Prevalence and Predictors of Sperm Banking in Adolescents Newly Diagnosed With Cancer: Examination of Adolescent, Parent, and Provider Factors Influencing Fertility Preservation Outcomes

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ABSTRACT

Purpose
To estimate the prevalence of sperm banking among adolescent males newly diagnosed with cancer and to identify factors associated with banking outcomes.

Patients and Methods
A prospective, single-group, observational study design was used to test the contribution of sociodemographic, medical, psychological/health belief, communication, and developmental factors to fertility preservation outcomes. At-risk adolescent males (N = 146; age 13.00 to 21.99 years; Tanner stage $3$), their parents, and medical providers from eight leading pediatric oncology centers across the United States and Canada completed self-report questionnaires within 1 week of treatment initiation. Multivariable logistic regression was used to calculate odds ratios (ORs) and 95% CIs for specified banking outcomes (collection attempt vs no attempt and successful completion of banking vs no banking).

Results
Among adolescents (mean age, 16.49 years; standard deviation, 2.02 years), 53.4% (78 of 146) made a collection attempt, with 43.8% (64 of 146) successfully banking sperm (82.1% of attempters). The overall attempt model revealed adolescent consultation with a fertility specialist (OR, 29.96; 95% CI, 2.48 to 361.41; $P = .007$), parent recommendation to bank (OR, 12.30; 95% CI, 2.01 to 75.94; $P = .007$), and higher Tanner stage (OR, 5.42; 95% CI, 1.75 to 16.78; $P = .003$) were associated with an increased likelihood of a collection attempt. Adolescent history of masturbation (OR, 5.99; 95% CI, 1.25 to 28.50; $P = .025$), banking self-efficacy (OR, 1.23; 95% CI, 1.05 to 1.45; $P = .012$), and parent (OR, 4.62; 95% CI, 1.46 to 14.73; $P = .010$) or medical team (OR, 4.26; 95% CI, 1.45 to 12.43; $P = .008$) recommendation to bank were associated with increased likelihood of sperm banking completion.

Conclusion
Although findings suggest that banking is underutilized, modifiable adolescent, parent, and provider factors associated with banking outcomes were identified and should be targeted in future intervention efforts.

INTRODUCTION

Over the past 40 years, survival rates for childhood cancer have dramatically improved, with one in 530 young adults in the United States identified as a survivor.1,2 Despite these advances, survivorship is commonly affected adversely by complications resulting from cancer treatment, including infertility.3 Alkylating agents and irradiation of the brain, spine, or pelvis/gonads have a doserelated risk of infertility, with higher cumulative dose and longer treatment yielding greatest risk.1-8 Because 50% of males surviving childhood cancer are at risk for infertility, interventions for fertility preservation (FP) should be offered to at-risk patients of reproductive age.9-12 Adolescents surviving cancer desire children and value parenthood.13 Among teenage males undergoing treatment, having children is
prioritized above making money, owning a home, faith, friends, or securing romantic relationships in the future. Seventy-six percent of childless males desire children in survivorship and prefer biologic offspring. Male survivors who experience treatment-related infertility are at increased risk for emotional distress, particularly those who were younger at diagnosis, desire children, or had been unaware that they are infertile.

Despite these risks, a minority of adolescents bank sperm. It is unclear why sperm banking (SB) is underutilized, particularly in light of the high priority survivors place on fertility and the psychological distress associated with fertility loss. Thus, the purpose of this study was to estimate the prevalence of collection attempts (CAs) and successful SB completion among at-risk adolescent males newly diagnosed with cancer, while identifying sociodemographic, medical, psychological/health belief, communication, and developmental factors among adolescents, parents, and medical providers that are best associated with banking outcomes.

**Participants**

To be eligible for this study, participants had to be male, newly diagnosed with a first cancer, and 13.00 to 21.99 years of age; have Tanner stage ≥ 3 disease; have been identified by his oncologist (or designee) as being at increased risk for treatment-related fertility loss; be proficient in speaking and reading English or Spanish; and possess the cognitive capacity to complete study questionnaires. From 2011 to 2014, a total of 183 adolescents were identified as being eligible across eight leading pediatric oncology institutions in the United States and Canada. Of those eligible, 180 were approached, 156 enrolled, and 146 returned completed study questionnaires (enrollment diagram shown in Fig 1). Participating sites (and the number of participants who completed questionnaires) included St Jude Children’s Research Hospital (n = 78), Children’s Healthcare of Atlanta (n = 20), City of Hope (n = 12), C.S. Mott Children’s Hospital/University of Michigan (n = 11), Cook Children’s Medical Center (n = 10), Hospital for Sick Children/SickKids (n = 7), Mattel Children’s Hospital/University of California Los Angeles (n = 5), and Primary Children’s Hospital (n = 3). In addition to adolescent participants, 144 parents/guardians (101 maternal, 42 paternal, and one survey completed collaboratively by both parents) and 52 medical providers also completed study questionnaires. On the basis of sensitivity analyses and 70.1% of the guardians (101 maternal, 42 paternal, and one survey completed collaboratively by both parents) and 52 medical providers also completed study questionnaires. The two binary study outcomes were CA (yes or no) and successful SB completion (yes or no). These outcomes were obtained from adolescent and parent study questionnaires. A CA was considered positive when an adolescent participant (or parent) endorsed one of the CA items (a) “Yes, I provided a sample” or (b) “No, I tried to but wasn’t able to provide a sample” or (c) “No, I provided a sample, but there was no sperm to bank in it.” SB completion was considered only when the response was “Yes” to this item.

**Measures: Primary Outcomes**

The two binary study outcomes were CA (yes or no) and successful completion of SB (yes or no). These outcomes were obtained from adolescent and parent study questionnaires. A CA was considered positive when an adolescent participant (or parent) endorsed one of the three following response options to “Have you banked your sperm?” (or “Did your son bank his sperm?”): (a) “Yes,” (b) “No, I tried to but wasn’t able to provide a sample,” or (c) “No, I provided a sample, but there was no sperm to bank in it.” SB completion was considered only when the response was “Yes” to this item.

**Measures: Independent Variables**

**Sociodemographic factors.** Adolescents, parents, and providers were asked to respond to a series of sociodemographic questions (eg, race, age, sex, education, household income) to describe the sample and examine the potential influence of these factors on banking outcomes.

**Adolescent factors.** Medical and developmental. Diagnosis and Tanner stage (3, 4, or 5) were obtained from the participants’ medical record or within the medical record, and adolescents were asked to self-report history of masturbation, nocturnal emission, and partnered sexual activity (yes or no). Adolescents were also asked to self-report whether they had been referred for an FP consultation (yes or no).
Communication. Adolescents were asked a series of yes or no questions regarding whether medical team members, parents, or other family members or friends had discussed their risk of infertility, their perception of fertility risk, and whether recommendations for SB were made. Adolescents also completed the communication, problem solving, affective responsiveness, and general functioning subscales from the McMaster Family Assessment Device.25

Psychological/health beliefs. Fertility and banking-related health beliefs were measured via sets of Likert-type items, which were adapted from previous research specific to the Health Belief Model.15,16-19 Perceived vulnerability was assessed using a five-item scale, which included content such as "Compared to other males who have never been treated for cancer, what is your risk of developing fertility problems in the future?" with responses ranging from 1 (much lower) to 5 (much higher). Perceived severity was also measured using a five-item scale that instructed adolescents to rate how much they agreed or disagreed with statements like "Infertility would be one of the hardest things to deal with in life" (1, strongly disagree to 5, strongly agree).

To measure perceived barriers, adolescents rated the importance of 28 potential barriers from 1 (very unimportant) to 4 (very important). Factor analysis revealed a four-factor structure, with barriers specific to influential authority figures (eg, medical team and parents), social influences (eg, friends, girlfriends or partners, siblings), concerns for future children (eg, child health, genetics, desire for children), and SB logistics (eg, cost, availability). To measure perceived benefits, adolescents completed six items on a scale of 1 (strongly disagree) to 5 (strongly agree) in response to statements such as "SB makes an infertile man a more desirable spouse." Self-efficacy was measured via four items regarding adolescent perceptions of their ability to complete aspects of SB, with response options ranging from 1 (definitely no) to 5 (definitely yes). Finally, cues to action were measured by asking participants to endorse sources of fertility-related information, choosing from seven medical, 12 family/friend, and six media sources. The numbers of sources endorsed were summed for a total score. Anxiety during the previous 7 days (ie, the interval between their diagnosis and SB decision) was also measured using the anxiety subscale of the Symptom Checklist 90-R.20,21

Parent factors. Communication. Parents were asked a series of yes or no questions regarding whether they had communicated with their son, his medical team, or other family members or friends about their son's risk of infertility, their personal perception of their son's fertility risk, and whether they or others had recommended SB for or to their son. Additionally, parents were asked whether their son had ever met with an FP specialist. Parents also completed selected subscales from the McMaster Family Assessment Device.25

Psychological/health beliefs. Parental versions of the aforementioned adolescent health belief scales were also completed, with "your son" replacing "you," as appropriate. Anxiety during the previous week was again measured using the anxiety subscale of the Symptom Checklist 90-R.21

Provider factors. Medical and developmental. In addition to rating the fertility risk status of a potentially eligible patient (0, no increased risk of infertility; 1, low but increased risk of infertility; 2, moderate risk of infertility; or 3, high risk of infertility secondary to cancer treatment), the provider also provided the adolescent's Tanner stage.

Communication. Providers were asked whether they had discussed fertility risk with the adolescent and/or with his parent(s) and whether they (or anyone else from the medical team) had recommended banking or made a referral for FP consultation (yes v no). Finally, providers completed a 12-item scale assessing their general comfort when communicating fertility risk and discussing SB with patients and families overall.32-33

Statistical Approach

To build the regression models with the most appropriate variables selected as covariates, a three-step statistical strategy was used incorporating missing data with multiple imputation, selecting variables with elastic net, and finally building the multivariable logistic regression model. Variables came from three different sources: adolescents, parents, and providers. Before the statistical analysis, 20 variables, which were either highly correlated with other covariates or had similar content to others factors, were removed to reduce collinearity. The first step was 20-iteration multiple imputation for missing nondemographic factors.38 A Markov chain Monte Carlo method was used to impute values, assuming an arbitrary missing pattern and the multivariable normal distribution of factors.37 Second, the elastic net method was used in each imputed data set to select final factors; covariates chosen by Bayesian information criteria ≥ 13 times (> 65% chance) were retained.38,39 Finally, the multivariable logistic models were fitted using these selected covariates in 20 imputed data sets. The results of the 20 imputations were combined, and aggregated statistical inferences were generated. The final results were presented in odds ratios (ORs) and 95% CIs.

RESULTS

Of the 146 adolescent participants, 78 (53.4%) made a CA. However, 14 of these patients did not successfully bank, because they were unable to collect a sample (n = 11) or their sample was
Sperm cryopreservation is effectively used to preserve fertility, and the utility of this approach has become more practical with improvements in assisted reproductive technologies. FP among patients with cancer has been associated with a variety of benefits, including reductions in fertility-related distress,40 promotion of decisional satisfaction, psychological relief,41 and optimism for the future,15,42 whereas fertility loss has been associated with significant psychological distress.43-45 Despite the advantages of banking, only 53% of study adolescents made a CA, with 44% successfully banking. Although these rates are broadly consistent with those reported in Europe and Asia,40,46,47 these findings suggest that SB is underutilized in this high-risk group.

Adolescent consultation with a fertility specialist was the most robust factor associated with making a CA. This finding is consistent with the adult literature, which has reported the absence of FP referral as a primary barrier to SB.50,42,48 In recent years, there has been an increase in the number of FP teams and specialists within children’s hospitals.49,50 These teams provide developmentally sensitive and specialized care and may be composed of psychologists, nurse educators, practitioners, social workers, patient navigators, geneticists, endocrinologists, urologists, and/or gynecologists who are trained and skilled in working with adolescents and their families specifically as regards FP. The utility of these intermediary teams (present at six of eight participating sites) is particularly important in managing this aspect of care, because many oncologists are uncomfortable discussing masturbation and the process of FP with younger patients.51,52 Adolescents who are resolute in their decision to engage or not engage in a CA do not typically receive an FP consultation. However, for those who are unsure or need more information, meeting with a fertility specialist seems to more often result in a CA. It should be noted that the association between meeting with a fertility expert and making a CA may have been confounded should adolescents have met with an FP specialist despite having already decided to make a CA.

With regard to adolescent-specific predictors, patient-reported history of masturbation was highly associated with successful SB, whereas higher Tanner stage was associated with increased rate of CAs. Adolescents experienced with masturbation have more insight into and clearer expectations regarding the demands associated with sperm collection. Males who are more physically mature should be particularly encouraged to make a CA, because 82% of attempters in this study successfully completed SB. It is important to query patients about history of masturbation when assessing SB candidacy among adolescents at diagnosis, and even though a patient may still be in the process becoming acquainted with his medical team, this study demonstrates it is possible.

Although masturbation could be considered a modifiable variable, teaching inexperienced males to masturbate extends beyond the limits of what most medical teams consider appropriate practice. Alternative FP methods can also be used among adolescents (eg, epididymal or testicular sperm extraction, electroejaculation).

Sperm Banking in Adolescents Newly Diagnosed With Cancer

### DISCUSSION

### Table 2. Logistic Regression Predicting CA Among at-Risk Adolescent Males Newly Diagnosed With Cancer (n = 148)

<table>
<thead>
<tr>
<th>Variable Description</th>
<th>β</th>
<th>SE</th>
<th>P</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fertility risk communication from provider</td>
<td>1.34</td>
<td>1.17</td>
<td>.251</td>
<td>3.82</td>
<td>0.39 to 37.71</td>
</tr>
<tr>
<td>Parent(s) recommended SB</td>
<td>2.51</td>
<td>0.93</td>
<td>.007</td>
<td>12.30</td>
<td>2.01 to 75.94</td>
</tr>
<tr>
<td>Medical team recommended SB</td>
<td>1.28</td>
<td>0.89</td>
<td>.148</td>
<td>3.60</td>
<td>0.63 to 20.49</td>
</tr>
<tr>
<td>Met with fertility specialist</td>
<td>3.40</td>
<td>1.27</td>
<td>.007</td>
<td>29.96</td>
<td>2.48 to 361.41</td>
</tr>
<tr>
<td>Health belief: benefits of banking</td>
<td>0.19</td>
<td>0.11</td>
<td>.085</td>
<td>1.21</td>
<td>0.97 to 1.51</td>
</tr>
<tr>
<td>Tanner stage</td>
<td>1.69</td>
<td>0.58</td>
<td>.003</td>
<td>5.42</td>
<td>1.75 to 16.78</td>
</tr>
</tbody>
</table>

### Table 3. Logistic Regression Predicting SB Outcome Among at-Risk Adolescent Males Newly Diagnosed With Cancer (n = 148)

<table>
<thead>
<tr>
<th>Variable Description</th>
<th>β</th>
<th>SE</th>
<th>P</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Banking self-efficacy</td>
<td>0.21</td>
<td>0.08</td>
<td>.012</td>
<td>1.23</td>
<td>1.05 to 1.45</td>
</tr>
<tr>
<td>Medical team recommended SB</td>
<td>1.45</td>
<td>0.55</td>
<td>.008</td>
<td>4.26</td>
<td>1.45 to 12.43</td>
</tr>
<tr>
<td>Parent(s) recommended banking</td>
<td>1.53</td>
<td>0.59</td>
<td>.010</td>
<td>4.62</td>
<td>1.46 to 14.73</td>
</tr>
<tr>
<td>History of masturbation</td>
<td>1.79</td>
<td>0.80</td>
<td>.025</td>
<td>5.99</td>
<td>1.25 to 28.50</td>
</tr>
</tbody>
</table>

Abbreviations: CA, collection attempt; CL, confidence limit; OR, odds ratio; SB, sperm banking.

*Adolescent report.

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but this occurs less frequently because of the invasive and expensive nature of these procedures. Other adolescent-specific modifiable factors were identified that should be targeted in SB efforts. Specifically, adolescents who have higher banking self-efficacy (eg, confidence in their ability to manually collect a sample) or recognize the benefits of SB are more likely to successfully complete SB or make a CA, respectively. These motivational factors seem to be important with regard to influencing banking outcomes among adolescents, suggesting that psychoeducational interventions targeting banking self-efficacy and the perceived benefits of banking may translate into increased rates of SB and CAs.

Parent, as compared with medical team, recommendation to bank was the most robust factor associated with CAs. Parent support in decision making has been frequently associated with SB but this is the first study to quantify the magnitude of this effect. Although parent consent and patient assent for banking must be secured among minors, the influence of parent recommendation on CA decision making was observed irrespective of patient age.

Regarding limitations, the study relied on adolescent and/or parent self-report of CA and SB completion, rather than verifying these outcomes in the medical record. However, the 100% agreement between patient and parent reports (when available) on these outcomes reduces misclassification concerns. The benefits of using a standardized approach in assessing Tanner stage across sites are also noted. Despite being the largest prospective data set of its kind to our knowledge, there are power limitations associated with a sample of 146 adolescents. Binary variables are at particular risk for low cell frequencies, resulting in larger-than-expected CIs (eg, adolescent history of masturbation). This suggests additional, larger studies examining SB in this population are warranted. Even though elastic net is an appropriate approach when analyzing data with a large number of correlated covariates relative to the sample size, the possibility of overfitting the models cannot be ruled out. Finally, collection of questionnaires before treatment initiation would have been a better temporal study design for examining predictors of SB, but this was logistically difficult given the short time interval between diagnosis and treatment initiation. Future research should also consider the effect of program factors on SB outcomes (eg, on-site collection availability, financial support for banking costs, institutional climate regarding adolescent fertility preservation), and interventions to increase SB and decisional satisfaction (regardless of banking outcome) should be tested in the future as a means to improve patient care.

Guidelines for FP have been developed by the American Society of Clinical Oncology, National Comprehensive Cancer Network, American Academy of Pediatrics, and American Society of Reproductive Medicine. Despite the applicability of these guidelines to adolescents with cancer, SB remains underutilized. This study reports on the adolescent, parent, and provider factors that affect these outcomes and identifies specific modifiable factors that should be targeted in future interventions. SB is not the appropriate choice for everyone, but timely communication regarding fertility risk, familial counseling, and recommendations for FP consultation are requisite irrespective of estimated risk, prognosis, or provider beliefs. By participating in these discussions, not only are we empowering adolescents to engage in their own health care, but we may also be affecting important quality-of-life and family-building outcomes in cancer survivorship.

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Sperm Banking in Adolescents Newly Diagnosed With Cancer

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