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HOW I APPROACH

Fertility preservation in pediatric central nervous system tumors: A report from the Children's Oncology Group

James Felker[1,2] | Kari Bjornard[3,4] | Allison Close[5] | Josuah Chavez[6] | Eric J. Chow[7] | Lillian R. Meacham[8] | Karen Burns[9]

[1]Division of Hematology/Oncology, Department of Pediatrics, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA

[2]UPMC Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania, USA

[3]Division of Hematology/Oncology, Department of Pediatrics, Indiana University School of Medicine, Indianapolis, Indiana, USA

[4]Riley Hospital for Children at Indiana University Health, Indianapolis, Indiana, USA

[5]Division of Hematology/Oncology, Helen DeVos Children's Hospital, Michigan State University College of Human Medicine, Grand Rapids, Michigan, USA

[6]Division of Hematology/Oncology, Helen DeVos Children's Hospital, Grand Rapids, Michigan, USA

[7]Fred Hutchinson Cancer Center, Seattle Children's Hospital, Seattle, Washington, USA

[8]Aflac Cancer and Blood Disorders Center, Children's Healthcare of Atlanta, Pediatric Hematology/Oncology/BMT, Emory University Atlanta, Atlanta, Georgia, USA

[9]Department of Pediatrics, Cancer and Blood Diseases Institute, Cincinnati Children's Hospital Medical Center, University of Cincinnati School of Medicine, Cincinnati, Ohio, USA

Correspondence
James Felker, University of Pittsburgh, UPMC Children's Hospital of Pittsburgh, 4401 Penn Ave, Pittsburgh, PA 15224, USA.
Email: James.felker@chp.edu

Lillian R. Meacham and Karen Burns are the co-senior authors for this work.

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Abstract

The Oncofertility Consortium Pediatric Initiative Network has published recommendations about the risks of infertility due to gonadotoxic therapy. We abstracted gonadotoxic therapies from central nervous system (CNS) Children's Oncology Group (COG) protocols between 2000 and 2022. We assigned them as unknown, minimal, significant, or high levels of increased risk for gonadal dysfunction/infertility. Seven of 11 CNS protocols placed patients at a high level of risk in at least one treatment arm. Males (7/11) were most commonly at a high level of risk, followed by pubertal females (6/11) and prepubertal females (5/11), highlighting the importance of pre-treatment counseling regarding fertility preservation interventions in this population.

KEYWORDS
brain and spinal cord tumors, fertility preservation, oncofertility

Abbreviations: CED, cyclophosphamide equivalent dosing; CNS, central nervous system; COG, Children's Oncology Group; CSI, craniospinal irradiation; HSCT, hematopoietic stem cell transplant; PIN, Pediatric Initiative Network.

1 | INTRODUCTION

Effective treatments for pediatric central nervous system (CNS) tumors have reduced mortality by 50% (1969–2018), resulting in as many survivors as leukemia and lymphoma patients.[1–3] Many of the patients who survive, however, are left with significant toxicities related to treatment from surgery, chemotherapy, and radiation therapy.[4] The gonads are particularly sensitive to treatment, specifically alkylator and heavy metal chemotherapy, and radiation therapy.[5–9] Additionally, radiation to the hypothalamus increases the risk of central hypogonadism, compounding the risk of infertility.[10] Several national organizations have developed guidelines for assessing treatment-related gonadotoxicity of cancer treatments based on type and dose of alkylator and heavy metal therapy, radiation site and dose, and sex of the patient.[11–13] These organizations also set guidelines for counseling patients on their risk for future fertility and the possibility of preserving their fertility prior to cancer-directed therapies.[14] Pediatric cancer care providers have become more aware of these risks, and counseling has increased over time.[15] However, given the fragmented care and the possibility of misinterpretations of risks at individual institutions, we set out to guide centers on risk of infertility/gonadal dysfunction based on phase III Children's Oncology Group (COG) CNS protocols.

As previously reported, the Pediatric Initiative Network (PIN) of the Oncofertility Consortium developed stratification for risk of infertility/gonadal dysfunction through a working group of multidisciplinary clinicians and researchers who were members of the PIN.[16] Reviewing the literature related to fertility outcomes in pediatric cancer patients, the group identified alkylating agent and heavy metal exposure, hematopoietic stem cell transplant (HSCT), radiation therapy to either the gonads directly or the hypothalamus and retroperitoneal lymph node dissection as risk factors for infertility/gonadal dysfunction.[5–8,17–19] The working group was able to assign risk levels (*minimally*, *significantly*, or with a *high* level of increased risk for infertility) based on sex and pubertal status (Figure 1A,B) and treatment exposures.[16] These guidelines were developed to provide a common language and definition of risk levels so that clinical care and research could be standardized. It is this risk stratification schema guideline that fertility counseling for pediatric patients is rooted.

The COG is the largest pediatric cancer group in North America, Australia, and New Zealand. It is responsible for most phase III clinical trials in pediatric patients in these regions. Even when open clinical trials are not available, most institutions will utilize closed treatment protocols to treat patients as per a previous trial based on the current knowledge of the results.[20] Furthermore, in survivorship, many patients who need counseling about their risk for infertility/gonadal dysfunction were treated on trials that are now closed, but may have received treatment on an arm or aim that is not considered the current standard of care. Because of these complexities and the ubiquity of COG trials, we reviewed all frontline phase III COG CNS protocols between 2000 and 2022 to assess the gonadotoxic risk for each treatment arm. We hope to provide access to the calculated levels of risk for all phase III CNS protocols so that providers who may not be familiar with reading COG chemotherapy road maps in these trials, or the provider who is not familiar with the risk stratification system, can use the information provided to assist them in counseling their patients about associated risks for infertility/gonadal dysfunction.

2 | MATERIALS AND METHODS

2.1 | Data abstraction

Phase III, new diagnosis CNS tumor treatment protocols from 2000 to 2022 were identified using the COG members' website. The authors divided the protocols into arms. An arm of the protocol was defined to include any variations in chemotherapy or radiation that made a treatment plan unique within that protocol. Protocols were evaluated for gonadotoxic therapies (alkylating agents, heavy metals, HSCT, or hypothalamic or gonadal radiation), and cumulative alkylating agent dose was calculated based on the planned alkylator therapy and

(A)

Female Risk Chart			Minimally Increased Risk	Significantly Increased Risk	High level of Increased Risk
Alkylators CED gm/m2		Prepubertal	CED < 8	CED 8-12	CED > 12
		Pubertal	CED < 4	CED 4-8	CED > 8
Heavy Metal mg/m2			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 Gy	30-39.9 Gy	≥ 40 Gy

(B)

Male Risk Chart		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	0.2-0.6 Gy	0.7-3.9 Gy	≥ 4 Gy
	Hypothalamic	26-29.9 Gy	30-39.9 Gy	≥ 40 Gy
Surgery			RPLND	

FIGURE 1 Level of risk for gonadal failure/infertility above that of the general population: (A) female risk level; (B) male risk level. Reprinted with permission. CED, cyclophosphamide equivalent dosing; RPLND, retroperitoneal lymph node dissection.

TABLE 1 Risk of future infertility or gonadal dysfunction for Children's Oncology Group phase 3 treatment protocols for newly diagnosed medulloblastoma.

	Gonadotoxic therapy							Level of risk for future infertility/gonadal dysfunction[a]		
Protocol and therapy arms	Alkylator (CED g/m^2)	Cisplatin (mg/m^2)	Carbo[b] (yes)	CSI Rad	Local Rad	WVR	PF Rad	Prepubertal females	Pubertal females	Males
ACNS0331										
Standard dose CSI, TB radiation	13.2	450		[c]	[c]			High[d]	High[d]	High[d]
Standard dose CSI, PF radiation	13.2	450		[c]			[c]	High[d]	High[d]	High[d]
Reduced dose CSI, TB radiation	13.2	450		[c]	[c]			High[d]	High[d]	High[d]
Reduced dose CSI, PF radiation	13.2	450		[c]			[c]	High[d]	High[d]	High[d]
ACNS0332										
Regimen A	12	450		[c]			[c]	High[d]	High[d]	High[d]
Regimen B	12	450	Yes	[c]			[c]	High[d]	High[d]	High[d]
ACNS0334										
Regimen A	100.8	315	Yes					High	High	High
Regimen B	100.8	315	Yes					High	High	High
ACNS2031										
Average risk	13.2	450		[c]	[c]			High[d]	High[d]	High[d]
Low risk	13.2	450		[c]	[c]			High[d]	High[d]	High[d]

Abbreviations: carbo, carboplatin; CED, cyclophosphamide equivalent dose; CSI, craniospinal irradiation; PF, posterior fossa; Rad, radiation; TB, tumor bed; WVR, whole ventricular radiation.

[a]Level of risk is defined as *minimal*, *significant*, *high* level of increased risk (see Figures 1 and 2) or unlikely to be at risk as they are not identified as gonadotoxic by COG guidelines.

[b]Carboplatin is not risk stratified by dose.

[c]Radiation dose varies based on tumor site, plan. If radiation field includes hypothalamus, the level of risk will increase in dose-dependent manner (see Figure 1).

[d]Patients are considered high risk based on chemotherapy alone; however, additional additive risk may be conferred by radiation depending on radiation field, dose, and modality of radiation.

converted to cyclophosphamide equivalent dosing (CED).[7] Dosing in mg/m^2 was utilized for risk stratification, and any dosing in mg/kg was converted to mg/m^2 using the 30-rule.[21] Relapsed trials, pilot studies, and ancillary studies not containing chemotherapy, and phase I–II studies were excluded. All data were reviewed and abstracted by two authors, while a third author was utilized to evaluate and resolve any discrepancies. Individual treatment arms listed in the protocols along with specific permutations in therapy are outlined in Tables 1–4.

2.2 | Risk assignment

Similar to prior published reports, risk levels (*minimal*, *significant*, *or a high level of increased risk for gonadal dysfunction/infertility*) were assigned by two authors based on the previously published PIN Risk Stratification System (Figure 1A,B) for prepubertal females, pubertal females, and males.[16,22,23] Any discrepancies in risk assignment were resolved through team consensus. High-risk therapy includes treatment that exceeds a CED of 4 g/m^2 in males, 8 g/m^2 in pubertal females (Tanner 2 breast development or greater), 12 g/m^2 in prepubertal females, or any HSCT (myeloablative or reduced intensity) containing at least one alkylating agent or total body irradiation (TBI). High-risk therapy also includes gonadal radiation exposure (direct or indirect) of ≥15 Gy in prepubertal females, ≥10 Gy in pubertal females, and ≥4 Gy in males or hypothalamic radiation of ≥40 Gy in both males and females. Patient regimens without one of the gonadotoxic exposures listed in the PIN Risk Stratification System were considered unlikely or unknown to place patients at risk for gonadal dysfunction/infertility.[16]

3 | RESULTS

In total, 11 protocols with 41 treatment arms were reviewed. The median CED dose used on a treatment arm in a CNS tumor protocol is 10 g/m^2, with a maximum dose of 100.8 g/m^2. Overall, seven of 11 (64%) CNS tumor protocols had at least one group in a treatment arm that placed patients at *high* level of increased risk. Males were most commonly at a *high level of* increased risk with at least one *high*-risk treatment arm in seven of 11 protocols (64%), followed by pubertal females and prepubertal with at least one *high-risk* treatment arm in six of 11 (55%) and five of 11 (45%), respectively (Figure 2).

TABLE 2 Risk of future infertility or gonadal dysfunction for Children's Oncology Group phase 3 treatment protocols for newly diagnosed glioma.

	Gonadotoxic therapy							Level of risk for future infertility/gonadal dysfunction[a]		
Protocol and therapy arms	Alkylator (CED g/m^2)	Cisplatin (mg/m^2)	Carbo[b] (yes)	CSI Rad	Local Rad	WVR	PF Rad	Prepubertal females	Pubertal females	Males
ACNS0822										
Arm A	0	0			[c]			Unlikely[d]	Unlikely[d]	Unlikely[d]
Arm B	0	0			[c]			Unlikely[d]	Unlikely[d]	Unlikely[d]
Arm C	0	0			[c]			Unlikely[d]	Unlikely[d]	Unlikely[d]
ACNS1831										
Arm 1	0	0	Yes					Minimal	Minimal	Minimal
Arm 2	0	0						Unknown[e]	Unknown[e]	Unknown[e]
ACNS1833										
Arm 1	0	0	Yes					Minimal	Minimal	Minimal
Arm 2	0	0						Unknown[e]	Unknown[e]	Unknown[e]
ACNS1931										
Arm 1	0	0						Unknown[e]	Unknown[e]	Unknown[e]
Arm 2	0	0						Unknown[e]	Unknown[e]	Unknown[e]

Abbreviations: Carbo, carboplatin; CED, cyclophosphamide equivalent dose; CSI, craniospinal irradiation; PF, posterior fossa; Rad, radiation; WVR, whole ventricular radiation.

[a]Level of risk is defined as *unlikely*, *minimal*, *significant*, *high* level of increased risk (see Figure 1) or unknown to be at risk as they are not identified as gonadotoxic by COG guidelines.

[b]Carboplatin is not risk stratified by dose.

[c]Radiation dose varies based on tumor site, plan. If radiation field includes hypothalamus, the level of risk will increase in dose-dependent manner (see Figure 1).

[d]Level of risk not high based on cumulative chemotherapy, but risk may be increased due to radiation depending on radiation site, plan (see Figure 1).

[e]Gonadotoxic risk with selumetinib is not established and therefore the level of risk is listed as unknown.

3.1 | Medulloblastoma

Four medulloblastoma protocols with 10 arms were reviewed (Table 1). One hundred percent (4/4) of medulloblastoma protocols included a *high* level of increased risk arm for males, prepubertal females, and pubertal females. The CED range for medulloblastoma protocols was 12–100.8 g/m^2. In addition, three of four (75%) of the protocols had craniospinal irradiation (CSI), and all protocols contained heavy metal chemotherapy, further increasing the risk for infertility beyond the risk associated with alkylators alone.

3.2 | Glioma

We reviewed four glioma protocols with nine treatment arms (Table 2). Most upfront glioma studies had no planned alkylating agents, and were designated unlikely or would place patients at *minimal level of* risk for infertility/gonadal dysfunction. Two out of the four (50%) glioma protocols had an arm that had heavy metal chemotherapy, and three of four (75%) protocols had a targeted therapy (selumetinib) for which there are limited data on both the short- and long-term gonadal effect, and the level risk for selumetinib is listed as unknown level of risk for gonadal dysfunction/infertility.

3.3 | Germ cell tumors

Germ cell tumors had one phase III CNS protocol subdivided into four regimens with 12 arms reviewed (Table 3). Six out of the 12 arms (50%) have at least one arm that puts males at *high* level of increased risk. No treatment arms meet the threshold for *high* risk for females, but six of 12 arms put pubertal females in the significant level of increased risk category. The CED range was 0–4 g/m^2. All patients received either CSI, whole ventricular radiation, or local radiation, and depending on the location, this may put individual patients in a different risk category.

3.4 | Atypical teratoid rhabdoid tumor and ependymoma

Two CNS protocols subdivided into 10 arms were reviewed (Table 4). Seven out of the 10 arms (70%) put males and pubertal females at a *high* level of increased risk. Five out of the 10 arms (50%) put prepuberal females at *high* level of increased risk, with an additional two arms placing them at significant increased risk. The CED range was 0–97.2 g/m^2. Nine out of 10 arms (90%) had heavy metal chemotherapy. Patients receiving either CSI or local radiation may increase to a higher risk category depending on the dose to the hypothalamus.

TABLE 3 Risk of future infertility or gonadal dysfunction for Children's Oncology Group phase 3 treatment protocols for newly diagnosed CNS germ cell tumors.

	Gonadotoxic therapy							Level of risk for future infertility/gonadal dysfunction[a]		
Protocol and therapy arms	Alkylator (CED g/m^2)	Cisplatin (mg/m^2)	Carbo[b] (yes)	CSI Rad	Local Rad	WVR	PF Rad	Prepubertal females	Pubertal females	Males
ACNS0232										
Regimen A										
Local	0	0			[c]	[c]		Unlikely[d]	Unlikely[d]	Unlikely[d]
Occult multifocal	0	0			[c]	[c]		Unlikely[d]	Unlikely[d]	Unlikely[d]
Disseminated	0	0		[c]	[c]			Unlikely[d]	Unlikely[d]	Unlikely[d]
Regimen B CR reduced radiation										
Local	0	0	Yes		[c]			Unlikely[d]	Unlikelyd	Unlikely[d]
Occult multifocal	0	0	Yes		[c]	[c]		Unlikely[d]	Unlikely[d]	Unlikely[d]
Disseminated	0	0	Yes	[c]	[c]			Unlikely[d]	Unlikely[d]	Unlikely[d]
Regimen B PR/SR reduced radiation										
Local	4	200	Yes		[c]			Minimal[d]	Significant[d]	High[e]
Occult multifocal	4	200	Yes		[c]	[c]		Minimal[d]	Significant[d]	High[e]
Disseminated	4	200	Yes	[c]	[c]			Minimal[d]	Significant[d]	High[e]
Regimen B PR/SR/PD standard radiation										
Local	4	200	Yes		[c]	[c]		Minimal[d]	Significant[d]	High[e]
Occult multifocal	4	200	Yes		[c]	[c]		Minimal[d]	Significant[d]	High[e]
Disseminated	4	200	Yes	[c]	[c]			Minimal[d]	Significant[d]	High[e]

Abbreviations: Carbo, carboplatin; CED, cyclophosphamide equivalent dose; CNS, central nervous system; CR, complete response; CSI, craniospinal irradiation; PD, progressive disease; PF, posterior fossa; PR, partial response; Rad, radiation therapy; SR, stable response; WVR, whole ventricular radiation.

[a]Level of risk is defined as *unlikely*, *minimal*, *significant*, *high* level of increased risk (see Figure 1) or unknown to be at risk as they are not identified as gonadotoxic by COG guidelines.

[b]Carboplatin is not risk stratified by dose.

[c]Radiation dose varies based on tumor site, plan. If radiation field includes gonadal tissue or hypothalamus, the level of risk will increase in dose-dependent manner (see Figure 1).

[d]Level of risk not high based on cumulative chemotherapy, but risk may be increased due to radiation depending on radiation site, plan (see Figure 1).

[e]Patients are considered high risk based on chemotherapy alone; however, additional additive risk may be conferred depending on radiation field, dose, and modality of radiation.

4 | DISCUSSION

We assigned levels of gonadotoxic risk using the PIN risk stratification for newly diagnosed CNS tumors in current-era phase III trials.[16] Our review shows that most CNS tumor protocols placed patients at a *high* level of increased risk for gonadotoxicity according to the PIN risk stratification. When stratified by sex and pubertal stage, planned treatment places a patient at a *high* level of increased risk in five of 11 (45%) protocols for prepubertal females, six of 11 (55%) protocols for pubertal females, and seven of 11 (64%) protocols for males The *high* level of increased risk for gonadotoxicity makes it essential that patients with CNS tumors receive risk-adapted counseling prior to initiation of therapy or at different time points when treatment plans change. When comparing the highest possible CED among protocol arms containing alkylating agents, the median CED dose in CNS tumor protocol arms is 10 (interquartile range [IQR]: 0–13.2) g/m^2, with a maximum of 100.8 g/m^2, compared to leukemia/lymphoma protocols where the median CED is 3 (IQR: 0–3.6) g/m^2, with a maximum of 13.2 g/m^2, and solid tumor protocols where the median CED is 0.5 (IQR: 0–14.5)g/m^2, with a maximum of 70.6 g/m^2.[22,23] The high gonadotoxic risk dosages seen in CNS tumor protocols compared to solid and leukemia lymphoma protocols are secondary to increased use of radiation-sparing chemotherapy in infants with high-dose chemotherapy and stem cell rescue.

CNS tumor treatments present unique challenges and barriers to fertility preservation. First is a difficulty in timing. Patients presenting with CNS tumors often do so urgently, requiring emergent neurosurgical intervention. Many patients end up transitioning to rehabilitation units while recovering from significant neurologic deficits related to tumors and surgery. Furthermore, the final pathology, especially with modern molecular techniques, can take several weeks, which can mean a final treatment plan and CED risk is not known until right before radiation or chemotherapy starts. Patients with CNS tumors, in some instances, are initially seen by neurosurgery and physical medicine and rehabilitation and not seen by oncology until final diagnosis. The multidisciplinary team, coupled with the complexity of care of these

TABLE 4 Risk of future infertility or gonadal dysfunction for Children's Oncology Group phase 3 treatment protocols for newly diagnosed atypical teratoid rhabdoid tumor and ependymoma.

	Gonadotoxic therapy							Level of risk for future infertility/gonadal dysfunction[a]		
Protocol and therapy arms	Alkylator (CED g/m^2)	Cisplatin (mg/m^2)	Carbo[b] (yes)	CSI Rad	Local Rad	WVR	PF Rad	Prepubertal females	Pubertal females	Males
ACNS0333										
Infratentorial, M0, age <6 months	97.2	210	Yes					High	High	High
Infratentorial, M0, age >6 months	97.2	210	Yes		[c]			High[d]	High[d]	High[d]
Supratentorial, M0, age <12 months	97.2	210	Yes		[c]			High[d]	High[d]	High[d]
Supratentorial, M0, age >12 months	97.2	210	Yes		[c]			High[d]	High[d]	High[d]
Disseminated, any age	97.2	210	Yes	[c]	[c]			High[d]	High[d]	High[d]
ACNS0831										
STR	2	0	Yes	[c]				Minimal[e]	Minimal[e]	Minimal[e]
STR + maintenance	10	400	Yes	[c]				Significant[e]	High[d]	High[d]
GTR1 (anaplastic), GTR2, NTR infratentorial	2	0	Yes	[c]				Minimal[e]	Minimal[e]	Minimal[e]
GTR1, GTR2, NTR infratentorial + maintenance	10	400	Yes	[c]				Significant[e]	High[d]	High[d]
GTR1 (classical histology), supratentorial	0	0		[c]				Unlikely[e]	Unlikely[e]	Unlikely[e]

Abbreviations: Carbo, carboplatin; CED, cyclophosphamide equivalent dose; CSI, craniospinal irradiation; GTR, gross total resection; M0, no metastatic disease; NTR, near total resection; PF, posterior fossa; Rad, radiation therapy; STR, subtotal resection; WVR, whole ventricular radiation.

[a]Level of risk is defined as *unlikely*, *minimal*, *significant*, *high* level of increased risk (see Figure 1) or unknown to be at risk as they are not identified as gonadotoxic by COG guidelines.

[b]Carboplatin is not risk stratified by dose.

[c]Radiation dose varies based on tumor site, plan. If radiation field includes hypothalamus, the level of risk will increase in dose-dependent manner (see Figure 1).

[d]Patients are considered high risk based on chemotherapy alone; however, additional additive risk may be conferred depending on radiation field, dose, and modality of radiation.

[e]Level of risk not high based on cumulative chemotherapy, but risk may be increased due to radiation depending on radiation site, plan (see Figure 1).

patients, can lead to delays in the referral of patients to fertility preservation teams, leaving little time for fertility preservation interventions. Appropriate and timely fertility preservation conversations require that all parties, neurosurgery, physical medicine and rehabilitation, and neuro-oncology, be aware of the risks to fertility with treatment as well as the windows of time between diagnosis and start of treatment that can be used for infertility risk counseling and fertility preservation. Multidisciplinary care can ensure a timely referral with an increased likelihood of success before initiating gonadotoxic therapy.

In addition, there can be several dilemmas and ethical concerns to consider in this patient population. Neurologic deficits, including motor or cognitive, may complicate decisions about fertility preservation.[24] It may be difficult to obtain a semen specimen for sperm cryopreservation in patients with neurologic debilitation. For those pubertal male patients, an alternative way of collecting, such as electroejaculation, testicular sperm aspiration, or testicular sperm extraction, could be considered.[25] Adolescent and young adult patients who would typically be involved in shared decision-making with their families about fertility may be temporarily incapacitated by their tumor or resultant surgery (e.g., those with posterior fossa syndrome), requiring family members to intuit what the patient may want.[26] In addition to these situations, long-term follow-up of adult survivors of brain tumors has estimated that about one quarter of survivors are not able to live independently.[27] Furthermore, childhood CNS tumors are the leading cause of cancer death, and some patients, like those with diffuse intrinsic pontine glioma, will not survive despite modern advances.[2] In complex fertility cases, an ethicist can assist the fertility preservation team or be available for consults to help with fertility decisions.

There are several endocrinologic concerns to consider in this population. When risk stratifying patients for gonadotoxicity, discussing the risk of central hypogonadism is essential. The tumor or surgery itself may have damaged the pituitary gland or hypothalamus and caused central hypogonadism prior to any treatment.[28] Furthermore, many of the protocols we reviewed include CNS radiation, and may confer additional risk if the radiation doses to the hypothalamus reach greater than 22 Gy in women and more than 26 Gy in men according to the PIN stratification, with the risk of gonadotropin deficiency increasing from 7.8% to 22.7% after doses of greater than 40 Gy in both sexes in longitudinal studies of survivors.[10,29] It is essential to counsel patients, however, that lower doses of radiation could still lead to central hypogonadism, and all patients should follow-up regularly with an endocrinologist post treatment to screen for these hypothalamic-pituitary late effects issues. For patients who desire a biological child and who have not received significant gonadotoxic

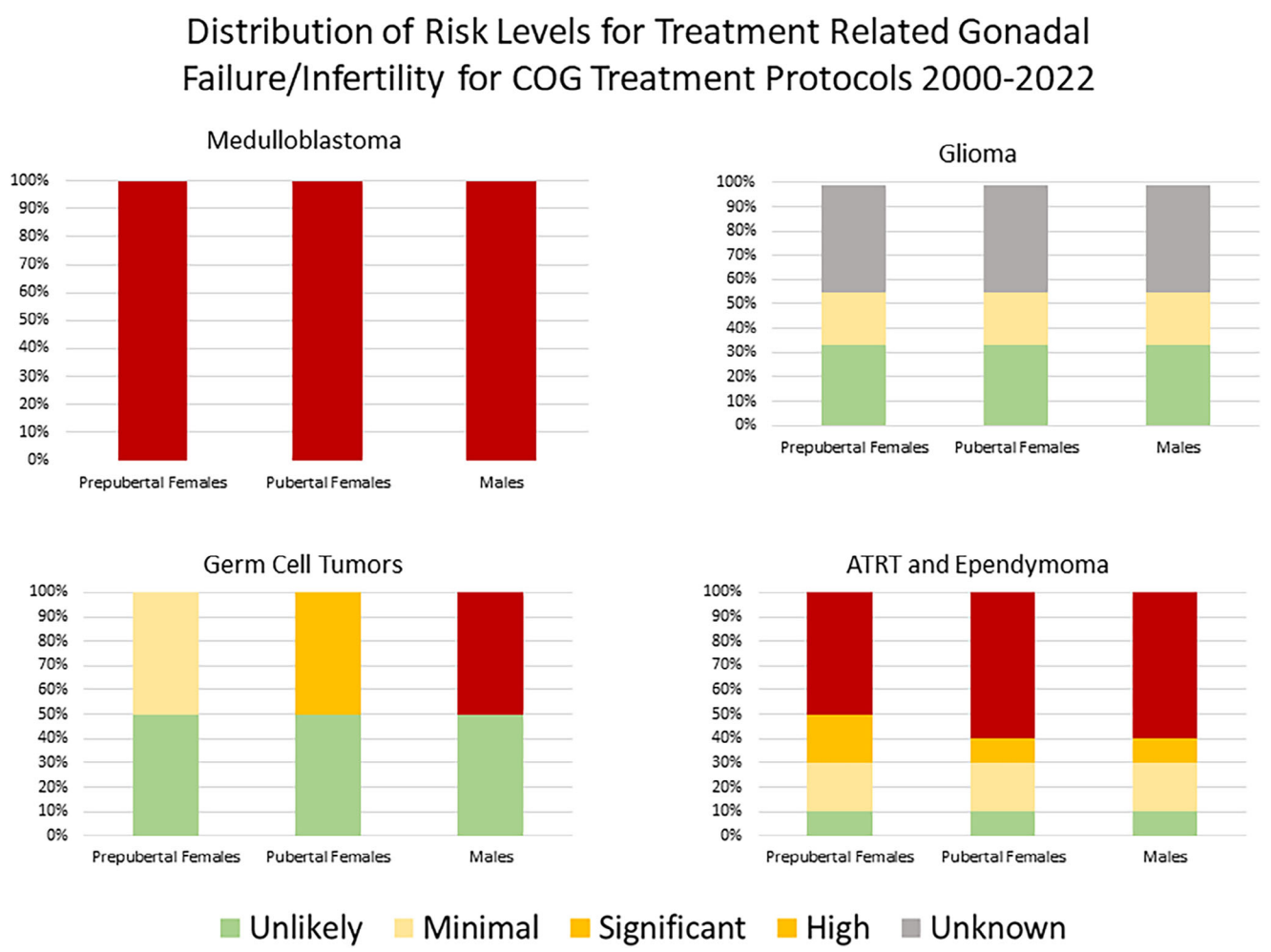

FIGURE 2 Distribution of risk levels for treatment-related gonadal failure/infertility for COG treatment protocols 2000–2022.

therapy, there is a theoretical option for ovulation/spermatogenesis utilizing a portable pump delivering gonadotropin in a pulsatile fashion.[30] In addition to the impact of CNS radiation on future fertility, scattered radiation dosage from spinal radiation may affect ovarian function. Fertility preservation teams may need to work closely with the radiation oncologist and the dosimetrist on the dose of radiation to the ovaries, which is essential in determining risk. If this is unavoidable and the patient is not receiving additional gonadotoxic chemotherapy, shielding or a laparoscopic transposition/oophoropexy could be done prior to radiation to move the ovaries out of the field of radiation.[31]

Another factor to consider is whether the patient will receive proton or photon radiation. Proton radiation is a form of external beam radiotherapy using a large particle (protons) instead of photons to treat the patient. The benefit of proton therapy is less or no scattering of the doses past the target point. This may eliminate any radiation to the ovaries in spinal radiation, and limit the scatter doses to the hypothalamus in patients receiving radiation elsewhere in the brain. Studies in standard-risk medulloblastoma showed a significantly lower risk of long-term sex hormone deficiencies in patients who had received proton therapy compared to conventional photon therapy.[32] While proton therapy seems promising to prevent longer term hormone side effects, there still is a need for prospective trial data to show a definitive benefit.[32] The fertility consultant should be aware of the difference in radiation fields between these two modalities; however, the patient should be counseled that long-term data are limited. Overall, in CNS tumors where radiation therapy is a mainstay of treatment in many types of tumors, the fertility preservation team must work closely with a radiation oncologist to discern the planned doses to the hypothalamus/pituitary and gonads.

Recently, the addition of targeted treatments for brain tumors has revolutionized treatment for many subtypes of low-grade glioma. The discovery of the ubiquitous mutations in the RAS/MAPK pathway in both neurofibromatosis (NF)-related and non-NF-related gliomas and recent trials have shown these tumors respond highly to using BRAF inhibitors or MEK inhibitors.[33,34] However, the long-term risk to fertility associated with these agents is not clear. Patients receiving these agents are counseled about the potential teratogenicity while on these medications and instructed to avoid getting pregnant (or partners pregnant) and to stop treatment if they are interested having offspring.[35] Unfortunately, a large percentage of patients relapse even with short times without the inhibitor, making it difficult to impossible to find a window of time off these chronic therapies in which to

be able to pursue fertility preservation procedures. This may lead to a difficult choice for affected patients between treating the brain tumor and attempting to get pregnant. If having a biologic child is a priority, for female patients, oocyte retrieval and cryopreservation and use of a gestational carrier could be considered. Pre-clinical data in rats have shown MEK inhibition increases cystic follicles and decreases corpora lutea.[36] For males, there are pre-clinical data in rats that the BRAF inhibitors impair spermatogenesis with continued disruption up to 4 weeks after stopping the drug.[35] In terms of longer term fertility issues, there are no human data. Because of this uncertainty, all patients initiating treatment with these inhibitors should be offered fertility counseling.

Finally, we reviewed only phase 3 CNS clinical trials at COG. CNS tumor treatment often includes protocols not in phase 3 trials or protocols outside the COG. Because of the numerous trials and limitations of this review, it is crucial to understand the PIN risk factors in CNS tumors and be able to apply them to other neuro-oncology protocols. Furthermore, many patients, unfortunately, experience relapse and potential change in therapeutic plan; therefore, at every time point, it is essential to re-evaluate the cumulative risk factors and, when necessary, adjust the level of risk for gonadotoxicity/future infertility/with the fertility preservation team.

5 | CONCLUSIONS

This article aims to provide guidance for risk counseling in patients receiving COG-based therapy for CNS tumors, joining recently published articles that also summarized the risk associated with COG phase III hematologic malignancies and solid tumors.[22,23] These recommendations can be used throughout the patient's journey, from diagnosis to survivorship. We recommend that most patients with CNS tumors are offered fertility risk counseling prior to treatment, which should include the potential range of gonadotoxicity associated with the proposed treatment. Additionally, we suggest that these discussions should occur continuously throughout the patient's care, as there may be opportunities for fertility preservation after treatment. For future COG and international protocols, we hope that fertility risk will be included as appendices to aid centers in uniform risk stratification and global risk counseling.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

ORCID

James Felker https://orcid.org/0000-0003-4585-8126
Kari Bjornard https://orcid.org/0000-0002-2881-0027
Allison Close https://orcid.org/0000-0002-0976-4723
Karen Burns https://orcid.org/0000-0002-7296-4226

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