

Virtual Mentor

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CLINICAL CASE

Communicating Risk of Infertility to Adolescents Prior to Chemotherapy

Commentary by John Hutter, MD, and James L. Klosky, PhD

Andrew, 13, was recently diagnosed with acute myelogenous leukemia (AML). At his second appointment with the pediatric oncologist he and his parents were told about the standard induction treatment for AML: chemotherapy with a combination of anthracycline and cytarabine. The oncologist, Dr. Kessler, described the various side-effects of this course of treatment, including infertility. Andrew and his parents understood, and, after asking a few questions about scheduling, they agreed to start chemotherapy as soon as possible.

Later, while Andrew was out of the room, Dr. Kessler told his parents that if Andrew banked some sperm prior to the initiation of chemotherapy he would be able to have biological children in the future, in the event that his sperm became infertile secondary to his chemotherapy. She explained that banking sperm was a fairly simple procedure, requiring only that Andrew masturbate to produce the semen from which the sperm would be extracted to be frozen and stored. There was a banking facility nearby, which she could contact if Andrew's parents were interested in learning more about the process. She asked their permission to speak with Andrew about the risks and benefits of sperm banking.

To Dr. Kessler's surprise, Andrew's parents not only refused their permission, but reacted to her proposal with horror. "We've worked hard to raise our son to be a good boy who would never think about doing anything as inappropriate and immoral as masturbation," said Andrew's father. "Yes," his wife agreed, "suggesting to Andrew that he masturbate would upset him, so we insist that you not say anything about this to him. He has accepted that he might be infertile after this treatment is finished; let's just leave it like that, and hope for the best." Dr. Kessler agreed, and the appointment came to an end.

Commentary 1

by John Hutter, MD

In responding to the queries posed by this scenario, it is essential to consider the importance of context in applying ethical principles. The concept that context is part of ethical decision making dates back to Aristotle's *Nichomachean Ethics* and means simply that what is right under certain circumstances might be wrong when circumstances differ. Let's begin by exploring aspects of this scenario that define its context.

Andrew is newly diagnosed with acute myelogenous leukemia, a life-threatening malignancy requiring immediate treatment. If the proposed sperm-banking procedure were to delay antileukemia treatment, Andrew would be at greater risk than a patient with a newly diagnosed malignancy that posed less immediate danger.

A second contextual consideration is the universality of the proposed sperm-banking intervention. Is this a procedure that is routinely and consistently performed for all newly diagnosed adolescents with cancer? While banking of sperm has been strongly recommended for adolescent males about to undergo therapy that may affect fertility, a substantial number of adolescent male cancer patients do *not* undergo the procedure prior to the institution of therapy. Sperm banking is not routinely employed for various reasons, including, as I mentioned, the immediacy of required anticancer therapy, lack of emphasis on fertility preservation in oncology training programs, and procedure costs, which often place an additional burden on families. The lack of universal application of the proposed procedure lends support to the argument that parental consent be required for a minor undergoing this intervention, even if the intervention were both desired by the minor patient and potentially of some benefit.

A third context factor is Andrew's pubertal development and ability to provide an ejaculate sperm sample. Although not specifically stated, let's assume that his physician had established that Andrew had sufficient pubertal development and ejaculate capabilities to carry out the banking procedure. This factor, albeit obvious, is a good example of the context concept, i.e., what's right to propose to a pubertal adolescent about sperm banking may not be appropriate for a prepubescent child. Similarly, Andrew's age and stage of development should be considered; approaches to early adolescents may differ from those proposed to adolescents more advanced in their cognitive and emotional development.

The risk for Andrew in declining sperm banking also requires evaluation [1]. The overall risk of azoospermia following chemotherapy treatment of adolescents and young men has been best studied in Hodgkin's disease. Azoospermia rates as high as 90 percent have been observed after multiple cycles of chemotherapy that includes alkylating agents, but declines to 30 to 50 percent when patients receive three cycles or fewer of chemotherapy or are treated with regimens that do not include an alkylating agent.

Factors that influence the risk of infertility after chemotherapy include the age and sex of the patient, type of chemotherapeutic agent, and dose intensity. Younger patients generally have a lower risk of infertility than older individuals. Males have a slightly greater risk of infertility than females who receive an identical treatment regimen. It is difficult to apply fertility-risk data to current therapies because many of the treatment regimens for which the fertility outcomes have been calculated have been supplanted by newer regimens with improved cancer survival outcomes. Hence, exact risk of infertility from the regimen proposed for treatment of Andrew's acute

myelogenous leukemia (anthracycline and cytarabine) remains incompletely defined but might carry a lower risk than treatment regimens that include alkylating agents.

Most likely, Andrew will remain capable of sperm production after a single chemotherapy cycle with anthracycline and cytarabine, but several small studies have suggested there is an increased risk of transient aneuploidy of sperm following chemotherapy administration. In considering a recommendation for Andrew prior to the initiation of chemotherapy, one must also take into account that sperm motility in leukemia patients may be lower than normal prior to treatment. Disease-related decreased sperm motility, when combined with the urgent need for treatment that may preclude obtaining multiple samples for banking, and Andrew's age (13 years) increase the possibility that the sample obtained will not be adequate in both sperm numbers and function. Studies of successfully banked sperm, however, demonstrate that adolescents with cancer have the same sperm DNA viability as normal controls.

Decision Making in Stressful Times

The diagnosis of a life-threatening illness in a child or adolescent is extremely stressful for a family. Parents are faced with a situation that is out of their control and may also feel that they did something wrong that contributed to the illness. A high level of stress may influence the parents' responses to the sperm-banking recommendations. Treating oncologists should appreciate how their own inherent beliefs about what is in the patient's best interest can influence their acceptance of a parental response. For example, would one's opinion about Dr. Kessler's acceptance of Andrew's parents' decision be altered if the parents had said, "We are refusing sperm banking because we appreciate the urgency of commencing chemotherapy and don't want to risk any delays"? While we might find the latter response less disquieting and more acceptable because it is more consistent with the context of our own beliefs, the response still generates the same end result—namely a parental request to exclude Andrew from a medical decision-making process.

Adolescent Assent

A key question posed by the scenario is the degree to which we respect adolescent autonomy in medical treatment choices, which has implications for ethical decision making, constitutional rights of individuals, and legal policy making. When does a child or adolescent have the capability to fully comprehend and appropriately weigh the short- and long-term risks and benefits of medical treatment and procedures? At what point should the inherent right of adults to consent to and refuse medical treatment be extended to children? What level of information about a medical condition and its treatment should be routinely shared with a child or adolescent?

The legal age for independent decision making has customarily been set at 18, but some younger individuals have greater capacities for decision making than some adults. Furthermore, state legislative policies have extended legal decision making to adolescents younger than 18 (referred to as mature or emancipated minors) when they are serving on active duty in the military, self sufficient, married, or when it is thought that obtaining parental consent would hinder or delay necessary treatment

for specified disorders, most frequently substance abuse, contraception, and sexually transmitted diseases. State policies have also been highly variable in definitions of mature minors, enumerations of medical conditions to which minors can consent, and responses to parental requests for treatment information.

Parents' right to make decisions for their minor children is well established in common law and the U.S. Constitution. And through a doctrine of *parens patriae*, the state also has a clearly identified obligation to protect children and adolescents independent of parental approval. In medical decision making, *parens patriae* has mainly been applied only: (1) when seeking required parental approval would hamper a minor from receiving necessary medical treatment, e.g., treatment of a sexually transmitted disease; (2) when parental refusal of treatment would jeopardize the life of the child, e.g., refusal to treat juvenile diabetes; and (3) in attempts to define the rights and societal obligations afforded to children with terminal illness.

The right of refusal exercised by Andrew's parents requires respect. While one may not agree with their decision, they are exercising their fundamental right to refuse an intervention that lacks sufficient established benefit for Andrew for the state to step in and contravene their decision. Their request, however, does not fully abrogate Dr. Kessler's responsibilities in seeking to ensure what is best for her patient. A statement issued by the AAP Committee on Bioethics in 1995, noted that "the pediatrician's responsibilities to his or her patient exist independent of parental desires or proxy consent" [2]. The ethical dilemma as to whether Andrew should be afforded the opportunity to be presented with important medical information remains unresolved, at least temporarily.

One may also wonder whether Dr. Kessler "did the right thing" by electing to have an initial conversation with Andrew's parents, excluding him from the process. Parent-physician discussions that exclude the child and early adolescent are frequently held for delivering the initial diagnosis in serious and life-threatening conditions because doing so allows parents to express their fears and concerns freely, which they might not do in the presence of their child. Such conversations are usually followed by discussions with the child or adolescent and include both information and assent for treatment. Excluding the patient, however, provides at least tacit deferral to the parents as ultimate decision makers, perhaps contributing to the ethical dilemma.

What course of action would I have pursued if I were the oncologist encountering Andrew and his family for the second time? Given the context of Andrew's age, life-threatening illness urgently requiring therapy, and respect for parental rights, I concur with Dr. Kessler's decision to accept, at least initially, the parents' refusal to discuss the therapeutic option, one that is not universally employed and has only incremental benefit. I would remain concerned, however, about continuing on a course where medical options were not discussed with Andrew. The nature of Andrew's illness will most likely require me to have at least daily contact with him and his family during the next several weeks. During this time, I would emphasize to

the parents the importance of sharing information with Andrew about his treatment and obtaining appropriate assent. As my relationship with Andrew and his family strengthens, I would seek to provide the parents with additional information about sperm banking to further educate them and resolve their misconceptions. If treatment is successful, Andrew will be in remission and medically more stable in approximately 1 month. Perhaps by this time the parents will be less stressed and more informed about sperm banking and will recognize the importance of sharing medical information with Andrew enough to permit a discussion with him on this subject.

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Commentary 2

by James L. Klosky, PhD

The American Society of Clinical Oncology asserts that oncologists have a responsibility to discuss infertility risk with all patients treated during their reproductive years and that these discussions should take place as early as possible [1]. At the same time, physicians are charged to “do no harm.” If Andrew’s parents believe that their son will get upset at the suggestion of fertility preservation outside of the context of marriage, the physician’s duty to discuss risk must be balanced with the potential of causing psychological harm to both patient and family. Dr. Kessler, the oncologist in this case, is further challenged due to her unfamiliarity with this family (second appointment) and her surprise regarding the parents’ insistence that sperm banking not be addressed with their son. There are many factors that influence an adolescent’s candidacy for sperm banking including cancer diagnosis, treatment acuity, age, Tanner stage, religious orientation, cognitive functioning, and emotional maturity. I provide recommendations specific to this case study, but they may be generalized to other adolescent patients.

Communicating Fertility Risk in the Pediatric Oncology Setting

We know that both Andrew and his parents were present during the review of potential infertility as a result of his treatment for AML. Later, Dr. Kessler chose to

initiate the discussion of sperm banking when Andrew was outside of the clinic room, and, because of his parents' insistence, she agreed to refrain from further sperm-banking discussions. In retrospect, Dr. Kessler should have made a brief statement on sperm banking at the time of fertility-risk disclosure in the presence of both Andrew and his parents. Ideally her statement would have included the information that sperm banking is often recommended prior to the initiation of AML treatment to preserve the patient's ability to father children in the future, as she was describing the various body systems affected by AML treatment. The advantage of this brief introduction is that it exposes the patient and his parents to the idea of fertility preservation without demanding an immediate response from them. Upon completion of the late-effects review, Dr. Kessler could have inquired globally whether the family had questions about "anything that I reviewed today," thus creating another opportunity for sperm-banking discussions in a low-demand context. This approach would have also increased the likelihood of private discussion between Andrew and his parents, which in turn could have facilitated more expedient sperm-banking decision making and improved decision satisfaction regardless of the outcome.

It is not uncommon for teenagers and their parents to be highly distressed at the time of cancer diagnosis and during informed-consent and assent processes. In particular, difficulty in remembering and processing information related to cancer survivorship is often reported when the acute focus of the family is on cancer cure. To redress this problem, oncologists and their medical teams frequently assess and reassess the family's understanding of cancer treatment and provide a stream of supplemental information on treatment-related topics designed to facilitate prompt and informed decision making and psychological adaptation to diagnosis.

Correcting Misconceptions, Promoting Flexible Thought, and Making Effective Referrals

Prior to a diagnosis of pediatric cancer, most families have never considered banking sperm. Furthermore, when teenagers think about reproduction, most focus on avoiding pregnancy—not preserving fertility. Consequently, many families are unacquainted with the process, demands, or options related to sperm banking and may be quick to make judgments or develop misconceptions regarding this sensitive topic. It's in these cases that oncologists (or other members of the medical team) can significantly influence the decision-making process by sensitively querying familial rationales for not banking sperm, while at the same time correcting any misconceptions that the family (or parents in this case) may have.

The case study indicates familial communication about sexual behavior in Andrew's family is poor and lacks recognition (or knowledge) of normal psychosexual development. Andrew's parents have made two errors that can be modified. First, there is an assumption that by banking sperm, reproduction will take place outside of the confines of marriage. A clinician could reframe this assumption and explain that by banking sperm, Andrew and his future wife will maintain the option of having biological children (and grandchildren) in the future. Although it was not explicitly

stated, it appears that both of Andrew's parents object to the traditional method of collecting sperm (i.e., masturbation). Information on epididymal sperm aspiration, testicular sperm aspiration, or electroejaculation (all of which can take place under sedation) could have been highlighted as "nonsexual" options that could be exercised with their consent and Andrew's assent.

Information of this sort could have also influenced Andrew's father, who views his son as a "good boy who would never think about doing anything like that." Rather than resigning to this rigid style of thinking (good boy versus bad boy), the physician could encourage Andrew's father to think more flexibly and consider sperm banking as a function of fatherhood and human development. Instead of focusing on the psychosexual, physical development could be emphasized with brief education addressing Tanner stage and secondary male characteristics (increased muscle mass, body hair, and deepening voice) as markers of impending manhood. If Andrew's father seems receptive to this line of counseling, Dr. Kessler could go further and introduce or normalize the involuntary experience for nocturnal emission as the body's way of demonstrating its biological readiness for fatherhood. Questioning resistant parents about their own identity as parents and interests in grandparenting can also facilitate a productive discussion about sperm banking as a means of salvaging their child's fertility after cancer treatment.

Even senior oncologists with well-developed clinical acumen encounter families who identify barriers to sperm banking, including familial religious orientation, culture, tradition, socioeconomic status, perceptions of fertility risk, communication style, psychological functioning, and, as in this case study, refusal to discuss the pros and cons of sperm banking with the patient. When families present these or other barriers that fall outside of the medical scope, they should be referred to others within the hospital system who are trained in addressing the identified sperm-banking barrier(s). For example, families who are motivated to bank sperm but are conflicted due to their religious beliefs (masturbation, use of assistive reproductive technologies, etc.), should be referred to a hospital chaplain. Families experiencing banking-related conflict or anxiety should be referred to a clinical psychologist. Referral to social work is indicated if concerns develop regarding sperm banking, storage costs, or transportation to the fertility clinic.

A referral to a psychologist could have been helpful in reducing Andrew's parents' anxiety, which in turn affects flexible thinking. Furthermore, the consulted psychologist could facilitate increased communication among family members on topics such as infertility concern, sperm banking, discomfort with decision process, or the promotion of decision-making satisfaction regardless of the sperm-banking outcome. By utilizing a "barrier interventionist," Dr. Kessler may have maximized the likelihood of Andrew banking sperm.

Conclusion

Sixty-seven percent of male cancer survivors desire children and prefer biological offspring whenever possible [2-4]. Survivors who experience infertility are at

increased risk for emotional distress, including sadness and anger, particularly when fertility information was withheld at diagnosis [2, 5-9]. Infertility-related distress is a long-term issue that impairs intimate relationships and other quality-of-life outcomes up to 10 years post-cancer treatment among young adults [10]. One way to avoid these and other undesirable outcomes of infertility is to bank sperm. Currently, sperm banking among adolescent males is underutilized, although the reasons for this are not well understood.

This case represents a realistic situation that many of us encounter and struggle to resolve. It is our duty to communicate risk of infertility in a timely fashion and to recommend sperm banking when indicated. But in order to promote sperm banking among uninformed families, we must also correct misconceptions, promote flexible thinking, make effective referrals, and follow up with adolescents and families within the ethical confines of pediatric care [11]. Although it is often thought that sperm banking must take place prior to the initiation of cancer therapy, animal modeling suggests that developed sperm are stored in the epididymis up to 14 days prior to ejaculation, suggesting that sperm samples provided within 2 weeks of treatment initiation can be used [12, 13]. For those who initially refuse sperm banking, efforts to promote banking should continue during the first few weeks of treatment before the patient becomes azoospermic.

Sperm banking is not appropriate for everyone, and the needs of individual patients must be considered. Whether the goal is to improve decisional satisfaction, emphasize the possibility of fertility maintenance, or develop more flexible ideas of parenting, the goal of improving quality-of-life outcomes across all cancer survivors remains.

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