

# Enhancing Evidence for Preconception and Prenatal Counseling on Obstetrical Risks After Cancer

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In this issue of the Journal, Zgardau and colleagues (1) present a detailed assessment of obstetric and perinatal outcomes after childhood and adolescent cancer in Ontario, Canada. Included cancers were diagnosed at ages younger than 21 years during 1985-2012. The majority cancer types were leukemias or lymphomas (47.5%), followed by central nervous system tumors (18.7%), and all other cancer types combined (33.9%). Using data from a single-payer insurance program, the investigators compared obstetric and perinatal outcomes between female cancer survivors and a comparison population of women without cancer, matched 5:1 on age and postal code, and within the survivor population.

Many, but not all, of the current findings align with the recent recommendations from the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG) on counseling and surveillance of obstetrical risks for childhood, adolescent, and young adult cancer survivors diagnosed before age 25 years (2). Among the IGHG recommendations, obstetrical risks supported by high levels of evidence included increased risk of premature birth and low birthweight after abdominopelvic radiotherapy (vs no radiotherapy) and the absence of elevated risk for congenital anomalies (either compared with noncancer populations or specific to receipt of ovarian-abdominal radiotherapy) (2). IGHG recommendations were based, in part, on results from previous cohort studies that demonstrated a strong association between prior pelvic irradiation and low birthweight (<2500 g) and/or premature birth (<37 weeks) (3-6).

The Ontario analysis provides additional support that congenital anomalies are not more common in the offspring of cancer survivors (1). This finding provides continued reassurance for a common concern of survivors and their partners and adds weight to the evidence underpinning the IGHG recommendations. The authors did observe an elevated risk of preterm birth among cancer survivors compared with the noncancer comparison group, but it did not appear strongly associated with abdominopelvic radiotherapy. In the Ontario analysis, preterm

birth risk was highest among recipients of hematopoietic stem cell transplant (HSCT), with a greater than threefold increase in the risk of preterm birth associated with autologous HSCT and greater than eightfold increase associated with allogeneic HSCT (1). Exclusion of the HSCT population did not fully mitigate the higher preterm birth risk in the cancer vs noncancer group, indicating additional contributing factors beyond HSCT. Finally, the authors observed an elevated risk of cardiac morbidity in unadjusted models (1), providing indirect support for the IGHG's recommendation for cardiomyopathy surveillance as part of preconception or first trimester care for survivors who received chest radiation or anthracycline-based chemotherapy (2).

During the 1985-2012 diagnosis period, embryo cryopreservation would have been the only nonexperimental fertility preservation strategy available to postpubertal female patients. Oocyte cryopreservation was considered experimental in 2008 (7) and was available as a protocol-based procedure at some institutions. This position was modified by the American Society of Reproductive Medicine in 2013, when the experimental label for this procedure was removed (8). The report by Zgardau et al. (1) does not specify whether these options were available to patients in this setting, but in contemporary patient groups, fertility counseling around these strategies is recommended for postpubertal adolescents. Prepubertal patients may also consider ovarian tissue cryopreservation (9). The expansion of fertility preservation services presents new challenges for health equity, because services are rarely covered by insurance (in the United States) and existing fertility and financial support and advocacy programs cannot reach all patients.

In the Zgardau et al. (1) analysis, all multivariable models adjusted for income quintile and rurality a priori. Young cancer survivors in Ontario were more likely than their matched noncancer counterparts to be in higher income strata but were similarly likely to be rural residents. Other sociodemographic characteristics, including Ontario's visible minority designation, are not provided. In the United States, health equity in both cancer (10) and obstetrical care (11) are ongoing concerns

because outcomes are worse in both domains for minoritized survivors by racial, ethnic, economic, sexual orientation, and gender identities. These challenges have been recognized by the American Society of Clinical Oncology as both a specific concern for fertility preservation (9) and for cancer control broadly (10). Studies that can reflect the experiences of minoritized populations are necessary to address health inequities that may otherwise be overshadowed by the larger numbers in majority groups.

Although the IGHG provides recommendations for counseling around obstetrical risks for cancer survivors diagnosed before age 25 years, similar recommendations are not widely available for cancer survivors diagnosed at older reproductive ages. The American Society of Clinical Oncology Clinical Practice Guideline for Fertility Preservation in Patients With Cancer (8,9) provides recommendations around fertility preservation counseling for cancer patients diagnosed during, or before, reproductive ages but does not synthesize evidence regarding potential pregnancy and obstetrical risks. A recent systematic review and meta-analysis summarized perinatal complications for female cancer survivors broadly but pooled estimates from studies of survivors diagnosed before the ages of 21 or 15 years and studies that extended diagnosis age to approximately age 40 years (12).

Across North America, secular trends towards older ages at marriage and childbearing result in a higher proportion of young adults being diagnosed with cancer before starting or completing their childbearing plans. Relative to younger cancer survivors, intervals between the end of cancer treatment and desire for pregnancy for older reproductive-age patients may be shorter by necessity to stay within physiologically fertile windows. In addition, solid tumors such as breast, colon, or gynecologic malignancies, and their corresponding treatments and potential threats to maternal and perinatal outcomes, are not well represented in younger patient groups and warrant specific consideration. Synthesized evidence on perinatal and postpartum risks for cancer survivors diagnosed during the full range of reproductive years is necessary to inform preconception and prenatal counseling for all reproductive-age survivors.

Pregnancies that are never clinically observed are not at risk for perinatal complications in existing health records and data linkages. The Ontario cohort (1), and others before, illustrate later ages at first pregnancy and lower cumulative incidence of pregnancy for cancer survivors compared with age-matched women without cancer. In this analysis, treatment-related factors associated with a decreased risk for a recognized pregnancy included HSCT, alkylating agent chemotherapy, and cranial radiation. To fully support cancer survivors, it is also essential to consider the indirect consequences of an early cancer diagnosis, including disruptions to relationships (13,14), impacts on sexual health (15), and the potential for financial hardship (16), as additional challenges to parenting goals. The report by Zgardau et al. (1) adds to the weight of evidence that can be summarized to inform clinical care, which in turn will be essential to disseminate beyond oncology to reach primary care and obstetrics and gynecology providers. The majority of cancer survivors will pursue their reproductive goals after leaving oncology care as a first point of contact, emphasizing the essential nature of the transition and communication between oncology and other health-care specialties to support the needs and well-being of survivors.

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## Data Availability

No data are presented in this editorial.

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