

Chapter 12

Today's Research, Tomorrows Cures: The Ethical Implications of Oncofertility

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In contemporary society, translational medical research is the name of hope itself. For many, advances in modern medicine can be seen as a steady progression of science over dreadful and intractable illnesses, especially illness of children and young adults. Advances in the creation of families and protection of children have most clearly marked medicine's success. Yet every scientific discovery and medical advance carries with it the inevitable dilemmas of choice and power. This chapter will look carefully at the effect on treatment when two trajectories of translational research converge to form a new field of inquiry—the field of oncofertility—and explore the ethical and social implications of the power that such research will create.

Over the last 30 years, advances in reproductive technology have changed the event of infertility from a crisis of faith and generativity to a treatable medical condition. A breakthrough development in reproductive technology occurred with the historic birth of Louise Brown in 1978 through in vitro fertilization (IVF). Although infertility remains prevalent and is emotionally difficult for those it affects, it is now often curable, with nearly 85% of persons seeking treatment able to produce a child [1]. The advancements of assisted reproductive technology (ART), and particularly IVF, have increased the number of women who able to become pregnant using gametes from her and her partner, or by using donor sperm or eggs. It is, by many accounts, one of the measurable, tangible narratives of medical success, becoming so normative that in 2003, 112,872 ART cycles were carried out in the U.S. alone, resulting in 35,785 live births and 48,756 infants born using the techniques developed for the treatment of infertility [2].

This story of breakthrough advances in treating infertility parallels another—the successful treatment of previously fatal cancers, particularly cancers in children. Most people today who are diagnosed with cancer survive, with 5-year survival rates being well over 80% for many forms of cancer [3]. The idea of cancer has shifted from that of a death sentence to that of a chronic disease that will need to be monitored over the long term. With the increase in successful treatment of cancer patients, medical teams must now focus not only on the short-term treatments, but also anticipate long-term quality-of-life issues for their patients in the world beyond the “cure.” As survivors of cancer treatment are returned to the trajectory of their lives, they develop similar goals for education, career, and family life that their healthy peers and family members enjoy. Yet some of these goals are simply unattainable, for side effects of the chemotherapy or radiation that saved their lives has often compromised or eliminated their fertility.

For children and adults faced with a sudden cancer diagnosis, the immediate priority is survival and support for the difficult time period surrounding treatment. But the coincident infertility created by advances in cancer treatment often paradoxically create a patient of a different sort—

an infertility patient. At this juncture, the medical disciplines of oncology and infertility have become intertwined, and a new area of medicine, oncofertility, emerges.

With this new field comes new issues: complex dilemmas and ethical and practical issues that arise when discussing fertility preservation in the context of cancer are only the first horizon of our moral concern. The concerns around these topics deepen when the wider social implications of this work are considered. The medical breakthroughs created in oncofertility are a portal to a far wider prospect. Using the techniques described in this book, can gametes be preserved against a host of physical and social events that will compromise fertility, often with the same prospective statistical certainty as chemotherapy and radiation?

Finally, as basic research on human embryonic stem cells accelerates, a rate-limiting step is the acquisition of human eggs from women for research, especially for the creation of disease-specific cell lines for the study of early cellular reprogramming and for the creation of patient-specific histocompatible tissue. As the debate about how to obtain human oocytes for research and for potential cures intensifies, serious moral issues about the risk of multiple egg extraction emerge. It has not escaped our attention that the creation of a stable, renewable, and plentiful source of human ova has the potential to relocate and transform the entire debate about egg acquisition for research or therapy. Such an advance could solve several of the ethical complexities of stem cell research by ensuring the just, safe, and scalable acquisition of eggs.

The questions of fertility preservation have an obvious threshold consideration— they are strongly affected by the sex of the participant. For men, sperm can be safely retrieved, frozen, and stored once a boy begins to produce spermatocytes (see Brannigan, this volume, for further discussion). Unfortunately, options for women facing cancer treatment are less reliable. Mature human oocytes cannot be effectively frozen, stored, and thawed because of the fragility of the human egg cell [4,5]. For a woman facing fertility-impairing cancer treatment, a male partner or willingness to use donor sperm, the time to safely delay cancer therapy, and a cancer that will not grow in response to hormonal treatments makes her a candidate for ovarian hyperstimulation and emergency IVF. Ideally, this results in embryos for potential future use (see Agarwal and Chang, this volume, for further discussion). This option is currently the most widely used and proven method for preserving fertility, however, it has limitations, can be emotionally and physically difficult, is a viable option for only a fraction of patients, and carries some risk to the patient. Scientific expertise and technical advances have begun to overcome many of the obstacles of female fertility preservation in the face of cancer, with the goal of offering solutions that are feasible for a wider range of patients [5].

Expanding Options for Women – Follicle Preservation and Maturation

Should more be offered and attempted? Biomedical research in the field of oncofertility has begun to extend experimental research to explore this question. Could ovarian tissue containing immature ovarian follicles be frozen, stored, and then thawed, matured, fertilized, and result in successful pregnancy [6–8]? Was this idea both practical and ethical? Yet offering the procedure is itself an ethical problem: the techniques available are experimental, and participation in research protocols offers limited hope for the participants today, while holding the promise of developing options for future patients [8]. The complexity of the decisions for both patients and

their families increases yet further in the case of childhood cancer, when the child's assent and parental consent for the child patient's participation in research come into play [9]. The best interest of the child now must simultaneously be held in balance with the best interest for the adult the child will hopefully become.

In this chapter, we uncover the core themes that have emerged and reflect on how the canonical literature on the topic is reinforced or altered by new work in oncofertility. First, we explore infertility as a disease state or disability. Why is it important to continue research on fertility preservation? Does the loss of fertility for any reason have a moral high priority and deserve allocation of resources and health care dollars? We then look at an instance whereby the technology of ovarian cryopreservation and maturation will have particular ethical considerations: the case of fertility preservation and research in children. What special considerations surround cancer, fertility, and research involving children? Is it appropriate to be concerned with a child's future reproduction or treatment-related infertility? How might the issue be approached to avoid discomfort with regarding children as future sexual beings? Lastly, these questions are used to frame the potential next uses of an emerging ability to cryopreserve ovarian tissue for future transplantation or maturation of primordial follicles in vitro. The potential of these techniques is far-reaching, not only because it may provide a new choice for fertility preservation for girls and women with cancer, but also because it has the potential to revolutionize fertility treatments for other reproductive-age women, change the nature of egg donation, reduce the number of unused embryos in infertility clinic freezers, and influence the acquisition of embryonic stem cells.

A Prairie Horizon: The Long View of Research on Fertility

The landscape of reproduction has shifted throughout history, both as an adaptation to circumstances and as a reaction to advances in technology. The scientific breakthrough of efficient ovarian tissue cryopreservation and in vitro maturation [7] of human female gametes will likely change the horizon of this landscape in the near future. The purpose of this chapter is to provide roots for the utilization of this technology. By reflecting on ethics literature, historical precedents, recommended medical practices, and desires of cancer survivors, we will frame some of the important questions about advancing fertility preservation treatments and anticipate future dilemmas.

The development of ovarian cryopreservation represents a significant step forward for fertility-preserving options for cancer patients who are either sexually immature, do not have a partner at the time of diagnosis and/or do not wish to use donor sperm, or who are not able to or choose not to delay treatment for emergency IVF [5–7]. In the scenario that this treatment becomes readily available for humans, a patient could elect to have one ovary removed by laparoscopic (minimally invasive) surgery and cryopreserved. If she chooses to start a family and is unable to do so without assistance, a piece of the ovarian tissue would be thawed, the follicles matured and fertilized in vitro, [10] and then introduced into her uterus as in current IVF protocols. Alternatively, the tissue could be transplanted into the patient and matured prior to IVF [11]. If the patient no longer has a uterus or is not able to carry a pregnancy, the embryos could be gestated by a surrogate.

Cryopreserving immature follicles would have several distinct advantages for cancer patients or any woman needing an oophorectomy. First, it allows her to bank her own gametes, allowing her to have her own genetic offspring in the future if she chooses. Second, if she is eligible for emergency IVF but does not have a partner, it gives her the opportunity to wait until she has a partner. She also can choose against the delay of her own cancer treatment and have an alternative to emergency IVF. Third, it will likely eliminate the risk of reintroduction of malignant cells back into the patient [5,12]. Fourth, it may decrease the number of embryos made with each cycle, thus eliminating the dilemma of what to do with unused embryos once a pregnancy has been achieved. Fifth, it allows her to delay childbearing until an age that approximates that of the normal population. Female survivors of cancer treatment may recover normal ovarian function early in their reproductive life, but they often experience premature ovarian failure by their thirties [13]. The subsequent pressure to reproduce may hasten her choice of a partner or restrict the other life choices of education and career that her peers enjoy.

Despite the medical breakthrough that this technology represents, let us ask a priori the questions: Is the premise of infertility research a just and prudent use of research resources and attention? Why is it important to focus research and offer new reproductive technologies (NRT)? Many would argue that IVF research is precisely the sort of highly technological medicine that drives up health care costs by focusing on desire instead of need. In a world that has significant infant mortality and orphans in need of homes, should medicine continue to refine this field? Let us turn to the defenses as mounted in the literature by Daniel Brock and John Robertson.

The right to reproduce is regarded as an important freedom within society that is seldom questioned or restricted. This reflects a long-standing sense of a procreative respect for the “right to reproduce” as a moral imperative, often defended as bearing on autonomy, identity, self-determination, and dignity [14]. Our cultural value of being able to have one’s own genetic children is clearly displayed as the emotional reaction of an individual or couple to their own infertility.

When discussing the rights of individuals, it is customary to describe them in terms of negative and positive rights. The right to procreate is inherently regarded as a moral “negative right”, which is to say that others have a duty to not interfere with this right unless there is sufficient and weighty moral ground to do so. For example, individuals and the government should not sterilize citizens against their will nor interfere with an individual’s access to NRTs. The right to procreate has not, however, been afforded the status of a “positive right.” This would propose that others must act in a way to secure this right and guarantee the right to NRTs to anyone who needs them regardless of cost. The designation of this claim is certainly a matter of current debate given the prevalence and emotional consequences of infertility. By recognizing the fact that reproductive technologies are not widely available or funded, however, we do not intend to make an argument against insurance coverage of reproductive technologies. It is beyond the scope of this chapter to discuss social injustices with regard to access to health care services for fertility, contraception, or other mechanisms of “procreative liberty” as described by John Robertson [15]. The fact that infertility treatments are covered by insurance in a minority of states in the U.S. or that citizens are not accustomed to expecting these services should not pave the way for this precedent to become ingrained in our social thinking [14].

If a moral right protects procreation by coital means, then one can extend this right to also protect non-coital reproduction [15]. The desire for an infertile person or couple to reproduce is rooted in the same desire to parent as it is for a couple that can coitally reproduce: to rear children that are genetically related to one or both of the parents. The fact that the individual or couple is infertile should not exclude them from an experience that is the norm for people in their lifetime [15]. In this case, the disability is an inability to coitally produce children, and to disqualify them from treatment would be tantamount to denying any medical treatments that aim to approximate normal life. If insurance will cover the diagnosis and treatment of the sequelae of chemotherapy or radiation, for example lung or heart problems, it follows that infertility as a consequence of treatment should also be covered. Furthermore, many medical conditions, such as hypertension, diabetes, arthritis, and cancer have associated genetic predispositions as well as behavioral influences. Why should other medical conditions that also have genetic or behavioral components, such as premature ovarian failure, immotile sperm, or delayed childbearing not be allocated the same status with regard to health care dollars? The direct consequences of infertility may not be life threatening, but many medical conditions that hinder quality of life are readily treated and covered [14]. Perhaps the limited allocation of health care dollars for this service is biased by the decision being made by a portion of the population that has already reproduced, thus they know they will not need these services [14].

As Daniel Brock notes:

“Norman Daniels has argued that the importance of health care for justice lies most fundamentally in its securing and protecting for individuals access to the normal range of opportunities in their society. Health care can often prevent, restore, or limit the loss of normal function that is the typical mark of disease. While we tend to associate equality of opportunity most commonly with education and work, it is not limited to those venues. NRT’s often represent the means by which the opportunity to bear and raise children can be restored to infertile individuals. The moral importance—on grounds of equality of opportunity and justice—of doing so depends largely on the relative importance of parenting within the normal life plans of most people. This suggests that infertility is a disability whose alleviation by means such as NRT has a very high moral priority.” [14]

For the authors of this chapter, the case for allowing women to have children after cancer treatments presents a compelling case for research. In the case of cancer when the cure may cause harm, we argue that there is a duty to prevent damage or repair that which is damaged by treatment, when possible. Infertility is understood as a disease of reproductive-age individuals that can often be overcome by medical treatment, and it is just to allocate resources to its research and treatments. There is yet another reason to actively pursue this research. It is our contention that the growing search for oocytes for stem cell research presents another, non-rights-based argument for continuation. Thus, we can focus on the particular case of oncofertility, while understanding that the research has a mutable future.

The Role of Oncologists and Infertility Specialists

In large part, the most profound ethical issues when a new treatment is developed are the presentation of the advance without fictions or promises. The issue of realistic consent is the second ethical problem in oncofertility. Cancer and its aftermath present a difficult case, with a long history of invasive, risk-laden treatments. Patients depend on their physician to present to them their illness, educate them about treatment, and expect to be warned about side effects of

the treatment. Developing a clear ethical interaction can be complicated by the swiftness of new research as well as its uncertain application.

As this technology goes forward, it is also imperative that appropriate patients have access to information regarding experimental fertility-preserving techniques. Oncologists who treat reproductive-age patients or patients who have not yet reached sexual maturity need to not only be aware of the potentially gonadotoxic effects of treatments in order to discuss treatment related infertility with patients, but also should be aware of both established and experimental fertility preserving options for both male and female patients [9,12]. Studies suggest that oncologists either explain sub-optimally the potential of treatment-related infertility, or fail to do so at all (see Snyder, this volume, and Clayman, Galvin, and Arntson, this volume, for further discussion). This can be attributed to a number of factors, including an appropriate focus on treatment and cure of the cancer, lack of physician knowledge about available methods to preserve fertility, physician judgment about patient prognosis, or discomfort with broaching the subject with patients or their parents, as in the case of children. While oncologists may get the appropriate training in fellowship programs to discuss well established methods of fertility preservation such as sperm banking and oophoropexy, they may lack appropriate training and knowledge about newer techniques, particularly those that are experimental [9,12].

Ongoing training and effort on the part of the practitioner will ultimately be required to stay abreast of experimental techniques, particularly in the case of children and women without partners who will need to store gametes, not embryos. The American Society of Clinical Oncology (ASCO) recognizes the scope of this problem and has published “Recommendation on Fertility in Cancer Patients” that emphasizes the importance of early discussion and referral to appropriate resources for all patients of reproductive age. In the case of children or women who cannot or do not wish to freeze embryos, the patients should also be referred to appropriate specialists and centers capable of carrying out institutional review board (IRB)- approved protocols when established methods do not exist [12]. The process of patient education about fertility preservation prior to cancer treatment will ultimately require a combination of approaches that involve education by patient advocacy groups and also a sea change within the climate of oncology practice [12].

Unfortunately, the measure of damage and the need for restoration of function is often hard to quantify. It is often difficult to place a number on the risk of infertility for any given patient and the type of treatment he or she is to receive. The fertility status of the patient after treatment will vary greatly depending on sex, age, dose and duration of chemotherapy or radiation treatments, method of administration, field of radiation, and the pre-treatment fertility status of the individual [5–7,12] (see Gracia and Ginsberg, this volume). For experimental fertility-preserving techniques, it is impossible to quantify success as there is no current success rate to offer to the patient. The patient who is offered the opportunity to enroll in experimental trials must explicitly understand that the true benefit may not be available within his or her reproductive life span, yet may contribute to the development of an option for other patients in the future. Experimental techniques should only be undertaken at appropriate research centers under IRB-approved protocols. Oncologists must work closely with the reproductive endocrinologists and with psychosocial providers in order to be able to refer as needed and help to develop an appropriate treatment plan and refer patients to clinical trials [6,7,12,16].

Reproductive endocrinologists need to not only be aware of both established and experimental options, but also have an increased awareness of the patient that is facing the crisis of cancer simultaneously with the potential crisis of infertility. Full consideration of the cancer diagnosis, consultation with the patient's oncologist, the range of fertility preserving options, and the patient's desires for future fertility will inform the appropriate plan. Infertility training programs should work to increase exposure of training fellows and obstetrics and gynecology residents to oncology patients seeking fertility preservation in order to improve patient referral to appropriate trials and specialized centers in the future [6,7,12] (also see Kondopalli, this volume, for further discussion).

From the beginning of the consent process, the patient must be presented with any and all options available to either preserve fertility or pursue other means to have children, including adoption, egg donation, and surrogacy. The distinction between established and experimental options must be made clear and the patient must consent for any research that will be done on their tissue. Patients must clearly understand how long the tissue will be stored by the research team and made aware of their options for storage after that time has expired. Although the current research (including developments in the mouse) is promising [10,11], we must bear in mind that in vitro maturation is still experimental and should be presented as such without giving the patient false hope. Furthermore, the older the patient is, the less likely the experimental technique will be available to her in her reproductive years. Directives about how to handle the tissue posthumously in the event of the patient's death should be included with the consent to obtain the tissue. These directives need to specify if a partner or spouse may use the tissue for IVF after the death of the patient. In the case of children, the age at which the patient will have access to use the tissue to initiate a pregnancy and if parents have any right to the tissue needs to be established prior to obtaining the ovarian tissue [9,16,17].

Ethical concerns regarding the theoretical increased risk of cancer in a child born to a cancer survivor, due to a possible genetic predisposition, have been discussed by other researchers [16,18]. A discussion of the estimated risk to patient's offspring should be part of the informed consent process prior to ovarian cryopreservation, but does not preclude the patient's access to these services. Physicians have also questioned if it is ethical to allow a patient to reproduce when they may have a reduced life-span, thus leaving a child with only one parent. Although the loss of a parent is undeniably stressful for a child, the ethical analysis provided in other works [19] argues that this burden does not exceed other stresses children may experience in their lifetime and does not yield a convincing argument to deny cancer survivors access to reproductive services.

Ethical Issues in the Case of Childhood Cancers

The Special Case of Young Girls

When faced with the diagnosis and treatment regimes for pediatric cancer, parents face a particular burden of choice. They will be asked not only about the range of treatment options for their child, but also about somewhat disquieting options regarding the theoretical adult that their child may become, if she survives. Such a complex set of dilemmas is overwhelming. Parents

must contemplate the problem of the best interests of the child at two completely different times of life, one of which is entirely abstract. They must negotiate the needs of a desperately (and suddenly) sick child in need of urgent treatment and their desire to believe the treatment will be successful and it will allow the child to live and grow. Parents then must hold a distant and often conflicted vision about the child's future, where he or she is an adult who will make choices about education, family, and career—indeed, as sexually active adult men and women desiring children of their own. The choice to engage in an utterly experimental intervention, minor surgery, and a set of complicated conversations about the future is a unique responsibility for parents of children with cancer.

It was because of these very difficulties that our research turned to this question. In understanding this ethical question, we turned to a logical cohort most likely to give thoughtful answers: women and their parents who had faced cancer in the past. Choosing families who had faced pediatric cancer, we asked whether such conversations and the experiment proposed—even if no hope for translation to clinical use was offered—would be warranted. The research strongly indicated that this difficult conversation is critical. The respondents indicated that careful consideration of even experimental fertility preservation ought to be presented (see Nieman et al., this volume).

For some physicians and parents, the concern about discussing a child's future fertility is unalterably a discussion that sexualizes a young child and attempts to predict her reproductive choices. While acknowledging this, we argue that an alternative view is possible, that of the preservation of organ function, in much the way other organs are protected and restored after cancer therapies damage them; the ovary, after all, is a reproductive organ. In the view of many, it is a morally distinction function, for an ovary contains gametes, whose special status has long been considered distinction and who cells are entities deserving of special concern and respect, a fact that cannot be ignored when ovarian tissue is stored or used.

The goal of cancer treatment is cure with the least amount of damage to the rest of the organs in the body. With this model, any discussion with parents and the child should include a discussion of the effort to minimize damage and the associated advantages and risks. In the case of ovaries, which are particularly susceptible to damage by chemotherapy and radiation, one option for preserving function is to remove ovarian tissue or an entire ovary for cryopreservation.

The risks and benefits of fertility-preserving surgery can be explained in an age-appropriate manner in order for her to give assent. The surgery is being done to protect the cells in an organ that may allow the child to have children in the future if she chooses. If the surgery is not done, then there is an estimated risk she will not have her own children, and she will need to choose from other options such as adoption, egg donation, or childlessness. We cannot guarantee she can have her own genetic children if the surgery is performed, nor can we guarantee she will or will not be able to bear her own genetic children if the surgery is not done. Preserving the ovary simply increases the chance that she will be able to have her own genetic children if she chooses to do so in the future.

Research in Children

The special problem of research in children is central to our ethical concern – both because research will have to be done long in advance of therapeutic use, as described above and that in all cases, the surgical intervention necessary will raise unique ethical questions of how any pediatric research is framed. Ethical guidelines for research in children must strike a balance between the need to improve treatments for children with protection of the individual child. IRBs are able to approve pediatric research in three risk and benefit categories under federal regulations: (1) studies that offer participating children a prospect of direct benefit, (2) studies that do not offer a prospect of direct benefit but pose only minimal risk, and (3) studies that do not offer a prospect of direct benefit and pose a minor increase over minimal risk [20].¹ As a result, the enrollment of children in clinical research is highly dependent on regulators at each institution and how they struggle to interpret risk and benefit guidelines [21].² While it is understood that it is important to protect children from excessive risks in research, it is also important to consider that an overestimation of the risks will prevent important advances in pediatric treatments [22].

Research with children requires their assent, which differs from the consent obtained from the patient's parents or an adult patient [9]. Informed consent has two main components: that the patient has comprehension or understanding of the treatment and that the consent is freely given [23]. Assent is “a child's affirmative agreement to participate in research.” The process of assent from a child acknowledges both their legal status as a minor and also their decreased decision-making capacity or ability to comprehend a treatment [9].

The requirement of assent may be waived by the IRB only in cases when the research “offers a prospect of direct benefit that is important to the health or wellbeing of the children and is available only in the context of research” [21]. We fully understand that children may not have the capacity to understand the nature of rare but serious risks, and thus the consent to this intervention must be a parental decision for younger girls.

In the case of oophorectomy for fertility preservation in girls with cancer, the treatment may or may not provide direct benefit to the child, and will put the child at above minimal risk compared with that of daily life. The federal guidelines are vague in how to assess capacity for assent and how much information about risks should be given to children asked to assent. Based on the recommendation of the American Academy of Pediatrics (AAP) and the National Commission, it is appropriate to obtain assent³ from children 7 years of age and older. Parental consent must also be given. As described above, the need for the surgery may be presented as part of the

¹ Minimal risk is defined as “ordinarily encountered in daily life or during the performance of routine physical or psychological test” (22).

² A recent study of how IRB chairpersons applied these guidelines yielded highly variable results, revealing either overestimation of tests that are considered routine, or underestimations of risks of daily life, such as riding in a car in rush-hour traffic (22).

³ The components of competent assent are (1) rudimentary understanding of the procedures, that is, what subjects will be required to do, or what will be done to them, if they participate; (2) basic comprehension of the general purpose of the research; and (3) a preference to participate in the research. The result is a lower level of requirement of comprehension than consent and the expression of a preference to participate. As the age and development of the child advances, appropriate respect needs to be given to the child or adolescent assent for treatment (29).

treatment package and in an age-appropriate manner that describes the protection of organs involved in reproduction. Both assent and consent must be obtained in order for the surgery to be performed. For children under age 7, parental consent is sufficient if a reasonable person would agree that the potential benefit to the child justifies the potential risks [21,22]. Further guidelines need to be developed on the nature of explicit information that must be provided to children about risks in order to obtain assent.⁴ The age at which a pediatric patient would have access to the tissue to initiate a pregnancy and if parents have any right to the tissue needs to be established prior to obtaining the ovarian tissue [16,24].

Why is it important to involve children in the decision about their treatment or research protocol at all? Although legal requirements may apply, the ethical analysis and psychological benefits to involvement of children in such decisions yield far more compelling arguments. Just as in the treatment of adults, it is important to respect the child's autonomy, dignity, individuality, and opportunity for self-determination. The psychological literature supports that children involved in their treatment decisions have the positive benefits of feeling effective, competent, and in control and may experience better self-esteem, decreased anxiety, and decreased depression as a result. In cases where research may not directly benefit the patient but may benefit future patients in a similar situation, participation in research may allow the adolescents to feel altruistic and as if they are contributing to society and scientific knowledge. This may also be the first major decision, not only in the course of disease treatments, but in a long life of difficult decisions, and allowing the patient to make the decision in a supportive environment may have long-lasting benefits [25].

Assessing the Intervention: A Community Consent Process in Action

At the beginning of the project of ovarian preservation, the primary ethical concern was that a procedure that was not even entirely dependable in the murine model would be offered to young girls and their families who were already facing enormous and difficult decisions about cancer chemotherapy. Was such a request itself even ethical? Or would the very notion of the question be too difficult to bear? Reflecting on this, we decided to go to the people most directly involved – for the only expertise that actually mattered here was the expertise of patients and families.

As new technologies emerge, it is important to have the experience of survivors and their families inform the approach taken with patients who may qualify for experimental fertility-preserving techniques. Literature on childhood cancer often focuses on the scientific, ethical, and legal considerations for fertility preservation [9,16,17], but rarely on the attitude and opinions of parents or survivors with fertility concerns or fertility-preserving options at the time of diagnosis [12]. One recent focus group study on female adult survivors of childhood cancer and their parents, however, has looked at parents' and survivor's concerns regarding cancer-related infertility (see Nieman et al., this volume). The study finds that although the parents acknowledged that they were overwhelmed with information at the time of their daughter's

⁴ The recommendation from the National Commission and the AAP is that assent be obtained from children ages 7 and older, but a recent study found that only 20% of IRBs follow this recommendation. This study also found that approximately 25% of IRBs are not requiring investigators to inform children of serious, however rare, risks. This is a deviation from the normal analogous regulations for children developed from adult requirements, but the requirement of serious risks explained to children is not explicitly recommended in guidelines (21).

cancer diagnosis, they agreed that fertility preserving options, even if experimental, should be presented as part of the “treatment package” for all children with cancer, similar to how clinical trials are presented to parents. Survivors and parents said that they would have given serious consideration to participation in a fertility preserving study. Survivors also indicated that helping medical advancement, helping other women in the future, and the possibility that it might help them have a child were all potential benefits of participating in a study. Parents also raised concerns about exposing their daughter to another surgery that could be potentially emotionally and physically draining as well as harmful. But these parents also indicated that they would have like more information and believe that, in hindsight, they would have considered having their daughters participate in the study if it had been available at the time of diagnosis. This research indicates that patients and their families will likely be interested in information about fertility-preserving options at the time of diagnosis and prior to the initiation of chemotherapy and radiation, even if they are experimental, and that patients faced with similar fertility damaging therapy may choose to participate if presented with this option. (For further discussion of this focus-group study, see Kinahan, Didwania and Nieman, this volume and Nieman et al., this volume).

The Ethical Implications for a New Terrain: Therapy or Enhancement?

While we have argued that offering an experimental intervention and pursuing research in oncofertility is fully warranted when done under the norms and policies we suggest above, we are aware of the obvious implications of this research. Do our arguments apply to the use of cryopreservation of ovarian tissue for any cause that might imperil fertility? For any use of the matured eggs, including stem cell research? Let us address each question separately.

It is an understandable therapy to attempt to preserve the potential to have genetic children for a cancer patient, but should this therapeutic intervention be extended to women who may face infertility due to other causes? Must there be an immediate or iatrogenic threat to fertility in order for a woman to choose to preserve it? Although we acknowledge that this may be an infrequently requested service, the arguments in favor or against such a practice are important to consider as technologies to store female gametes improve. An extension of the risk/benefit analysis for fertility preservation surely must include other circumstances that threaten fertility or delay childbearing. In order to explore this idea, we discuss both the established method of banking embryos by cryopreservation, and then ask if the principles that apply to embryo storage would extend to male or female gametes.

For example, what if a woman knew that her ability to have children may be impacted by a need for extended professional training or graduate education, a duty to serve in the armed forces or foreign service, or engagement in precarious occupations such as space travel or radiation research? Her risk of infertility will be markedly increased either due to her age or her exposure to hazards, perhaps even approximating the risk of infertility presented to a patient being treated with chemotherapy or radiation. As a society we have clearly become comfortable with a woman’s choice to use contraception to prevent pregnancy. The preservation of fertility could be argued as the extension of reproductive choices [15]. Perhaps few women would consider the risk, time commitment, and cost of ovarian hyperstimulation to retrieve eggs for IVF and storage of embryos without demonstrated infertility. But would the ability to store eggs instead of

embryos, analogous to storage of sperm, make this option more tempting? Is a law student required to partner before she has children, or a Navy recruit with six years to serve actually “socially infertile” due to obstacles imposed by society?

By the criteria of effectiveness, safety, and ability to pay, IVF could be offered to anyone who requests it. The idea of 25-year-old women preserving fertility by freezing embryos would be disconcerting to many, but a 25-year-old woman undergoing hyperstimulation to help an infertile couple create embryos is current practice. Does the ethical dilemma lie in the storage of embryos that may not ever be used, or in preserving female fertility for “lifestyle” reasons? Who should make the distinction between “lifestyle” and the circumstances of an individual’s life that threaten fertility or delay childbearing for any reason, such as finding a partner late in life, pursuing a challenging career, or recovering from an illness? That moral values undergird access to fertility treatments is a largely undescribed issue, yet single mothers and same-sex couples often are sometimes denied fertility services – are they also “socially infertile?”

The American Society for Reproductive Medicine (ASRM) currently recommends against offering ovarian and oocyte cryopreservation as a means to defer reproductive aging based on the current risk-to-benefit ratio and experimental status of the techniques [7]. It remains, however, that the body of work that represents oncofertility is striving to improve techniques to acquire and store gametes until they are established rather than experimental. The storage of gametes, unlike the creation and freezing of embryos, is less ethically problematic for practitioners and society. Sperm banking has been an established technique that is not currently met with much deliberation or protest. As techniques to bank gametes for women emerge, the practical advantages should be weighed against the risk of obtaining the ovarian material. Fertility specialists, women who seek the procedure, and ethicists will need to consider the risk-to-benefit ratio at which fertility preservation could be offered at the request of a healthy patient. We would add that a fair debate about the propriety of the storage of ovarian material would re-open a debate that must include storage of sperm. In light of new data linking conditions such as autism and schizophrenia to paternal age > 40 [26], the request for sperm storage by healthy men in their thirties may increase in frequency.

Such a debate walks the familiar fence line of all enhancement debates – where does normal aging become a risk factor in the newly framed disease of infertility? The statistics are startling. Approximately 12% of U.S. women of childbearing age have received infertility services [2], and married women in their thirties who have not yet had a child have a 20–25% rate of infertility after 12 months of unprotected intercourse [27]. Assuming in vitro maturation would allow a woman to conceive by IVF in the future, there could be distinct advantages to a woman storing ovarian tissue in her twenties. It would literally stop the clock and the aging events that begin to increase rates of infertility in older women. The ovary is removed when she is sexually mature and in her reproductive prime, when she has more follicles than she will in her thirties, her ovary has not become resistant to the hormones that mature eggs each month, and the younger eggs are less likely to have chromosomal abnormalities. At what risk-to-benefit ratio, considering the risk of surgery, the success of the preservation, and risk of infertility, could she elect to have this surgery at age 25?

Since ovarian cryopreservation is experimental, it will first be offered to patients who have an iatrogenic threat to their fertility [6,7]. But once the method is no longer considered experimental and its success rate begins to approximate current IVF techniques and normal monthly fecundity, then it is reasonable that access be considered under guidelines similar to other ARTs.

Furthermore, as hormonal and physical markers are improved to assess the potential of maturing follicles, only the best candidates will be fertilized, ideally leading to fewer embryos created each cycle. This could virtually eliminate the dilemma of what to do with unused embryos once a pregnancy has been achieved, and to the creation of a new source of eggs for stem cell research.

Recalling a Complex History

Nearly 30 years has passed since the birth of Louise Brown, a breakthrough in medicine and a startling change in the meaning and construction of fertility. Then an experimental technique of IVF, now a routine medical treatment for infertility, the disaggregation of the steps of ovulation, fertilization, implantation, and embryonic development allowed each step to be studied in the in vitro clarity of the lab. The remarkable success of the technique and its eventual commonality allow a certain level of complacency about the extraordinary difficulty of its technical and social achievement.

In their book *A Matter of Life*, Steptoe and Edwards record March 1968 as the first IVF procedure using eggs from a woman who needed her ovary removed for medical reasons. In the subsequent months, they worked with ovaries from 12 women who needed medically indicated oophorectomy, and performed 56 in vitro fertilizations for a paper published in *Nature* in 1969. It was only after several years of working out the details of acquiring in vivo matured oocytes and achieving fertilization that the first trial transfer of any embryo back to the mother was made (January 1972). The first pregnancy was not achieved until the summer of 1975 and was not carried to term. An unspecified number of patients and embryos, and trial and error, resulted in the pregnancy of Lesley Brown with Louise in December of 1977, and the historic birth in 1978 [28].

It is important to note that Steptoe and Edwards only briefly tried IVF in nonhuman primates and discovered that technical difficulties prevented the technique to be efficient or a good research model. Since the mouse model worked well, and as they had desperate couples willing to try their last hope at biological children, they moved straight to efficient fertilization and embryo transfer in humans. This is an important detail, for it set the precedent for all future IVF interventions, many of which would move directly into clinical use as a matter of practice guidelines rather than in controlled, double-blinded clinical trials. In a sense, the entire IVF enterprise has been an extended clinical trial, but without the standard guidelines, IRBs, and DSMBs. Much of the work was advanced in the private commercial sector. Yet IVF is now an established technique that has a monthly success rate, according to the CDC, that approximates, or even exceeds, normal human fecundity. We wish to note that such an advance did in fact rest on a certain degree of public trust, the willingness of women to be human subjects, and scientific risk.

As we gaze on the possibility of a radically new landscape in human reproduction, not only for cancer survivors, but for all women, we need to re-state the need for the clearest oversight and

regulations. Can we turn to this complex history, and yet remain cautious about its shortcomings in this parallel case? We argued that this is the case, as in IVF, non-human primate trials may prove inconclusive or unsustainable. We argue that, as in IVF, other mammalian models may prove sufficient to allow a move to human trials, especially given that the proposed technique of in vitro maturation can be considered a scientifically logical extension of IVF techniques used with regularity today. For the research to proceed in humans will require IRB-approved trials, using standards of quality that current protocols for embryo transfer require in order to give the optimal chance for normal, healthy offspring. Initial patient selection would be limited to women who would not otherwise have the opportunity to have genetic offspring.

Regulatory norms are only a part of the picture. A remarkable advance in so basic a human activity requires a wide-ranging ethical debate about the nature, goal, and meaning of the science. The debate will concern the issues we have summarized here: cancer and its meaning, infertility and its construction, pediatric research, justice issues, iatrogenic harms, and resultant duties. Yet more will be required. This further disaggregation of human reproduction is, after all, about women, families, and how we bring children into the world. The complex negotiation of new roles and the complex and delicate new science offer unprecedented hope and unprecedented responsibilities.

Conclusion

This chapter discusses a subset of the ethical issues surrounding the expanding field of oncofertility. Fertility preservation will continue to be a concern of many adult oncology patients, but also of pediatric patients as they become adult survivors of their childhood cancer. We establish that work in both fertility preservation in the face of iatrogenic threat to fertility and infertility research hold a moral high priority. Fertility preservation procedures for both children and adults should be routinely discussed with patients whose disease treatment may impair fertility, but only be offered in the context of specialized research centers and IRB-approved protocols. Furthermore, patients should understand the limitations of what can be offered at the time of their treatment. Although current experimental fertility preservation protocols should be reserved for individuals who face iatrogenic threat to fertility, we acknowledge that these techniques may not be considered experimental in the near future and may be requested in the context of life circumstances that delay childbearing, to create stem cells, or in conjunction with alternative IVF protocols. We encourage an ongoing discussion between physicians, ethicists, and society at large that carefully weighs the risk-to-benefit ratio of the uses of these technologies in the context of other fertility protocols that are currently routinely offered, such as ovarian hyperstimulation, sperm donation, and embryo storage. As oncofertility grows as a multidisciplinary field, ethics will be a constitutive part of the discussion and research. In this chapter, our aim was to outline some of the more pressing issues regarding ovarian tissue preservation and maturation of oocytes in vitro, particularly with regard to cancer diagnosis and in children. As the techniques put forth in this volume become mainstreamed into medical care, a goal of oncofertility is to continually reassess ethical issues as breakthroughs in the laboratory become instituted at the bedside.

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