Chapter 19

Oncofertility and Informed Consent: Addressing Beliefs, Values, and Future Decision Making

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T.K. Woodruff et al. (eds.), *Oncofertility*, Cancer Treatment and Research 156, 249
DOI 10.1007/978-1-4419-6518-9_19.

http://www.springerlink.com/content/978-1-4419-6517-2#section=759973&page=1

Introduction

Imagine every parent's nightmare. . . your sweet, vibrant daughter has just been diagnosed with cancer. The doctor is talking to you, but all you hear is "cancer" and all you can think about is the possibility that she may die. Now that the diagnosis is made, the doctor is anxious to begin treatment. He is describing the treatment, its benefits and burdens, and the schedule. Suddenly, though the "c-word" continues to buzz in your ears, you hear the side effects of treatment – hair loss, nausea, fatigue, weight loss, and infertility. "Infertility?! My baby may never be able to have babies?!" You have not yet processed the diagnosis, or come to terms with your child's mortality, and now this. Before you have even consented to the cancer treatment, the doctor is asking if you would like to enroll your daughter in an oncofertility research protocol. It means delaying treatment and further taxing her (and you) physically and emotionally. Time is of the essence, since the cancer treatment must begin as soon as possible. Not one decision but two, and both seem impossible.

The informed consent process is the backbone of physician–patient communication, and although fundamental to the practice of medicine, this process is completely inadequate in so many ways. Since the Supreme Court ruled that "Every human being of adult years and sound mind has a right to 1914 Scholendorff case, informed consent has determine what shall be done with his own body" in the been a legal standard for assuring that patients are informed, understand the information provided, and are afforded the opportunity to make autonomous decisions [1].

As a conversation between people, the informed consent process is imperfect. A good process involves disclosing information about the patient's condition, need for treatment, treatment options, risks, and benefits of those options; assuring that the patient understands that information; and allowing the patient or family member as the patient's surrogate to make a voluntary decision. Numerous questions plague the process: How much information must a physician disclose? How great must a risk be to necessitate disclosure? How can patient understanding be assured? Such questions reflect the formal process as it has evolved legally and ethically, but do not begin to get at broader issues. Clinical oncofertility trials provide an interesting context for considering the adequacy of the informed consent process. Is informed consent truly possible when making "a high-

stake, time-sensitive, emotionally charged, nested decision"? [2]. Difficulties for patient/family decision making lie in at least three areas:

(1) ability of the patient/family to understand the nature of treatment and research;
(2) ability to distinguish the treatment and research, particularly in assessing risks/benefits each; and
(3) ability to account for both the immediate and long-term implications of the decisions made.

Each of these demonstrates the frailty of the informed consent process and the tenuous nature of some of the decisions patients or their families make. Much has been written about the first two issues particularly in relation to the limits of informed consent following serious diagnosis in the research context. For example, informed consent requires that patients have adequate knowledge to make informed decisions. This means that the information be disclosed and understood. Yet, studies indicate that patients may not have the necessary knowledge or may not understand what they have been told [3, 4]. Further, studies suggest that a "therapeutic misconception," in which a potential research subject conflates the separate goals of treatment and research, may complicate informed consent for research trial enrollment [5, 6, 7].

My focus will be on the third issue, one that is particularly poignant in the context of oncofertility research and will require longitudinal study as (and if) oncofertility treatments move from the domain of research into standard practice. Such consideration is essential for adequate informed consent, as a decision to enroll in a study now will impact decisions made over the patient's lifetime. Understanding the implications of the decision requires an examination of the conditions under which the decision is made. Among these conditions are beliefs about the goals of the research (i.e., individual fertility preservation) and the emotional stake the patient and her family may have in the decision. Once made, the decision will likely require future decision making. I will briefly consider each issue in an effort to frame its significance for informed consent.

The Belief that Fertility Is Preserved: Immediate Risk for Future Benefit

The newly diagnosed cancer patient learns that her treatment may leave her infertile. Good statistics on the likelihood of this, if they are available, may still be unclear as they apply to populations and not individuals. The oncofertility trial appears to be the young patient's best, and perhaps only hope, of assuring future fertility. To make a decision, the patient/family must assess their beliefs about fertility and understanding of the research. At least four related considerations seem important in this scenario.

First, is the physician willing to offer a fertility preservation procedure such as ovarian tissue cryopreservation? With many cancers, immediate treatment is desirable, if not necessary, to avoid additional risks from the cancer itself. A physician may believe that the potential to save the patient's life takes precedence over all other considerations. In the physician's risk/benefit analysis, potential or even likely infertility may simply be a price paid for preserving life. This is separate from the patient's/family's own calculus but may profoundly affect whether the patient is even offered fertility preservation

options. Some physicians act as technicians, merely offering and objectively explaining all treatment options available so that the patient/family is solely responsible for decision making. Others more paternalistically direct treatment, while still others seek to counsel and negotiate with patients. The course of the conversation results from the physician's beliefs and type of physician he/she is [8].

The physician's concerns about impact of the research on treatment may be compounded by a second concern: Is the procedure likely to result in fertility preservation? Both physician and patient must assess the trade-off between the delay of cancer treatment and potential for fertility preservation. Ovarian tissue cryopreservation does not guarantee that the patient will be able to have her own babies in the future. Even if the research demonstrates success, similar success for a particular patient is not assured. Efforts to preserve fertility have no therapeutic value for the treatment of cancer, may interfere with the initiation of cancer treatment, have independent risks, may result in unacceptable side effects, and ultimately may not pay off. One study found that research participants did not understand that clinical trial treatment is not standard treatment and may involve additional risk [9]. For some, the risks beyond the impact that participation in the study will have on the cancer treatment may not be acceptable. For example, beyond the usual risks associated with a surgical procedure, removal of an ovary or part of an ovary may result in early menopause and its attendant risks for the patient. This might be weighed against the potential risk of infertility and the potential for success of the developing oncofertility technologies. Consideration of these risks is necessary though may be difficult to separate from the larger context of the risks and benefits embedded in the cancer treatment. Others argue that clinical research trials are consistent with therapy and may be good therapy themselves [10]. While this argument pertains to clinical trials for the primary diagnosis, in this case a clinical trial for an experimental cancer treatment, it more broadly suggests an independent value for clinical trials. A patient worried about her future fertility may fare better in her cancer treatment if this concern is addressed.

Addressing a patient's concerns about future fertility, however, may entail actually thinking about the future, not just the more imminent possibility of infertility. With most cancers, the primary concern is preserving life and restoring the patient to a cancer-free existence. The infertility issue may be a significant distraction, which may be either positive or negative. For some, the opportunity to deal with a different problem may be welcome relief from dwelling on the cancer diagnosis. For others, however, it may mask important issues that the patient/family must understand in making any treatment or research decision. Considerations of fertility are inherently matters for long-term thinking, particularly in the case of a child or adolescent patient. Decisions about bearing children will usually not be made for years or even decades. Pursuing fertility preservation could become important symbolically; it represents a normal, healthy future in which starting a family is possible. Whether this representation is realistic or optimistic is necessarily part of a good informed consent process. From a research perspective, the patient's enrollment in a research protocol may be of great benefit whether the patient lives or dies or goes on to make use of the opportunity for bearing children or not. But for the patient, participation in the protocol may only be valuable, setting aside general arguments about the importance of altruistic behavior, if there will be a real opportunity

to benefit from it in the future. Considerations of the symbolic value of the procedure, i.e., “what does it mean to the patient?” are likely to impact the decision to participate.

Finally, risks, benefits, and symbolism aside, the decision-making process cannot avoid addressing the fundamental question: Does the patient want babies? While some girls declare their desire for a baby from the moment they pick up their first doll, most will not have seriously considered this even in the abstract. Thus, the entire decision about participation hinges on anticipating future desires. Even those girls who claim to have no desire for children may want to maintain the option, recognizing that they may change their minds. If the families are involved in this decision-making process (and they likely are given that the patient is a minor), it may be difficult to separate a parent’s desire for future grandchildren from the patient’s wishes. This may lead to conflict if the patient prefers to focus on the present treatment of her disease while the parents insist that she consider her future or vice versa. While the parents retain decision-making authority, such weighty decisions about life and death and procreation suggest the need to include the minor in the process, as developmentally appropriate. Indeed, the American Academy of Pediatrics recognizes the important role of the minor in medical treatment decision making and calls for patient assent for treatment [11]. Consent and assent require concrete decisions about abstract situations and beliefs that may not yet be clear.

Emotional Implications of the Decision-Making Process

Among the risks and benefits that might be discussed as part of the informed consent process are the emotional implications of the decisions to be made. At least two warrant consideration: the very role of emotions in this decision-making process and the relationship this decision has to the child’s sexuality.

Any decision about infertility will likely be as subject to emotions as to rational considerations, even without the greater context of cancer treatment. The decision can be dressed in the language of logic, with a recitation of benefits and risks and an accounting of personal values. But, fundamentally, the decision to have a child is among the most emotion-laden decisions one can make and any decision that relates to childbearing seems likely to be as emotional. That does not mean that there are not good and bad reasons, pros and cons, arguments from responsibility and obligation, considerations of context, and other elements of objective argumentation, but ultimately, it comes down to whether one wants a child or not. Desires often exist independent of good judgment. To further complicate matters, in this case the decision is probably not yet about whether the patient wants a child, but about what the child is likely to want in the future. Emotional decisions may not reflect an individual’s core values or may not be reflective at all. It seems logical, in the face of immediate jeopardy to one’s fertility, to reach for an insurance policy, to take action that might preserve the option of having children in the future. But it may be just as logical to refuse enrollment in an oncofertility trial out of a reasonable preference to commence with the cancer treatment as soon as possible, to worry about living first and having babies later. Which is more logical? In the end it may not matter as the emotional reaction – panic, desire, fear of infertility, or dying – may be the true arbiter of decision making. Emotional response is certainly human and can be

very valuable, but may not suggest the decision one would otherwise make in less difficult and urgent circumstances. As Jodi Halpern notes,

> . . . while emotions might help us notice what is morally or humanly relevant, they are not always reliable indicators of our deep and long-standing values. Consider how romantic passion or fear of loss compel our actions and even give us a sense of certainty – and yet both can also feel quiet alienating in retrospect. The strength of an emotional feeling does not necessarily reveal how integral the emotional view is to our internal beliefs and values [12].

When a weighty decision must be made quickly, with little time or energy for rational analysis, emotion may become the primary guide. It may not lead one astray, but can explain emotional anguish later on. Acknowledging this possibility, if not accounting for it, seems a necessary part of the informed consent process.

In addition to the emotions triggered by the possibility of infertility are those due to the discussion itself. Any discussions related to fertility may be difficult or at least uncomfortable. Parent and child are forced by circumstances to discuss the child's fertility, a topic inextricably linked to sexuality. After just facing a child's mortality, they now must also consider the child as a sexual being. Usually, the preference is for adults to make decisions about childbearing for themselves when the time comes. However, when cancer treatment in a young or adolescent girl poses the risk of infertility, suddenly she is forced to consider very adult topics, without the benefit of whatever preparation the status of adulthood confers or from the context of a committed relationship in which family planning ideally occurs. Parents are also put in the position of making decisions that only indirectly bear on them. While some parents may be overbearing in their pursuit of grandchildren, they usually do not have to make decisions that will affect whether biologically related grandchildren are even a possibility. Through this emotion-laden lens, it seems impossible that the family, and the child herself, will ever see this young patient in the same way again. A child involved in the decision-making process may come to view herself as more adult, more capable of making decisions, including those about sex, or may be troubled by her inability to deal with such weighty issues. Parents may also view the child differently, perhaps more mature or more vulnerable.

Debates about sex education and the human papilloma virus (HPV) vaccine may be instructive. The HPV vaccine was developed to prevent the spread of the virus linked to cervical cancer and is ideally targeted to 8- to 10-year-old girls who are less likely to be engaged in the sexual activity that could expose them to HPV.
Parental response to the vaccine has been mixed. Parents are divided on when sex education should begin and the responsibility of the parents in providing the education. When the HPV vaccine was introduced, parents were concerned that it would prompt earlier discussions about sexuality than they were prepared for and could serve to encourage their young daughters to have sex. Studies on the implications of the HPV vaccine suggest that families may not be ready. One study, for example, found that some parents preferred to delay immunization and the sex education they believed should accompany it, at least until secondary school. The investigators note, "Some parents were unable to acknowledge that their children could be regarded as sexual and therefore there was no need for a vaccine to protect against [a sexually transmitted disease]" [13]. Other

parents preferred that the vaccine be offered to younger children or babies to limit the child's curiosity and circumvent the need for discussion about sexuality. Similarly, the unavoidable link between fertility and sexuality may intensify emotions and cloud judgment about both cancer treatment and fertility preservation choices. In addition to discussing treatments, research, and the benefits and burdens of each, the family may need help sorting out their emotional responses.

Future Decisions

Electing to preserve fertility feels like a final decision. Decision made, the patient undergoes a procedure to attempt to preserve her fertility, removing all or part of an ovary, banking eggs, or creating and banking embryos. Once done, she can proceed with her cancer treatment. If the cancer treatment is successful and the patient survives, however, the story is only just beginning. At some point, whether it turns out that she is infertile or not, she must decide what to do with that stored material.
For a young girl, it may be decades before she wants or needs the materials. In the meantime, she and/or her parents must make decisions about storage and ultimately, she or someone else must decide what to do with the materials.

Fertility preservation procedures may include storage for some limited time, at least while a research protocol is active, but eventually the former patient/family must make decisions about ongoing storage. Storage fees may amount to thousands of dollars before she is ready to use the materials. This may feel like money well spent for someone rendered infertile by their cancer treatment who desires a baby or a waste for someone whose fertility persists despite treatment or decides she does not want children; such is the nature of any "insurance policy." The storage issue may seem easy, but can force the former patient to revisit her illness experience and question her desires, on an annual basis. Interviews of women who stored embryos after in vitro fertilization (IVF) illustrate the potential emotional burden. One woman was asked about surplus embryos at the beginning of the IVF process, but says she was unable to consider embryos she might not want or need when her focus at the time was on having children she so desired. When the first bill for the extra embryos arrived after she had children, she said, "I was petrified. . . There was no practical reason to keep them. I just wasn't ready to make the decision not to keep them." Each year she pays $600 for her inability to decide what to do [14].

Even if the fee is not a factor, long-term storage raises other questions. A young girl may not be ready or interested in having children for 10, 20, or even 30 years. Will the tissue still be viable? The experience with frozen ovarian tissue is too recent to know, but frozen sperm has proven viable for up to 21 years [15]. How will freezing and thawing affect the tissue? Will using the tissue be safe after extended periods of storage? What if the storage facility goes out of business, suffers a power outage, etc.? Once the patient is ready, will she have the means to make use of the materials? None of the questions have answers at this time, but will require consideration at some point. The concern now is whether these questions merit consideration before enrolling in a fertility preservation protocol.

Beyond the question of storage and maintenance are questions about disposition of the materials. The research protocol may address the issue at the time of enrollment. In the event that the patient dies, the patient/family may be asked to select either donation for research purposes or destruction of the remaining tissue that was collected for research. Whatever box was checked may no longer reflect the family's preferences after the death of the patient or the patient's expressed wishes before her death. These preferences may include options not offered at the outset of the trial. Further, the tissue designated for the patient's own use is sent to a third party storage facility and is never under the purview of the researchers, though it may be subject to particular requirements of the storage facility or fertility center. Can a living patient or a family direct that the materials be used in other ways, for example, donated to the patient's sister or even to a stranger, for procreative purposes? The history of IVF is full of tales of individuals fighting over what is to become of frozen embryos. The IVF experience also demonstrates that a number of frozen embryos exist in limbo, abandoned, and unfunded by their creators. The Ethics Committee of the American Society for Reproductive Medicine considers embryos abandoned after 5 years of unpaid bills and futile efforts to contact those responsible for the embryos [16]. According to this standard, the facility may then thaw and discard the embryos. Yet, the storage facilities appear to have been largely paralyzed to act on the policy [17]. One study indicates that most clinics (95%, 166 clinics) attempt to contact the people who have stored embryos regarding disposal, even if the consent to future disposal had already been provided in writing. Most of those (66%, 110 clinics) did not proceed with disposal if those who created the embryos could not be reached [18]. The researchers describe a sense of reverence for these embryos, which persists even in disposal processes that may resemble religious ceremonies. While the same moral weight may not attach to ovarian tissue, comparable emotional import might, occasioning similar controversies and familial distress. Or, it may be that the disposal of preserved ovarian tissue is more like the disposal of frozen sperm or even the disposal of other unwanted tissue removed during surgical procedures. The reaction will likely vary with the context of the disposal and the personality of the family. Regardless, a full informed consent process may have to acknowledge the need for future decisions about storage and disposal.

Conclusion

No informed consent can cover everything, but legally and ethically, physicians and researchers are obligated to disclose information relevant to decision making, assure the patient/family understanding, and support the process of making a voluntary decision. Decisions about undergoing fertility preservation procedures highlight some of the shortcomings of the informed consent process and raise questions about the very possibility of an adequate informed consent. Generally the process focuses on the immediate treatment and/or research options, but for some decisions this may not be enough. Decisions about oncofertility research and treatment require attention to personal values, emotions, and implications for long-term decision making, and these discussions take time. In studies of clinical research decision making for minor patients, parents consistently cite the need for more time to make the trial decision [19–25]. "[P]hysicians should plan the consent process in such a way as to allow for as much time for decision-

making as possible within the limits of the child's medical condition and the particular trial protocol being offered" [26]. Unfortunately, this important discussion often must occur quickly, perhaps over only hours or days. Is it possible to address or even raise these issues under the pressure of time and serious diagnosis? This is more than just a rhetorical question. For informed consent to avoid being relegated to mere legal requirement, this process of communication must be recognized as a fundamental driver of the physician–patient relationship and quality health care. Short time frames and urgent decisions are no excuse for insufficient efforts to convey the magnitude and implications of the decisions to be made. The patient and her parents, overwhelmed by their situation and the decisions they must make, need help navigating the issues they must consider. It is the physician who is best situated to help them make these decisions. The impossible can only come to seem possible with the best communication under the circumstances. This means at least disclosing answers to questions the patient/family will likely not know to ask and helping them understand what they are doing, well before seeking signatures on an informed consent form.

Acknowledgments This research was supported by the oncofertility consortium NIH 8UL1DE019587, 5RL1HD058296.

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