A dozen years of ovarian tissue cryopreservation at a pediatric hospital: tracking program and patient metrics while adapting to increasing needs

Kathryn L. McElhinney, M.D.,[a,b,c] Tara Kennedy, B.S.,[a,b] Erin E. Rowell, M.D.,[a,b,c] and Monica M. Laronda, Ph.D.[a,b,c,d,e]

[a] Department of Surgery, Division of Pediatric Surgery, Feinberg School of Medicine, Northwestern University, Chicago, Illinois; [b] Fertility & Hormone Preservation & Restoration Program, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois; [c] Stanley Manne Children's Research Institute, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois; [d] Department of Pediatrics, Division of Endocrinology, Feinberg School of Medicine, Northwestern University, Chicago, Illinois; and [e] Department of Obstetrics and Gynecology, Feinberg School of Medicine, Northwestern University, Chicago, Illinois

Objective: To review the program and patient metrics for ovarian tissue cryopreservation (OTC) within a comprehensive pediatric fertility preservation program in its first 12 years of development.
Design: Retrospective review.
Setting: A tertiary children's hospital in a large urban center between March 2011 and February 2023.
Patients: Pediatric patients who underwent OTC.
Interventions: Unilateral oophorectomy for OTC.
Main Outcome Measures: Patient demographics and clinical course information were collected for analysis.
Results: A total of 184 patients underwent OTC in the first 12 years. One hundred fifteen patients were prepubertal at the time of OTC, and 69 were postpubertal. In total, 128 patients (69.6%) received part of their planned therapy before OTC. Starting in 2018, 104 participants (92.0%) donated tissue to research, 99 participants (87.6%) donated blood, and 102 (90.2%) donated media to research. There was a decrease in the median age of patients who underwent OTC from 16.4–6.6 years and an overall increase in the proportion of patients per year that were prepubertal. Forty-eight (26.0%) patients who underwent OTC were outside referrals and traveled from as far as Seattle, Washington.
Conclusion: During the first 12 years of this program, oncofertility research increased, annual tissue cryopreservation cases increased, and the median age of those who underwent OTC decreased. The program was adapted to build a stand-alone gonadal tissue processing suite and specialized in prepubertal ovarian tissue processing. The program will continue to adapt to patient needs in the upcoming decades because restoration technologies advance through research supported by this and collaborating programs. (F S Rep® 2024;5:197–204. ©2024 by American Society for Reproductive Medicine.)
Key Words: Pediatric oncofertility, ovarian tissue cryopreservation, fertility preservation, gonadotoxic therapy

Received August 25, 2023; revised February 9, 2024; accepted February 13, 2024.
E.E.R. and M.M.L. should be considered similar in author order.
Supported in part, by the National Institutes of Health's National Center for Advancing Translational Sciences, grant number (TL1TR001423, to K.L.M.).
Supported in part, by the Gesualdo Foundation Research Scholar funds (to M.M.L.).
The data underlying this article cannot be shared publicly for the privacy of individuals who participated in the study. The data will be shared, on reasonable request, with the corresponding author.
Correspondence: Monica M. Laronda, Ph.D., Fertility and Hormone Preservation and Restoration Program, Ann and Robert H. Lurie Children's Hospital of Chicago, 225 E Chicago Ave, Box 63, Chicago, IL 60611 (E-mail: mlaronda@luriechildrens.org).

F S Rep® Vol. 5, No. 2, June 2024 2666-3341

https://doi.org/10.1016/j.xfre.2024.02.009

Fertility preservation (FP) is a key component of comprehensive care for patients who are at increased risk of developing premature gonadal insufficiency because of their treatments for malignant, genetic, or rheumatologic conditions. Rates of survival for pediatric cancers have improved, and aggregate 5-year survival rates now exceed 80% with most patients living into adulthood (1). Sixty percent of survivors of pediatric cancers will have a serious long-term complication that may include infertility (2–11). Alkylating chemotherapeutics or radiation fields that include the hypothalamus or gonads cause a significantly increased risk for premature gonadal insufficiency and/or infertility (4–6, 8, 10–14). The American Society of Clinical Oncology, the National Comprehensive Cancer Network, the American Academy of Pediatrics, and the American Society for Reproductive Medicine (ASRM) recommend comprehensive FP counseling to any patient whose anticipated treatment increases their risk of infertility (15–18).

First described in 1996, ovarian tissue cryopreservation (OTC) is the only modality for FP in patients who have not yet progressed through puberty (19, 20). Additionally, the nature and urgency of starting treatment may not allow the time required for ovarian stimulation and oocyte retrieval for egg cryopreservation, which is not recommended after the initiation of chemotherapy and radiation. For those patients, OTC is an option for FP before the onset of treatment (20–22). Ovarian function is then restored by ovarian tissue transplantation (OTT) into either orthotopic or heterotopic locations (23–25). More than 140 live births have been reported from OTT after OTC as of 2020 (26). In 2019, the ASRM removed the experimental label from OTC; however, there is an understanding among pediatric providers and researchers that important research must continue to define and improve OTC and OTT outcomes, especially in pediatric and adolescent individuals where only a few OTTs have been described (18, 27, 28).

In 2011, the Ann and Robert H. Lurie Children's Hospital of Chicago (Lurie Children's) joined Northwestern University's Oncofertility Consortium to offer OTC as an FP option for pediatric patients at increased risk of infertility. In the subsequent 12 years, unilateral oophorectomy followed by OTC was performed for 184 patients. This study retrospectively reviewed the program and patient metrics with the goal of highlighting significant research and patient care milestones.

MATERIALS AND METHODS

Unilateral oophorectomy and OTC

Pediatric girls whose treatment was determined to have a significantly increased risk or a high increased risk of infertility qualified to be included in this study (14, 29). All prepubertal patients and postpubertal patients who could not delay the start of their treatment were offered OTC. All OTC procedures were conducted under the Lurie Children's institutional review board (IRB) protocol (prepubertal IRB No. 2014–15534 and 2018–1509, postpubertal IRB No. 2011–14420 and 2017–1149). All families and patients aged 18 years and older provided written informed consent for OTC and the collection of research specimens. When appropriate, minor patients provided written assent. All patients who underwent OTC had a unilateral oophorectomy (30, 31). This was most often performed laparoscopically, but it could occur also during a laparotomy when there was concurrent tumor resection. When possible, oophorectomy was performed under the same anesthesia as that needed for another procedure, such as central venous port placement or bone marrow biopsy. After the ovary was retrieved, a 3–4 mm punch biopsy was taken and sent for routine pathology examination. Previous protocols under the Oncofertility Consortium (2011–2016) used 20% of the processed ovarian tissue for research. When the patient and family consented to donate tissue after 2018, a second 3–4 mm punch biopsy was taken for research purposes. Some of the donated biospecimens were processed in a research laboratory for ongoing studies, although others were cryopreserved, flash-frozen, or otherwise appropriately processed and stored for future studies. Patients who had undergone previous treatment with alkylating chemotherapy were asked to donate a punch biopsy to research. When the ovary was small, the research tissue sample was forgone when $<80\%$ of the tissue would be left for the patient's future use. The ovary was transferred to the Northwestern Medicine Embryology and Andrology Laboratory (2011–11/2020) or the Lurie Children's Gonadal Tissue Processing Suite (GTPS, 12/2020–present) in OFC holding media (Sage/Origio No. ART-8040). The cortex of the ovary was thinned to 1.5–2.0 mm and cut into strips that were 3–5 mm wide. Strips were incubated in OFC cryopreservation and freezing media (Sage/Origio ART-8050) and then cryopreserved in cryovials using a controlled rate freezer (32, 33). The vials of cryopreserved tissue are transferred to ReproTech, LLC, for long-term storage.

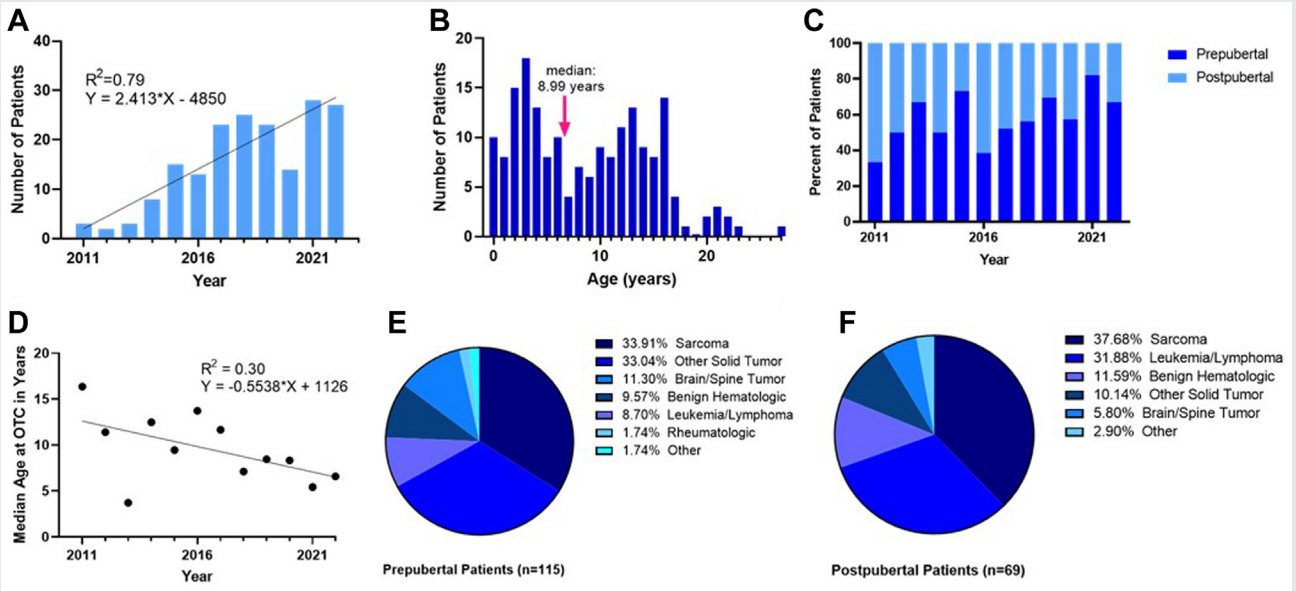
Review of patient demographics and clinical characteristics

A retrospective review was conducted of all patients who underwent OTC at Lurie Children's from March 2011 to February 2023. Each 12-month interval is from March through February of the following year (i.e., the year 2011 refers to March 2011 through February 2012). The electronic medical record was used to collect patient demographic data, referral information, diagnosis, and clinical data, date of procedure, and whether patients donated specimens for research. Data on the total number of patients undergoing OTC annually, diagnosis, previous treatment, and pubertal status at the time of OTC and referrals were also collected.

Statistic analysis

All statistical analyses were performed using Graph Pad Prism 9 (GraphPad Software, San Diego, CA). All regressions were performed using a linear regression. R Statistical Software (v4.2.1; R Core Team 2022) was used to

FIGURE 1



(**A**) Number of ovarian tissue cryopreservations (OTCs) annually from March 2011 to February 2023. The 12-month period refers to March through February of the following year (i.e., the year 2011 refers to March 2011 through February 2012). (**B**) Histogram of patients by age in years at the time of OTC. The median age at the time of OTC was 8.99 years. (**C**) Proportion of prepubertal vs. postpubertal OTCs by year when the procedure was performed. (**D**) The median age at OTC by year. (**E**) Diagnoses in prepubertal and (**F**) Postpubertal patients undergoing OTC.

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construct the referral map in Supplemental Figures 1A and 1B, (available online).

RESULTS

Patient demographics and diagnosis

A total of 184 patients underwent OTC at Lurie Children's from 2011–2022, with a general trend of increasing total cases annually over the 12-year period (slope = 2.4) (Fig. 1A). The median age at OTC was 8.99 years (range, 0–27 years) (Fig. 1B). One hundred fifteen (62.5%) patients were prepubertal, and 69 (37.5%) were postpubertal at the time of OTC. The proportion of prepubertal vs. postpubertal patients varied each year (Fig. 1C). However, there was a general trend toward younger patients undergoing OTC over time (slope = -0.55) (Fig. 1D). Most patients identified as White (73.2%), with 8.2% identifying as Black, 5.4% identifying as Asian and 13.2% identifying as another race. Most patients were non-Hispanic (75.5%), with 15.8% identifying as Hispanic or Latino, whereas 8.7% did not disclose.

The most common primary diagnosis in patients who underwent OTC was sarcoma, followed by other solid tumors, leukemia, and lymphoma. This differed between prepubertal and postpubertal patients. Prepubertal patients were most often diagnosed with other solid tumors—typically Wilm's tumor or neuroblastoma—then sarcoma (Fig. 1E). This was then followed by a brain or spine tumor. Postpubertal patients were primarily diagnosed with sarcoma, followed by leukemia or lymphoma, and then a benign hematologic condition (Fig. 1F).

Patient clinical course

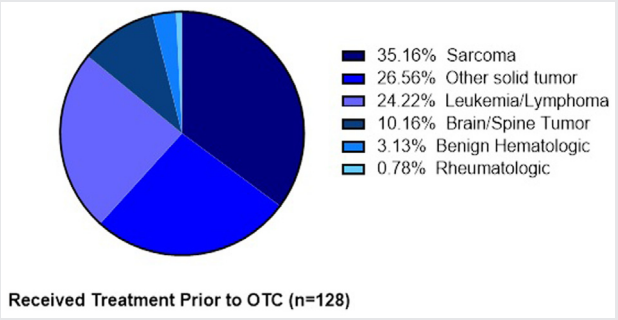
Referrals for OTC were received from centers across the country, although most referrals were received from centers in the Midwest (Supplemental Fig. 1, available online). Most patients who underwent OTC were already receiving care for their principal diagnosis at Lurie Children's Hospital at the time of referral: 139 (74.7%) patients were referred for OTC while receiving care at Lurie Children's Hospital, whereas 47 (25.3%) patients were referred from outside institutions (Supplemental Fig.1C, available online).

In total, 128 (69.6%) patients received part of their planned therapy before OTC either because of an urgent need to start gonadotoxic treatment because of cancer or because of families requiring additional time to consider FP options (Fig. 2). This included 80 (69.6%) prepubertal patients and 48 (69.6%) postpubertal patients. Most OTC procedures occurred under one anesthetic exposure, coordinated with another procedure related to the patient's principal diagnosis: 61.4% (63.5% prepubertal and 58.0% postpubertal) were performed with cohort procedures, which included a port placement, bone marrow biopsy, lumbar puncture, or gastrostomy tube placement.

Donations to research

Beginning in 2018, patients could donate specimens to the foundational research laboratory, including tissue biopsies, blood specimens, and media containing discarded stroma collected during tissue processing that would typically be discarded after processing the ovary for cryopreservation (Fig. 3).

FIGURE 2



The diagnoses of patients who underwent gonadotoxic treatment before undergoing ovarian tissue cryopreservation (OTC). These patients often required starting gonadotoxic treatment immediately because of their condition, or families requested more time to decide on pursuing fertility preservation. All patients who received treatment before OTC were diagnosed with a malignancy.

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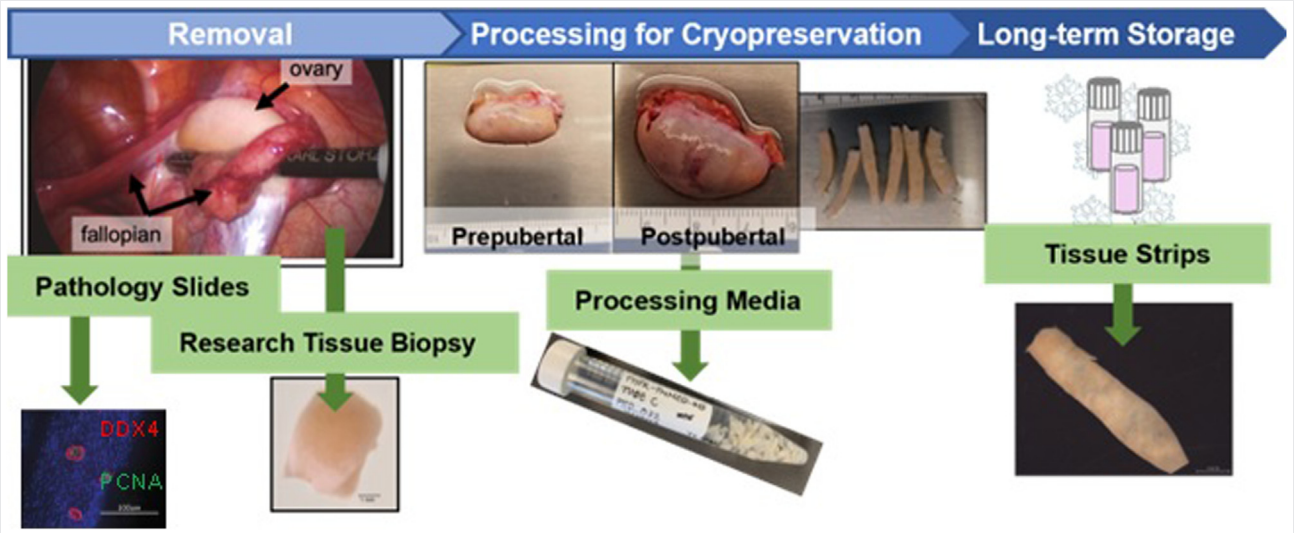
A tissue specimen donation was specifically requested from patients who underwent gonadotoxic therapy before OTC to assess the effects of treatments on the pediatric ovary. One hundred thirteen patients underwent OTC between 2018 and 2022, of whom 104 (92.0%) donated tissue to research. Of those who donated to research, 52 (50.0%) of these participants had a previous treatment. Ninety-nine (87.6%) participants donated blood, and 102 (90.2%) donated media for research.

Key milestones and publications during the first 12 years of the program

The first OTC case at Lurie Children's (then called Children's Memorial Hospital) occurred in March of 2011. The Oncofertility program at Lurie Children's collaborated with the neighboring adult hospital, now called Northwestern Medicine, to process ovarian tissue for OTC, and research tissue was donated to Northwestern University. The ASRM removed the experimental label from egg cryopreservation in 2012 (34). In 2016, Lurie Children's identified key translational and clinical research initiatives and named the Fertility & Hormone Preservation & Restoration (FHPR) Program as one initiative. Support for the FHPR program included establishing a basic and translational research program at the Stanley Manne Children's Research Institute and included administrative support within Pediatric Surgery for clinical research and patient care goals. With this expansion, additional protocols for gonadal tissue cryopreservation supported translational and clinical research for gonadal cryopreservation for patients with a difference (disorder) in sex development and the first surgery for gonadal tissue cryopreservation under the difference (disorder) in sex development -specific research protocol was performed in 2018 (35, 36). In addition, in 2018, OTC surgical case volume exceeded 30 cases in 1 year, which strained the tissue processing capability of the adult embryology laboratory and initiated discussions to build a pediatric-focused laboratory for processing ovarian tissue for OTC within Lurie Children's. The GTPS was opened within the sterile core of the operating room and received appropriate Federal Drug Administration and Illinois Department of Public Health registrations. During

FIGURE 3



The workflow and types of samples that can be donated to research. Patients and their families are given the option to donate ovarian tissue, used processing media, and tissue strips that will otherwise not be used. Patients who have received previous treatment with alkylating chemotherapy are asked, as part of their consent, to donate an ovarian punch biopsy to research. Additionally, patients and families can donate blood at the time of surgery.

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this time, in December 2019, the ASRM released its committee opinion, which removed the experimental label from OTC as a means of FP in patients with ovaries (18). The GTPS opened to accept the first ovary for processing in December 2020, amidst the coronavirus disease of the 2019 global pandemic.

DISCUSSION

The Children's Oncology Group 2003 Report on Long-term Follow-up Guidelines suggests monitoring fertility and hypogonadism in survivors of childhood cancer (37). Professional societies, such as the ASRM and the American Society for Clinical Oncology, shortly followed the Children's Oncology Group by recommending that all new patients with a cancer diagnosis be informed of the risks of infertility and their options for FP before cancer treatment (15, 38). Therefore, a comprehensive pediatric care program includes the ability to offer inclusive and timely discussions about the potential increased risk of future infertility or sex hormone deficiencies.

Comprehensive FP consultations must be supported by the opportunity to undergo FP procedures. These procedures can include testicular tissue cryopreservation, sperm cryopreservation, OTC, or egg cryopreservation, depending on the patient's gonads and pubertal status. Discussions during consultation with patients and their families can be difficult as medical, ethical, social, religious, and cultural factors must be considered (39–41). When appropriate, patients are included in these discussions directly with their parents because it has been shown previously that adolescent patients have a strong desire to participate in discussions about FP (42). These discussions involve looking to the future in patients who may have a difficult diagnosis or are unsure when they plan to become biologic parents in the future (43). Alternative options to traditional childbearing must be also presented and considered, such as adoption, egg and sperm donation, and surrogacy (44–46). Although the preservation of ovarian tissue does not commit a patient to having biologic children, it does provide them with additional potential opportunities to have biologic children in the future. Most patients and families wish to have the option to safeguard their future fertility when faced with gonadotoxic treatments (39, 47). For many patients, OTC is the modality that, at present, provides the greatest possibility for restoring future fertility. However, patients and families should be counseled that OTC does not guarantee future biologic children as a result of the decision to cryopreserve their tissue (26).

The Northwestern University Oncofertility Consortium was established in 2007. Lurie Children's (previously Children's Memorial Hospital) formally joined the Oncofertility Consortium in 2010. At the time, ovarian transposition and embryo cryopreservation were the only nonexperimental options for individuals with ovaries with fertility-threatening diagnoses or treatments (34, 48, 49). Ovarian tissue cryopreservation offered an alternative option for patients who could not delay treatment for ovarian stimulation, did not want to use a current partner or sperm donor for embryo cryopreservation, or were advised against ovarian stimulation for hormone-responsive cancers. Additionally, OTC was the first option for FP in prepubertal patients (20–22). The OTC protocol was opened at Lurie Children's in 2011, and the first patient was enrolled in March 2011. There have been several events that have led to an increase in access to FP for pediatric patients with ovaries. The ASRM removed the experimental label of egg cryopreservation in 2012, making ovarian stimulation and egg cryopreservation more appealing to individuals who did not want to freeze embryos but could undergo ovarian stimulation for FP. One group of reproductive endocrinologists from the Icahn School of Medicine at Mount Sinai reported that before the removal of the experimental label of egg cryopreservation, no insurance companies offered coverage for egg cryopreservation (50). In the years since, there has been a steady increase in the percentage of cases of egg cryopreservation covered by insurance, with 42.7% of cases covered by insurance in 2022. They also report a steady increase in egg cryopreservation cases, with 119 egg cryopreservation procedures performed in 2012 and 684 procedures performed in 2022. Another group from the University of Pennsylvania showed that women with insurance coverage for egg cryopreservation were more likely to present for counseling about egg cryopreservation and then ultimately move forward and complete ovarian stimulation and egg cryopreservation (51). This change in practice may have contributed to the overall shift in the proportion of OTC cases from postpubertal, adolescent, and adult patients to prepubertal patients, which was seen also in the Oncofertility Consortium cohort overall (52). Illinois residents and many patients who sought care at Lurie Children's were affected by HB2617, which mandated that health insurance must cover FP services for iatrogenic infertility in 2017 (53). In December 2019, the ASRM released its committee opinion, which removed the experimental label from OTC as a means of FP in patients with ovaries (18). We believe that the removal of the experimental label from OTC will lead to a similar trend, because what was seen after the experimental label was removed from egg cryopreservation increased insurance coverage and overall increased access to this form of FP.

Another shift in OTC utilization may have been a consequence of demonstrating that laparoscopic oophorectomy can be safely performed in young infants (30). The FHPR program has a standardized approach to unilateral oophorectomy for OTC to optimize the amount of ovarian tissue available for cryopreservation and future OTT (30). Other institutions have opted for an ovarian biopsy or a partial oophorectomy. However, there are notable disadvantages to these approaches. Ovarian biopsy or partial oophorectomy increases the risk of thermal damage to the ovarian cortex—both within the tissue taken for cryopreservation and what remains intact within the patient. In addition, there has been a reported increased risk of hemorrhage in cases of ovarian biopsy (54). Additionally, performing a partial oophorectomy or biopsy is technically challenging, particularly in the prepubertal patient where the ovary and body habitus are small. Unilateral oophorectomy allows for the storage of more cortical tissue and more future attempts at OTT, while leaving the remaining ovary untouched and a potential site for

orthotopic transplantation (54–56). After patients undergo a unilateral oophorectomy, the remaining ovary undergoes compensatory changes, leading to similar hormone production and rates of fertility when compared with patients who have not undergone oophorectomy (57). Patients who underwent unilateral oophorectomy for reasons other than OTC experience menopause 1.8 years earlier than their peers who still have both ovaries; however, the difference is small and likely not clinically significant (58, 59). Long-term patient follow-up within the FHPR program is ongoing to compare gonadal function in those who had OTC and who had similar diagnoses and treatments but did not opt for OTC.

The FHPR program's research efforts support future innovations in fertility and hormone preservation and restoration with donated human specimens (60, 61). Most patients and families elect to donate research specimens. Access to pathology specimens has enabled robust characterization of follicle density and depth of primordial follicles within the tissue to define best practices in ovarian tissue processing for OTC (62). We were also able to define changes in the gross and subanatomic features of the human ovary across the pubertal transition and support our collective efforts to define terms and definitions that consider the ovary across stages of development (62–64). The media that is used during the ovarian tissue processing for OTC is discarded unless otherwise donated to research. These media samples contain ovarian interstitial cells and cumulus-oocyte complexes that support current and future research into the growth and maturation of oocytes from prepubertal and adolescent ovaries, with and without previous chemotherapy treatments (65). Serum from donated blood specimens is used to create hormone benchmarks across the pubertal transition and to test modalities for monitoring serum levels using protein-saver cards previously standardized for the adult population (66). Finally, peripheral blood mononuclear cells from donated blood specimens are used to make patient-derived human induced pluripotent stem cells for future research into cell-based hormone replacement therapies (67, 68).

In addition to our own work, there has been increasing interest and awareness on the topic of pediatric FP and OTC, as demonstrated by the increase in publications on the subject annually from 2011 through 2022 (Supplemental Fig. 2 and Supplemental Table 1, available online). This increase in the literature available since the beginning of this program and the willingness of families to travel nationally for FP support the increasing interest and support of OTC by patients and their families (Supplemental Figures 1 and 2). This awareness coincided with the growth of worldwide Oncofertility Consortium participation and an increase in reported patients undergoing successful OTT that restored ovarian hormones and produced biologic children (61, 69–73). Ongoing efforts by organizations, such as the Alliance for FP are also improving access to FP options by advocating for legislation at the state level to mandate insurance coverage for FP procedures (74). Presently, OTT is the only option for reintroducing native ovarian hormone function after a patient experiences premature ovarian insufficiency (23). Since 2016, there have been 5 individuals, including one reported in the lay press, who had undergone OTT after an OTC at age of <14 years. This has resulted in 3 live births and the induction of puberty in 2 adolescent girls (69–73). Future work within our program includes optimizing fertility and hormone restoration rates through implementing and optimizing OTT for patients who underwent OTC as a child or adolescent. We are the largest children's hospital in our area and offer risk assessment, education, and counseling to every patient at risk of premature ovarian insufficiency. Additional work needs to be done to make patients and physicians at other institutions aware of fertility risks, the FP option, and that OTC is available at Lurie Children's and other institutions in the country. Future directions for our program include collaborative efforts with other institutions to offer unilateral oophorectomy locally to patients who may not otherwise be able to travel for this procedure, allowing their ovary to be shipped for processing and cryopreservation at Lurie Children's. This is a prevalent model in Denmark, Germany, and the United Kingdom and would expand access to this unique pediatric-focused program to more diverse families outside of this large academic institution (13, 75, 76). No patients to date have used the OTC tissue preserved within our program for restoration. However, we anticipate that some of our oldest patients, or those who had undergone OTC in the earlier years, may request OTT for fertility and hormone restoration soon. This program will continue to contribute valuable information on processing, cryopreservation, and outcomes while serving these patients in the fertility and hormone preservation and restoration process.

CONCLUSION

Ovarian tissue cryopreservation cases in the FHPR program have increased over the past 12 years as the median age at FP by OTC has decreased. These changes coincide with several pivotal changes within the field, including increased availability of oncofertility information in the form of clinical and translational literature publications, an increased number of reported live births after OTT, an increased number of OTT in individuals who were aged <14 years at the time of OTC, and changes in professional society guidelines that expanded access and acceptability of OTC. It is believed that advocacy will continue to increase access to OTC through mandated insurance coverage using legislation at both the state and federal levels. Data will continue to be collected to drive this field, with a particular focus on options for achieving puberty and live births with OTT for patients who were prepubertal at the time of OTC.

CRediT Authorship Contribution Statement

Kathryn L. McElhinney: Investigation, Writing – review & editing, Writing – original draft, Visualization, Formal analysis, Data curation, Software, Validation. **Tara Kennedy:** Investigation, Writing – review & editing, Methodology, Investigation, Data curation, Software, Validation. **Erin E. Rowell:** Investigation, Writing – review & editing, Supervision, Resources, Data curation, Conceptualization, Funding

acquisition. **Monica M. Laronda:** Investigation, Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Data curation, Conceptualization, Funding acquisition.

Declaration of Interests

K.L.M. has nothing to disclose. T.K. has nothing to disclose. E.E.R. has nothing to disclose. M.M.L. has nothing to disclose.

REFERENCES

1. Armenian SH, Landier W, Hudson MM, Robison LL, Bhatia S. on behalf of the COG Survivorship and Outcomes Committee. Children's Oncology Group's 2013 blueprint for research: survivorship and outcomes. Pediatr Blood Cancer 2013;60:1063–8.
2. Alessi I, Caroleo AM, de Palma L, Mastronuzzi A, Pro S, Colafati GS, et al. Short and long-term toxicity in pediatric cancer treatment: central nervous system damage. Cancers 2022;14:1540.
3. Bath LE, Anderson RA, Critchley HO, Kelnar CJ, Wallace WH. Hypothalamic–pituitary–ovarian dysfunction after prepubertal chemotherapy and cranial irradiation for acute leukaemia. Hum Reprod 2001;16:1838–44.
4. Chemaitilly W, Mertens AC, Mitby P, Whitton J, Stovall M, Yasui Y, et al. Acute ovarian failure in the childhood cancer survivor study. J Clin Endocrinol Metab 2006;91:1723–8.
5. Cooke-Barber J, Scorletti F, Rymeski B, Eshelman-Kent D, Nagarajan R, Burns K, et al. Long-term follow-up of surgical outcomes for patients with Wilms tumor and neuroblastoma. Cancer 2021;127:3232–8.
6. Gleeson HK, Shalet SM. The impact of cancer therapy on the endocrine system in survivors of childhood brain tumours. Endocr Relat Cancer 2004;11:589–602.
7. Hsiao W, Lapite A, Faig W, Abdel-Megid M, Carlson C, Hobbie W, et al. Long-term kidney and cardiovascular complications in pediatric cancer survivors. J Pediatr 2023;255:89–97.e1.
8. Hudson MM, Ness KK, Gurney JG, Mulrooney DA, Chemaitilly W, Krull KR, et al. Clinical ascertainment of health outcomes among adults treated for childhood cancer. JAMA 2013;309:2371–81.
9. Parisi GF, Cannata E, Manti S, Papale M, Meli M, Russo G, et al. Lung clearance index: a new measure of late lung complications of cancer therapy in children. Pediatr Pulmonol 2020;55:3450–6.
10. Sklar CA, Mertens AC, Mitby P, Whitton J, Stovall M, Kasper C, et al. Premature menopause in survivors of childhood cancer: a report from the childhood cancer survivor study. J Natl Cancer Inst 2006;98:890–6.
11. Thomson AB, Critchley HOD, Kelnar CJH, Wallace WHB. Late reproductive sequelae following treatment of childhood cancer and options for fertility preservation. Best Pract Res Clin Endocrinol Metab 2002;16:311–34.
12. Hutchcraft ML, McCracken K, Whiteside S, Lustberg M, Lindheim SR, Nahata L, et al. Current fertility preservation options for female patients with hodgkin lymphoma. Obstet Gynecol Surv 2020;75:683–91.
13. Jensen AK, Rechnitzer C, Macklon KT, Ifversen MRS, Birkebæk N, Clausen N, et al. Cryopreservation of ovarian tissue for fertility preservation in a large cohort of young girls: focus on pubertal development. Hum Reprod 2017;32:154–64.
14. Meacham LR, Burns K, Orwig KE, Levine J. 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 2020;9:662–6.
15. Lee SJ, Schover LR, Partridge AH, Patrizio P, Wallace WH, Hagerty K, et al. American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. JCO 2006;24:2917–31.
16. National Comprehensive Cancer Network. NCCN guidelines version 1.2019 adolescent and young adult oncology. Available at: https://www.nccn.org/professionals/physician_gls/pdf/aya.pdf.
17. Klipstein S, Fallat ME, Savelli S. Committee on Bioethics, Section on Hematology/Oncology, Section on Surgery. Fertility preservation for pediatric and adolescent patients with cancer: medical and ethical considerations. Pediatrics 2020;145:e20193994.
18. Practice Committee of the American Society for Reproductive Medicine. Fertility preservation in patients undergoing gonadotoxic therapy or gonadectomy: a committee opinion. Fertil Steril 2019;112:1022–33.
19. Hovatta O, Silye R, Krausz T, Abir R, Margara R, Trew G, et al. Cryopreservation of human ovarian tissue using dimethylsulphoxide and propanediol-sucrose as cryoprotectants. Hum Reprod 1996;11:1268–72.
20. Dolmans MM, Falcone T, Patrizio P. Importance of patient selection to analyze in vitro fertilization outcome with transplanted cryopreserved ovarian tissue. Fertil Steril 2020;114:279–80.
21. Donnez J, Dolmans MM, Demylle D, Jadoul P, Pirard C, Squifflet J, et al. Live-birth after orthotopic transplantation of cryopreserved ovarian tissue. Lancet 2004;364:1405–10.
22. Johnson EK, Finlayson C, Rowell EE, Gosiengfiao Y, Pavone ME, Lockart B, et al. Fertility preservation for pediatric patients: current state and future possibilities. J Urol 2017;198:186–94.
23. Christianson MS, Oktay K. Advances in fertility-preservation surgery: navigating new frontiers. Fertil Steril 2019;112:438–45.
24. Oktay K, Buyuk E, Rosenwaks Z, Rucinski J. A technique for transplantation of ovarian cortical strips to the forearm. Fertil Steril 2003;80:193–8.
25. Oktay K, Buyuk E, Veeck L, Zaninovic N, Xu K, Takeuchi T, et al. Embryo development after heterotopic transplantation of cryopreserved ovarian tissue. Lancet 2004;363:837–40.
26. Donnez J, Dolmans MM. Fertility preservation in women. N Engl J Med 2017;377:1657–65.
27. Rowell EE, Duncan FE, Laronda MM. ASRM removes the experimental label from Ovarian Tissue Cryopreservation (OTC): pediatric research must continue. Available at: https://www.fertstert.org/news-do/asrm-removes-experimental-label-ovarian-tissue-cryopreservation-otc-pediatric-research. Accessed May 3, 2023.
28. Nahata L, Woodruff TK, Quinn GP, Meacham LR, Chen D, Appiah LC, et al. Ovarian tissue cryopreservation as standard of care: what does this mean for pediatric populations? J Assist Reprod Genet 2020;37:1323–6.
29. Green DM, Liu W, Kutteh WH, Ke RW, Shelton KC, Sklar CA, et al. Cumulative alkylating agent exposure and semen parameters in adult survivors of childhood cancer: a report from the St Jude Lifetime Cohort Study. Lancet Oncol 2014;15:1215–23.
30. Rowell EE, Corkum KS, Lautz TB, Laronda MM, Walz AL, Madonna MB, et al. Laparoscopic unilateral oophorectomy for ovarian tissue cryopreservation in children. J Pediatr Surg 2019;54:543–9.
31. Rowell EE, Corkum KS, Even KA, Laronda MM. Ovarian tissue health after laparoscopic unilateral oophorectomy: a porcine model for establishing optimized fertility preservation techniques in children. J Pediatr Surg 2020;55:1631–8.
32. Tsui E, McDowell H, Laronda M. Slow freeze (cryopreservation) protocol for human ovarian tissue. Available at: https://www.protocols.io/view/slow-freeze-cryopreservation-protocol-for-human-ov-csfkwbkw. Accessed May 3, 2023.
33. Dissection of a whole ovary in preparation for cryopreservation. Available at: https://www.youtube.com/watch?v=yxuy-KniU24. Accessed May 3, 2023.
34. Gianaroli L, Racowsky C, Geraedts J, Cedars M, Makrigiannakis A, Lobo R. Best practices of ASRM and ESHRE: a journey through reproductive medicine. Hum Reprod 2012;27:3365–79.
35. Johnson EK, Finlayson C, Finney EL, Harris CJ, Tan SY, Laronda MM, et al. Gonadal tissue cryopreservation for children with differences of sex development. Horm Res Paediatr 2019;92:84–91.
36. Harris CJ, Corkum KS, Finlayson C, Rowell EE, Laronda MM, Reimann MB, et al. Establishing an institutional gonadal tissue cryopreservation protocol for patients with differences of sex development. J Urol 2020;204:1054–61.
37. Children's Oncology Group. Late Effects and Nursing Committees. Late Effects Screening Guidelines. Available at: http://survivorshipguidelines.org/?. Accessed July 31, 2023.
38. Ethics Committee of the American Society for Reproductive Medicine. Fertility preservation and reproduction in cancer patients. Fertil Steril 2005;83:1622–8.
39. Crawshaw M. Psychosocial oncofertility issues faced by adolescents and young adults over their lifetime: a review of the research. Hum Fertil 2013;16:59–63.

40. Long CJ, Ginsberg JP, Kolon TF. Fertility preservation in children and adolescents with cancer. Urology 2016;91:190–6.
41. Allingham C, Gillam L, McCarthy M, Zacharin M, Jayasuriya S, Heloury Y, et al. Fertility preservation in children and adolescents with cancer: pilot of a decision aid for parents of children and adolescents with cancer. JMIR Pediatr Parent 2018;1:e10463.
42. Quinn GP, Murphy D, Knapp C, Stearsman DK, Bradley-Klug KL, Sawczyn K, et al. Who decides? Decision making and fertility preservation in teens with cancer: a review of the literature. J Adolesc Health 2011;49:337–46.
43. Knapp CA, Quinn GP, Murphy D. Assessing the reproductive concerns of children and adolescents with cancer: challenges and potential solutions. J Adolesc Young Adult Oncol 2011;1:31–5.
44. Kemertzis MA, Ranjithakumaran H, Hand M, Peate M, Gillam L, McCarthy M, et al. Fertility preservation toolkit: a clinician resource to assist clinical discussion and decision making in pediatric and adolescent oncology. J Pediatr Hematol Oncol 2018;40:e133–9.
45. Kim J, Mersereau JE. Early referral makes the decision-making about fertility preservation easier: a pilot survey study of young female cancer survivors. Support Care Cancer 2015;23:1663–7.
46. Letourneau JM, Ebbel EE, Katz PP, Katz A, Ai WZ, Chien AJ, et al. Pretreatment fertility counseling and fertility preservation improve quality of life in reproductive age women with cancer. Cancer 2012;118:1710–7.
47. 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 2016;29:585–98.
48. Backhus LE, Kondapalli LA, Chang RJ, Coutifaris C, Kazer R, Woodruff TK. Oncofertility consortium consensus statement: guidelines for ovarian tissue cryopreservation. Cancer Treat Res 2007;138:235–9.
49. Practice Committee of the American Society for Reproductive Medicine. Ovarian tissue cryopreservation: a committee opinion. Fertil Steril 2014;101:1237–43.
50. Bergin K, Wiseman C, Levin I, Baird M, Lee J, Sekhon L, et al. A decade of planned oocyte cryopreservation: decreasing age, increasing access to care, and improving prognosis. Fertil Steril 2023;120(Suppl):e42–3.
51. Schon SB, Shapiro M, Gracia C, Senapati S. Medical and elective fertility preservation: impact of removal of the experimental label from oocyte cryopreservation. J Assist Reprod Genet 2017;34:1207–15.
52. Armstrong AG, Kimler BF, Smith BM, Woodruff TK, Pavone ME, Duncan FE. Ovarian tissue cryopreservation in young females through the Oncofertility Consortium's National Physicians Cooperative. Future Oncol 2018;14:363–78.
53. Gabel R, Andersson SA, Fine L, Hoffman J, Zalewski MJ, Cassidy KM, et al. INS CD-FERTILITY PRESERVATION. Available at: https://www.ilga.gov/legislation/BillStatus.asp?DocNum=2617&GAID=14&DocTypeID=HB&LegID=103887&SessionID=91&GA=100. Accessed July 31, 2023.
54. Corkum KS, Laronda MM, Rowell EE. A review of reported surgical techniques in fertility preservation for prepubertal and adolescent females facing a fertility threatening diagnosis or treatment. Am J Surg 2017;214:695–700.
55. Cohen HL, Tice HM, Mandel FS. Ovarian volumes measured by US: bigger than we think. Radiology 1990;177:189–92.
56. Cohen HL, Shapiro MA, Mandel FS, Shapiro ML. Normal ovaries in neonates and infants: a sonographic study of 77 patients 1 day to 24 months old. AJR Am J Roentgenol 1993;160:583–6.
57. Dao KA, Tadros S, Chan S, Poremski PM, Squires JH. Pediatric ovarian volumes measured at ultrasound after contralateral unilateral oophorectomy. Pediatr Radiol 2019;49:632–7.
58. Gasparri ML, Ruscito I, Braicu EI, Sehouli J, Tramontano L, Costanzi F, et al. Biological impact of unilateral oophorectomy: does the number of ovaries really matter? Geburtshilfe Frauenheilkd 2021;81:331–8.
59. Rosendahl M, Simonsen MK, Kjer JJ. The influence of unilateral oophorectomy on the age of menopause. Climacteric 2017;20:540–4.
60. Ataman LM, Ma Y, Duncan FE, Uzzi B, Woodruff TK. Quantifying the growth of oncofertility. Biol Reprod 2018;99:263–5.
61. Smith BM, Duncan FE, Ataman L, Smith K, Quinn GP, Chang RJ, et al. The National Physicians Cooperative: transforming fertility management in the cancer setting and beyond. Future Oncol 2018;14:3059–72.
62. Tsui EL, Harris CJ, Rowell EE, Laronda MM. Human ovarian gross morphology and subanatomy across puberty: insights from tissue donated during fertility preservation. F S Rep 2023;4:196–205.
63. Tsui EL, O'Neill KE, LeDuc RD, Shikanov A, Gomez-Lobo V, Laronda MM. Creating a common language for the subanatomy of the ovary. Biol Reprod 2023;108:1–4.
64. O'Neill KE, Maher JY, Laronda MM, Duncan FE, LeDuc RD, Lujan ME, et al. Anatomic nomenclature and 3-dimensional regional model of the human ovary: call for a new paradigm. Am J Obstet Gynecol 2023;228:270–5.e4.
65. Amargant F, Zhou T, Yuan Y, Nahar A, Krisher R, Spate L, et al. FGF2, LIF, and IGF1 (FLI) supplementation during human in vitro maturation enhances markers of gamete competence. Hum Reprod 2023;38:1938–51.
66. McDade TW, Woodruff TK, Huang YY, Funk WE, Prewitt M, Kondapalli L, et al. Quantification of anti-Müllerian hormone (AMH) in dried blood spots: validation of a minimally invasive method for assessing ovarian reserve. Hum Reprod 2012;27:2503–8.
67. Schwartz GB, Kubo H, Laronda MM. Generation of two human induced pluripotent stem cell lines from a patient with complete androgen insensitivity syndrome with a hemizygous single nucleotide variant in the androgen receptor (AR) gene. Stem Cell Res 2021;55:102441.
68. Laronda MM, Burdette JE, Kim J, Woodruff TK. Recreating the female reproductive tract in vitro using iPSC technology in a linked microfluidics environment. Stem Cell Res Ther 2013;4(Suppl 1):S13.
69. Demeestere I, Simon P, Dedeken L, Moffa F, Tsépélidis S, Brachet C, et al. Live birth after autograft of ovarian tissue cryopreserved during childhood. Hum Reprod 2015;30:2107–9.
70. Donnelly L. Woman gives birth to baby using ovary frozen in her childhood in "world first." The Telegraph. Available at: https://www.telegraph.co.uk/news/2016/12/14/woman-gives-birth-baby-using-ovary-frozen-childhood-inworld/. Accessed March 15, 2023.
71. Ernst E, Kjærsgaard M, Birkebæk NH, Clausen N, Andersen CY. Case report: stimulation of puberty in a girl with chemo- and radiation therapy induced ovarian failure by transplantation of a small part of her frozen/thawed ovarian tissue. Eur J Cancer 2013;49:911–4.
72. Matthews SJ, Picton H, Ernst E, Andersen CY. Successful pregnancy in a woman previously suffering from β-thalassemia following transplantation of ovarian tissue cryopreserved before puberty. Minerva Ginecol 2018;70:432–5.
73. Poirot C, Abirached F, Prades M, Coussieu C, Bernaudin F, Piver P. Induction of puberty by autograft of cryopreserved ovarian tissue. Lancet 2012;379:588.
74. Alliance for Fertility Preservation. State Laws & Legislation [Internet]. [cited 2023 Nov 28]. Available from: https://www.allianceforfertilitypreservation.org/state-legislation/.
75. Lakhoo K, Davies J, Chakraborty S, Berg S, Tennyson R, Fowler D, et al. Development of a new reproductive tissue cryopreservation clinical service for children: the Oxford programme. Pediatr Surg Int 2019;35:1271–8.
76. Van der Ven H, Liebenthron J, Beckmann M, Toth B, Korell M, Krüssel J, et al. Ninety-five orthotopic transplantations in 74 women of ovarian tissue after cytotoxic treatment in a fertility preservation network: tissue activity, pregnancy and delivery rates. Hum Reprod 2016;31:2031–41.