A woman’s ability to become pregnant, carry the pregnancy successfully, and give birth to a healthy child are all paradoxically threatened by many of the cancer treatments that enable girls to survive to adulthood. Like Hurricane Katrina, pediatric cancer is a tempest that leaves a concealing flood of acute treatment effects in its wake. Chronic problems only appear as the waters recede. Or perhaps the story of Noah’s ark is a more apt metaphor of preserving fecundity for the new world that emerges after the deluge. Surveys of the large cohort of the Childhood Cancer Survival Study (CCSG), supplemented by clues from small, clinical case series, are helping us to chart the altered childbearing landscape for women treated in childhood and adolescence.

This current report concludes that children of female survivors of pediatric cancer have a moderately higher risk of being born preterm compared with children of siblings (1). However, most of this risk is concentrated in children whose mothers had radiation before menarche that included the uterus in the field. These findings, based on self-report questionnaires and medical record reviews for 1264 female survivors, tally with previous observations that radiation reduces uterine capacity and blood supply, especially when administered before adolescence (2,3). A previous report from the CCSG on pregnancy outcome also showed a trend to higher rates of miscarriage or low birth weight babies in women treated in childhood with pelvic radiation, although treatment with chemotherapy alone did not increase adverse pregnancy outcomes (4). Adding to this optimistic picture of childbearing potential, only 6.3% of the women in CCSG who were over age 18 but within 5 years of their cancer diagnosis had suffered acute ovarian failure (5), suggesting that most could expect to be fertile. In that report as well, women who had received ovarian radiation accounted for a disproportionate number of those with infertility.

It would be premature, however, to symbolize the fecundity of survivors of childhood cancer with rainbows or with storks bringing leafy twigs. Fewer girls or teens have high doses of radiation to the pelvis or abdomen currently than during the years when CCSG participants were treated, but chemotherapy regimens using high-dose alkylating agents have become more frequent, presumably increasing the rates and extent of ovarian damage (5). The CCSG surveys could not assess potential infertility directly. Acute ovarian failure is only the most severe marker of diminished ovarian reserve. The number of viable follicles can be reduced by low doses of radiation to the ovaries or exposure to chemotherapy, shortening a cancer survivor’s years of fertility (6). The mean age ± standard deviation of survivors with normal menses in the CCSG cohort was 29.6 ± 7.4 years compared with 32.9 ± 6.8 years for those in acute ovarian failure. The report focuses on the fact that women with ovarian failure were slightly older when treated for cancer but ignores the larger and more important gap in the current age of the two groups. Ominously, smaller studies using physiologic assessment of ovarian reserve suggest that many young survivors may experience permanent, premature ovarian failure in their 30s.

Dutch researchers studying 134 young female survivors of childhood cancer used self-report and hormonal assays of estradiol and follicle-stimulating hormone (FSH) to show that 8% already were experiencing ovarian failure and another 23% were at imminent risk of permanent, premature menopause (7). The mean age of...
women with abnormal hormonal profiles was 30 at the time of the investigation compared with 25 for those with normal hormonal levels. Treatment after puberty does appear more destructive to the ovaries, however, producing a 45% rate of imminent ovarian failure compared with 16% when treatment was in earlier childhood. It is unclear how to weigh the inexorable loss of a reduced pool of ovarian follicles versus the long-term impact of treating ovaries during a period of maximum sensitivity to damage.

A Danish study (8) measured ovarian volume and the number of antral follicles in 21 survivors with a median age of 23 years. Only women who had normal FSH levels and regular menstrual cycles were included. Yet, compared with an age-matched control group, the pediatric cancer survivors had significantly smaller ovaries and fewer follicles. Their menstrual cycle length was also significantly shorter, another sign of premature ovarian aging. Our current measures are crude in predicting premature, permanent ovarian failure (9), but these observations suggest that we should inform survivors interested in childbearing that their window of fertility may be considerably narrower than normal. Having regular menstrual cycles, or even normal FSH levels before age 30, does not indicate a normal ovarian reserve.

Pediatric cancer survivors also may be at higher risk for pregnancy complications than the CCSG reports would suggest. The current publication (1) focused on the 65% of pregnancies that resulted in live births, excluding the unsuccessful 35%. The earlier CCSG survey of pregnancy outcome also reported a 15% rate of miscarriage and a 17% rate of medical terminations (4). Female siblings had a significantly higher rate of live births per pregnancy than the cancer survivors. Even if there is little evidence for a high rate of early miscarriage due to genetic damage to oocytes after cancer treatment (1), the physical stress of pregnancy can trigger cardiomyopathy or pulmonary hypertension caused by occult damage from chest irradiation or anthracyclines (10,11). Young women who have survived cancer appear to be overly concerned about the risk of birth defects or cancer for their offspring but are unaware of the advisability of consulting a high-risk obstetrician as part of planning a pregnancy (12). Pregnancy also exacerbates the already grim risk of breast cancer for young women treated for Hodgkin lymphoma with chest irradiation and anthracyclines (13).

Recent surveys suggest that adolescent female patients and their parents (14) as well as pediatric oncologists (15) want to preserve postcancer fertility. Given the complex terrain our young survivors need to traverse, we should design patient and professional education materials that map out the paths to making informed decisions.

REFERENCES