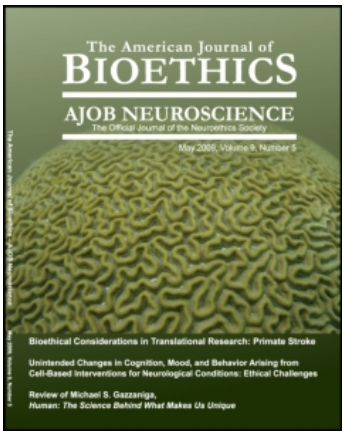

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Waiting to be Born: The Ethical Implications of the Generation of "NUBorn" and "NUAge" Mice from Pre-Pubertal Ovarian Tissue

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Target Article

Waiting to be Born: The Ethical Implications of the Generation of "NUBorn" and "NUAge" Mice from Pre-Pubertal Ovarian Tissue

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Oncofertility is one of the 9 NIH Roadmap Initiatives, federal grants intended to explore previously intractable questions, and it describes a new field that exists in the liminal space between cancer treatment and its sequelae, IVF clinics and their yearning, and basic research in cell growth, biomaterials, and reproductive science and its tempting promises. Cancer diagnoses, which were once thought universally fatal, now often entail management of a chronic disease. Yet the therapies are rigorous, must start immediately, and in many cases result in premature failure of the body's reproductive ability. In women, this loss is especially poignant; unlike the routine storage of sperm, which is done in men and boys facing similar treatment decisions, freezing oocytes in anticipation of fertility loss is not possible in most cases, and creating an embryo within days of diagnosis raises significant moral, social and medical challenges. Oncofertility is the study of how to harvest ovarian tissue in women facing cancer to preserve their gametes for future use with IVF, thus allowing the decisions about childbearing to be deferred and reproductive choices to be preserved. The research endeavor uses the capacity of the ovarian follicle to produce eggs *in vitro*. Developing the human follicle to ovulate successfully outside the body is scientifically difficult and ethically challenging. Infertility is linked to long-standing religious and moral traditions, and is intertwined with deeply contentious social narratives about women, families, illness and birth. Is the research morally permissible? Perhaps imperative if understood as a repair from iatrogenic harms? How are considerations of justice central to the work? How will vulnerable subjects be protected? What are the moral implications of the work for women, children and families? What are the implications for society if women could store ovarian tissue as a way of stopping the biological clock? What are the moral possibilities and challenges if eggs can be produced in large quantities from a stored ovarian tissue?

Keywords: Oncofertility, Fertility Preservation, Cancer, IVF, Ethics

INTRODUCTION

In contemporary society, translational medical research is the name of hope itself. The banners at our medical school proclaim: "today's research, tomorrow's cures" and who could not yearn for that to be swiftly true? For many, the advances in modernity can be seen as a steady progression of science over dreadful and intractable illnesses, especially illnesses of children and young adults. At the same time, in the last 30 years, advances in reproductive technologies have changed the event of infertility from a crisis of faith and generativity to a diagnosable and treatable medical condition. Although infertility remains prevalent and fraught with emotional difficulties, seen as an organic, medical issue it is now often curable, "producing" a child for the majority of women seeking treatment. It is these advances in the creation of families and protection of children that have most clearly marked medicine's success. This article explores the ethical implications of new research, funded by one of NIH's Road Map Initiatives to address intractable problems, which will attempt to build on the complexities of treating one condition: infertility, engendered by the success in treating another condition: cancer, by the use of basic research on cell growth, biomaterials and reproductive medicine.

The Narrative of IVF

The advancements of assisted reproductive technology (ART) and *in vitro* fertilization (IVF) have increased the

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number of women able to become pregnant using her own gametes, or by using donor eggs. It is, by many accounts, one of the measurable, tangible narratives of medical success, becoming so normative that in 2005, 134,260 ART cycles were carried out in the U.S. alone, resulting in 38,910 live births and 52,041 infants (CDC 2005) born using the techniques developed for the treatment of infertility. By 2001, 500 children worldwide had been born using ART with pre-implantation genetic diagnosis (PGD) (ASRM June 2006 PGD practice guidelines) a technique that can now be described as a genre of preventative medicine—with PGD, couples who carry lethal or debilitating inheritable diseases can select an embryo who does not carry the genetic markers for the disease. The practice of IVF is so widespread that the success rate for achieving successful pregnancy with IVF is now equivalent to the rate of normal sexual reproduction.

This marks a dramatic change in the physical and the social narrative of family and reproduction. This deconstruction of the reproductive process into its simplest parts: gametes, stored embryos, and surrogate wombs, has progressed to such an extent that the event of IVF has become an ordinary, albeit costly, beginning of many pregnancies.

Cancer Narratives

The story of IVF parallels another—the treatment of previously fatal cancers, particularly cancers in children. As the 5-year survival rates of children treated for cancers often exceeds 70% (American Cancer Society [ACS] 2003), the diagnosis of cancer for patients and their families has shifted from that of a death sentence to that of a chronic disease necessitating management over the long term. With the increase in successful treatment of these patients, medical teams must focus not only on short-term treatments, but also anticipate long-term quality of life issues for their patients, in the world beyond "cure". As survivors of any cancer treatment are returned to the trajectory of their lives, they develop the 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 reproductive potential.

For families of young children and young adults facing a sudden cancer diagnosis, the immediate priority is survival and support during the difficult time period surrounding treatment. But the coincident infertility caused by the advances in cancer treatment that allow for successful recovery paradoxically create a patient of a different sort—an infertility patient. At this juncture, the medical disciplines of oncology and infertility intertwine, and a new area of medicine, Oncofertility, is born. Yet it is a commonplace that every scientific advance bears with it the inevitable dilemmas of choice and complexities of power that all discoveries carry. It is nearly a commonplace in bioethical literature to call out the phrase that is used in so many of our papers, "the promise and the peril" to greet any new technology (count of internet citations at the time of writing this paper: 1,770,000).[1] This paper will look carefully at the coincidence of treatment when two trajectories of translational research converge within the field of Oncofertility and explore the ethical and social implications of the power that such research will create.

More than the science research is waiting to be born as well: complex dilemmas, 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. Oncofertility treatment is a portal for a far wider prospect: using the techniques described in this paper, 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 just 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, via somatic cell nuclear transfer (SCNT) of patient-specific histocompatible tissue. As the debate about how to obtain human oocytes for research and for potential cures intensifies, serious moral issues regarding 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 would entirely solve at least one aspect of the ethical complexities of stem cell research—how to acquire eggs justly, safely and scalably.

Here we report and reflect on one further step in the deconstruction of the process of reproduction: the successful freezing, maturation and use of pre-pubertal ovarian tissue. Proven in the mouse model, the research is the basis of one of the NIH new "Roadmap" Projects, a key component in the Oncofertility Consortium National Research Project called *The Oncofertility Consortium: Fertility Preservation for Women* (National Institutes of Health 2008). Creating a new interdisciplinary field of "Oncofertility" places it in the very center of some passionate debates in the field of bioethics: the development and exchange of human eggs; the issue of consent in pediatric experimentation; the question of the "therapeutic misconception" in translational research; and the dilemmas inherent in powerful cancer treatments.

This work is unlike the anecdotal reports in which fertility clinics have allowed (with intermittent success in a handful of cases) an individual woman to create a set of eggs, which are then frozen and used for insemination and implantation at a later time, for it seeks to overcome the substantial scientific and technical problems involved in storing eggs, even immature eggs, for later use. First reported

1. Jonathan B. Tucker and Raymond A. Zilinskas, "The Promise and Perils of Synthetic Biology," The New Atlantis, Number 12, Spring 2006, pp. 25–45. . . . To give only one recent example.

in an article quietly published June 23, 2006, by Xu and colleagues at Northwestern University, this work is the latest accomplishment of a multiyear research program devoted to the successful maturation of immature ovarian follicles from mice (Xu et al., 2006). The use of a biomaterial support matrix provided the breakthrough in the growth and maturation of good quality eggs from an immature starting pool. It also permitted the first imagination about translating the work from the bench, through biomaterials, to the bedside of women (and potentially girls) who are facing life-preserving but fertility-threatening cancer treatment. Remarkable not only for its innovative vision, this project is also notable because from the very beginning of the work, Woodruff and her colleagues understood the ethical dilemmas at the heart of their research, asked for interdisciplinary participation in the project from its earliest stages and suggested a concurrent research project in the ethics of Oncofertility. The Center for Bioethics, Science and Society has been asked to consult, shape and reflect upon this project from its inception three years ago, as members of a University wide collaboration that involves extensive study across several disciplines: ethics, sociology, engineering and molecular biology. Another aspect of this effort entails the careful creation of a bench side consultation process for the work, involving a national oversight committee of bioethicists, feminist philosophers, physicians, religious studies scholars and legal theorists (Magnus et al. 2006).

While the project of maturing immature follicles from ovarian tissue is surely a remarkable concept, the uncoupling of specific bodies and babies from their mothers is surely not new. Among the oldest narratives of antiquity, including the Hebrew Scripture, are ones of surrogacy and of wet nurses, accounts of remarkable pregnancies in elderly women and the use of medications to facilitate the process. Not only these narratives serve as a precedent for contemporary discourse about advanced reproductive technology; other core tropes from biblical texts discuss similar chronicles. When the scientists first described the idea of storing immature eggs for an imagined future use, the story of Joseph came immediately to mind. Thus was begun what we called the Joseph Project, informally and metaphorically named to recall the Biblical story of Joseph, who called for the storage of grain in the midst of seven years of a plentiful crop in preparation for a prophesied seven year famine, an enormous social endeavor undergone on the basis of a dream. The Joseph Project is a consideration of both the norms and rationale for the specific use of this technology in cancer, for the future application of this research to young girls facing a life-preserving but future fertility-threatening treatment, or life event. We understood from the beginning that such research would have broader implications. Such a methodology could be used both in human reproductive decisions and many stem cell therapies, both of which use the human embryo created *in vitro* and struggle with a shortage of eggs so intense that even payment for egg exchange has been proposed (Hyun 2006).

THE JOSEPH PROJECT

This project was initiated by Woodruff and her colleagues to address a specific and important limitation of cancer therapy. Advances in cancer therapy have slowly moved the diagnosis of cancer away from being a death sentence, and living a full life after cancer treatment is now a real possibility for many patients. For women of reproductive age, a diagnosis of cancer now confronts them with two threats. The first is one's own mortality, and the second is the possible end of one's reproductive life, since many cancer regimens risk harming or destroying a woman's limited supply of ova. Unlike men, who can choose to freeze and store sperm for later use with results, women cannot easily or routinely store ova, and the process rarely results in a pregnancy. While some reports of children born from frozen ova do exist, the process of thawing and fertilizing eggs remains difficult. What is not known is whether freezing eggs for the many years between cancer diagnosis and the time that a woman would choose to use them will yield healthy and functional eggs, thus defining one of the puzzles of the researchers.

Moreover, as the survival rates for several childhood cancers have increased, an unprecedented number of children are now offered the reality of an adulthood in which they could be expected to grow to maturity, essentially cured of a childhood disease. Yet the very therapy that saves their lives—chemotherapy or radiation therapy, often coupled with bone marrow transplants—may destroy their reproductive capacity. Today, women who want to bear their own genetic children after cancer treatment may need to use donor eggs and artificial reproductive technologies (ART) such as IVF to achieve pregnancy. A woman facing a cancer diagnosis is thus forced to immediately decide whether or not to undergo what is called "emergency IVF." This is a process to hyperstimulate ovulation, fertilize the resulting eggs with someone's sperm, (either her partner's or a donor's), and create and then freeze the resulting embryos. The successfulness of the stimulation process is fraught with uncertainty: While the optimistic goal is getting 8–10 eggs, the number of eggs yielded is highly variable and dependent upon the specific patient, and may result in a small and finite number of embryos that will be available for attempts at future transfer and pregnancy. The entire process involves the delay of cancer treatment in favor of two weeks of daily injected hormonal fertility treatments, a difficult and sometimes impossible decision to make—which itself may put a woman at increased risk and in some cases is not an option at all, or not physically feasible. For many, the social unfeasibility alone creates an insurmountable barrier. Alternatively, ovarian tissue can be removed immediately, within days of cancer diagnosis and cryopreserved. Could the ovarian tissue later be thawed and could the physical properties of the tissues be stimulated, *in vitro*, to produce oocytes? In these cases, asked the researchers, could the women store and then later use their own eggs, and perhaps have many chances, instead of only one, at IVF? Such an intervention would have to be initiated prior to one's cancer treatment,

and would require the removal of an ovary, or at least a portion of an ovary.

Woodruff had long been interested in how eggs mature, and how ovarian cancer represented a fundamental malfunction of this complex and delicate process. She was committed to turning her basic research into therapies. As an ethicist, I (Zoloth) was asked to reflect on the implications of their latest finding, that cultured eggs (oocytes) could be fertilized and transplanted into mice, which them gave birth to mice that themselves are capable of generating live, apparently normal offspring (Xu et al. 2006). Colleagues at Northwestern were then drawn together to consider these issues. In our reflections, we wished to distance ourselves from many of our other colleagues, whose work would lay claim to a terrain of moral anxiety in which each new advance in reproductive biological research calls into question fundamental aspects of social organization (Lauritzen 2005; Kass 2004; Fukayama 2002). This was, after all, a method for improving the lives of cancer patients facing sequelea from medicine's very advances. Yet, we too had our concerns. While the trajectory of this research has led rather inexorably but logically from its beginnings in the first surrogate mothers of antiquity, toward Louise Brown (the first IVF baby), this last step surely ought to raise significant ethical inquiry. For if these techniques are as successful in humans as they have now been shown for the mouse, then an *unprecedented choice* will be available to women and girls—it will be possible to selectively remove an ovary, store the tissue and recover eggs for use with *in vitro* fertilization (IVF) at a later time with an ease currently applied to well accepted IVF techniques. Like men, women could do this long in advance of a relationship with a partner.

THE PROCESS OF THE RESEARCH: BIOLOGY MEETS NANOTECHNOLOGY

The ability to store or bank eggs, as is currently possible with sperm, is hampered by the complexity of normal egg growth and maturation. In the ovary, each oocyte is surrounded by specialized support cells, granulosa and theca cells, which together form a spherical follicle. Because the cells within the follicle produce various hormones that help the oocyte to grow and mature, the structure of the follicle and the arrangement of cells within the follicle must be maintained in order for the egg to develop properly and attain the capacity for fertilization. Current methods of growing follicles or oocytes outside of the body do not provide the three-dimensional follicle structure necessary to facilitate egg growth—eggs are typically grown in two dimensional Petri dishes. Dr. Woodruff's group, working together with Dr. Lonnie Shea in the department of Chemical and Biological Engineering, developed a synthetic nanofiberbased material (an alginate hydrogel), which could encapsulate an entire follicle, maintain its shape and cell-cell interactions, and therefore allow the oocyte to grow and mature *in vitro* but as if in a rounded tissue capsule. The researchers' latest accomplishment was the production of live offspring from mouse oocytes grown within this three-dimensional culture system, thus establishing a novel core technology for the storing of tissue and maturation of eggs for future IVF. The first two mice born from this in follicle maturation (IFM) technology were named NUBorn and NUAge (NU=Northwestern and the thus the title of this paper). This work has been translated to human (cancer patients both newly diagnosed and recurrent cancer patients) and non-human primate (rhesus) follicles where growth of the immature follicles and retrieval of mature eggs has been possible.

ETHICAL ISSUES RAISED BY THE RESEARCH

This project raises both practical and metaphysical ethical questions. The first of these are a cascade of informed consent and informed refusal issues for the removal of ovarian tissue. This is the sort of consent, made under conditions of new diagnosis, that makes any decision by an adult women difficult, especially if she does not have a partner with whom she would want to create an embryo *right now*. However, it is particularly complex when the patient in question is a child, given the series of pediatric consent/assent required for any pediatric interventions (Kohrman et al. 1995). For the family confronting cancer in their child, the crisis of survival would likely dominate the discussion. Yet, the researcher would then have to ask for consent for a procedure valuable only in a far distant future, on behalf of a theorized or imagined family. The procedure requires surgery—some risk, some pain and recovery time—although does not involve the risk of high dose, injectable, exogenous hormones that would be needed to mature eggs *in vivo* in infertile or marginally fertile women. At the time when the Joseph Project was first imagined, and in its preliminary stages, the ethical question was deepened by the tremendous uncertainty of its application, for the idea was only theoretical—no eggs had been matured, much less been fertilized. As *the Joseph Project,* our metaphor also reflected this theoretical dimension, for the retrieval and storage of ovarian follicles would take place years before we would know if the "families-after-cancer" scenario would be successful and if the human follicles would mature and produce eggs. Unlike many other pediatric interventions, this one required ones' moral imagination to consider not only the best interests of the child at the present time, but also of the adult person that that child would (hopefully) become in the far future. Thus exists a doubled consideration, for in addition to the undercurrent of anxiety that the child will not survive, there is the need to simultaneously retain and abandon the sense of innocence of the child, while introducing the violation and risk of surgery and the consideration of the child's future sexual preferences, plans and reproductive life. This was the social cost of concretizing the hope into intervention—the future being begins to advocate for a claim on the being in the present (an interesting variant on the issue of intergenerational promises and claims).

In this target essay, we briefly set forward some initial questions suggesting the work that will need to be done as we consider the ethical, legal, and social implications of

the research. To map the field, we looked broadly at both clinical and intellectual issues in cancer research and care for survivors of cancer and their fertility. We suggest there were a series of ethical issues framing the moral aspects of the work.

First, therapies of the late 1990s had reconfigured the disease "cancer" from an end-of-life crisis to a life-threatening event that called for rehabilitation and the resumption of a new life, perhaps with some disability or level of chronicity. But in so doing, patients had taken a serious risk. Even in effective and well managed treatments, there were side effects from the intervention, and these were treated (and covered by insurance) for they were considered part and parcel of the therapy itself. Yet, when Woodruff raised the issue of ovarian tissue retrieval to save follicles, freeze them, and mature eggs in an effort to treat infertility that was the result of cancer therapy, the issue of payment for that part of the process was suddenly questioned. Should this be a lab cost? Would that be an unfair incentive? Should the insurance company cover the cost? Was this akin to early bone marrow transplants, especially ones that were undergone (as in sickle cell anemia) to avoid more costly procedures in the future?

Second, we looked carefully at the assumption that a critical part of a human life is the ability to bear genetic children and the loss of that ability is a medical problem with a medical solution. When, exactly, does infertility become a condition outside of normal species function, and when does it become normal for women past the normative childbearing age? 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: by age 33, there is a 20–25% risk that all women will need some type of reproductive assistance (Chandra et al. 2005). Assuming *in vitro* maturation would allow a woman to conceive by IVF in the future, there could be distinct advantages for a woman to store ovarian tissue in her 20's. It would literally stop the clock and the aging events that begin to increase rates of infertility among older women. The ovary is removed when a woman is sexually mature and in her reproductive prime: she has more follicles than she will in her 30's, 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, lowering the risk of genetic errors leading to genetic diseases. Given the low risk of surgery and an approximately 20–25% risk of later infertility, can she elect to have this surgery at age 25? Should limits be set for this technology's use in cancer survivors alone? Are other uses permissible? What of the idea of preservation for social or protective reasons? What about for other life-threatening events? We were lead to consider the limits of the use of this technology, in a debate akin to the coincident debates about therapy versus medical enhancement in general. If such interventions are limited, how could this be done in the climate of IVF and ART as it now exists, and how should such regulation be defined and maintained?

Third, as it relates to the use of the *in vitro* culture technology described by Xu and colleagues, we speculated on the impact of follicle banks to store immature ova on stem cell research as well as for fertility research. As basic research on human embryonic stem cells accelerates, a rate limiting step is the just 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, via SCNT, of patient specific histocompatible tissue. As we have noted above, having a new source for human ova that avoids the hyperstimulation of a woman's reproductive cycle may also create a way to avoid the propagation of a competitive market in which healthy young women are urged and paid (up to $100,000 per cycle for selected colleague coeds, The Daily Northwestern 2008) to hyperovulate so that their eggs can be used in labs for stem cell research and clinics for *in vitro* fertilization.

Fourth, this problem, even for ethicists who, as we do, support the basic premise of the research, raises serious philosophical problems. There is no question that this method suggests a deepening of the post-modern ideas of the body as a set of parts, and how such reconsideration impacts the meaning and value of each part and of our sense of the whole self. This sense of "Lego-land" is a feature of all discourse about synthetic biology and technology, but perhaps it occurs most forcefully in the area of the self.

Fifth, we considered a cascade of standard issues about informed consent and refusal, which are also a part of the work as it moves into clinical trials. For example:

- Should the time and kinds of treatment for the cancer be altered by the harvest of the ovary?
- For whom is the risk of surgery justified?
- For whom is the risk of treatment delay justified?
- What percentage of the stored tissue should be kept for private use versus research to validate the procedure?
- How do we protect (or can we protect?) against the stress of the decision making itself and the stress of newly acquired infertility, and how do we ensure that this does not unfairly coerce enrollment in the research or offer false hope for either one's fertility or the cancer therapy?
- What should be the role of IVF clinics in policy and politics as we reflect on the research?
- How should the providence of the gametes be considered if the person cannot or does not use them. For example, in the event of death, can others use them, and with what constraints? In the event of changing one's mind, could they be used for research?
- What is the nature and meaning of asking permission to do research that is *not at this time feasible* and whose parameters are constantly mutable as the technology itself develops?
- Was the fact that IVF developed in precisely this way a substantive precedent for this case, or just a bad example?

In their book *A Matter of Life*, Steptoe and Edwards (1980) record March, 1968 as the first *in vitro* fertilization

of 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 (Edwards, Bavister, and Steptoe 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, trial and error, resulted in the pregnancy of Lesley Brown with Louise in December of 1977, and her historic birth in 1978.

It is important to note that Steptoe and Edwards (1980) only briefly tried IVF in non-human primates and discovered that technical difficulties prevented the technique from being efficient or providing a good research model. Since the mouse model worked well, and 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 moved directly into clinical use as a matter of practice guidelines rather than conducting controlled, double-blinded clinical trials. In a sense, the entire enterprise has been an extended clinical trial, but without the standard guidelines, IRBs and DSMBs—as much of the work was advanced in the private, commercial sector.

ASSESSING THE INTERVENTION: A COMMUNITY CONSENT PROCESS IN ACTION

Our group was particularly concerned about the pediatric patients facing cancer. Who decides in the case of young girls, and how can assent actually be obtained in such a theoretical case? How does the decision making process change as the child grows? How can a family make the calculation as they struggle to see the child both as herself and deal with the meaning of the imagined sexual adult person that this work implies that child will become? It was because of these very difficulties that our research first turned to this question. In understanding this ethical question, we turned to a logical cohort most likely to give thoughtful answers—women and their mothers 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. Our research strongly indicated that this difficult conversation is critical: the careful consideration of even experimental fertility preservation ought to be presented, indicated our respondents.

At the beginning of the project of ovarian preservation, the primary ethical concern we had was that even the offer of such research raised the distinct possibility of utterly false hope. Since the procedure was not even entirely dependable in the murine model, could it be offered to young girls and their families who were already facing enormous and difficult decisions about cancer treatment? Was such a request itself even ethical? Or would the very notion of the question be too difficult to bear? In reflection on this, we decided to turn to the people most directly involved and ask them, for the only expertise that actually mattered here was the pragmatic expertise of patients and families.

Literature on childhood cancer often focuses on the scientific and ethical considerations for fertility preservation, but rarely on the attitudes and opinions of parents or survivors regarding fertility concerns or fertility preserving options at the time of diagnosis. A focus group of adult survivors of childhood cancer and their parents was conducted in order to explore how the risk of infertility was dealt with at the time of diagnosis, and how that as changed as the once children have grown into healthy adult women (Nieman et al. 2007). Survivors have reported that dealing with infertility as a result of cancer treatment can be as difficult as facing the cancer and treatment that rendered them infertile. Few options currently exist to preserve female fertility, and fewer existed for many adult female survivors at the time of their childhood cancer diagnoses. As new technologies emerge, it is important to have the experiences of survivors and their families inform the approach taken with patients who may qualify for experimental fertility preserving techniques.

In the study reported by Nieman and colleagues (2007), four focus groups were recruited to explore the attitudes and opinions on fertility at the time of diagnosis and at present. In order to qualify for participation, the female survivors had to be diagnosed with cancer from age 13–21, be English speaking, and willing to participate in tape recorded focus groups. The parents of these patients formed two focus groups separate from their daughters, the surviving patients. The topics of the focus groups were:

1. Short and long term concerns at the time of the patient's (or daughter's) diagnosis.
2. Attitudes about fertility at the time of diagnosis and presently.
3. Reactions to proposed research in ovarian tissue cryopreservation with the intent to preserve fertility.

For the third topic, the survivors and their patients were given a brochure to read about the proposed research. The age of the survivors at the time of the focus groups was 23–36, with 5 of the 10 survivors currently unaware of fertility status, and 3 of the 10 reporting successful conception and delivery of a child at the time of the study.

Parents of the survivors consistently reported that although they were well informed about the treatment regime, they do not remember much decision-making about the treatment to take place. They viewed this as the provider's role to choose the appropriate treatment, putting the provider in the role as primary decision maker. Furthermore, parents of survivors felt that fertility issues were rarely discussed by the team prior to treatment, and when concerns of infertility were raised, it was often after treatment had begun or in the context of deciding to do

another treatment cycle. The importance that parents report they would have placed on fertility at the time of diagnosis ranged from "very important" to "not that important," but the majority agreed that questions about their daughters' fertility status has grown increasingly important as the survivors become adults. The fertility status was only known in approximately 30% of the survivors participating in this study, and they were all fertile. As a result, the concern about fertility may have been underestimated in this particular study.

The focus groups were also presented with information about research and experimental techniques that could potentially give options to young girls facing cancer. Although parents acknowledged that they were overwhelmed with information at the time of their daughter's 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 similarly 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 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.

Both survivors and their parents developed similar questions about the risk of infertility with treatment and the risks of only having one ovary after cryopreservation. Parents in particular raised concerns about exposing their daughter to another surgery that could be potentially emotionally and physically draining as well as harmful. Despite their concerns, parents indicated that they would have liked more information and believed 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 focus group addressed some important issues regarding cancer survivors' (and their parents') attitudes about fertility preserving research. The results indicate 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 these options are experimental, and that patients faced with similar fertility damaging therapy may choose to participate if presented with this option. Considering the retrospective nature of the focus group and their comments about the overwhelming amount of information and anxiety at the time of diagnosis, it is likely that the willingness to participate in the research at the time of diagnosis could differ in current patients. Despite their memories of crisis at the time of diagnosis, the focus groups' responses indicated that options should be discussed at the time of diagnosis.

The focus groups answered the questions "Would you have liked the option to be presented?" and "Would you have considered participating?" in a very general sense. More specific questions, however, are still unanswered. For example, if a physician could predict fairly accurately the likelihood of the patient's infertility, what percent chance of infertility would be the threshold for a patient to decide to participate in the study? What is a physician's threshold of suspected risk of infertility for the patient that influences if experimental fertility preserving options are offered to the patient? The difficulty in answering these questions is compounded by the difficulty in predicting infertility for any given cancer treatment regimen. The goal of cancer treatment is to cure with the least amount of damage to the rest of the organs in the body—including the delicate structures of the gametes. It is a difficult goal to achieve. The variables of age, chemotherapy and radiation regime, and individual physiology can all influence both the primary outcome of curing cancer as well as secondary outcomes, such as reproductive potential.

Yet we anticipate that full informed consent will be difficult to achieve. For some physicians and parents, the concern about discussing a child's future fertility is unalterably a discussion that sexualizes a young child, and predicts her reproductive choices or even her sexual orientation. While acknowledging this, we argue that an alterative 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, the ovary has a morally distinctive function: an ovary contains gametes, whose special status has long been considered distinction and who cells are entities deserving of special concern and respect (The Belmont Report [National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research 1979]), a perspective that cannot be ignored when ovarian tissue is stored or used.

THE PROBLEM OF JUSTICE

We also considered the range of wider social issues in our research. First among these were the issues of justice and access to this technology. Cancer and infertility are conditions that afflict all women equally, traversing class, race and ethnic lines. But social and economic distinctions generally determine health care access, and in America, this often plots closely to ethnicity and race. Despite the fact that some states (our state, Illinois, for example) mandate insurance coverage for IVF in public policies, IVF remains difficult to finance and support. The private "market" for donor eggs alone leads to a formidable cost barrier for most couples and IVF is understood as a treatment out of reach of lower income or uninsured populations. But access to IVF as a part of cancer "survivorship" (the current term of art) may be a different sort of justice question. What should be the role of economic factors, incentives and distribution costs? How should the project seek to address health care and social disparities driven by race and ethnicity, class or gender? Who should bear the cost of research? Who should profit, if anyone? Who owns the tissue? Is this research just given other possible uses of scarce resources for families? How can vulnerable subjects be assured of continuing access to health care and support after their tissue is retrieved?

What would be the regulatory framework needed to keep women from selling ovarian tissue to IVF clinics and labs? How should we even think about this practice, to frame the questions of need, loss, and desire?

In the years since the Woodruff lab first proposed its work, rapid progress has been made, providing proof of principle research. Now that the first mouse and monkey *in vivo* models demonstrate successful live births, and human models show success *in vitro*, it is time for a wider consideration of the very real issues that we face prior to initiating clinical trials in humans. Our first priority is to the families who will be facing the choice to pursue this option, and the educational efforts that will be aimed at them. It is imperative that this be a high priority, for there is a real concern on our part that the technology not be sensationalized into a polarizing public debate about the far future of the research. We believe that early limits and a careful consideration of appeals that would transgress that limit are in order. A thoughtful, wider community education and dialogue should focus on the use of this technology in circumstances where women face the destruction of fertility.

The literature on enhancement however, has demonstrated how difficult such a strategy can be, for what begins as a therapy can quietly be used in other situations, which may be less desperate, more socially constructed and thus seen as less reasonable. Yet descriptions of why this is the case have proven elusive. At issue will be the nature of our ability to set limits on technology in its first years, and how new technology creates meaning by redefining the possible trajectory of any woman's life—raising issues for some about the nature of limits themselves. We understand that the idea of infertility and of generativity was long linked to fragility, survival after catastrophe, and the destruction of family. This technology touches on many of our most powerful tropes of antiquity and of modernity's dark history. Our use of the metaphor of Joseph, which occurs in three Abrahamic faith traditions, suggests that we may have the social resources to address this with rational discourse.

Allowing ovarian tissue containing immature follicles to be harvested as part of a routine IVF process could ultimately mean that far fewer embryos would need to be created, since this new technology would preclude the need to immediately produce embryos for freezing in the hopes that one or two will be successfully gestated and delivered. The non-use of harvested eggs is so similar to the non-use of eggs that occurs every single month for all normally ovulating women that it would render that act far less vexing than the process of creation and destruction of embryos in the treatment of infertility (Doerflinger 2004; Callahan 2003)

Precisely because this research has the potential for such expansion and because of its anticipated high profile status in the coming years, it is important to reflect on these questions long before the technology is available in the clinic. This project could change the futures of young women who face cancer by restoring their capacity for childbearing, a goal that all could agree is a good one. These developments could also become the single biggest change since the birth control pill in how women construct their reproductive life choices. And it could shift a difficult debate in stem cell research toward resolution. There is much to be done, for basic research is indeed a "rough beast . . . waiting to be born" (in all the complexity of that allusion). This research draws from both the sources of our scripture and our dreams, the narratives of families, handmaidens, mandrakes, visions of survival against all odds. Yet it alerts us, by its very power, to the possibility of darkness, promises and perils indeed.[2] We are suggesting an early articulation and expansion of these questions will allow our research in ethics to proceed simultaneously with, and not behind, the science as it emerges. It is our hope that this work will be understood as one more research direction that allows us to reconsider new human possibilities with thoughtfulness, compassion, and humility. ■

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2. "The darkness drops again; but now I know
That twenty centuries of stony sleep
Were vexed to nightmare by a rocking cradle,
And what rough beast, its hour come round at last,
Slouches towards Bethlehem to be born?

W.B. Yeats, *The Second Coming* (1920)

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