well. How can uterine function be measured, quantified, and assessed? Ovarian function can be approximated with serum studies and ultrasound measurements, but uterine function is not as easily estimated. Endometrial biopsies can be used to compare molecular, histologic, or proteomic changes, but what of the myometrium? Furthermore, even if no changes are seen at the level of the endometrium or myometrium, one may argue that the only true test of uterine function is live birth—an often impractical endpoint. In parallel with an investigation into the causative mechanisms of chemotherapy-induced damage to the uterus, an exploration of novel methods to study uterine function is pressing.

Finally, among survivors of childhood and adolescent malignancy, a basic question arises: can the gonadotoxic effects be separated from the uterine effects of chemotherapy? If a regimen damages the gonads and creates an environment deficient in sex steroids, the development of the uterus must be affected. Although the effects of adult-onset cancer and treatment can be studied by comparing pregnancy rates among women using oocyte donors for cancer- and noncancer-related reasons, this would not be sufficient to study a childhood or early adolescent insult. As we wade through these and many other unanswered questions about the effects of chemotherapy on the uterus,

the study by Garg et al (1) sheds light on some aspects of this vast issue.

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