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The Survivorship Care Gap:

After Childhood and AYA Cancers, How to Keep Survivors in Follow-Up Care

BY SARAH DIGIULIO

Experts call the prevalence of undiagnosed disease in survivors of childhood cancers "concerning"—and say the challenges of keeping survivors of childhood, adolescent, and young adult cancers in long-term follow-up care throughout their lives are likely to blame. More on the solutions most likely to improve patient outcomes… *Page 8*

Survey: 1 in 3 Community Cancer Centers Involved in Merger, Acquisition, or Affiliation Last Year p.16

Lymphoma Specialists Lament Decision to Discontinue the Underprescribed Drug p.18

Breast Cancer Cosmetic Outcomes Found Worse with APBI than with WBI p.32

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Study: Majority of Menstruating Women Who Survive Childhood Cancer Can Achieve Pregnancy

BY HEATHER LINDSEY

"A more comprehensive understanding of infertility after cancer is crucial for counseling and decision-making about future conception attempts and fertility preservation."

While women who survive childhood cancer have an increased risk of infertility, nearly two-thirds of those who tried unsuccessfully to become pregnant for at least a year eventually conceived, according to new data. According to the study, published in the August issue of *Lancet Oncology* (***2013;14:873-881***), this rate is comparable to that of eventual pregnancy among all clinically infertile women.

The authors, led by Lisa Diller, MD, Chief Medical Officer of Dana-Farber/Boston Children's and Medical Director of the David B. Perini, Jr., Quality of Life Clinic at Dana-Farber Cancer Institute, note that this is the first large-scale study of female childhood cancer survivors to examine outcomes for those who had infertility (defined as attempting to conceive for a year or more without success).

"The research indicates that pregnancy in menstruating survivors is clearly a possibility," Diller said. "Our data suggest that early attention to fertility can increase pregnancy rates in these patients."

LISA DILLER, MD: "The research indicates that pregnancy in menstruating survivors is clearly a possibility. Our data suggest that early attention to fertility can increase pregnancy rates in these patients."

One of the most important takeaway messages of this study is that an overwhelming majority of patients treated for cancer at a young age will not have fertility problems," said Jared Robins, MD, a reproductive endocrinologist at the Women & Infants Center for Reproduction and Infertility in Providence, RI. "It's an important point that the diagnosis of cancer in childhood does not mean these girls will have fertility problems as survivors."

That being said, though, he added, these individuals do have a higher risk of infertility than women who aren't childhood cancer survivors, so physicians should think about ways to preserve fertility at the time of diagnosis.

The Data

The researchers—first author was Sara E. Barton, MD—assessed data from the Childhood Cancer Survivor Study, a cohort of five-year survivors from 26 institutions in the United States and Canada who were under age 21 when diagnosed between 1970 and 1986.

A total of 3,531 sexually active female survivors, aged 18 to 39, completed a baseline questionnaire about their medical care, reproductive history, and demographics between November 1992 and April 2004. The median age at the time of the questionnaire was 27.6.

The diagnoses included were leukemia, central nervous system cancer, Hodgkin and non-Hodgkin lymphoma, Wilms' tumor, neuroblastoma, soft-tissue sarcoma, and bone tumors.

The team also used an alkylating agent score to quantify drug exposure and estimated doses of radiation to the ovaries, uterus, and hypothalamus-pituitary.

Overall, about 13 percent of the women who survived childhood cancer had clinical infertility—i.e., trying to conceive for at least a year without success—and about 16 percent were affected by total infertility, which included both clinical infertility and ovarian failure.

In a comparison group of 1,366 sisters of childhood cancer survivors with a medium age of 28.9, 10 and 10.8 percent of them experienced clinical and total infertility, respectively.

JARED ROBINS, MD: "It's an important point that the diagnosis of cancer in childhood does not mean these girls will have fertility problems as survivors."

Compared with their siblings, the cancer survivors had a significant increased risk (relative risk [RR] of 1.54) of total infertility, including women who were clinically infertile, or trying to conceive for at least one year, and reporting ovarian failure.

Compared with their siblings, survivors also had a significant increased RR of 1.48 of clinical infertility. This risk was more pronounced in those younger than 24 (RR 2.92), than in those 25 to 29 (RR 1.61) and 30 to 40 (RR 1.37).

Among survivors of childhood cancer who had been trying unsuccessfully to get pregnant for at least a year, 64 percent conceived after about another six months, compared with an average of five months for clinically infertile women in the control group who eventually conceived.

Women whose cancer was treated with alkylating-agent chemotherapy or high-dose radiation to the abdomen or pelvis were most at risk of infertility, the researchers reported.

The study also showed that only 42 percent of cancer survivors who sought

continued on page 27

→SLEDGE

continued from page 25

effective. If this has not yet happened, it is in part related to lack of interoperability between the EHR systems. Crossing town from one practice or hospital to another is frequently to enter a deep electronic chasm. The best you can hope for is that you live in a place where monopoly prevails. Epic (and I really don't mean to pick on Epic) has the EHR franchise for Stanford, UCSF, and Kaiser Permanente, among other local concerns, so the Bay area is relatively integrated from an EHR standpoint.

But this is not the case everywhere. And without interoperability (which EHR vendors pretty much all passively or actively oppose) the promise of EHRs will continue to be largely theoretical. Gandhi's famous response when asked what he thought about Western civilization comes to mind: "It would be a good idea."

ASCO has devoted significant resources (significant for ASCO if trivial for the EHR vendors) to creating CancerLinQ, its rapid learning health care system. My sense, in my brief experience with Epic and my older relationship with Cerner, is that the EHR vendors have not thought through the needs of specialties, perhaps because their principal relationship is to hospital corporations.

Electronic health records are an important component of any rapid learning system, perhaps the central component. CancerLinQ will ultimately need to interact with a whole slew of EHR vendors. Will it be embraced, or strangled? Or just ignored? We'll see. In the meantime, I will continue to plod through my dictations.

→FERTILITY

continued from page 26

treatment for infertility were prescribed medication, compared with 75 percent in the sibling group. Sixty-nine percent of survivors and 73 percent in the control group were likely to seek medical help for their infertility.

Survivors Less Likely to Receive Fertility Drugs

Diller said she is unsure why cancer survivors were less likely to receive medication for their infertility. "We didn't ask survey participants about this," she said, theorizing, though, that fertility experts were unaware of the type of data presented in the study and assumed that fertility agents were ineffective in this patient population.

Additionally, noted Charles Shapiro, MD, Chair-elect of the Survivorship Committee of the American Society of Clinical Oncology and Director of Breast Cancer Research at Ohio State University Comprehensive Cancer Center-Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, because cancer survivors may have comorbidities such as heart, lung, or thyroid disease, physicians may be reluctant to prescribe medications or patients may be wary of potential drug side effects.

Another theory, he continued, is that endocrinologists counseling these women may possibly have been less likely to prescribe drugs such as clomiphene because of biases about inducing a pregnancy in a cancer survivor or being concerned that fertility drugs might cause harm in these patients.

JOY M. FULBRIGHT, MD, noted that the harvest and cryopreservation of eggs is no longer considered experimental.

Current Cancer Therapies Still Impact Fertility

Diller said that while the patients in the studies were diagnosed decades ago, "we still, unfortunately, often have to use the same therapies that put fertility at risk as we did in the 1970s and '80s, including alkylating agents and radiation because the cure rate is usually higher."

Oncologists especially avoid radiation, but sometimes they can't when trying to achieve a cure, she explained.

REBECCA BLOCK, MSW, PHD: "There almost can never be enough reminders about fertility preservation because with improved survival rates, young children grow up to lead full lives,"

Pediatric oncologists also try to limit the use of alkylating agents as much as possible, noted Joy M. Fulbright, MD, a pediatric oncologist/hematologist at Children's Mercy Hospitals and Clinics in Kansas City. This tends to be an option in patients with Hodgkin lymphoma; however, these drugs are still commonly used to treat sarcomas and as pretreatment for bone marrow transplants, she said.

Working together, fertility specialists and oncologists can shield the ovaries and minimize uterine exposure to radiation therapy, Robins said. "We can also discuss different treatment regimens and whether they are ovarian toxic."

Protecting Fertility in Pediatric Patients

For adolescent patients, while cancer treatments aren't much different, fertility-preservation options have changed and now include egg preservation and ovarian tissue preservation, Diller said.

> The researchers say that this is the first large-scale study of female childhood cancer survivors that examines the outcomes for those who experienced infertility.

The harvest and cryopreservation of eggs is no longer considered experimental and takes at least two weeks of the patient's time before treatment gets under way, Fulbright explained. If patients are prepubescent, oncologists might suggest ovarian tissue cryopreservation, although this is still experimental and fairly expensive because insurance generally doesn't cover the procedure, she said.

"This study is old in terms of when patients were treated," Robins noted. "If we were to do this study today, the pregnancy rates would be even better because we have such a great awareness of fertility preservation."

Moreover, Fulbright added, adult survivors have more options for fertility treatment than existed 10 or 20 years ago.

Patient Communication and Survivorship

"In some ways there can't be enough reminders about fertility preservation because with improved survival rates, young children grow up to lead full lives," said Rebecca Block, MSW, PhD, a psychosocial researcher working in adolescent and young adult oncology and studying decision-making about fertility preservation in young women with cancer for the Knight Cancer Institute at Oregon Health & Science University. "As soon as a child or adolescent is diagnosed, we start to think about what their life could look like."

Of particular note, patients and their families need to be given information about the impact of pelvic irradiation and exposure to alkylating chemotherapeutic agents on fertility, Denise Rokitka, MD, MPH, Director of the Pediatric Long-Term Follow-Up Clinic at Roswell Park Cancer Institute, said via email. While this risk is difficult to estimate, education regarding the possibility of infertility and discussion about possible fertility options is extremely important, she added.

In the Diller study, female cancer survivors without the risk factors of pelvic irradiation and exposure to alkylating agents still had a lower fertility rate than their sibling counterparts, Rokitka pointed out. "Therefore, it is important to educate all cancer survivors, not just those deemed at high risk."

> Women whose cancer was treated with alkylating agent chemotherapy or high-dose radiation to the abdomen or pelvis were most at risk of infertility.

Continuing Research

Diller said she would like to see further research examining pregnancy rates in a newer cohort of patients who have undergone in vitro fertilization. Determining the pregnancy rates in women who underwent egg harvesting as young cancer patients also needs to be explored, she said.

Continued research and improved availability of fertility-preservation techniques will be important in overcoming the late complications of infertility experienced by survivors, Rokitka concluded.