ORIGINAL RESEARCH

Caregiver attitudes toward testicular tissue cryopreservation in prepubertal male cancer/HSCT patients

A non-metropolitan, Canadian cohort

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ABSTRACT

INTRODUCTION: Prepubertal males undergoing cancer treatment or hematopoietic stem cell transplant (HSCT) are at risk of infertility but currently have no fertility preservation (FP) options. Immature testicular tissue cryopreservation (TTC) has been used for successful pregnancies/live births in animal models. Human TTC for experimental biobanking is currently being planned at select Canadian sites, with potential for expansion. Canadian patients/caregivers from metropolitan centers have previously demonstrated interest. To build an equitable national strategy, it is prudent to capture attitudes from caregivers from non-metropolitan sites. The aims of this study conducted in Saskatchewan were to describe the attitudes of caregivers of prepubertal male cancer/HSCT patients toward TTC and to measure caregiver willingness thresholds to consent to testicular biopsy for TTC.

METHODS: A questionnaire with demographic information, rank-order list regarding perceived barriers to TTC, and open-ended question was administered to caregivers of prepubertal cancer/HSCT patients at our tertiary pediatric hospital. An additional theoretical threshold setting exercise was conducted.

RESULTS: Fifty-two caregivers participated (response rate 85.2%; 73.5% female; age 37 years; 78% White; 18% Indigenous; all five income quintiles represented). Caregiver attitudes were child-focused (risk/benefit of procedure) rather than caregiver-focused (travel, cost.) On average, caregivers endorsed willingness to accept TTC in the setting of: minimum 26% chance of infertility from treatment; maximum 29% chance of biopsy complications; minimum 18% chance of future FP use; maximum $616 annual storage cost; and maximum 7.4 hours driving time.

CONCLUSIONS: Caregivers across Saskatchewan demonstrated interest in TTC. These results can inform efforts to expand TTC options and equitable access for prepubertal cancer/HSCT patients.

INTRODUCTION

Male patients who undergo cancer treatment and/or hematopoietic stem cell transplant (HSCT) during childhood or adolescence can experience fertility issues due to treatment-related azoospermia, oligospermia, sexual dysfunction, and growth/puberty delays.[1] As pediatric cancer outcomes improve and HSCT indications expand to more malignant and non-malignant indications, fertility preservation (FP) has become an increasingly important issue for patients/caregivers.

Oncofertility counselling is a recommended standard of care for all pediatric cancer and HSCT patients, including those where no FP option is available;[2] however, lack of FP options remains a barrier for health care providers (HCPs) to initiate these discussions. In particular, there are no clinical FP options available for prepubertal male patients.[3] In primate models, sperm matured from prepubertal testicular tissue has been used for successful-term pregnancies.[4] Early-phase clinical trials exist outside of Canada that are studying this process with human tissue; however, there is a paucity of immature tissue available.[5] There is potential to expand current FP options in Canada to include testicular tissue cryopreservation (TTC) for biobanking and/or experimental use but there is limited data regarding caregiver attitudes toward experimental TTC options.[6]

In 2016, a Canadian study demonstrated significant patient/caregiv-

er desire to participate in experimental TTC options.[6] Additionally, the thresholds at which patients/caregivers were willing to theoretically accept TTC (in terms of potential use of the tissue, testicular biopsy complications, and cost) were far less conservative than the thresholds at which HCPs reported that they would be willing to offer it.[6] This study was conducted a decade ago in three large metropolitan areas (Toronto, ON; Hamilton, ON; and Vancouver, BC) and excluded patients who underwent HSCT.[6] Experiences from caregivers from non-metropolitan areas in less densely-populated provinces are critical to inform plans to expand equitable FP options for all Canadian children/adolescents impacted by cancer or who undergo HSCT.

The aim of this cross-sectional pilot study conducted in Saskatchewan was to describe the attitudes of caregivers of prepubertal male patients who were recently diagnosed with cancer and/or underwent stem cell transplant for any indication toward TTC for biobanking/experimental use. Our primary aim was to describe caregiver attitudes using a quantitative survey and a single open-ended question. Our secondary aim was to measure the willingness of caregivers to accept the theoretical risk of testicular biopsy for TTC with respect to five conditions of care: chance of infertility due to the underlying treatment, complications from the biopsy, potential for future FP use, annual storage cost, and driving time to access the procedure. Our exploratory aim was to determine if caregiver demographic or clinical variables were predictive of willingness thresholds in the above domains.

METHODS

Recruitment and study visit

With institutional research ethics board approval (USask #BEH-5476), caregivers (parents and/or legal guardians/substitute decision-makers) were recruited in the provincial pediatric oncology/hematopoietic stem cell transplant outpatient clinic at the Jim Pattison Children's Hospital in Saskatoon from May 30 to August 4, 2025. Caregivers of biologic male patients (with testes) who were either diagnosed with cancer and/or underwent a stem cell transplant for any indication aged 12 or under (date of cancer diagnosis or date of transplant, whichever occurred more recently) within the last five years were eligible to participate. Institutional clinic schedules were screened weekly to identify eligible caregivers. Potential participants were contacted by the study team via telephone using a standardized script 48 hours prior to their child's appointment to introduce the study.

Caregivers who expressed interest were approached in person during their child's appointment. After obtaining informed consent, participants completed a demographic form and questionnaire. The questionnaire included questions regarding their child's diagnosis and treatment; rank-order list regarding perceived barriers to TTC; and an open-ended question: "Please describe your thoughts, feelings, or experiences related to this topic. You may include any details that you determine to be important." Caregivers could select "I don't know" or leave questions blank.

Threshold setting exercise

Following questionnaire completion, a study team member conducted the threshold setting exercise using a standardized digital slide deck presentation (methodology modified from Gupta et al., with permission from the original corresponding author). The researcher introduced the concepts of FP and TTC using a standardized script. Caregivers were given a theoretical scenario in which they had another male child diagnosed with cancer or who was to undergo HSCT.

Probabilities of five conditions of care associated with TTC were set at appropriate baseline levels that reflected prior published data (infertility from underlying treatment: 50%, biopsy complications: 1%, odds of using tissue for future FP: 15%, storage cost: $350/year, and driving time: one hour). Caregivers were given the options to proceed with testicular biopsy (yes) or decline testicular biopsy (no) for their child.

For each condition of care, thresholds were determined by either increasing or decreasing the variable by set increments until the caregiver changed their response. For instance, if a caregiver initially responded with "yes" at baseline of 50% chance of infertility from the underlying treatment, the researcher would lower the risk of infertility from baseline by increments of 10% until the caregiver switched to "no." Conversely, if the caregiver responded with "no" at baseline of 50% infertility, the researcher would increase the risk of infertility from baseline by 10% increments until the caregiver switched to "yes." If a caregiver did not change their original answer, the exercise stopped when the minimum or maximum incremental value for that condition was reached (i.e., 0% or 100% chances of infertility from underlying treatment, biopsy complications, and use of tissue for future FP; $50 or $900 for annual storage cost; and one or 10 hour(s) driving time).

The maximum annual storage cost was increased from Gupta et al to account for inflation and higher cost of living over the last decade. The process was repeated for

each variable, with the other four variables set at baseline. The study visit was conducted in English. Caregivers who were not fluent in English were excluded.

Data analysis

Descriptive statistics were calculated for all variables, with continuous variables reported as mean ± standard deviation (SD) and median with interquartile range (IQR), and categorical variables as frequencies and percentages. Univariate analyses were conducted to determine if caregiver demographics or clinical variables were predictive of TTC willingness thresholds.

Variables for univariate analyses included child's age at diagnosis, child's diagnosis, caregiver age at time of survey, self-reported caregiver race/ethnicity and Indigenous identity, home residence population size, and self-reported household income quintile. Variables were determined a priori based on previously identified factors that influenced caregiver threshold responses at large metropolitan Canadian sites,[6] as well as to examine the impacts of accessing care for equity-deserving populations within our province (including Indigenous patients and those from rural/remote areas).

Diagnosis category was expanded from Gupta et al to include caregivers of males who had undergone HSCT for underlying non-malignant diagnoses. Given the non-normal distribution of willingness threshold variables and ordinal nature of several predictors, non-parametric tests were employed. Wilcoxon Two-Sample tests (Mann-Whitney U) were used for comparisons between two groups (parent sex/gender, Indigenous status). Kruskal-Wallis tests were used for comparisons across multiple groups (child's diagnosis, parent race, household income, population). Spearman's rank correlation coefficients assessed the relationship between child's age at diagnosis and willingness thresholds. All tests were two-sided with statistical significance set at p=0.05. Analyses were conducted using SAS software.

Qualitative responses to the open-ended question were transcribed by D.E.H. Two authors (D.E.H. and P.R.D.) independently reviewed the transcripts to generate keywords and codes, then jointly reviewed and consolidated keywords and codes to synthesize themes as per Naeem et al.[7]

RESULTS

Caregiver demographics and clinical variables

Of 61 eligible caregivers invited to participate, 52 participants completed study visits (response rate 85.2%.)

Table 1. Caregiver demographics and clinical variables

Caregiver demographics	n (%)
Age, years, median (IQR)[a]	37 (34.5–39.5)
Sex[b]	
Male	13 (26.5)
Female	36 (73.5)
Self-reported race/ethnicity[c,d]	
White	39 (78.0)
Asian, South Asian, or Southeast Asian	9 (18.0)
Black, African, or Caribbean	1 (2.0)
Arab	1 (2.0)
Self-reported indigenous identity (including First Nations, Metis, Inuit)[e]	
Yes	9 (17.6)
No	42 (82.4)
Highest level of education completed	
Not yet completed high school	1 (1.9)
High school	7 (13.5)
College/vocational	21 (40.4)
Undergraduate degree	9 (17.3)
Graduate/doctoral degree	14 (26.9)
Employment status, current[e]	
Full-time work (>40 hours per week)	32 (62.8)
Part-time work (<40 hours per week)	7 (13.8)
Employed, not currently working	4 (7.8)
Not currently employed	8 (15.6)
Self-reported household income quintile[f]	
1st quintile (<$36 000 CAD)	4 (8.5)
2nd quintile ($36 000–$59 500 CAD)	7 (14.9)
3rd quintile ($59 501–$89 000 CAD)	7 (14.9)
4th quintile ($89 001–$133 500 CAD)	10 (21.3)
5th quintile (>$133 500 CAD)	19 (40.4)

[a]n=23 missing; [b]n=3 missing; [c]n=2 missing; [d]caregivers could select more than one option if applicable; [e]n=1 missing; [f]n=5 missing; [g]included blinatumomab; [h]excluded central venous catheter placement; [i]included Car-T cell therapy. CNS: central nervous system; HSCT: hematopoietic stem cell transplant; IQR: interquartile range.

In our cohort, the majority of respondents were female, White, and employed full-time or part-time. Notably, 18% identified as Indigenous, First Nations, Metis, and/

Table 1 (cont'd). Caregiver demographics and clinical variables

Caregiver demographics	n (%)
Population size, primary residence	
200 000–500 000	30 (57.7)
10 000–49 999	6 (11.5)
5000–9999	1 (1.9)
1000–4999	9 (17.3)
<999	6 (11.5)
Clinical variables	
Child's age at diagnosis/HSCT, years, median (IQR)	4 (2–8)
Child's age at time of survey, years, median (IQR)	7 (5–9)
Child's diagnosis	
Leukemia/lymphoma	33 (63.4)
CNS tumor	10 (19.2)
Solid tumor	5 (9.6)
Other	4 (7.8)
Child's treatment modality[d]	
Chemotherapy[g]	46 (86.5)
Surgery[h]	22 (42.3)
Radiation therapy	7 (13.5)
Targeted therapy	8 (15.4)
Stem cell transplant[i]	8 (15.4)
Immunotherapy	2 (3.8)

[a]n=23 missing; [b]n=3 missing; [c]n=2 missing; [d]caregivers could select more than one option if applicable; [e]n=1 missing; [f]n=5 missing; [g]included blinatumomab; [h]excluded central venous catheter placement; [i]included Car-T cell therapy. CNS: central nervous system; HSCT: hematopoietic stem cell transplant; IQR: interquartile range.

or Inuit. All five socioeconomic quintiles were represented. While 57.7% of our cohort lived in Saskatoon or Regina (populations 378 475 and 291 187, respectively),[8] the remainder lived outside of urban centres (population <49 999.) Nearly one-third of caregivers (28.8%) were from rural areas (populations ≤4999), with 11.5% from communities with 999 people or less (Table 1).

Threshold setting exercise and rank order of perceived barriers

Median willingness thresholds to accept TTC were: minimum 26% chance of infertility from underlying treatment; minimum 18% chance of using tissue for future FP; maximum 29% chance of biopsy complications; maximum $616 annual storage cost; and maximum 7.4 hours driving time (Table 2).

When asked to rank factors influencing potential decision to consent to TTC if available, caregivers ranked chance of infertility from underlying treatment, potential for future use of tissue for FP, their child's health status (at time of biopsy), and potential biopsy complications as the most important. Logistics and cost were ascribed mid-level importance. Personal belief systems and travel were ranked as the least important factors (Table 3).

On exploratory univariate analyses, male caregivers endorsed greater willingness to pay higher annual storage cost (p=0.029). Additionally, caregivers from smaller communities endorsed willingness to accept a higher biopsy complication rate (p=0.002) and a longer travel time (p=0.02). Other variables were not predictive of willingness to accept TTC in the remaining domains.

Qualitative responses to open-ended question

Upon inductive thematic analysis of responses to open-ended question, D.E.H. identified seven codes and P.R.D. identified five codes. Agreement/overlap was achieved for all 12 codes. They were consolidated into eight codes, from which five themes emerged. Weighing risks/benefits, caregivers would prioritize life-saving cancer therapy/HSCT for their children; however, they also endorsed the importance of FP. They acknowledged that they were overwhelmed at the time of their child's cancer diagnosis/HSCT, which may have impacted decision-making. To that end, some reported that TTC may provide caregiver reassurance by facilitating deferred decisions and future discussions involving their children. Overall, caregivers expressed both regret that their children did not have a TTC option and hope for future options for others (Table 4).

Table 2. Caregiver willingness thresholds to theoretically accept TTC

Conditions of care	Median (IQR)	Minimum	Maximum
Minimum acceptable risk of infertility from underlying treatment	26% (10–30%)	10%	100%
Maximum acceptable risk of testicular biopsy complications	29% (10–33%)	1%	100%
Minimum acceptable probability of future use of tissue for fertility preservation	18% (5–25%)	5%	95%
Maximum acceptable annual storage cost	$616 ($450–900)	$50	$900
Maximum acceptable driving time to access procedure	7.4 hours (5–10 hours)	1 hour	10 hours

TTC: testicular tissue cryopreservation.

Table 3. Caregiver rank of factors that would have impacted their decision to consent to TTC for their child if it had been available

Factor (mean ranking)
Chance of decreased fertility from underlying treatment (2.33)
Chance of using tissue for future fertility preservation (2.58)
Child's health status (2.59)
Risk of biopsy complications (2.64)
Cost (5.19)
Logistics (5.42)
Belief Systems (6.58)
Travel (7.02)

1: most important, 8: least important, barriers determined a priori based on prior published literature. Mean rankings are reported, lower scores correlated with greater perceived importance.

DISCUSSION

This cross-sectional study described attitudes of caregivers in Saskatchewan toward TTC, procurement (via biopsy) and storage of immature testicular tissue from prepubertal cancer/HSCT patients for experimental biobanking and research purposes. We surveyed caregivers, as they would be the primary decision-makers regarding testicular biopsy for their children.

Saskatchewan (1.2 million population) has a single tertiary pediatric hospital (Jim Pattison Children's Hospital) and a single private reproductive clinic (Aurora Reproductive Care), both in Saskatoon. The provincial pediatric hematology/oncology program also operates a satellite site in Regina. Fertility consultation is covered universally by provincial health insurance; however, FP procedures and tissue storage costs are paid out-of-pocket by families. Philanthropic funding is often accessed to reduce costs to patients/families, although not guaranteed. This financial barrier is consistent across Canada, with some variability.

Additionally, pediatric/adolescent patients from Saskatchewan who require stem cell transplant are referred to sites in Calgary (Alberta Children's Hospital) or Winnipeg (The Children's Hospital of Winnipeg), which are approximately 589 km and 769 km from the Jim Pattison Children's Hospital in Saskatoon, respectively. Care costs are fully covered by inter-provincial agreements. Pre- and post-transplant care is provided in Saskatchewan, while conditioning, transplant, and acute inpatient care are provided in Calgary or Winnipeg until engraftment. Typically, patients/families spend 3–4 weeks as an inpatient and an additional 1–2 months as an outpatient out-of-province. This model is similar to other Canadian jurisdictions, including sites in Ontario, Quebec, Alberta, and the Atlantic provinces.

Notably, our cohort included representation from equity-deserving populations, such as caregivers who identified as Indigenous, First Nations, Metis, or Inuit, and caregivers from rural/remote locations. Nearly one-third of caregivers (28.8%) were from rural areas (populations <4999), with 11.5% from communities with 999 people or less. This represents a much higher proportion than recent national estimates of 18% of Canadians living in rural/remote areas.[9]

The clinical characteristics of their children's illnesses were representative of the national landscape, with leukemia/lymphoma the most frequent diagnosis category and CNS tumors as the next most frequent diagnosis category. Of note, 15.4% underwent HSCT, and this group also included non-malignant diagnoses, such as aplastic anemia, immunodeficiencies, and sickle cell disease.

Responses to rank-order list and open-ended question demonstrated that caregiver attitudes toward TTC were child-focused rather than caregiver-focused. Caregivers identified that clinical variables, namely the risks and benefits of the procedure, would have the greatest impact on their decision-making. Logistics and cost were ascribed medium importance, while personal beliefs and travel were ranked as least important. As one caregiver responded, "Our decisions would always be based on what is best for our son."

Caregivers emphasized a clear prioritization of curative/life-saving therapy for their children; however, caregivers also highlighted the importance of onco-fertility. One caregiver wrote, "When our child was originally diagnosed, it was a whirlwind of appointments…It is easy for some [information] to get lost or to be missed, but I would consider [onco-fertility] to be extremely important. A parent needs clear, concise information [regarding] the importance and timeline…It is hard for a parent to focus on anything else when their child is fighting for their life because everything else feels less important in comparison."

To that end, caregivers also reported that TTC may mitigate their decisional regret and guilt, facilitate future conversations with their children, and potentially allow their children to make their own reproductive decisions later in life. Data from pediatric cancer survivors clearly support these concepts. Onco-fertility counseling (with or without tissue storage) is therapeutic and reduces

later anxiety and regret for pediatric cancer patients, even if no FP option is undertaken.[2]

Willingness thresholds for our cohort were similar to prior published data from large, metropolitan, Canadian centers, with the exception of maximum acceptable annual storage cost ($616 vs. $500 per year), despite comparable household income distribution, including a similar proportion of caregivers in the highest income quintiles.[6] Higher overall household income did not correlate with higher acceptable annual storage cost in our cohort. These results may reflect overall inflation and rising costs of living over the last decade.

Caregivers ranked travel as the least important factor influencing potential decisions around TTC, and, on average, endorsed a willingness to drive up to 7.4 hours to access the procedure. Additionally, caregivers from smaller communities were willing to accept longer travel time (p=0.02). A caregiver expanded, "With [baseline] treatment, travel happens [anyway]."

Given that many caregivers in our province were already accustomed to travel within the province to reach centralized resources or to neighboring jurisdictions to access additional subspecialized care, the perceived barrier of travel for potential TTC may have been mitigated. A study conducted at BC Children's Hospital suggested that families of pediatric/adolescent cancer patients traveled far distances within BC to access limited early-phase clinical trials at a centralized tertiary children's cancer center for relapsed or hard-to-treat cancers.[10,11]

Overall, Canadian patients/families from less densely populated areas may be willing to travel far distances within regions to access specialized pediatric cancer and urologic care, especially since many are accustomed to doing so at baseline. As many pan-Canadian studies focus on addressing inter-provincial travel barriers to accessing specialized pediatric oncology resources,[10] it is important to capture these nuanced perspectives from caregivers from non-metropolitan areas of lower population density.

Our study also expanded upon prior published data by including caregivers of prepubertal males who underwent HSCT for non-malignant conditions. Indications for HSCT for non-malignant conditions (including hemoglobinopathies and immunodeficiencies, many of which are X-linked and affect prepubertal males disproportionately) have broadened, such that more pediatric patients are encountering treatments that may impact fertility.[12] Child's diagnosis was not predictive of willingness thresholds in any condition of care, but it is possible that our cohort was too small and heterogenous to test for such differences. Additionally, the children of some caregivers in our cohort underwent HSCT for malignant cancer diagnoses, which may have confounded analysis.

Interestingly, male caregivers in our cohort were willing to pay higher annual storage fees (p=0.029), and caregivers from smaller communities were willing to accept higher complication rates (p=0.002). Inductive thematic analysis of qualitative responses did not identify particular reasons for these trends, suggesting areas of potential further study.

Table 4. Inductive thematic analysis of caregiver responses to open-ended questions

Theme	Code	Illustrative quotes
Endorsed the importance of oncofertility	Importance of oncofertility	"I would consider this to be very important. A parent needs clear, concise information on the importance and timeline… before treatment begins."
Weighing risks and benefits, would prioritize life-saving therapy	Risks vs. benefits	"Our decision would always be based on what is best for our son. If risks outweighed benefits, we would never even consider it."
	Prioritization of child's health/life-saving therapy	"It is hard for parents to focus on anything else when their child is fighting for their life."
		"Parents will always choose their child's life over fertility in future."
Acknowledgement that overwhelming time at pediatric cancer diagnosis/stem cell transplant may impact decision-making	Overwhelmed at diagnosis/time of HSCT	"When our child was originally diagnosed, it was a whirlwind of appointments… It is easy for some information to get lost or be missed… so many decisions must be made at that time."
TTC may provide caregiver reassurance by facilitating deferred discussions/decisions (involving child in future)	Facilitate decision deferral	"The decision to participate would simply enable the child to make that reproductive decision later in life."
		"I would not be upset with my son if even after doing this and spending the money, he chooses not to have a kid. At least they have an option."
	Provide reassurance	"This option may bring comfort or reassurance."
		"This option could ease some of the fear [regarding] future conservations with their children when they get older."
Wished they had an option, expressed hope and desire for future access for others	Desire for access/regret	"From diagnosis at age 3, to relapse at age 7, and now post-treatment at age 10, I wouldn't change treating him, it felt like a necessary sacrifice… but the option to preserve fertility would have been wonderful."
	Hope for future	"I hope this comes to Canada in the near future."
		"Positive, hopeful for future opportunities…"

HSCT: hematopoietic stem cell transplant; TTC: testicular tissue cryopreservation.

Limitations

This study included a heterogeneous cohort with a small sample size, which limited our ability to draw conclusions regarding the impact of caregiver demographics or clinical variables on caregiver willingness thresholds in regard to potential TTC. It would be beneficial to expand to other Canadian sites of similar size and demographics to better characterize the experiences of patients and families who live outside of large metropolitan areas.

We used driving time as a surrogate for travel distance, as Saskatchewan is Canada's only land-locked province. This data may not be generalizable to other centers (particularly coastal regions), as travel may be more complex.

As we lacked the resources to conduct the study visit with translation services for caregivers who spoke languages other than English, we may have excluded caregivers, including those who were new to Canada.

Lastly, we explored caregiver attitudes by asking caregivers of prepubertal male patients who were undergoing or had recently undergone cancer treatment or HSCT to respond to a theoretical scenario. Their responses may not fully reflect the real-time, prospective decisions of other caregivers if offered TTC in the future.

CONCLUSIONS

Our study confirms that caregivers who live in non-metropolitan, Canadian regions display interest in TTC for experimental biobanking for pre-pubertal males diagnosed with cancer and/or undergoing HSCT. Caregiver attitudes were child-focused. Travel time to access such subspecialty care was not endorsed as a barrier for these caregivers, particularly for those who live in the smallest communities. These results can help inform equitable national strategies to address existing gaps in fertility care for Canadian children undergoing cancer treatment and HSCT for malignant and non-malignant diseases.

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