

Oncofertility: Fertile Ground for Conflict Between Patient Autonomy and Medical Values

SARAH K. WALSH,^a ELIZABETH S. GINSBURG,^{a,b} LISA SOLEYMANI LEHMANN,^b ANN H. PARTRIDGE^{a,b}

^aDana-Farber Cancer Institute and ^bBrigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA

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ABSTRACT

Oncofertility is a unique, multidisciplinary field that serves to bridge the gap between available fertility resources and the special reproductive needs of cancer patients. Oncofertility is a growing field due to the increasing number of survivors, development of new oncologic therapies, extension of duration of therapies, and development and refinement of reproductive therapies. While the technologies and demand for services expand, clinicians need to be appropriately prepared for dealing

with various clinical scenarios that may require ethical deliberation. Three real cases are presented in which the patient wishes to pursue reproductive assistance, but her decision is met with hesitance or uncertainty by her care team. Discussion of these clinical scenarios highlights ethical implications of oncofertility practice and serves to highlight the need for the establishment of multidisciplinary care teams and guidelines to support both clinicians and patients. *The Oncologist* 2017;22:860–863

Implications for Practice: The growing field of oncofertility is ripe for conflict between patient autonomy and medical values due to the nature of cancer and associated threat on an individual's health and survival, as well as the personal significance of childbearing. Cases are presented and ethical implications are discussed to further explore the inherent difficulties in oncofertility practice and guide clinicians in similar situations. Developing guidelines and establishing multidisciplinary teams to facilitate oncofertility discussions and care, as well as training of clinical team members, may improve patient safety, well-being, and satisfaction within the context of fertility decision making, care, and outcomes.

INTRODUCTION

As improvements in reproductive medicine develop, fertility preservation is becoming more widely available, further prioritized by medical professionals, and increasingly utilized by special patient populations such as young women and girls with cancer. The interdisciplinary field of oncofertility links oncologists and infertility specialists to address the complex fertility issues of cancer patients, and to help this population preserve the ability to parent biological children. However, oncofertility also raises ethical dilemmas for health care providers.

Improved oncologic therapies and surveillance have led to increased cancer survival rates [1], resulting in more women able to pursue childbearing after cancer treatment, as well as a patient and provider mindset that may be more focused on survivorship outcomes early on in the diagnosis and treatment period. Longer treatment periods, as seen in the recent trend of breast cancer survivors undergoing longer durations of hormonal treatment [2], are not only creating more survivors, but are extending the age of childbirth opportunity into the years of naturally diminished fertility.

With the varied complexities of cancer patients and the personal and sociological weight of fertility decisions, conflict between patient autonomy and medical values should be expected in the field of oncofertility. Scenarios may in particular present a clash of patient autonomy and physicians' duty of nonmaleficence, including not offering seemingly counter-indicated procedures even when patients are willing to risk their health to preserve fertility or have a child. Additionally, both provider and patient experience a range of concerns and emotions. Young female cancer patients may face worry and psychological distress surrounding fertility decisions, and decisions are often made under substantial uncertainty and risk [1]. Clinicians overall may be reluctant not only due to their personal feelings, but in part due to their relative lack of knowledge about available fertility resources for this population and about the general novelty of these technologies [1]. All of these factors demand the establishment of oncofertility ethics guidelines that multidisciplinary care teams can reference and share with patients in these situations.

Correspondence: Ann H. Partridge, M.D., Dana-Farber Cancer Institute, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts 02215, USA. Telephone: 617-632-3800; e-mail: ahpartridge@partners.org Received November 29, 2016; accepted for publication December 13, 2016; published Online First on April 13, 2017. ©AlphaMed Press 1083-7159/2017/\$20.00/0 <http://dx.doi.org/10.1634/theoncologist.2016-0373>

We present three cases that illustrate some of the ethical dilemmas that accompany oncofertility practice. For none of these cases is there one right answer; rather, they set the stage for discussion of inherent ethical dilemmas in this relatively new field and offer practical guidance for management.

CASE 1

A 23-year-old single woman with severe common variable immunodeficiency with IgA deficiency and autoimmune cytopenias with significant neutropenia was a candidate for potentially curative allogeneic stem cell transplantation. The patient had previously undergone several immune-directed therapies without remission, and planned to proceed with stem cell transplantation with an unrelated donor after conditioning chemotherapy and total body irradiation. The conditioning regimen would render her sterile. The patient underwent fertility counseling and expressed interest in oocyte cryopreservation. At the time of presentation, the patient had an absolute neutrophil count of less than 100, was severely thrombocytopenic, and was red blood cell transfusion dependent. The safety and outcome of fertility preservation treatments in the context of her disease were discussed, particularly the risk of infection and/or bleeding as a result of egg retrieval or laparoscopy (if ovarian tissue cryopreservation was chosen). In addition, the possible, though rare, risk of hyperstimulation could require delaying her transplant several weeks.

Is It Ethical to Deny Fertility Preservation to Patients When Such Treatment May Carry Substantial Risk to the Patient's Life?

To make clinical decisions in the context of vexing ethical dilemmas, we should consider Beauchamp and Childress's four guiding principles of medical ethics: respect for autonomy, non-maleficence, beneficence, and justice [3]. However, the balance between patient autonomy and nonmaleficence can be difficult to achieve in cases of medically complicated patients when the intervention required for fertility preservation can be potentially life threatening. Intervention in this case with ovarian stimulation and oocyte cryopreservation would delay the transplant and increase risk of serious infection, possibly leading to death. Most fertility preservation treatments can potentially delay cancer treatment [2]. In these complicated cases, providers are faced with difficult decisions and patients may be in danger, either directly from the procedures or as a result of delaying needed treatments.

Retaining the ability to conceive a child is a major quality of life issue for many women, including those with cancer, sometimes even to the extent of influencing treatment decisions [2, 4]. As infertility may weigh heavily on a given patient, providers must include weighing potential harms and benefits, as well as patient preferences during the treatment planning discussion [2]. Providers should engage in a process of shared decision making with patients to ensure that they understand the severity of risks, motivation for pursuing fertility preservation, and alternative parenting options.

While some patients may want to pursue fertility treatments even in the face of limiting their own life expectancy, in rare circumstances clinicians may be justified in refusing to offer fertility treatment. Gracia et al. [5] point out that denying fertility preservation treatment would be inarguably ethical if it was known to what extent a patient's health would suffer as a result of treatments; however, this is usually uncertain.

Nonetheless, it is impossible to know how a patient will react to a given drug or procedure, but medical evidence, risk assessment, and judgment are used to determine the best method of treatment. Ideally, the decision of eligibility for fertility preservation should be left to a multidisciplinary team including the patient, a medical oncologist, a reproductive endocrinologist, and a psychologist or other mental health provider, guided by written protocols that can be shared with patients [6].

In a medical climate that frequently allows patients to assume varying degrees of risk in order to improve quality of life, such as in the case of a face transplant or post-mastectomy breast reconstruction, some may rightfully argue that prioritizing life prolongation over an elective procedure is unethical and antiquated. However, the ethical dilemma here is not whether or not harm is acceptable in the face of patient autonomy, but rather how much harm is acceptable. Similarly, it must be considered how much beneficial influence the elective procedure would have on quality of life. In rare cases such as this, a patient's wishes may demand that a provider allow harm too great to justify. Physicians have a professional duty not to offer counter-indicated procedures, even when requested by autonomous patients. Determining and generalizing set guidelines to all patients within disease centers may be difficult, but is necessary to guide practice, establish ethical and responsible standards, determine when procedures are counter-indicated, and protect patients.

CASE 2

A 32-year-old married woman with advanced triple negative breast cancer wished to transfer her previously frozen embryos to a gestational carrier. With disease progression and the possibility of having only limited life expectancy, the patient struggled with the decision to start a family. She felt confident that her husband and family members could care for a child, but she did not want her child to resent her for starting a family knowing her dim prognosis. The patient had several panic attacks around upcoming treatment appointments, with some of them leading to hospitalization. Her cancer was mildly progressing in the setting of her first-line chemotherapy, and the patient expressed that she was sick of receiving only bad news and that the possibility of starting a family was one thing that made her feel happy and hopeful.

Should Emotional and Psychological Well-Being be a Consideration When Deciding Whether or Not to Support a Patient to Pursue Assisted Reproduction?

This case illustrates the burdens of a cancer diagnosis, which can cause an individual significant stress and anxiety, as well as feelings of sadness and hopelessness. For some patients, the decision to have a child can give them a sense of hope and control in the face of living with cancer. While providers should respect patient autonomy, it is crucial to develop a strong patient-provider relationship in which both parties can openly and honestly discuss issues such as prognosis, motivation for having a child, cost of procedures, and future arrangements for the child in the case of death. In the face of both cancer and infertility, emotions will undeniably play a role in decision making. Providers should not seek to divorce emotions from decision making, but rather distinguish them from underlying issues that could be addressed through counseling. After thorough discussions have taken place, evidence has shown that

most patients in this clinical situation ultimately will decide against pursuing reproductive measures [6]. The purpose of counseling should not be to dissuade these patients from pursuing parenthood, but rather to help patients clarify the optimal course of action. Counseling in this context can aid in facilitating difficult discussions between the patient and family members around the patient's eventual death. In this scenario, the decision ideally rests with the willingness of the husband and family to raise the child in the likely event of the mother's very premature death. The care team's role is mainly to ensure that all parties understand the ramifications and are comfortable with their decisions, and to support the patient and family.

CASE 3

A 37-year-old married woman with nodal recurrence of ER/PR+ human epidermal growth factor receptor 2 negative breast cancer presented desirous of fertility preservation prior to potentially curative treatment. She was without evidence of disease otherwise and had not previously pursued fertility preservation. She underwent a cycle of ovarian stimulation and attempted embryo cryopreservation, which was cancelled due to poor response. She then underwent axillary dissection and radiation and began treatment with leuprolide and anastrozole. She discontinued systemic therapy within a few years, insisting that she was done putting her childbearing on hold. She was unable to conceive on her own and requested fertility treatment. High risk obstetrical consultation with restaging scans, social work consultation, and reluctant agreement of her oncologist led her to undergo two IVF cycles, and she conceived on the second cycle. Unfortunately, in the early first trimester she developed respiratory symptoms that led to the discovery of metastatic disease to the lungs. Initially the patient was determined to carry the pregnancy despite the need for anti-cancer therapy to treat her symptomatic metastatic disease.

Should Cancer Patients with High-Risk, Though Potentially Curative, Disease Be Supported to Pursue Fertility Preservation, Be Assisted in Becoming Pregnant, or Be Supported in the Decision to Stay Pregnant if Disease Recurs During Pregnancy?

Having a child is highly valued in terms of quality of life for many people, cancer patients included, and society is generally accepting of the idea of cancer patients seeking fertility preservation [7]. However, if a patient with limited life expectancy is able to have a child, it is an unfortunate reality that she may die shortly after the birth. In such a scenario, the burden of an individual's choice may be unjustly placed elsewhere, such as on the child or the surviving spouse. The Ethics Committee of the American Society for Reproductive Medicine concludes that the argument citing child welfare as a reason against reproduction is not persuasive for three main reasons [8]. First, the risk of cancer recurrence may not be extremely high in a given patient; second, the child will likely have a meaningful life even if he or she loses a parent; third, children experience stress and sorrow from a variety of circumstances in their lives that might be comparable to a parental death [8]. In cases 2 and 3, the first reason is less valid because we are not dealing with the average cancer patient, but rather women who have a high risk for or known metastatic disease. Nevertheless, despite the likelihood of an

approaching parental death, a child can still cope and have a meaningful life. Thus, respecting a patient's ultimate choice to reproduce in these cases is ethical as long as the surviving family is willing to care for the child after the patient's death.

Case 3 also highlights the dilemma of a woman who wants to keep a pregnancy despite significant risk to her physical well-being from her disease, and an inability to treat her appropriately while pregnant. This scenario may seem similar to that in case 1, but the major difference is that here the patient is refusing treatment rather than requesting it. All patients who have decision-making capacity have an ethical and legal right to refuse any treatment, even that which is life-sustaining. A pregnant woman's decision to refuse systemic chemotherapy in order to preserve the life of her fetus may be difficult for providers to accept, but it is nevertheless ultimately the patient's decision. Providers should clearly communicate to such a patient what her prognosis is with and without treatment so that she can make a truly informed decision. If treatment only provides a marginal benefit in terms of life expectancy, it may be reasonable for a patient to refuse treatment with the hope they will survive long enough to give birth to a healthy child. Here, guidelines should be established that ensure a shared process of decision making involving patient, family, and medical stakeholders, with additional input from tumor and ethics boards if necessary.

CONCLUSION

Ethically complex situations may be resolved optimally through open communication, counseling, understanding of patients' prognosis and values, and collaboration with a multidisciplinary health care team that places the patient at the center of the team [6]. While the majority of these cases must be dealt with on a case-by-case basis weighing the risks, benefits, preferences, prognosis, and psychosocial well-being of each individual, we can make some recommendations on the course of action for these women and patients like them.

Case 1 highlights the difficult dilemma of allowing a patient to undergo a potentially harmful procedure. In cases of considerable risk, a line of eligibility can and must be drawn in order to guide decision making, which can be transparent to patients. Until we have a national forum that includes providers and patients developing guidelines, provider groups within disease centers must decide on these guiding protocols. In this patient's case, her health care team decided that the risk of infectious complications would be too high at an absolute neutrophil count below 500. The multidisciplinary care team ultimately decided that fertility preservation conferred excessive risk in the context of the patient's disease and refused to proceed with treatment, adding that she could consider getting a second opinion. The patient disagreed with the team's decision, saying that this should be her decision, but ultimately stated that she had decided not to move forward with fertility preservation due to financial costs, noting irritation that her providers had not told her early on that payment for egg freezing was due up front.

This outcome highlights another question: what is the provider's obligation in discussing the costs of fertility treatments with patients and aiding in obtaining financial resources? While the intricacies of this consideration may be beyond the scope of this article, patients clearly need a comprehensive understanding of the financial realities of fertility procedures before decisions can be fully informed. Financial costs associated with fertility preservation have proven to be a barrier for young

adult female cancer survivors considering fertility assistance [9]. Because cost can be such an influential factor, either the physician or someone else from the care team, such as a social worker or a fertility program nurse navigator, should ensure that the patient is knowledgeable in this area and has the resources to seek and advocate for financial assistance.

In situations such as case 2, which highlights both the role of mental health and a limited lifespan in clinical decision making in oncofertility, we recommend that patients be referred first to counseling. The presence of psychological and emotional issues does not necessarily rule out a patient as a candidate for fertility preservation. While leaders may be able to come to agreement on the extreme ends of the spectrum of psychological disease as to who should not move forward with fertility preservation, most cases must be considered on a case-by-case basis, utilizing psychological counseling and supports throughout the process. This woman recently decided to pursue parenthood and had embryos transferred to a gestational carrier who has an ongoing pregnancy. Presently the patient is undergoing third-line chemotherapy treatment. The patient is also under psychiatric care for her anxiety disorder, which has been stable recently. In these cases, reliance should be less on set guidelines and more on guiding procedures for management of such medical ethics issues as they arise, including discussion, collaboration, and support within a multidisciplinary team. As these decisions are often inherently stressful and emotional, referral to counseling should be considered with all patients and required for those who exhibit psychological or emotional disturbances. Together, the counselor and patient may come to a more thoughtful decision, and the counselor can share the patient's progress with the multidisciplinary team.

Case 3 presents a woman who wished to become pregnant despite high risk for metastatic disease, and then desired to keep a pregnancy despite the development of symptomatic advanced disease. Many compelling ethical arguments were discussed, but ultimately length of life is not a justifiable reason to deny fertility treatment. After many discussions with her oncologist, and due to the fact that it was unclear that she would live long enough for the fetal viability without treatment of the metastatic disease, the patient and her husband decided to terminate the pregnancy to allow for treatment. She received a number of palliative therapies and ultimately succumbed to the disease. While life expectancy is not a reason in and of itself to deny fertility treatment, it may impact the patient and

family's decisions. Referral to counseling for the patient and/or the surviving spouse or family may also be considered and encouraged in these cases in order to ensure that all parties are knowledgeable and comfortable with the decision.

These cases highlight potential dilemmas in which the balance between patients' preferences and autonomy conflict with clinicians' values and responsibilities. While advocating for the development of guidelines to help clinicians contend with these cases, we also recognize the contradiction this poses in the face of the gray areas outlined in the cases here, and thus these guidelines may be limited in scope. In addition to informing clinicians of basic good clinical practice within the field, the establishment of guiding principles for the management of such cases should serve to start a national conversation on the topic and also help providers determine when cases are gray or not, and thus when they should be brought to an ethics committee or a multidisciplinary team for further input. Clinical experience in dealing with such dilemmas with a collaborative team approach including the patient at the center should help lead to thoughtful resolution and will better shape the way providers resolve ethical conflicts surrounding oncofertility in the future. In addition to clinical experience, oncology providers who have poor knowledge of oncofertility issues should take advantage of oncofertility continuing medical education opportunities, as a lack of knowledge and understanding in this area can disadvantage patients who would benefit from having meaningful discussions about fertility with their providers. Ultimately, as oncofertility grows, it is essential that providers are trained to deal with these situations and that research and conversation are prioritized to help clarify ethically responsible clinical practice.

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