Title

Infrastructure of Fertility Preservation Services for Pediatric Cancer Patients: A Report From the Children's Oncology Group.

Journal

JCO Oncology Practice, 18(3)

ISSN

2688-1527

Authors

Frederick, Natasha N
Klosky, James L
Meacham, Lillian R
et al.

Publication Date

2022-03-01

DOI

10.1200/op.21.00275

Peer reviewed

original contributions

Infrastructure of Fertility Preservation Services for Pediatric Cancer Patients: A Report From the Children's Oncology Group

Natasha N. Frederick, MD, MPH[1,2]; James L. Klosky, PhD[3,4]; Lillian R. Meacham, MD[3,4]; Gwendolyn P. Quinn, PhD[5]; Joanne Frankel Kelvin, MSN, RN[6]; Brooke Cherven, PhD, MPH, RN[3,4]; David R. Freyer, DO, MS[7,8,9]; Christopher C. Dvorak, MD[10]; Julienne Brackett, MD[11]; Sameeya Ahmed-Winston, CPNP-PC[12]; Elyse Bryson, MMS[3]; Eric J. Chow, MD, MPH[13]; and Jennifer Levine, MD, MSW[14]

QUESTION ASKED: What is the availability of fertility preservation (FP) services across Children's Oncology Group (COG) institutions and what are the infrastructure-related barriers inhibiting patient access?

SUMMARY ANSWER: Current infrastructure to support FP for pediatric, adolescent, and young adult oncology patients across COG institutions is inadequate. Key infrastructure-related barriers include cost of FP, inadequate knowledge or training of staff to educate and provide fertility risk assessment and access to preservation strategies, inadequate staffing, and coordination logistics with reproductive specialists.

WHAT WE DID: We sent a survey to the 220 COG member institutions that included questions on institutional characteristics, structure and organization of FP services, and barriers to FP.

WHAT WE FOUND: Of the 144 (65.5%) programs that returned surveys, we found that only 53 (36.8%) reported having a dedicated FP person or team to meet with pediatric oncology patients to discuss infertility risk and available FP options, which is notable as the presence of an FP team was independently associated with an institution being able to offer oocyte or embryo cryopreservation, ovarian tissue cryopreservation (OTC), and testicular tissue cryopreservation. Notably, only 26 (18.1%) participating institutions offered all current nonexperimental FP interventions (sperm banking, oocyte or embryo cryopreservation, and OTC).

BIAS, CONFOUNDING FACTORS: Although two thirds of COG institutions participated in this study, it is unclear if the data presented here are reflective of those institutions that did not participate and thus may over-represent or under-represent FP services and infrastructure-related barriers to FP. Additionally, the field of FP is constantly evolving and the status of OTC changed from experimental to nonexperimental in December 2019 after completion of data collection, limiting interpretation of responses in relation to this procedure. Survey methodology does not allow for more in-depth and nuanced assessments of current programs in place, which may be helpful in identifying key elements of program success and how these elements may be adapted for use at other programs.

REAL-LIFE IMPLICATIONS: Although national organizations, including the ASCO, the National Comprehensive Cancer Network, and the American Society for Reproductive Medicine, have issued guidelines recommending fertility risk assessment and discussion of preservation options for newly diagnosed patients with cancer before the start of treatment as standard-of-care practice since 2006, COG institutions as a whole do not have the infrastructure to offer FP practices to patients, including providing access to standard-of-care FP interventions. This survey identified the development of dedicated FP teams that engage reproductive specialists and non-MD members as a modifiable factor associated with increased patient access to FP procedures.

CORRESPONDING AUTHOR

Natasha N. Frederick, MD, MPH, Center for Cancer and Blood Disorders, CT Children's Medical Center, 282 Washington St, Hartford, CT 06106; e-mail: nfrederick@connecticutchildrens.org.

ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and disclosures are available with the complete article at ascopubs.org/journal/op.

Accepted on September 30, 2021 and published at ascopubs.org/journal/op on October 28, 2021: Full-length article available online at DOI https://doi.org/10.1200/OP.21.00275

CARE DELIVERY

original contributions

Infrastructure of Fertility Preservation Services for Pediatric Cancer Patients: A Report From the Children's Oncology Group

Natasha N. Frederick, MD, MPH[1,2]; James L. Klosky, PhD[3,4]; Lillian R. Meacham, MD[3,4]; Gwendolyn P. Quinn, PhD[5]; Joanne Frankel Kelvin, MSN, RN[6]; Brooke Cherven, PhD, MPH, RN[3,4]; David R. Freyer, DO, MS[7,8,9]; Christopher C. Dvorak, MD[10]; Julienne Brackett, MD[11]; Sameeya Ahmed-Winston, CPNP-PC[12]; Elyse Bryson, MMS[3]; Eric J. Chow, MD, MPH[13]; and Jennifer Levine, MD, MSW[14]

abstract

PURPOSE Fertility preservation (FP) services are part of comprehensive care for those newly diagnosed with cancer. The capacity to offer these services to children and adolescents with cancer is unknown.

METHODS A cross-sectional survey was sent to 220 Children's Oncology Group member institutions regarding institutional characteristics, structure and organization of FP services, and barriers to FP. Standard descriptive statistics were computed for all variables. The association between site-specific factors and selected outcomes was examined using multivariable logistic regression.

RESULTS One hundred forty-four programs (65.5%) returned surveys. Fifty-three (36.8%) reported a designated FP individual or team. Sperm banking was offered at 135 (97.8%) institutions, and testicular tissue cryopreservation at 37 (27.0%). Oocyte and embryo cryopreservation were offered at 91 (67.9%) and 62 (46.6%) institutions, respectively; ovarian tissue cryopreservation was offered at 64 (47.8%) institutions. The presence of dedicated FP personnel was independently associated with the ability to offer oocyte or embryo cryopreservation (odds ratio [OR], 4.7; 95% CI, 1.7 to 13.5), ovarian tissue cryopreservation (OR, 2.7; 95% CI, 1.2 to 6.0), and testicular tissue cryopreservation (OR, 3.3; 95% CI, 1.4 to 97.8). Only 26 (18.1%) participating institutions offered all current nonexperimental FP interventions. Barriers included cost (70.9%), inadequate knowledge or training (60.7%), difficulty characterizing fertility risk (50.4%), inadequate staffing (45.5%), and logistics with reproductive specialties (38%-39%).

CONCLUSION This study provides the most comprehensive view of the current landscape of FP infrastructure for children and adolescents with cancer and demonstrates that existing infrastructure is inadequate to offer comprehensive services to patients. We discuss modifiable factors to improve patient access to FP.

JCO Oncol Pract 18:e325-e333.

INTRODUCTION

Given the excellent outcomes among children and adolescents diagnosed with cancer, attention is increasingly placed on mitigating late effects and improving quality of life post-treatment.[1] It has been well established that exposure to chemotherapy such as alkylating agents, as well as therapeutic irradiation involving the gonads, may adversely affect the reproductive function of both males and females. Sperm banking has long been the standard of care (SOC) to preserve fertility before gonadotoxic exposures in postpubertal males. For postpubertal females, established SOC options include oocyte and embryo cryopreservation. In December 2019, the American Society of Reproductive Medicine deemed ovarian tissue cryopreservation (OTC) a nonexperimental fertility preservation (FP) intervention for prepubertal and postpubertal females at high risk of infertility from cancer treatment.[2,3] Testicular tissue cryopreservation (TTC), which remains an experimental procedure, is the only option to preserve reproductive germ cells in prepubertal male patients.[4] As gonadal dysfunction and infertility are key concerns for young survivors and their families, access to FP procedures is critical for providing comprehensive cancer care.[5]

The ASCO first published guidelines detailing the components of FP services for at-risk patients in 2006 followed by updates in 2013 and 2018.[6] The National Comprehensive Cancer Network and the American Society of Reproductive Medicine subsequently followed suit.[7,8] Broadly, the guidelines include (1) discussion of risks of infertility with patients pretreatment;

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on September 30, 2021 and published at ascopubs.org/journal/op on October 28, 2021: DOI https://doi.org/10.1200/OP.21.00275

(2) discussion of FP options with at-risk patients (or parents or guardians of children and adolescents) before treatment; and (3) and referral of interested patients to reproductive specialists. Despite the introduction of guidelines over 15 years ago, studies continue to show that FP services are inadequately provided to adolescent and young adult patients newly diagnosed with cancer.[9,10] This is particularly concerning, given that surveys document that adolescents and young adults prioritize fertility risk conversations and potential pursuit of preservation strategies before initiation of treatment.[11-13] Although several studies have shown that establishing structured FP services increases both patient satisfaction and FP utilization rates, their general availability and uptake in pediatric oncology programs are not well defined.[14-17] As such, the primary objectives of this study were to describe the composition and availability of FP services across Children's Oncology Group (COG) institutions and to identify the relevant infrastructure-related barriers.

METHODS

Fertility Survey

A cross-sectional survey distributed to COG member institutions was used to collect data between May and December 2018. In the absence of validated surveys, a multidisciplinary group of experts in FP, including pediatric oncologists, endocrinologists, advanced practitioners, psychologists, and nurses, developed a survey for this study. It consisted of 77 questions pertaining to institutional size and type of institution, presence and characteristics of designated FP person or team to address FP with patients, FP services available to patients, practices around FP risk assessment, counseling, and participation in preservation strategies, and barriers to FP (survey instrument available as a Data Supplement, online only). Before dissemination, the survey was pilot-tested with clinicians for content, clarity, and ease of completion. This feedback was used to make survey modifications based on group consensus. Four demographic questions and 27 infrastructure-related questions (including presence of FP person or team, FP team members, access to reproductive specialists, availability of specific FP services or procedures, availability of financial support, FP documentation and education, and infrastructure-related barriers) form the basis of this report. FP services presented in the survey included sperm banking, testicular sperm extraction, testicular sperm aspiration, electroejaculation, TTC, oocyte or embryo cryopreservation, and OTC. TTC and OTC were both experimental procedures at the time of the survey.

All surveys were administered electronically through REDCap (Research Electronic Data Capture), a secure, Health Insurance Portability and Accountability Act–compliant web application for building and managing online surveys and databases. Surveys were sent in May 2018 to a designated individual at each of the 220 COG member institutions, either the COG Principal Investigator, or an individual identified by the Principal Investigator as knowledgeable about FP. Individuals completing the survey were encouraged to obtain input from their colleagues to ensure the data were complete and accurate. If no response was received, a maximum of four follow-up e-mails with a survey link were re-sent, with final data entry completed by December 31, 2018. The study was approved by the institutional review board at the Fred Hutchinson Cancer Research Center. All respondents provided informed consent.

Data Analyses

Returned surveys were reviewed for completeness and confirmation that only one set of answers was received from each COG institution. Demographic data on nonresponders were not available for comparison. As a surrogate, we examined the number of COG registrations and enrollments to therapeutic and nontherapeutic studies between responding and nonresponding sites. Standard descriptive statistics were computed for all variables. The association (odds ratio [OR] with 95% CI]) between potential site-specific factors and selected outcomes were examined for male and female FP procedures separately using logistic regression. Factors found to have associations with $P < .1$ were then included in adjusted models. P values were two-sided, with values $< .05$ considered significant. All analyses were conducted using Stata (version 16, College Station, TX).

RESULTS

One hundred forty-four institutions completed the survey for an overall response rate of 65.5% (144 of 220). Of these, most (n = 89, 61.8%) were part of self-identified academic medical centers (Table 1). Responding sites had higher COG registrations and enrollments to therapeutic and nontherapeutic clinical trials compared with nonresponders (Appendix Table A1, online only).

FP Team

Fifty-three institutions (36.8%) reported having a designated individual or team to address FP with patients and families. Institutions that had a larger volume of cancer diagnoses (> 120/year) more commonly (57.9%) had an FP individual or team in place compared with medium or smaller sites (28.0% *v* 30.4%, respectively; $P = .007$). Twelve (8.3%) institutions reported being in the process of establishing a designated FP individual or team. Fifty-eight institutions (40.3%) reported not having a formal FP team but had some process in place to address FP; 82.8% of these sites saw ≤ 120 new cancer diagnoses per year. Twenty-one (14.7%) institutions reported no team or process in place; 90.4% of these sites saw ≤ 120 new cancer diagnoses per year.

Teams varied in composition. Forty-four (83.0%) reported physician representation, but with varied specialties.

TABLE 1. Characteristics of Participating COG Institutions (N = 144)

Characteristic	No. (%)
Clinical setting (allowed to choose more than one)	
Academic medical center	89 (61.8)
Comprehensive cancer center	27 (18.8)
Freestanding children's hospital	42 (29.4)
Children's hospital within and adult medical center	49 (34.0)
NCORP	13 (9.0)
Community hospital	15 (10.4)
No. of new cancer diagnoses per year	
< 60 (small)	56 (38.9)
61-120 (medium)	50 (34.7)
> 120 (large)	38 (26.4)
Fertility preservation champion or team present	53 (36.8)
Survivorship program present	129 (89.6)

Abbreviations: COG, Children's Oncology Group; NCORP, NCI Community Oncology Research Program.

Reproductive endocrinology and infertility (REI) physicians were the most represented (n = 32, 60.4%) followed by oncologists (n = 30, 56.6%), urologists or andrologists (n = 22, 41.5%), survivorship or late-effects physicians (n = 17, 32.1%), and pediatric or adolescent gynecologists (n = 15, 29.4%). Among respondents, REI, pediatric or adolescent gynecologists, and urologists or andrologists were available on site, 52.1%, 62.0%, and 86.6%, respectively. However, the likelihood of having REI or urologists or andrologists on site did not differ among sites with or without a designated fertility team, whereas sites with a fertility team more commonly reported adolescent gynecology on site (77.4% *v* 52.8%; $P = .004$). Additional FP team members included other clinicians (physician assistants, nurse practitioners, and registered nurses; n = 38, 71.7%), psychologists or social workers (n = 15, 10.4%), and patient navigators or coordinators (n = 11, 7.6%).

Reproductive Services

Sperm banking was offered at 135 (97.8%) sites (Table 2). Thirty (24.6%) reported having a sperm bank on site. Thirty-four (25.4%) offered electroejaculation or vibratory stimulation. Testicular sperm aspiration and testicular sperm extraction were offered by 26 (18.1%) and 31 (21.5%) institutions, respectively. TTC was offered at 37 (27%) sites. Seventeen programs (12.3%) referred patients to another institution for TTC. In multivariable analyses, the availability of TTC was independently associated with large institution (> 120 new patients/year) size (OR, 3.3; 95% CI, 1.2 to 9.3 *v* institutions with < 60 patients/year) and the presence of an FP person or team (OR, 3.3; 95% CI, 1.4 to 97.8; Table 3). In analyzing the associations between TTC and specific FP team members, those teams that contained a urologist more commonly offered TTC (OR, 12.4; 95% CI, 3.4 to 46.0). Institution type (ie, academic center *v* not; children's hospital *v* not) and inadequate staffing were not associated with the offering of TTC (data not shown).

Oocyte and embryo cryopreservation were offered to postpubertal females at 91 (67.9%) and 62 (46.6%) institutions, respectively (Table 2). For the purposes of FP, sites referred to REI within their institution (n = 56, [38.9%]), at another institution (n = 39, [27.1%]), or at a private practice (n = 34, [23.6%]). OTC was offered at 64 (47.8%) sites: 34 (25.4%) by referral to another institution, 18 (13.4%) under an institutional review board–approved protocol, and 12 (9.0%) as a clinical service. In multivariable analyses, oocyte and embryo cryopreservation were independently associated with large (> 120 new patients/year) institutions (OR, 5.6; 95% CI, 1.5 to 21.6 *v* < 60 patients/year), presence of an FP person or team (OR, 4.7; 95%, CI, 1.7 to 13.5), presence of REI as part of the FP team (OR, 13.4; 95% CI, 1.7 to 107.4), and the presence of nonphysician clinicians on the team (OR, 3.5; 95% CI, 1.1 to 11.5; Table 3). Institution type (ie, academic center *v* not; children's hospital *v* not) was not associated with the offering of oocyte or embryo cryopreservation (data not shown). OTC availability was associated with the presence of an FP person or team (OR, 2.7; 95% CI, 1.2 to 6.0), including specifically REI, gynecologists, and nonphysician team members.

Overall, noninvestigational FP options were more widely available for males (sperm banking at 97.8% of institutions) compared with females (oocyte or embryo cryopreservation at 70.4% of institutions), $P < .001$. FP options deemed experimental at the time of the survey were more widely available to females (OTC at 47.8% of institutions) compared with males (TTC at 26.8% of institutions), $P < .001$. Twenty-six institutions offered current SOC services, including sperm banking, oocyte or embryo cryopreservation, and OTC, with the caveat that OTC was not deemed SOC at the time of the survey. A higher proportion of these programs identified as large institutions ($P < .001$) and having an FP person or team ($P < .001$), including REI, urology or andrology, adolescent gynecology, and nonphysician providers (eg, patient navigator or coordinator, and nursing).

Documentation and Education

Routine documentation of FP discussions in the medical record was reported by 101 programs (70.4%), whereas 28 (19.9%) reported having a template for FP documentation. Overall, 35 (24.5%) reported that documentation of FP discussions was mandated. Documentation was not significantly associated with oocyte or embryo cryopreservation, OTC, or TTC. In providing education regarding FP, 80 (55.6%) used materials developed by other groups (eg, Livestrong/Fertile Hope or the Oncofertility Consortium), whereas 34 (23.6%) reported use of materials created by their own institution. The format of educational materials included written materials (n = 34), video-based (n = 5),

TABLE 2. Reproductive Services Available or Offered at COG Institutions (N = 144)

Service	No. (%[a])
Sperm banking for postpubertal males	
Yes	135 (97.8)
No	3 (2.2)
Type of sperm banking facility used	
Our institution has a sperm bank on site	30 (24.6)
We refer to a sperm bank outside of our institution	92 (75.4)
Electroejaculation or vibratory stimulation	
Yes	34 (25.4)
No	100 (74.6)
Other sperm collection procedures	
TESA	26 (18.1)
TESE	31 (21.5)
TTC	35 (24.3)
None of the above	77 (53.5)
TTC for prepubertal males	
Under a research protocol	14 (10.1)
Clinical service	6 (4.3)
Refer to another institution	17 (12.3)
Not available	17 (12.3)
Oocyte cryopreservation for postpubertal females	
Yes	91 (67.9)
No	43 (32.1)
Embryo cryopreservation for postpubertal females	
Yes	62 (46.6)
No	71 (53.4)
OTC	
Under a research protocol	18 (13.4)
Clinical service	12 (9.0)
Refer to another institution	34 (25.4)
Not available	70 (52.2)
Oophoropexy before pelvic radiation with possible ovarian exposure	
Yes	107 (81.1)
No	25 (18.9)

Abbreviations: COG, Children's Oncology Group; OTC, ovarian tissue cryopreservation; TESA, testicular sperm extraction; TESE, testicular sperm extraction; TTC, testicular tissue cryopreservation.

[a]Because of missing data, percentages may not be out of 144.

and web-based (n = 8). Seventy-eight programs (54.9%) reported provision of education resources to clinicians, with variable education formats (eg, grand rounds or other meetings, videos, and written materials).

Financial Considerations

Insurance covered the costs of sperm banking always at four (2.8%) sites and sometimes at 52 (36.1%) sites. A majority of sites (n = 85; 59.0%) reported that patients covered the cost of the sperm banking. Additional sources of funding at sites included institutional assistance (n = 30; 20.8%), third-party financial assistance (n = 59; 41.0%), discounted rates from sperm banks (n = 58; 40.3%), and philanthropy (n = 42; 29.2%). Coverage for embryo or oocyte cryopreservation followed similar trends as follows: insurance covered costs always at five (3.5%) sites and sometimes at 43 (29.9%) sites. Patients covered the costs at 68 (47.2%) of sites. Numbers of sites using additional sources of funding included institutional assistance (n = 15; 10.4%), third-party financial assistance (n = 44; 30.6%), discounted rates for drugs and reproductive endocrinology services (n = 31; 21.5%), and philanthropy (n = 21; 14.6%).

Additional Barriers to Providing Services

Respondents agreed or strongly agreed that the following additional infrastructure factors were barriers to providing FP services to their patients: covering the cost of FP procedures (70.9%), inadequate knowledge and training among medical teams about FP (60.7%), difficulty defining risk to fertility for an individual patient based on currently available medical literature (50.4%), inadequate staffing (45.5%), and logistics related to coordinating with REI (38.8%) and sperm banks (38.3%).

DISCUSSION

Since 2006, national organizations have issued guidelines recommending fertility risk assessment and discussion of preservation options for newly diagnosed patients with cancer as SOC before the start of therapy.[7,8,18] Pragmatically, this means a mechanism for FP referrals needs to be available at all institutions either within the institution or using an external resource. Having an established institutional infrastructure specific to FP facilitates meeting guideline recommendations, improving patient satisfaction, and using FP.[14-16,19] Yet, as the first study, to our knowledge, to describe the infrastructure landscape across a large number of pediatric hematology and oncology programs, this survey demonstrates significant variability in institutional FP infrastructure among COG institutions, with only 18% of the cohort offering all current SOC FP options (sperm or embryo or oocyte or OTC) in the pediatric and adolescent population. As > 95% of patients with childhood cancer in North America are treated at a COG-affiliated institution, this study provides the most comprehensive view of the current landscape of FP infrastructure for this population and an opportunity to consider ways to improve access.

Regardless of infrastructure, sperm banking was available at > 95% of the participating institutions via a variety of mechanisms. However, given the marked success, lack of invasiveness, and ability for sperm banking to be performed via mail-in kits, it is still notable that sperm banking was not universally available. The availability of SOC FP

TABLE 3. Program Characteristics Associated With Fertility Interventions

Program Characteristic	Embryo or Oocyte Cryopreservation OR (95% CI)[a]	OTC OR (95% CI)[b]	TTC OR (95% CI)[c]
Institutional size			
Small (< 60 new diagnoses per year)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Medium (60-120)	1.5 (0.6 to 3.5)	2.2 (0.9 to 5.3)	0.8 (0.3 to 2.5)
Large (> 120)	5.6 (1.5 to 21.6)	2.7 (0.95 to 7.8)	3.3 (1.2 to 9.3)
Presence of FP navigator or team *v* none	4.7 (1.7 to 13.5)	2.7 (1.2 to 6.1)	3.3 (1.4 to 97.8)
REI on team	13.4 (1.7 to 107.4)	4.5 (1.5 to 13.4)	NA
Gynecologist or urologist on team[d]	4.8 (0.5 to 41.5)	7.3 (1.4 to 37.7)	12.4 (3.4 to 46.0)
Nonphysicians on team	3.5 (1.1 to 11.5)	2.7 (1.1 to 6.9)	3.1 (1.2 to 7.9)

Abbreviations: FP, fertility preservation; NA, not available; OR, odds ratio; OTC, ovarian tissue cryopreservation; ref, reference; REI, reproductive endocrinology and infertility; TTC, testicular tissue cryopreservation.

[a]Adjusted for covariates listed plus gynecologist on site versus not.

[b]Adjusted for covariates listed plus site type (children's hospital *v* not) and gynecologist on site versus not.

[c]Adjusted for covariates listed plus site type (academic center *v* not) and urologist on site versus not.

[d]Gynecologist for embryo or oocyte cryopreservation or OTC, and urologist for TTC.

interventions for females was less accessible overall. Multiple factors likely contribute to this sex-based discrepancy in care, including the relative ease of collecting semen (most commonly through masturbation) that results in limited treatment delay. Mature oocyte cryopreservation involves ovarian stimulation with gonadotropins for 8-14 days and surgical retrieval of oocytes under transvaginal ultrasound guidance with sedation.

Conversely, OTC, experimental at the times of the survey, was more accessible to prepubertal female patients than TTC was to prepubertal male patients, likely because of its success in humans, whereas TTC has yet to result in a human birth.[20] Although individual institutions may not have the resources to support research for TTC, prior studies support the feasibility of partnership with larger centers offering this procedure through a standardized protocol with centralized processing or freezing.[21]

It is notable that access to embryo or oocyte cryopreservation, OTC, and TTC was all associated with the presence of dedicated FP personnel. Although being a larger site was also associated with the presence of a dedicated FP individual or team, this is one of the most modifiable factors for all size sites to improve access to FP services. The diverse representation of disciplines reported as on FP teams or as individuals suggests that there is no single configuration required of an FP team. We suspect that the different composition of existing teams reflects the heterogeneity among sites as well as team membership being composed of individuals who identify themselves as champions of FP. Although inadequate staffing was noted to be a barrier to providing FP services, it should be also noted that creative use of individuals sharing a full or partial FTE position is possible.[19] In the multivariable analysis, it was clear, however, that including REI, gynecologists and urologists or andrologists, and nonphysician members on the FP team did increase access to FP. Most sites refer patients outside of their own institution for both sperm banking and embryo or oocyte cryopreservation, and 40% of sites identified managing the logistics of coordinating care with sperm banks and reproductive endocrinology as a barrier to providing FP services. Thus, encouraging the participation of reproductive specialists on FP teams may help to streamline logistics.

Seventy percent of sites report routinely documenting FP discussions in the medical record, although only 24% reported a mandate to do so. Failure to document FP discussions means critical information about an individual's comprehensive cancer care is omitted from their record and limits the ability to accurately track patterns of discussion that occur within institutions.[22] Almost half of the respondents reported no structured educational opportunities on FP targeting clinicians, and noted inadequate knowledge and training about FP among the medical team to be the second most common barrier to providing FP services, a barrier that has previously been identified.[23] There remains a paucity of direct education for oncology physicians, including during fellowship training.[24] With the advent of virtual lectures, this deficit can in part be addressed by including experts in the area of FP among regular didactic sessions even among programs that currently lack formal FP programs. Although difficulty defining risk to fertility for an individual patient based on currently available medical literature was identified as a barrier by half of sites, guidelines have recently been published to help risk stratify exposures for female and male patients.[25]

Covering the cost of FP procedures was the barrier to providing FP services most commonly noted by sites. FP interventions were covered by insurance at extremely low rates with < 4% of sites reporting that insurance always covers SOC interventions and < 40% reporting that

insurance sometimes covers SOC interventions. At the time this survey was administered, six states were in the process of introducing or passing legislation mandating coverage of FP services, although most excluded public insurance and federally regulated insurance. At the time of this publication, 11 states have passed mandates with the same restrictions.[26] Data evaluating the impact of these changes are lacking, and this is a critical area for future study. In the absence of insurance coverage, alternative methods of helping patients pay for FP interventions have evolved. Although not all sites can rely on philanthropy and internal funding as reported by some sites, there is clearly room for sites to expand their use of third-party assistance programs and exploring discounted rates by reproductive specialists.[27]

Although two thirds of COG institutions participated in this study, it is unclear as to whether the data presented here are reflective of those institutions that did not participate and thus may over-represent or under-represent FP services and infrastructure related barriers to FP. Based on the data reflecting activity in COG, we hypothesize that the survey data may over-represent the totality of FP services and infrastructure across all institutions; however, caution is warranted when interpreting these results. Moreover, the field of FP is constantly evolving. Notably, the status of OTC changed from experimental to nonexperimental in December 2019 after completion of data collection, limiting interpretation of responses in relationship to this procedure. Additionally, survey methodology does not allow for more in-depth and nuanced assessments of current programs in place, which may be helpful in identifying key elements of program success and how these elements may be adapted for use at other programs. Nonetheless, the survey does establish a baseline for monitoring the evolution of FP services in the pediatric and adolescent cancer population.

In summary, pediatric oncology programs as a whole do not have the infrastructure to offer guideline-endorsed FP practices to patients, including providing access to SOC FP interventions. This survey identified the development of dedicated FP teams that engage reproductive specialists and non-MD members as a modifiable factor associated with increased access to FP procedures. Attention needs to be placed on creatively improving education through virtual modalities and increasing the rate of FP discussion documentation. Cost of covering FP procedures remains a major barrier to FP truly becoming a part of comprehensive cancer care, but state mandates are slowly beginning to address this issue. The current baseline established via this survey will allow for an understanding of how the recommended changes discussed impact infrastructure in the future. Additionally, better understanding of clinician knowledge gaps and clinician practices around FP communication will support increased patient access to these services.

AFFILIATIONS

[1]Center for Cancer and Blood Disorders, Connecticut Children's Medical Center, Hartford, CT
[2]University of Connecticut School of Medicine, Farmington, CT
[3]Aflac Cancer and Blood Disorders Center at Children's Healthcare of Atlanta, Atlanta, GA
[4]Department of Pediatrics, Emory University School of Medicine, Atlanta, GA
[5]Division of Medical Ethics, Departments of OB-GYN, Population Health, Grossman School of Medicine, New York University, New York, NY
[6]Memorial Sloan Kettering Cancer Center, New York, NY
[7]Cancer and Blood Disease Institute, Children's Hospital Los Angeles, Los Angeles, CA
[8]USC Norris Comprehensive Cancer Center, Los Angeles, CA
[9]Keck School of Medicine, University of Southern California, Los Angeles, CA
[10]Division of Pediatric Allergy, Immunology and Bone Marrow Transplant, University of California San Francisco, San Francisco, CA
[11]Department of Pediatrics, Baylor College of Medicine, Texas Children's Cancer and Hematology Centers, Houston, TX
[12]Center for Cancer and Blood Disorders, Children's National, Washington, DC
[13]Clinical Research and Public Health Sciences Divisions, Fred Hutchinson Cancer Research Center, Seattle, WA
[14]Weill Cornell Medicine, Division of Pediatric Hematology and Oncology, New York, NY

CORRESPONDING AUTHOR

Natasha N. Frederick, MD, MPH, Center for Cancer and Blood Disorders, CT Children's Medical Center, 282 Washington St, Hartford, CT 06106; e-mail: nfrederick@connecticutchildrens.org.

DISCLAIMER

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

EQUAL CONTRIBUTION

E.J.C. and J.L. are co-senior authors.

PRIOR PRESENTATION

Presented in poster abstracts at the American Society of Clinical Oncology Annual Meeting 2019, Chicago IL, May 31- June 4, 2019.

SUPPORT

Supported by the Children's Oncology Group under the National Cancer Institute of the National Institutes of Health award numbers U10CA180886UG1 CA189955. This research was funded in part through the NIH/NCI Cancer Center Support Grant P30 CA008748.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/OP.21.00275.

AUTHOR CONTRIBUTIONS

Conception and design: All authors
Financial support: Eric J. Chow
Administrative support: Eric J. Chow
Provision of study materials or patients: Gwendolyn P. Quinn, Julienne Brackett, Eric J. Chow
Collection and assembly of data: Natasha N. Frederick, Lillian R. Meacham, Gwendolyn P. Quinn, Brooke Cherven, Christopher C. Dvorak, Sameeya Ahmed-Winston, Elyse Bryson, Eric J. Chow, Jennifer Levine
Data analysis and interpretation: Natasha N. Frederick, James L. Klosky, Lillian R. Meacham, Gwendolyn P. Quinn, Joanne Frankel Kelvin, Brooke Cherven, David R. Freyer, Christopher C. Dvorak, Julienne Brackett, Sameeya Ahmed-Winston, Eric J. Chow, Jennifer Levine
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

REFERENCES

1. Armstrong GT, Chen Y, Yasui Y, et al: Reduction in late mortality among 5-year survivors of childhood cancer. N Engl J Med 374:833-842, 2016
2. Algarroba GN, Sanfilippo JS, Valli-Pulaski H: Female fertility preservation in the pediatric and adolescent cancer patient population. Best Pract Res Clin Obstet Gynaecol 48:147-157, 2018
3. Halpern JA, Das A, Faw CA, et al: Oncofertility in adult and pediatric populations: Options and barriers. Transl Androl Urol 9:S227-S238, 2020
4. Shetty G, Mitchell JM, Meyer JM, et al: Restoration of functional sperm production in irradiated pubertal rhesus monkeys by spermatogonial stem cell transplantation. Andrology 8:1428-1441, 2020
5. Gilleland Marchak J, Elchuri SV, Vangile K, et al: Perceptions of infertility risks among female pediatric cancer survivors following gonadotoxic therapy. J Pediatr Hematol Oncol 37:368-372, 2015
6. Oktay K, Harvey BE, Partridge AH, et al.: Fertility preservation in patients with cancer: ASCO clinical practice guideline update. J Clin Oncol 36:1994-2001, 2018
7. Coccia PF, Pappo AS, Beaupin L, et al: Adolescent and young adult oncology, version 2.2018, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 16:66-97, 2018
8. Practice Committee of the American Society for Reproductive Medicine: Fertility preservation in patients undergoing gonadotoxic therapy or gonadectomy: A committee opinion. Fertil Steril 112:1022-1033, 2019
9. Vesali S, Navid B, Mohammadi M, et al: Little information about fertility preservation is provided for cancer patients: A survey of oncologists' knowledge, attitude and current practice. Eur J Cancer Care (Engl) 28:e12947, 2019
10. Lampic C, Wettergren L: Oncologists' and pediatric oncologists' perspectives and challenges for fertility preservation. Acta Obstet Gynecol Scand 98:598-603, 2019
11. Frederick NN, Recklitis CJ, Blackmon JE, et al: Sexual dysfunction in young adult survivors of childhood cancer. Pediatr Blood Cancer 63:1622-1628, 2016
12. Benedict C, Thom B, Friedman DN, et al: Young adult female cancer survivors' unmet information needs and reproductive concerns contribute to decisional conflict regarding posttreatment fertility preservation. Cancer 122:2101-2109, 2016
13. Taylor JF, Ott MA: Fertility preservation after a cancer diagnosis: A systematic review of adolescents', parents', and providers' perspectives, experiences, and preferences. J Pediatr Adolesc Gynecol 29:585-598, 2016
14. Kelvin JF, Thom B, Benedict C, et al: Cancer and fertility program improves patient satisfaction with information received. J Clin Oncol 34:1780-1786, 2016
15. Lewin J, Ma JMZ, Mitchell L, et al: The positive effect of a dedicated adolescent and young adult fertility program on the rates of documentation of therapy-associated infertility risk and fertility preservation options. Support Care Cancer 25:1915-1922, 2017
16. Sheth KR, Sharma V, Helfand BT, et al: Improved fertility preservation care for male patients with cancer after establishment of formalized oncofertility program. J Urol 187:979-986, 2012
17. Lopategui DM, Ibrahim E, Aballa TC, et al: Effect of a formal oncofertility program on fertility preservation rates-first year experience. Transl Androl Urol 7: S271-S275, 2018 (suppl 3)
18. Oktay K, Harvey BE, Loren AW: Fertility preservation in patients with cancer: ASCO clinical practice guideline update summary. J Oncol Pract 14:381-385, 2018
19. Moravek MB, Appiah LC, Anazodo A, et al: Development of a pediatric fertility preservation program: A report from the Pediatric Initiative Network of the Oncofertility Consortium. J Adolesc Health 64:563-573, 2019
20. Gassei K, Orwig KE: Experimental methods to preserve male fertility and treat male factor infertility. Fertil Steril 105:256-266, 2016
21. Valli-Pulaski H, Peters KA, Gassei K, et al: Testicular tissue cryopreservation: 8 years of experience from a coordinated network of academic centers. Hum Reprod 34:966-977, 2019
22. Quinn GP, Block RG, Clayman M, et al: If you did not document it, it did not happen: Rates of documentation of discussion of infertility risk in adolescent and young adult oncology patients' medical records. JCO Oncol Pract 11:137-144, 2015
23. Quinn GP, Vadaparampil ST: Fertility preservation research, Fertility preservation and adolescent/young adult cancer patients: Physician communication challenges. J Adolesc Health 44:394-400, 2009
24. Frederick NN, Fine E, Michaud A, et al: Pediatric hematology and oncology fellow education in sexual and reproductive health: A survey of fellowship program directors in the United States. Pediatr Blood Cancer 67:e28245, 2020
25. Meacham LR, Burns K, Orwig KE, et al: Standardizing risk assessment for treatment-related gonadal insufficiency and infertility in childhood adolescent and young adult cancer: The Pediatric Initiative Network risk stratification system. J Adolesc Young Adult Oncol 9:662-666, 2020
26. Alliance for Fertility Preservation: State Laws and Legislation https://www.allianceforfertilitypreservation.org/advocacy/state-legislation
27. Omesi L, Narayan A, Reinecke J, et al: Financial assistance for fertility preservation among adolescent and young adult cancer patients: A utilization review of the Sharing Hope/LIVESTRONG Fertility Financial Assistance Program. J Adolesc Young Adult Oncol 8:554-559, 2019

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Infrastructure of Fertility Preservation Services for Pediatric Cancer Patients: A Report From the Children's Oncology Group

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/op/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Gwendolyn P. Quinn
Honoraria: Flo Health

Christopher C. Dvorak
Consulting or Advisory Role: Alexion Pharmaceuticals, Omeros
Research Funding: Jasper Therapeutics

Julienne Brackett
Research Funding: Bristol Myers Squibb

Sameeya Ahmed-Winston
Speakers' Bureau: Jazz Pharmaceuticals

Eric J. Chow
Research Funding: Abbott

Jennifer Levine
Stock and Other Ownership Interests: UMotif

No other potential conflicts of interest were reported.

APPENDIX

TABLE A1. COG Annual Clinical Trial Registrations and Enrollments

Registrations and Enrollments	Survey Responders (N = 144) Median (IQR)	Survey Nonresponders (N = 76) Median (IQR)	*P*[a]
COG registrations	33.5 (18-55)	23 (15-35)	< .001
COG enrollments on therapeutic trials	8 (5-16)	5 (2-9)	< .001
COG enrollments on nontherapeutic trials	44 (22-72.5)	26 (18-39)	< .001
COG total enrollments	55 (27-88.5)	32 (21-48)	< .001

Abbreviation: COG, Children's Oncology Group.
[a]*P* value is by Wilcoxon rank-sum test.