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Perspective

Standardizing Risk Assessment for Treatment-Related Gonadal Insufficiency and Infertility in Childhood Adolescent and Young Adult Cancer: The Pediatric Initiative Network Risk Stratification System

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Introduction

Continued advancements in therapy in pediatric and adolescent oncology have led to increasing numbers of patients achieving long-term survival. Consequently, conveying the late complications of treatment has become a regular discussion topic at the time of diagnosis. This is particularly relevent for gonadotoxicity as fertility preservation interventions exist to mitigate this late effect. Studies of self-reported infertility in survivors have assessed rates of 46% in males and 13% in females.[1,2] Crucial to these discussions is providing an estimate of the gonadotoxic risk that a particular treatment carries. Over time and across many studies, it has been demonstrated that cancer patients who are exposed to surgery involving the reproductive system, radiation to gonadal tissue or the hypothalamus and chemotherapy that depletes reproductive germ cells risk impairment to their fertility.[3–6] Among chemotherapy agents, the classes of drugs most likely to cause impairment are alkylating agents and heavy metals.

Further fine tuning an estimate of risk for a given individual has been a desirable but difficult goal. Studies from which risk factors are derived are either small in number, represent the experience at a single institution, rely on self-report, and/or are retrospective in nature. The study population is often heterogeneous and outcome measures vary across studies making direct comparisons of data difficult. The true outcomes of interest, that is, the ability or inability to become pregnant or sire a pregnancy usually occurs many years after cancer treatment, when patients are often no longer in contact with their oncology physicians.[7,8] Therefore, most studies of reproductive potential in survivors of childhood cancer use surrogate measures for infertility such as lack of pregnancy, acute ovarian failure, premature ovarian insufficiency, diminished ovarian reserve, oligo/amenorrhea, and elevated gonadotropins in females and elevated follicle stimulating hormones, oligospermia, or azoospermia in males [9–19] In addition, the prevalence of infertility can only be determined by knowing the number of survivors who, during the same period, were attempting pregnancy.

Finally, for females specifically, gonadotoxic therapies can variably deplete a female patient's nonrenewable ovarian reserve, further complicating risk stratification. When marked depletion of the ovarian reserve occurs secondary to cancer therapy, ovarian insufficiency can develop quite soon after the completion of therapy. For those in whom partial depletion occurs, a reproductive window large enough to fulfill their goals for biologic children before the onset of premature ovarian insufficiency (POI) may exist. This window of time may also be an opportunity for fertility preservation post-treatment. In this context, the definition of risk for POI clearly has different implications and yet is extremely difficult to quantify. In men, temporary azoospermia can occur for variable periods of time post-therapy and preclude siring a pregnancy even if permanent infertility is not the ultimate clinical outcome.

A first step in remediating the difficultites in estimating risk is to establish a standardized risk stratification model based upon currently available data to serve as a new baseline moving forward in clinical practice and research. Utilizing such a risk stratification model in clinical practice and across research studies can provide a platform for uniform clinical counseling and facilitate collaboration in and comparisons across research studies. To this end, the Best Practice Committee of the Pediatric Initiative Network (PIN) of the Oncofertility Consortium has developed such a risk stratification model for future gonadal insufficiency/infertility based on cancer treatment exposure.

The process for creating this model began with the creation of a working group composed of 27 clinicians and researchers from 15 institutions (Table 1). Current stratification systems in use were compared, national and international guidelines for long-term care were reviewed,[3–5] and a pertinent

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Table 1. Participants in the Risk Stratification Working Group of the Pediatric Initiative Network

Name	*Specialty*	*Institution*	*Role in fertility preservation*
Antoinette Anazodo, MD	Pediatric and adolescent oncology	Sydney Children's Hospital, Prince of Wales Hospital; University of New South Wales	Service development, educator, champion, and expert
Leslie Appiah, MD	Pediatric and adolescent gynecology	The University of Colorado Denver and Children's Hospital Colorado Cancer and Blood Diseases Center	Director, fertility preservation and reproductive late effects program
Kari Bjornard, MD, MPH	Pediatric hematology/ oncology	St Jude Children's Research Hospital	Oncology liaison to fertility clinic
Karen Burns, MD	Pediatric oncology	Cincinnati Children's Hospital Medical Center; University of Cincinnati College of Medicine	Codirector, comprehensive fertility care and preservation program
Brooke Cherven, PhD, MPH, RN	Pediatric and adolescent oncology	Children's Healthcare of Atlanta, Emory University	Nurse researcher in reproductive outcomes
Krista Childress, MD	Pediatric and adolescent gynecology	Children's Healthcare of Atlanta, Emory University	Member- fertility preservation team
Allison Close, MD	Pediatric hematology oncology	Helen DeVos Children's Hospital, Michigan State University	Leader of fertility preservation services
Daniel Green, MD	Pediatric hematology oncology	St Jude Children's Research Hospital	Clinical researcher in gonadal outcomes
Holly Hoefgen, MD	Pediatric and adolescent gynecology	Washington University School of Medicine	Codirector, integrated care & fertility preservation program
Yasmin Jayasinghe, PhD	Pediatric and adolescent gynecology	Royal Children's Hospital, University of Melbourne	Clinical lead fertility preservation service
Lisa Klimpel, NP	Pediatric, adolescent and young adult oncology	Children's Hospital of Orange County	Fertility program nurse practitioner leader
James Klosky, PhD	Pediatric psychology	Children's Healthcare of Atlanta, Emory University	Member-fertility preservation team
Mary Langevin, NP	Pediatric oncology	Children's Minnesota	Codirector AYA oncofertility/ preservation program
Jennifer Levine, MD MSW	Pediatric hematology oncology	Weill Cornell Medicine	Director, fertility preservation program and director of sSurvivorship
Veronica Gomez-Lobo, MD	Pediatric and adolescent gynecology	*Eunice Kennedy Shriver* National Institute of Child Health and Human Development	Director of pediatric and adolescent obstetrics/ gynecology
Lillian Meacham, MD	Pediatric endocrinologist	Children's Healthcare of Atlanta, Emory University	Director of the fertility preservation program
Molly Moravek, MD	Reproductive endocrinology and infertility	University of Michigan	Director fertility preservation program; IVF medical director
Leena Nahata, MD	Pediatric endocrinologist	Nationwide Children's Hospital	Director of fertility and reproductive health program
Kyle Orwig, PhD	Researcher, reproductive medicine	University of Pittsburgh	Director, fertility preservation program of UPMC
Olivia Prebus, RN	AYA oncology	Cook Children's Medical Center	Oncofertiltiy Nurse Navigator
Megan Pruett, NP	Pediatric endocrine nurse practitioner	Children's Healthcare of Atlanta	Member- fertility preservation team
Erin Rowell, MD	Pediatric surgery	Ann & Robert Lurie Children's Hospital	Director, fertility and hormone preservation and restoration program
Jill Samis, MD	Pediatric endocrinology	Ann & Robert H. Lurie Children's Hospital of Chicago	Member - fertility and hormone preservation and restoration program
Amanda Saraf, DO	Pediatric oncology	Riley Hospital for Children	Director of oncofertility

(*continued*)

Table 1. (Continued)

Name	*Specialty*	*Institution*	*Role in fertility preservation*
Hanna Valli-Pulaski, PhD	Researcher	University of Pittsburgh	Fertility preservation Program coordinator
Stacy Whiteside, NP	Pediatric and adolescent oncology	Nationwide Children's Hospital	Nurse practitioner/patient navigator fertility & reproductive health program
Mary Zelinski, PhD	Researcher	Oregon National Primate Research Center; Oregon Health & Science University	Ovarian tissue Cryopreservation research; Consultant to fertility preservation team

literature search was performed. The new proposed stratification guidelines were presented to the working group first by email and then discussed by conference call. Revisions were made in an iterative manner until consensus was obtained. Given the lack of adequate studies with self-reported infertility as an outcome, the percentage chance of infertility could not be assigned to the risk categories but instead terms describing the levels of risk were used: ''minimally increased risk,'' ''significantly increased risk,'' and ''high level of increased risk.'' Female risk stratification takes into account the different risk based on prepubertal vs pubertal status at the time of exposure to alkylators and radiation (Fig. 1). The male risk stratification does not vary based on age at exposure[13] (Fig. 2).

Perspective: Clinical Benefits of a Standardized Risk Stratification System

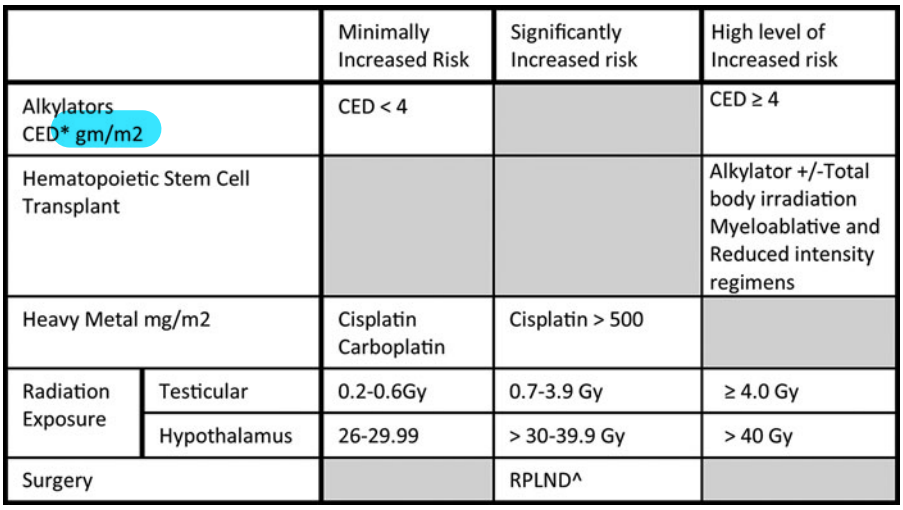
Providing an accurate assessment of risk to fertility is important for patient knowledge in the provision of informed consent. Current guidelines recommend that all levels of risk—from low to high—be conveyed to patients as part of comprehensive cancer care. Decisions to pursue fertility preservation require a patient-centered process involving the medical team that weighs the pros and cons of such interventions. This balance of pros and cons varies by risk for infertility, age, gender, and diagnosis among other factors. In general, the pros of pursuing fertility preservation are to mitigate the risk of permanent long-term gonadal damage. The drawbacks of pursuing fertility preservation interventions include unnecessary interventions in low risk situations, delaying the start of cancer fighting therapy, and cost as these interventions are expensive and often not covered by insurance.

Patients who have already progressed through puberty have standard of care options to preserve their fertility through cryopreservation of sperm, oocytes, or embryos. Recently, ovarian tissue cryopreservation has been deemed no longer experimental particularly in postpubertal females.[20] Male patients who have not yet gone through puberty have the choice of participating on a research protocol to freeze testicular tissue. The ability to provide accurate and consistent information will help providers work with families to make the best decision for their situation. Together they must weigh the risk of the procedure and any potential delay to cancer fighting therapy with the risk of permanent long-term gonadal damage.

This risk stratification system will allow clinicians to provide information to patients and families in a way that is comprehensive, uniform, and up to date across institutions. It allows for standardization of risk assessments in an area of medicine that continues to evolve. In addition, this standardization of the risk assessment across pediatric/AYA oncology institutions will provide continuity of care from diagnosis through survivorship, as patients often geographically relocate for school, work, or family. This will allow for consistent information regardless of institution should the patient and/or family need to transfer care.

			Minimally Increased Risk	Significantly Increased risk	High level of Increased risk
Alkylators CED* gm/m2		Prepubertal	CED < 8	8-12	> 12
		Pubertal	CED < 4	4-8	>8
Heavy Metal			Cisplatin Carboplatin		
Hematopoietic Stem Cell Transplant					Alkylator +/-Total body irradiation Myeloablative and Reduced intensity regimens
Radiation exposure	Ovary	Prepubertal		< 15 Gy	≥ 15 Gy
		Pubertal		< 10 Gy	≥ 10 Gy
	Hypothalamus		22-29.9	> 30-39.9 Gy	> 40 Gy

FIG. 1. Female level of risk for gonadal failure/infertility above that for the general population. *CED.[6] CED, cyclophosphamide equivalent dose.



		Minimally Increased Risk	Significantly Increased risk	High level of Increased risk
Alkylators CED* gm/m2		CED < 4		CED ≥ 4
Hematopoietic Stem Cell Transplant				Alkylator +/-Total body irradiation Myeloablative and Reduced intensity regimens
Heavy Metal mg/m2		Cisplatin Carboplatin	Cisplatin > 500	
Radiation Exposure	Testicular	0.2-0.6Gy	0.7-3.9 Gy	≥ 4.0 Gy
	Hypothalamus	26-29.99	> 30-39.9 Gy	> 40 Gy
Surgery			RPLND^	

FIG. 2. Male level of risk for gonadal failure/infertility above that for the general population. *CED.[6] CED, cyclophosphamide equivalent dose; ^RPLND, retroperitoneal lymph node dissection.

Perspective: Research Benefits of a Standardized Risk Stratification System

The field of fertility preservation continues to evolve with new methodologies originating as research studies. Since prepubertal patients do not produce oocytes or sperm, the options currently offered to these patients for fertility preservation are cryopreservation of ovarian tissue or testicular tissue. Ovarian tissue cryopreservation in prepubertal females and testicular tissue cryopreservation are considered investigational. Although the actual harvest of these tissues (typically a unilateral oophorectomy or a testicular biopsy) is not *per se* experimental, the cryopreservation and utilization of these tissues for future reproduction remain experimental, particularly for prepubertal patients. Active research in many laboratories is moving the field forward quickly.[21–26] Since the goal of harvest is ultimately the clinical use of the tissue to restore fertility, these interventions should be performed under the regulatory oversight of an Institutional Review Board (IRB), a Clinical Ethics and Novel Technologies Committee, or other appropriate regulatory body. The purview of this oversight is to determine whether the risks of infertility for a given group of patients are significant enough to justify intervention and that the benefits of preserving tissue for future use outweigh the risks of the surgical procedure to retrieve the tissue. An evidence-based risk stratification system helps to establish the tipping point between risk and benefit, which is necessary to identify and counsel patients who are eligible for experimental fertility preservation.

It is also necessary to continuously assess gonadal insufficiency and infertility outcomes for those patients treated on older treatment protocols as well as the infertility risks posed by each new treatment paradigm. The risk stratification system provides a benchmark for comparison that can be tested in preclinical animal models or in patient-focused clinical studies. Now that discussions of risk for infertility at the time of diagnosis have become more standardized and the fertility preservation community is well connected, collaborative research to combine patient data and proactively track reproductive outcomes is possible. Multi-institutional collaborations are necessary to represent the diversity of patients, diagnoses, and treatments with sufficient numbers to draw statistically significant conclusions about fertility risks.

Summary

The risk stratification model developed and presented here summarizes the currently available data for infertility risk in the pediatric and adolescent cancer population. Given the limitaitons already outlined, it is recognized as being both incomplete and imperfect. It is designed, however, as a critical start to creating a more complete and nuanced risk stratification system. We advocate the utilization of this model to promote uniform counseling, comparisons across research studies, and collaboration on infertility projects. In this manner, the data that evolve from the next generation of research studies will take us to the next level of understanding risk.

Author Disclosure Statement

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