Abstract

The last 5 years have seen a significant rise in the interest of fertility centers to provide care to young patients with diseases whose treatment may impair their future reproductive capacity. These diseases include cancer; rheumatologic diseases, including lupus, rheumatoid arthritis, ulcerative colitis; neurologic diseases, such as multiple sclerosis; and hematologic diseases, such as sickle cell anemia and thalassemia, which may require bone marrow transplant [1]. While fertility specialists are highly experienced in working with traditional infertility patients, they may not be as familiar with the needs of cancer patients, which often must be addressed on a much shorter time scale and in coordination with other clinicians and specialties.

Significant headway has been made to provide fertility specialists with tools that will assist them in meeting the unique needs of young patients faced with infertility. Though many reproductive specialists are now providing fertility-preserving treatments to young cancer patients, research indicates that many patients still do not receive adequate fertility information or referrals to reproductive services from their treating physicians [2, 3]. Access to fertility preservation interventions before treatment onset is a significant barrier to care and experienced fertility specialists have the opportunity to bridge that gap.

Fertility specialists wishing to provide fertility preservation care should be aware of treatment guidelines from the American Society for Reproductive Medicine (ASRM), the American Society of Clinical Oncology (ASCO), and the American Academy of Pediatrics (AAP) [4–6, 23]. The ASRM recommendations conclude that the various and diverse members of the treatment team—oncologists, surgeons, reproductive endocrinologists—have different responsibilities. Reproductive specialists play a unique role, as they are involved in both the initial fertility preservation procedure and later use of preserved gametes and tissues. Furthermore, fertility preservation procedures must be conducted in consultation with the patient’s disease specialist, such as an oncologist, and be coordinated with scheduled treatments. The ASRM guidelines also emphasize the importance of educating potential fertility preservation patients about the safety and efficacy of specific procedures,
and helping them understand the legal ramifications and requirements for minor patients. In particular, fertility specialists should communicate with patients about the risks of using experimental fertility preservation treatments, which currently include oocyte cryopreservation and ovarian tissue cryopreservation. Additional guidelines for ovarian tissue cryopreservation have also been developed [7].

Developing a seamless treatment team for young patients at risk of infertility from their disease or its treatment requires buy-in from a diverse group of stakeholders. These include the disease specialists, who, as the referring physicians, represent the gateway to fertility preservation for young patients. While these specialists should understand the role of fertility preservation and communicate basic information about these options, their principal role is to provide referrals to reproductive specialists in an appropriate and timely manner, and to work closely with the reproductive specialist to coordinate fertility preservation procedures with scheduled disease treatment, such as chemotherapy or radiation therapy. Additional team members include surgeons, psychologists and social workers, financial coordinators, legal experts, and laboratory personnel. Keeping this diverse group of professionals engaged in fertility preservation is key to providing streamlined care. This can be implemented through establishing standing meetings to discuss recent cases, research updates, and educational events.

The Oncofertility Consortium, with its National Physicians Cooperative has developed a series of tools for fertility programs to engage in research on experimental fertility preservation techniques and provide support to young patients. This joint effort between researchers and clinicians has led to a set of authoritative, shared resources developed for the betterment of the fertility preservation community. The following appendices include a variety of these tools, including sample institutional review board (IRB) templates—to provide experimental fertility preservation procedures to patients—as well as billing resources and additional information. Selected resources are available in the following appendices and on the Oncofertility Consortium website (http://oncofertility.northwestern.edu/files-npc-members). Through dissemination of these resources, the Oncofertility Consortium aims to speed the pace of research and rapidly transform clinical care to provide a full reproductive future for young survivors of cancer and other fertility-threatening diseases and treatments.

Resources for Ovarian Tissue Cryopreservation

Appendix A. Sample IRB Protocol: Ovarian Tissue Freezing for Fertility Preservation in Women Facing a Fertility Threatening Medical Diagnosis or Treatment Regimen

This sample IRB protocol can be used to initiate research on experimental ovarian tissue cryopreservation at an institution. The document should be used as a template and details can be modified to match the capabilities of an individual center and research program. IRB protocols for patient follow-up telephone scripts and an IRB submission checklist are available online.
Appendix B. Sample Consent Form: Ovarian Tissue Freezing for Fertility Preservation in Adult Women Facing a Fertility Threatening Medical Diagnosis or Treatment Regimen

This sample consent form includes the rationale and procedures involved in ovarian tissue cryopreservation for adult women. A parental consent form for this study and assent forms for individuals under age 18 are available online.

Resources for Oocyte Cryopreservation

Appendix C. Sample IRB Protocol: Oocyte Banking for Fertility Preservation in Women Facing a Fertility Threatening Medical Diagnosis or Treatment Regimen

This IRB protocol includes the purpose, objective, study design, and procedure used for sample oocyte cryopreservation investigations. Details of the study, such as location and methodology, can be modified based on institutional capabilities and current research.

Appendix D. Sample Consent Form: Oocyte Banking For Fertility Preservation in Women Facing a Fertility Threatening Medical Diagnosis or Treatment Regimen

This consent form for adult women wishing to engage in experimental oocyte cryopreservation includes details about the procedure for patients, storage of oocytes, financial information, and legal disclosures. Parental consent for minor patients and assent forms are available online.

Billing Resources

Appendix E. Letter Template: Provider Letter of Medical Necessity for Fertility Preservation Procedures

This letter can be used by health-care providers to call for insurance coverage of fertility preservation for a specific patient. The template includes the rationale for fertility preservation as well as attached professional guidelines. Letters should be modified for the appropriate insurance provider, clinician information, and patient case.

Appendix F. Letter Template: Patient Letter of Appeal for Fertility Preservation Procedures Template

Patients may use this letter as a template to appeal their insurance carriers to cover fertility preservation procedures. Providers can work with patients to provide the appropriate insurance and clinician contact and treatment information.

Additional Resources

Appendix G. Updating or Establishing Your FDA Registration
This document provides information for fertility centers that are involved in the processing or storing of donor tissues or cells to register with the US Food and Drug Administration (FDA), as required by FDA rule.

References

Appendix A
Sample IRB Protocol: Ovarian Tissue Freezing for Fertility Preservation in Women Facing a Fertility Threatening Medical Diagnosis or Treatment Regimen

Introduction

Although malignancy remains a critical health concern, significant medical advances in cancer detection and treatment have improved survival rates for patients. As patients live longer, the early and late consequences of cancer management are beginning to assume greater importance for survivors, their families, and providers. For instance, when considering the long-term sequelae of cancer therapy, infertility surfaces as a primary concern, particularly, among female survivors [50]. Unlike other late effects of cancer treatment, such as complications in cardiovascular or liver function, female infertility has biological and psychosocial implications that cannot be narrowly defined, nor easily addressed given the number of ethical and legal questions surrounding fertility preservation [32]. The acute ovarian failure to induced premature menopause and ultimately may result in difficulty with getting pregnant [28]. Particularly at risk are females who are older at the time of cancer diagnosis, those who have received abdominopelvic radiation or high doses of alkylating agents (particularly cyclophosphamide and procarbazine) and those diagnosed with Hodgkin lymphoma [5, 6, 20, 24, 45]. These concerns are not limited to cancer patients; treatment for other medical conditions such as rheumatoid arthritis and lupus may also result in infertility.

Traditionally, female cancer patients who wanted to have their own biological children in the future had limited options: protecting the ovaries from radiation and emergency in vitro fertilization (IVF) [25, 46]. Shielding a patient’s ovaries during radiation therapy has become common practice [39, 48]. However, emergency IVF, which relies on mature oocytes and sperm, is not always an option for young patients and those without a partner.

Mature oocytes can be retrieved following hormonal stimulation that is identical to that used for in vitro fertilization and cryopreserved [7]. Until recently, post-thaw recovery of cryopreserved oocytes with subsequent fertilization and embryo transfer lead to disappointing results [19, 22, 35, 51]. However, improvements in both freezing and thawing techniques for human oocytes necessitated by the ban in Italy
on freezing embryos (only eggs can be frozen) are currently leading to acceptable pregnancy rates [9, 2–4, 12, 33]. Like in vitro fertilization with freezing of embryos, the patient must undergo hormonal therapies to stimulate the growth of multiple follicles, followed by a surgical oocyte retrieval: A process that may take up to 3 weeks and can put the patient at risk of hyperstimulation syndrome. Therefore, the use of emergency IVF with the freezing of embryos or oocytes may delay the start of cancer therapies and may not be feasible for patients who have not yet reached puberty.

Fertility preservation options for female patients who cannot delay treatment or are too young to undergo hormonal stimulation rely upon ovarian tissue cryopreservation with subsequent transplantation and/or in vitro follicle maturation. Ovarian tissue containing immature oocytes (primordial, antral, and preantral follicles) has been successfully cryopreserved in several animal models including rodents, sheep, and nonhuman primates (Harp et al. 1995) [1, 16, 18, 30]. When thawed, this tissue can be grafted into a host with resumption of both endocrine and reproductive functions [31]. In 2004, the first successful application of this technology was reported in humans [11] using autologous orthotopic transplantation of frozen-thawed human ovarian tissue. In this study, the patient had return of endocrine function within 3 months of the transplant and achieved a spontaneous pregnancy. As of October 2007, there have been 12 reports of pregnancies (all but one spontaneous) following transplant of frozen/thawed ovarian tissue [10, 11, 26, 27, 38, 42–44] (Meirow et al. 2007; Anderson et al. 2007 Personal communication to J. Donnez). At least 13 more have been reported subsequently.

However, an important concern with transplanting ovarian tissue is the potential reintroduction of cancerous cells into a patient in remission, as seen in rodent lymphoma. Ovarian tissue transplant using this leukocyte-rich tissue may be contraindicated in patients with certain types of cancer [40, 41].

An alternative to transplantation of the ovarian tissue is isolation of the immature oocytes from the cryopreserved ovarian tissue and maturation in vitro with subsequent in vitro fertilization [29]. Traditional in vitro maturation systems make use of a two-dimensional culture [8, 15] that yields few oocytes that are viable, mature, or fertilizable. NU researchers [49] have demonstrated that a three-dimensional scaffold system using alginate, which may more closely mimic the in vivo ovarian physiologic conditions, produces a high follicle survival rate (93%) and oocyte maturation success (73%) in mice. Embryos derived from these oocytes were successfully fertilized in vitro and transferred to pseudopregnant female mice to produce live young. Both male and female offspring were also fertile. Parallel studies are underway in nonhuman primates. Ovarian follicles are contained in the cortex of the ovary. Large numbers of follicles can be obtained from strips of the ovarian cortex thus eliminating the need for hormonal stimulation of the ovary. Restoration of fertility and endocrine function made possible by maintaining the structural integrity of follicle using in vitro follicle maturation (IFM) could substantially improve the quality of life for women of reproductive age receiving cancer therapies which may otherwise impair ovarian function. Patient age, marital status, time available before treatment, and specific diagnosis are just a few of the factors that affect the choice of fertility preservation options in each individual patient.
**Purpose and Objective**

The primary objective of this study is to establish technologies that will enable long-term preservation of ovarian function, including the production of viable oocytes, through cryopreservation of ovarian tissue prior to chemotherapy, radiation, or treatment that is expected to reduce fertility. This study will provide research tissue for a national research repository that can be used to:

- Optimize techniques for freezing and thawing of ovarian tissue for use in transplant or in vitro follicle maturation (IFM).
- Investigate factors affecting successful maturation of immature follicles obtained from ovarian tissue including the use of three-dimensional biogel scaffolds, growth factors, hormones, and other culture conditions.
- Determine the efficacy of ovarian cryopreservation techniques.
- Provide long-term follow-up on patients who have ovarian tissue frozen for their own use.
- A substantial portion of the patient’s tissue will be cryopreserved and reserved for her own use.

*Significance:* Fertility preservation is an important quality-of-life issue for cancer survivors. While cancer treatments have become more efficacious, some can be expected to reduce fertility. This study will provide a pool of research ovarian tissue to use to develop and test methods to expand the range of fertility preservation options available to female cancer patients. At the same time, a substantial portion of the patient’s tissue will be cryopreserved and reserved for her own use.

*Preliminary Studies:* The investigators of the proposed study have extensive clinical or laboratory experience in the utilization of assisted reproductive technologies for infertile patients. The clinical investigators are fully trained and highly skilled in all the surgical procedures and clinical counseling needed in this study. The laboratory investigators of this study have extensive training in the physiology of oocyte and embryo development and have all the laboratory skills required for this study, including cell/tissue culture, culture and manipulation of gametes and embryos in vitro, and gamete/embryo cryopreservation. They also have extensive knowledge of the federal regulations governing reproductive tissue banking, tissue preparation and patient screening, and testing for long-term tissue banking.

[Insert preliminary studies]
Participant Selection

- **Inclusion criteria:**
  - Be female, 16–41 years of age.
  - Will undergo surgery, chemotherapy, drug treatment, and/or radiation for the treatment or prevention of a medical condition or malignancy expected to result in permanent and complete loss of subsequent ovarian function.
  - Have a medical condition or malignancy that requires removal of all or part of one or both ovaries.
  - Patients may have newly diagnosed or recurrent disease. Those who were not enrolled at the time of initial diagnosis are eligible if they have not received therapy that is viewed as likely to result in complete and permanent loss of ovarian function.
  - For patients undergoing elective removal of an ovary for fertility preservation only, have two ovaries.
  - Patients who already have stored cryopreserved ovarian tissue in a frozen state prior to undergoing cancer treatments (surgery, chemotherapy, or radiation) will be eligible for enrollment with informed consent.
  - Signed an approved informed consent and authorization permitting the release of personal health information. The patient and/or the patient’s legally authorized guardian must acknowledge in writing that consent for specimen collection has been obtained in accordance with institutional policies approved by the U.S. Department of Health and Human Services.
  - Are not a candidate for or choose not to utilize embryo or oocyte banking.

- **Exclusion criteria:**
  - Women with psychological, psychiatric, or other conditions which prevent giving fully informed consent.
  - Women whose underlying medical condition significantly increases their risk of complications from anesthesia and surgery.
  - Women who have a large mass in the ovary that is being removed will not be enrolled in the study. That is, ovarian tissue cryopreservation will not be performed on portions of an ovary that contained a large mass as experience in this study indicates that this tissue is not suitable for patient use in the future (contains limited or no follicles).
  - Serum FSH levels above 20 mIU/ml when no chemotherapy has been administered.
Study Design

Informed Consent and Survey

All potential participants will be informed of the risks of the planned treatment (surgery/chemotherapy/radiation) for subsequent infertility. Information about ovarian tissue preparation, freezing, and cryopreservation will be provided, and the experimental nature of ovarian tissue cryopreservation will be emphasized. They will be informed of the extent to which their participation in this study might be of benefit to them. In addition, they will be counseled prior to study entry for the unknown risk of possible genetic damage/fetal defects from cryopreservation and subsequent in vitro handling of the gametes and embryos. Clinical psychologists with extensive experience in issues related to assisted reproduction will be made available for counseling. A consent, assent, and parental consent form for the study are attached.

Collection of Ovarian Tissue

If the patient (and her parent/legal guardian, if under 18) chooses to participate and provides informed consent, she will be screened to determine eligibility and to determine if her medical condition significantly increases her risk of complications from surgery and/or anesthesia. The patient will also have a serum FSH drawn, on cycle day 3 where possible, as a marker of ovarian reserve to use in counseling her on her options.

Patients in four categories will participate in this study:

1. Patients who are having one or both ovaries removed for the treatment or prevention of a disease.
2. Patients who are having surgery to remove all or part of one or both ovaries for medical reasons where cryopreservation of the remaining limited portions of normal ovarian cortex is the only option for fertility preservation at the time (except that ovarian cortex from the ovary that contains the mass will not be cryopreserved).
3. Patients who are having surgery to remove all or part of one or both ovaries for medical reasons where cryopreservation of the remaining limited portions of normal ovarian cortex is the only option for fertility preservation at the time but who cannot or will not provide tissue to the research pool (except that ovarian cortex from the ovary that contains the mass will not be cryopreserved). These patients are willing to participate in the long-term follow-up described in this study.
4. Patients having one ovary removed electively, solely for the purpose of fertility preservation because they are not candidates for or choose not use more mature fertility preservation technologies.
Patients in Categories 1–3 will have surgical removal of their ovarian tissue using the methods determined by their surgeon based on their medical/surgical diagnosis or treatment.

Patients undergoing elective removal of an ovary (Category 4 above) will undergo a procedure called laparoscopy to remove the ovary. This surgery will be performed under general anesthesia and one ovary will be removed in total through an instrument channel employing standard techniques of operative laparoscopy. This surgical procedure is performed solely for fertility preservation but can potentially be coordinated with another procedure such as placement of a central line for future chemotherapy or laparotomy for another purpose. Although only one ovary will be removed, both of the patient’s ovaries must appear normal for the procedure to be completed. The ovary to be removed will be chosen at the time of surgery based on appearance and ease of removal. After the surgery is complete, the patient will not have any further procedures except for a routine postoperative visit. If indicated by the patient’s medical diagnosis, a small piece of the ovarian tissue will be provided to pathology for routine histological evaluation, and the remaining tissue will be processed for cryopreservation. If pathology finds evidence of cancer in the ovarian tissue provided at surgery, they may request that all of the patient’s tissue (even tissue that has been frozen for patient use) be returned to pathology for a more detailed examination. In this case, no tissue is available for the patient to use for fertility preservation purposes.

Despite a preoperative treatment plan to remove and cryopreserve ovarian tissue for fertility preservation, the surgeon or pathologist may determine intraoperatively that the entire ovary or a significant portion of the cortical tissue is needed for diagnostic purposes. Therefore, there may be no tissue available for cryopreservation for either patient use or research use. If only a small portion of the ovary is available after surgery or pathological sampling, then a determination will be made whether there is sufficient tissue available to freeze (see below).

**Study Procedures**

Ovarian tissues will be cryopreserved using modifications of the techniques described by Gosden et al. [16] or will be vitrified using a modification of the techniques of Kuwayama et al. 2007 [21, 34]. The ovary will be transported from the operating room to the designated laboratory for cryopreservation.

As part of the study protocol, a small fraction of the ovarian tissue, not to exceed 20% of the ovary and the immature eggs it contains (remaining after a portion has been provided to pathology, if indicated) will be provided to the National Physicians Cooperative of the Oncofertility Consortium for research purposes. The research tissue may be used fresh or may be frozen as described above. The remainder (majority) of the ovarian tissue will be cryopreserved for the patient’s own potential use in the future. Therefore, approximately 80% of the patient’s tissue will be frozen for her own use; she may utilize that tissue at any institution for any treatment
modality she chooses. The 20% of the ovary designated for research will go into a research pool and will be used for the research aims described above. None of the research tissue will be used for experiments that involve fertilization.

The ovarian cortex will be dissected from the medulla and cut into strips in culture/holding media, washed to remove blood cells, and passed through a series of cryopreservation solutions with increasing concentrations of cryoprotectants (including but not limited to propanediol, glycerol, or ethylene glycol, 0–15%; sucrose, 0–0.3 M) (freezing media). The tissues will be placed in cryovials or straws containing freezing media and frozen using a programmable freezer to cool tissues from 20°C to −40°C using defined ramps or vitrified directly or will be vitrified by direct plunge into liquid nitrogen. The vials or straws will be placed in liquid nitrogen for storage. The procedure for cryopreservation/vitrification may be modified as improvements become available.

Quality control procedures for the freezing and storage processes will be according to FDA regulations for reproductive tissues (Federal Register 21 CFR Part 1271 and Part 1270 [13]), guidelines of the American Association of Tissue Banks, and any other applicable federal, state, and local regulations. The designated Laboratory Director, John Zhang, Ph.D., is responsible for the overall quality control of all of these clinical laboratory activities, including ovarian tissue cryopreservation.

Minimum Amount of Ovarian Tissue: In order to ensure that the patient will have adequate tissue available for her own fertility preservation efforts, we define a minimum amount of tissue that must be available before the research portion can be obtained. This minimum is based on published information regarding amount of ovarian tissue required for two transplants of ovarian tissue (as the most conservative estimate of tissue needed to restore fertility). For this study, research tissue will not be removed unless there are at least six strips of cortical tissue measuring 2 × 0.5 cm. If less than six strips (worth of tissue) are available, then the patient will indicate in advance, in her informed consent, if she wants all of the tissue frozen for her own use or if she wants it all to be used for research.

Tissue Storage and Infectious Disease Testing

Ovarian Tissue Storage: All cryopreserved tissues obtained, including both the research portion (if frozen) and the patient portion, will be transferred to [name and location of storage facility] for storage and subsequent release. [Name of storage facility] is an FDA compliant and American Association of Tissue Banks accredited long-term storage facility for reproductive tissues. Based on the extended periods of time that these tissues are likely to be stored (patients may wait for 5 years from cancer treatment to be considered cancer free and begin a family; some may wait longer based on age), [name of storage facility] provides maximum flexibility for the patients involved. In this way, they can store tissues as long as they wish and ship them to a fertility treatment center of their choice at the time of use. The patient can determine how her own tissue will be used as technology changes and based on her unique circumstances. [Name of storage facility] does not perform fertility treatments and is not
affiliated with any fertility center, so there is no potential conflict of interest. Patients will execute a separate storage agreement with [name of storage facility] which defines the length of storage, shipping requirements, infectious disease screening, and disposition of the tissues in the event of their death.

Tissues designated for research and stored at [name of storage facility] will be allocated to investigators of NIH Oncofertility Consortium Grant by the Steering Committee of the Oncofertility Consortium.

Infectious Disease Screening and Testing: Banking and subsequent use of ovarian tissue is regulated by the Food and Drug Administration (FDA). In order to comply with current tissue banking regulations and to be prepared for any future changes in regulations while these ovarian tissues are in storage, patients will be tested and screened for a number of infectious diseases prior to banking ovarian tissue. All infectious disease testing will be performed at [name of testing facility]. The testing will include but not be limited to testing for hepatitis B and C and HIV. The screening and testing that will be performed are the same as would be performed on an anonymous reproductive tissue donor and include a physical examination and questions regarding potential high-risk behaviors. The testing that will be performed will be testing that is mandated for donors of leukocyte-rich tissues and must be performed within 7 days of tissue procurement. In this way, the tissue could potentially be used by the patient herself and it could also be suitable for use in another individual (such as a gestational surrogate) in the future if indicated by the patient’s medical diagnosis. (For example, use of in vitro maturation of follicles followed by IVF with embryo transfer to a gestational carrier for a patient without a uterus). In addition, a sample of the patient’s blood plasma will be stored with the ovarian tissue to permit any future testing required under federal tissue banking regulations. In spite of storing blood plasma, it is still possible that federal regulations may change and therefore, it may not be possible to perform the appropriate testing to permit heterologous use of the tissue in the future. Infectious disease testing is performed in this study to permit patient use of her own tissue and not for the purposes of research tissue or research study.

Clinical Data to Be Collected

Safety data

Adverse events after an elective laparoscopic oophorectomy (Category 3 Patients) will be identified using the Common Toxicity Criteria for Adverse Events (CTCAE). A copy of the CTC version 3.0 can be downloaded from the CTEP home page (http://ctep.info.nih.gov). All appropriate treatment areas should have access to a copy of the CTCAE version 3.0. The severity of the event should then be graded using the CTCAE criteria. Determination of whether the event was related to the surgical procedure and whether the adverse event was expected or unexpected will be made. Data on the time from surgery to start of definitive therapy (chemotherapy or radiation) will also be collected.
Appendix A

Other data to be collected

Age.
Diagnosis.
Treatment sequence associated with high risk of sterility.
Method of ovarian collection (laparotomy vs. laparoscopy).
Time from surgery to start of definitive therapy (chemotherapy or radiation).
Outcome: remission, relapse, or death.
Reproductive history before, during, and after cancer diagnosis with long-term follow-up.
Choices regarding use of cryopreserved stored tissues for fertility restoration.
Telephone script for long-term follow-up is attached.

Efficacy of Cryopreservation

In 1986, Chen reported the first successful attempt at cryopreserving and thawing a human oocyte resulting in a twin pregnancy after in vitro fertilization and embryo transfer. Progress in the field moved slowly for the next decade after murine data suggested that cryopreservation showed higher levels of chromosomal anomalies when compared with fresh eggs [17]. However, work in the early 1990s by Gook et al. demonstrated that cryopreservation was not as detrimental as originally thought, leading to renewed research interest in human oocyte cryopreservation [14].

By 2004, 100 human babies had been born from cryopreserved oocytes. These infants were produced with great inefficiency [47]. For instance, Marina and Marina [22] reported a 4% live birth rate from 99 oocytes frozen. Results with larger sample sizes were even less impressive. In fact, Porcu’s research group [35] reported only 16 pregnancies from 1,502 thawed oocytes (slightly more than 1%). Breakthroughs made by Italian researchers in optimizing freezing and thawing methods greatly improved pregnancy rates with mature human oocytes [2–4, 9, 12, 33] yielding pregnancy rates per thaw cycle of 19% and 22% per patient. However, these techniques make use of oocytes retrieved after hormonal stimulation utilized for in vitro fertilization which requires several weeks of treatment.

Cryopreservation of human ovarian tissue containing oocytes poses additional challenges. Oocytes have larger cell volumes, different freezing characteristics, and varying membrane permeability to cryoprotectants compared to ovarian tissue. Developing a method for tissue cryopreservation that permits recovery of a maximum number of mature follicles is one aim of this study. Tissue donated to the research pool will be frozen using varying cryopreservation methods and thawed to determine the efficacy of the freeze/thaw techniques. Follicles may be isolated from the thawed tissue and matured in vitro. The number of viable follicles isolated and their performance in culture will be recorded for each tissue specimen as indices of the efficacy of the cryopreservation process. Maturation of at least 50% of the oocytes/follicles recovered from the cryopreserved tissue is expected based on the literature. Data gathered from this research will assist in identifying and overcoming...
some of the challenges to successful freezing and thawing of tissue with subsequent in vitro maturation of follicles or oocytes.

### Feasibility of Three-Dimensional System for In Vitro Maturation of Immature Ovarian Follicles

Tissue provided to the research pool (no more than 20% of total tissue obtained from each patient) will be thawed as described by Gosden et al. [16]. Preantral and antral follicles (if available) will be isolated from the tissues and placed in culture. Factors that affect in vitro maturation of human oocytes will be investigated using the research tissue including but not limited to:

1. **Growth factors** such as IGF-1, IGF-2, EGF, GDF-9 and activin have been implicated in promoting follicular growth and oocyte maturation. These growth factors and others will be tested individually and in combination.
2. **Hormones** such as recombinant human FSH and LH will be included in the culture medium at different concentrations.
3. **Co-culture** of oocytes with certain somatic cells or cell lines is beneficial for in vitro maturation.
4. **Three-dimensional culture environment.** Under conventional culture conditions using plastic culture dishes, most types of cells will attach to the bottom of culture dish and spread. When follicular cells attach and spread on culture dishes, the 3-D structure of a follicle is lost and cellular contact between oocytes and surrounding follicular cells is disrupted, which may be detrimental to oocyte growth and maturation. In this study, preantral follicles will be encapsulated in biogel materials, such as agar or alginate, to prevent attachment and spreading of the follicular cells and maintain the three-dimensional structure of the follicle. Agar has been used successfully to culture hamster and human antral follicles [36, 37]. But it has a relatively high gel temperature (45°C), which may damage the cells during encapsulation. Alginate is a polysaccharide material which gels in the presence of calcium and causes less damage to the cells during the encapsulation process. Gels from both materials permit ready diffusion of growth factors, hormones, and other factors in and out of the follicle. The 3-D culture conditions needed to maximize in follicle maturation will be examined. Endpoints studied will include hormone production, follicle size and growth rate, oocyte maturity, structural changes using light and electron microscopy, and gene expression. None of the endpoints will involve fertilization of the oocytes.
Statistical Considerations and Data Management

Accrual

We estimate to accrue one patient per month.

Data Collection and Access

Participation in this research is confidential. All research tissues will be de-identified; participants will be identified by number and not by name. No information by which the patient can be identified will be released or published in connection with this study. Only the PI and coinvestigators will have access to files matching the patient with tissue specimen numbers. All data will be stored in a confidential database including the Cancer Central Clinical Database (C3D) provided by NIH/NCI for the Oncofertility Consortium. Data will be permanently stored by the PI and coinvestigators.

Risks: The patient’s participation in this study may involve the following risks. Most of these are related to the general risks of surgery.

- For patients undergoing elective laparoscopic oophrectomy that was required for fertility preservation only (Category 4 patients, see 6.2):
  1. Risks of laparoscopy: These include infection, damage to the patient’s internal organs, or bleeding problems as a result of insertion or manipulation of the laparoscopic instruments. The chance of the patient requiring hospitalization for complication(s) is about 1%. The patient’s chance of dying as a result of such complication(s) is less than 1 in 10,000.
  2. Risks of general anesthesia: The patient’s risk of death from anesthesia is less than 1 in 10,000.

- Removal of the ovary: There is a theoretical risk that the patient may experience a loss of fertility due to the removal of an ovary and/or may experience an early menopause caused by the loss of hormones produced by ovaries. The patient may regain spontaneous ovarian function. The surgery to remove tissue would then have been unnecessary. In addition, it is possible that the surgery itself could cause scar tissue or damage to the remaining ovarian tissue, so that chances for pregnancy could be reduced. These circumstances are very unlikely and much less likely than the patient’s chance of losing ovarian function as a consequence of her medical, surgical, or radiation treatment of her cancer or medical condition. She may also be at risk for the psychological consequences, including emotional upset, of having one ovary removed.

- Cryopreservation: Although care will be taken, damage to the removed ovarian tissue may occur during any part of the cryopreservation (freezing), shipping, or storage process. The effects of cryopreservation and long-term storage on human ovarian tissues are not known and possible damage to the tissues may occur. The risk of birth defect(s) and/or genetic damage to any child who may be born
following such a procedure is also unknown. However, thousands of children have been born worldwide from frozen embryos and eggs and there has been no report of increased risk of birth defects in these children. The ovarian tissue removed may not yield usable eggs, or pregnancy may not result when the eggs are ultimately used. Some patients may have particular risks associated with their underlying disease. If a cancer or other disease already affects the ovarian tissue, then it may never be possible to use the tissue in the future. This may not be known until the patient wishes to use her ovarian tissue. Tissue could be lost or made unusable due to equipment failure, or unforeseeable natural disasters beyond the control of this program.

- Infectious disease testing: Infectious disease testing may indicate that the patient has an infectious disease of which she was previously unaware and which may require treatment or may delay the start of her cancer or medical treatment. Although infectious disease testing will be performed within 7 days of removal of the ovary and additional plasma samples from the patient will be stored with her ovarian tissue, a future change in federal regulations for testing prior to use of this tissue may render the tissue unusable. Infectious disease testing and screening performed around the time of surgery may be inadequate to permit safe use of your tissue after the long-term storage of the tissue. While a sample of blood plasma will be stored to minimize this risk, the tests required in the future may require a sample other than plasma; the plasma sample may be inadequate or it may be lost or damaged during cryopreservation or storage. Infectious disease testing is only required for the patient to make use of her own tissue and is not required for use of the research tissue or the research study.

There may be no direct benefit to the patient from participating in this research study, but, as described above, there is a possibility that the portion of the tissue stored for her own use may eventually be used successfully to initiate a pregnancy. Participation in this research study may indirectly help other patients, who could benefit from ovarian tissue storage by helping to advance understanding of how to successfully freeze and thaw ovarian tissue in a manner that permits future use.

The use of ovarian transplant, in vitro maturation, or other new technology that cannot be envisioned now may allow the patient to use some of her cryopreserved and stored ovarian tissue in the future. However, this possibility cannot be assured and the patient will be thoroughly counseled about the experimental nature of this protocol.

The participant (and her parent/legal guardian, if under 18) has the alternative to choose not to participate in this study. Instead she may receive cancer treatment, chemotherapy, or radiation therapy, without undergoing surgery for the removal of one of her ovaries. If she is already undergoing surgery to remove all or part of her ovary (ovaries), she (and her parent/legal guardian, if under 18) can choose not to have the tissue cryopreserved. The patient may delay her treatment and undergo in vitro fertilization with freezing of embryos (not an option for patients under 18) or oocytes. There are no other alternative methods for preserving ovarian tissue available to the participant at this time.
Reimbursement and Research Cost

No direct reimbursement will be made to patients or their families. Patients in four categories will participate in this study:

1. Patients who are having one or both ovaries removed for the treatment or prevention of a disease.
2. Patients who are having surgery to remove all or part of one or both ovaries for medical reasons where cryopreservation of the remaining limited portions of normal ovarian cortex is the only option for fertility preservation at the time (except that ovarian cortex from the ovary that contains the mass will not be cryopreserved).
3. Patients who are having surgery to remove all or part of one or both ovaries for medical reasons where cryopreservation of the remaining limited portions of normal ovarian cortex is the only option for fertility preservation at the time but who cannot or will not provide tissue to the research pool (except that ovarian cortex from the ovary that contains the mass will not be cryopreserved). These patients are willing to participate in the long-term follow-up described in this study.
4. Patients having one ovary removed electively, solely for the purpose of fertility preservation because they are not candidates for or choose not use more mature fertility preservation technologies.

If the tissue does not meet the minimum quantity criteria (see 6.3), the patient will indicate in her consent form if the tissue is to be used entirely for research or reserved exclusively for her own use.

Hospital, Surgical, and Physician Costs

All costs will be billed to the patient or patient’s insurance. All noncovered services are the patient’s responsibility. Patients donating 20% of their ovarian tissue to the research pool will not be charged for the cryopreservation of their own tissue ($1,000), the first year of storage of their tissue or the shipping of the tissue to [name of storage facility] for storage.

Patient Tissue Storage

After the first year, all fees for the storage of the patient’s own tissue will be the patient’s responsibility (approximately $300/year). [Name of storage facility] has a financial assistance program in place to reduce this annual fee for those who can demonstrate financial need based on income.
Infectious Disease Testing

Infectious disease testing is required for storage and use of the patient’s own tissue and is not part of the research study. Infectious disease testing will be billed to the patient or patient’s insurance. Noncovered services are the patient’s responsibility.

Patients Who Do Not Contribute Tissue to the Research Pool

Patients who have insufficient tissue to contribute to the research pool despite agreeing to contribute to the pool will not be charged for the freezing of their ovarian tissue for their own use. Patients (and their parent/legal guardian, if under 18) requesting to have ovarian tissue frozen for their own use only (do not wish to contribute to the research pool but are willing to participate in long-term follow-up) will be charged for ovarian tissue freezing ($1,000). Patients who do not contribute tissue to the research pool will be financially responsible for the shipment of their tissue to long-term storage at [name of storage facility] (approximately $175) and its annual storage charge (approximately $300/year).

Provisions for Dealing with Research-Related Injury

In the event of injury or illness resulting from the research procedures, medical treatment for injuries or illness is available through the [name of fertility center].

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Appendix B
Sample Consent Form: Ovarian Tissue Freezing for Fertility Preservation in Adult Women Facing a Fertility Threatening Medical Diagnosis or Treatment Regimen

CONSENT FORM AND AUTHORIZATION FOR RESEARCH

Title: Ovarian Tissue Freezing For Fertility Preservation In Women Facing A Fertility Threatening Medical Diagnosis Or Treatment Regimen

Principal Investigator:

Supported by [or Funded by]:

You are being asked to take part in a research study. This document has important information about the reason for the study, what you will do if you choose to be in this research study and the way we ________________, would like to use information about you and your health.

What is the reason for doing this study?

You are being asked to participate in this research study because you are woman who will receive treatment for a medical condition which may result in infertility. You will be undergoing one of the following treatments and wish to preserve your ovarian tissue for the purpose of initiating a pregnancy in the future:

• Women who will undergo surgery, drug treatment, chemotherapy, or radiation therapy which is expected to result in a loss or impairment of ovarian function and/or infertility. Although not all surgery, drug treatment, chemotherapy, or radiation treatments affect fertility (the ability to become pregnant), the treatments you will receive are expected to affect your ovarian function and are likely to cause you to become sterile (unable to become pregnant) after therapy is finished.
- Women who will undergo surgery to remove one or both ovaries or portions of the ovaries as a way of treating or preventing a particular disease who wish to preserve their fertility.

At the present time, freezing of ovarian tissue is considered experimental and so thawing and subsequent use of the tissue to initiate a pregnancy must be performed as part of a research program. A portion of your ovarian tissue will be frozen for your own use and a portion will be donated to a research pool.

Your participation may advance our understanding of how to successfully freeze and thaw ovarian tissue in a manner that permits subsequent use by patients at some point in the future. Your participation may also advance our knowledge of how to successfully mature follicles and oocytes (eggs) that are contained in these tissues which may help others in the future. If tissue is frozen for your own use, you may have a means to restore your fertility in the future. However, there is a significant possibility that there may be no direct benefit to you from your participation in this research study.

What you will do if you choose to be in this study?

If you choose to participate in this study, and are interested in fertility preservation, a portion of your ovarian tissue will be cryopreserved and stored for your use later and you will donate a portion of your tissue for use in research. At the present time, freezing of ovarian tissue is considered experimental and so thawing and subsequent use of the tissue to initiate a pregnancy must be performed as part of a research program. You will determine how and at what institution you wish to use your own tissue in the future for the purposes of attempting to achieve a pregnancy. The number of visits will be determined by the surgical procedure performed. We will contact you by phone or mail until you have used your tissue or dropped out of the study to follow your medical and fertility status over time; ask questions about any future use of your frozen tissue and the possible outcomes of your fertility preservation treatment.

Procedures

For women who will receive chemotherapy, drug treatment or radiation therapy

Pre-Op Assessment: If you are enrolling in this research study because you are a woman who will be undergoing chemotherapy, drug treatment or radiation therapy prior to enrollment in the study, you will be evaluated by your oncologist or gynecologic surgeon and have some blood drawn (about two tablespoons) to confirm that you are eligible for this study. This blood will be used to measure FSH, a hormone in your blood, which gives us an indication of whether your ovary still contains a large number of healthy eggs. If this blood test indicates that you may not have healthy eggs remaining in your ovary, you will not be eligible for this study. You will also be evaluated by an anesthesiologist. If in his or her view, you would incur any additional risk of anesthesia by virtue of your disease or your general state of
health, you will not be enrolled. You may also meet with a clinical psychologist as part of your evaluation. This will require one or two additional office visits, each lasting between 30 and 60 min.

**Surgery:** You will undergo a procedure called a laparoscopy to remove one of your ovaries. A laparoscopy is a surgical procedure performed under general anesthesia (you will be asleep). This surgical procedure will be performed on you solely for the purpose of performing ovarian tissue cryopreservation which is an experimental procedure. It is not required for the treatment of your cancer.

A telescope-like instrument (a laparoscope) will be inserted into your abdominal cavity through a small (about half an inch) incision just below your navel. Two or three other such incisions may be made to permit the introduction of other instruments into your abdomen to allow the removal of your ovary. The technique for the removal of ovarian tissue by means of laparoscopy is based on well-established surgical approaches or techniques and has a very high likelihood of success.

Your surgery is planned to be performed as an outpatient procedure (will not require an overnight hospital stay). The duration of surgery is likely to be between 30 and 45 min. The recovery time required prior to either resuming normal activities or initiating chemotherapy or radiation therapy is expected to be 2–3 days. Your total time spent in the hospital will be about half a day. You should not plan on driving yourself home.

**For women who will have one or both ovaries or portions of their ovaries removed as treatment for a particular disease:**

**Pre-Operative Assessment:** If you are enrolling in this research study because you are having surgical removal of one or both of your ovaries or a portion of your ovaries as a way of treating or preventing a particular disease and wish to preserve your ovarian tissue for the purpose of initiating a pregnancy in the future, you will be evaluated by your oncologist or gynecologic surgeon and have some blood drawn (about two tablespoons) to confirm that you are eligible for this study. This blood will be used to measure FSH, a hormone in your blood, which gives us an indication of whether your ovary still contains a large number of healthy eggs. If this blood test indicates that you may not have healthy eggs remaining in your ovary, you will not be eligible for this study. Your surgery will be performed as your surgeon determines is appropriate for your medical condition.

**For all women having ovarian tissue cryopreservation:**

**Laboratory Procedures:** After surgery, a small piece of the removed ovary will be sent to the Department of Pathology and examined under a microscope, if this is indicated by your medical diagnosis. If it is performed, you will receive a copy of this report. A report that the tissue appears to be healthy is not a guarantee that the tissue is free of cancer cells, which could grow if the tissue were reimplanted in the future. However, if the Department of Pathology finds an abnormality in this sample that appears to be cancer, they may request that all of the tissue obtained during your surgery be returned to them for a more detailed examination. If this occurs, there may be no tissue remaining for fertility preservation purposes.
**Tissue Storage:** The remaining ovarian tissue will be frozen and stored in a number of separate vials. Later, one or more of the vials (never more than 20% of the total tissue and the immature eggs it contains removed) will be thawed to permit studies designed to determine how best to recover usable eggs from the tissue. Under certain circumstances, the tissue earmarked for scientific study may be studied prior to freezing. The research portion of the tissue will not be used for any studies that involve fertilization of the oocytes (eggs) it contains. The 20% of the tissue donated for research will not be usable by you.

The remainder of the ovarian tissue will be stored for your possible future use at an accredited long-term storage facility at [name of storage facility]. You will be asked to sign a separate storage agreement with [name of storage facility] that addresses the ownership, storage, shipping, and future disposition of your samples. There will be no charge for the freezing of your tissue, the first year of storage or the initial shipping of your tissue to [name of storage facility]. After the first year, you will be responsible for the annual storage fee (approximately $300) and any other charges accrued (e.g., shipping to another institution, at your request). Your tissue will only be stored at this institution for a short period of time following cryopreservation while shipment to [name of storage facility] is arranged. You will retain control over your tissues and may utilize them as you deem appropriate at the institution that you choose in the future. There is no limit as to how long your samples may be stored at [name of storage facility] provided your storage fees are paid annually after the first year. [Name of storage facility] has a financial assistance program in place for those who qualify.

During the period of time that your remaining tissue is stored, it is possible that technological advancements will progress for thawing stored ovarian tissues. If such advances take place and are found to be safe, you may request to thaw your tissue for reimplantation or egg recovery for the purpose of in vitro fertilization (IVF) in order to achieve pregnancy. At that time, your stored tissue will be transferred by [name of storage facility] to the facility of your choice at your request and at your expense. As part of your participation in this study, you will be updated on new options that are available for the use of your tissue and where those options are available. We cannot give you any information about the tissue that you donated to research since it will be de-identified (will not have your name attached to it). However, it is also possible that technological advancements to thaw the stored ovarian tissue may never occur and the tissue may not be usable. Although unlikely, it is also possible that these techniques may require approval by outside agencies (like the Food and Drug Administration) before they could be used to produce a pregnancy.

**Infectious Disease Testing:** Banking and subsequent use of ovarian tissue is regulated by the Food and Drug Administration (FDA). In order to comply with current tissue banking regulations and to be prepared for any future changes in regulations while your tissues are in storage, you will be tested and screened for a number of infectious diseases prior to banking your ovarian tissue.
These tests will include but not be limited to testing for HIV, hepatitis B and C based on current federal regulations. The screening and tests that will be performed are the same that would be performed on an anonymous reproductive tissue donor and will include a physical examination and questions about possible high-risk behaviors as well as blood tests. In this way, the tissue could potentially be used by you or would be suitable for use in another individual (such as a gestational carrier/surrogate) in the future, if your medical diagnosis indicates that this is necessary. Your ovarian tissue will be stored with tissue of the same infectious disease status. This infectious disease testing is only required because of the tissue that is being stored for your own use and not because you are donating tissue for research. This blood may be drawn after your surgery once the tissue has actually been obtained.

You will be tested for HIV. HIV is the term used for the virus that produces HIV infection and may ultimately lead to AIDS. Your blood will be taken to test for HIV. The study doctor must follow the Illinois AIDS Confidentiality Act (An Illinois law that sets up how HIV testing must be done and protects the confidentiality of information about someone’s HIV status.)

In addition, a sample of your blood plasma will be stored with your ovarian tissue to permit any additional future infectious testing required under federal tissue banking regulations. Current FDA regulations about required infectious disease testing for those storing tissues are specific and must be performed on a plasma sample that is obtained within 7 days of the tissue removal. If additional tests are required by the FDA in the future, this stored plasma might be used to perform those tests. However, in spite of storing blood plasma, the plasma sample may be inadequate to perform required testing under any new regulations and you may not be able to use your tissue in the future.

What are some of the risks and discomforts for people who are in this study?

Taking part in this study may involve the following risks:

Laparoscopy: Risks of the laparoscopy include infection, damage to your internal organs, or bleeding problems as a result of the insertion or manipulation of the laparoscopic instruments. Your chance of requiring hospitalization or more extensive surgery for the management of complications is about 1 in 1,000. Such complication(s) may necessitate a delay in further chemotherapy or radiation therapy treatments for your disease. Your chance of dying as a result of such complication(s) is less than 1 in 10,000. Minor complications, such as temporary pain or bruising at the incision sites, are common.

General Anesthesia: Your chance of dying from the anesthesia is less than 1 in 10,000. Minor complications, such as sore throat or short-term nausea, are quite common.
Elective (by choice) removal of an ovary: You have been invited to participate in this study because we expect that the treatment or surgery that you will undergo to treat your medical condition or cancer will significantly affect your future fertility. You should also know that it is possible to experience decreased fertility due to the removal of an ovary and/or to experience an early menopause caused by the loss of hormones produced by ovaries. Although we do not expect it, you may regain spontaneous ovarian function in spite of your medical treatments. If so, then for you, the tissue surgery would have been unnecessary. In addition, it is possible that the surgery itself could cause scar tissue or damage to the remaining ovarian tissue, so that chances for pregnancy could be reduced. These circumstances are very unlikely and much less than your chance of losing ovarian function as a consequence of your cancer or medical treatment. You are also potentially at risk for the psychological consequences, including emotional upset, of having one ovary removed.

Cryopreservation (freezing): Although care will be taken, damage to your removed ovarian tissues may occur during any part of the cryopreservation (freezing), shipping, and storage process. The effects of cryopreservation and storage on human ovarian tissues are not known and possible damage to the tissues may occur. The risk of birth defect(s) and/or genetic damage to any child who may be born following such a procedure is also unknown. However, thousands of children have been born following freezing of oocytes (eggs) and embryos and those freezing procedures have not resulted in an increased risk of birth defects.

The ovarian tissue removed may not yield usable eggs, or pregnancy may not result when the eggs are ultimately used. It is possible that medications you have taken may have some damaging effect on your ovary or egg quality. There are many medications whose effects on the ovary or egg quality are not yet known or have not yet been determined.

It is also possible that technological advancements to thaw the stored ovarian tissue may never occur and the tissue may not be usable.

Some subjects may have particular risks associated with their underlying disease. If a cancer or other disease already affects the ovarian tissue, then it may never be possible to use the tissue in the future. This may not be known until after you are healthy and wish to use your ovarian tissue.

Tissue could be lost or made unusable due to equipment failure, or unforeseeable natural disasters beyond the control of this program.

Infectious disease testing: Infectious disease testing and screening performed around the time of your surgery may be inadequate to permit safe use of your tissue after the long-term storage of the tissue. While a sample of your blood plasma will be stored to minimize this risk, the tests required in the future may require a sample other than plasma, the plasma sample may be inadequate or it may be lost or damaged in the cryopreservation or shipping process. Infectious disease tests will include but not be limited to testing for HIV, hepatitis B and C based on current federal regulations. Infectious disease testing may reveal an infection or disease of which you were previously unaware and which may require treatment. You will be tested for HIV. HIV is the term used for the virus that produces HIV infection and
may ultimately lead to AIDS. Your blood will be taken to test for HIV. The study doctor must follow the Illinois AIDS Confidentiality Act (An Illinois law that sets up how HIV testing must be done and protects the confidentiality of information about someone’s HIV status.)

**Emotional risks:** Your participation in this study may subject you to additional emotional risks beyond those directly related to your planned treatment.

**Tissue may be unavailable for freezing:** Although you may sign this consent, it is possible that there may be no tissue available for freezing. At the time of your surgery, if your surgeon or the pathologist (the physician who examines your tissue through the microscope) determines that all of your tissue is needed to diagnose your disease, then no tissue may be available for freezing. If that occurs you will not have any tissue frozen for your future use.

**There may not be enough tissue for both your use and for research:** If only a small portion of your ovarian tissue is available after your surgeon and the pathologist have made their determinations, there may not be sufficient tissue to both freeze tissue for your own use and to use for research. It is your choice what will be done under this circumstance and you will be asked below to indicate what you would want done in that circumstance.

**What are some of the benefits that are likely to result from my being in this study?**

Your participation may advance our understanding of how to successfully freeze and thaw ovarian tissue in a manner that permits subsequent use by patients at some point in the future. Your participation may also advance our knowledge of how to successfully mature follicles and oocytes (eggs) that are contained in these tissues which may help others in the future. If tissue is frozen for your own use, you may have a means to restore your fertility in the future. However, there is a significant possibility that there may be no direct benefit to you from your participation in this research study.

**What other procedures or courses of treatment might be available to me?**

You do not have to take part in this research study. In addition to being in this research study, the following treatment choices are available for your condition: You have the alternative to choose not to participate in this study. If you have a partner, you have the option of undergoing treatment with in vitro fertilization (IVF) in order to cryopreserve (freeze) embryos for future use (embryo banking). If you do not have a partner, you have the option of undergoing a modified form of in vitro fertilization
(IVF) in order to cryopreserve (freeze) eggs for future use (egg banking). Alternatively, you can make use of donor sperm and have conventional IVF with freezing of the resulting embryos. These procedures require several weeks to complete.

You also have the alternative of undergoing therapy with a type of medication called GnRH agonist (a protein which suppresses hormonal stimulation of your ovaries) prior to your cancer treatment. There is some evidence that such treatment reduces the risk of damage to the ovaries by either chemotherapy or radiation therapy. However, there have also been reports that its use may reduce the effectiveness of certain types of chemotherapy. This treatment is still considered experimental. It is not approved for this use at this time.

You also have the option of having your ovaries shielded from radiation or surgically moved to an area of the body away from the radiation (oophoropexy). The effectiveness of these procedures varies with the individual.

The ovarian tissue that is stored for your own use may be used for transplant back into your own body when you are ready to attempt to achieve a pregnancy. At the present time, approximately 25 pregnancies have occurred worldwide using this technique. (The reports of these pregnancies were “case reports” and so did not state how often this technique is successful.) Transplant of your own tissue cannot be used if you have a type of cancer in which your ovarian tissue might contain cancer cells that can “re-seed” your cancer in the future (such as ovarian cancer or some types of leukemia or lymphoma). At the present time, this procedure is not available at [name of institution] but is available at other institutions in the mid-West.

Your ovarian tissue may be thawed and the follicles and oocytes (eggs) it contains may be matured in the laboratory in a process called in vitro follicle maturation (IFM) and then fertilized using in vitro fertilization. At the present time, pregnancies have only been achieved in rodents using this technique and experiments in primates (monkeys) are continuing.

Freezing of ovarian tissue is available outside of this protocol (without participating in this study).

**Are there any financial costs to being in this study?**

**For women who will be receiving chemotherapy, drug treatment, or radiation therapy:**

You will receive no compensation for your participation in this study. You or your insurance company will be responsible for payment of all medications and medical care that would normally be part of the treatment or prevention of your condition, which may include the surgery to remove your ovary (ovaries), costs of infectious disease testing, and pathology. How much you have to pay depends on whether or
not you have health insurance and what costs your insurer will cover. If you have
any questions concerning your insurance coverage, you should speak to your health-
care insurance carrier.

If a portion of your tissue is donated to research, there will be no cost to you for
allowing the freezing of your tissue, its shipment to long-term storage, or the first
year of storage. The research portion of your tissue will be used only for research
and will not be sold. The research done with your tissue may lead to the develop-
ment of new products in the future. No compensation will be given to you now or in
the future for the use of these samples. The portion of your tissue that is for your
own use will remain under your control and expenses associated with any future use
of that tissue are your responsibility. As part of your participation in this study, you
will be updated on new options that are available for the use of your tissue and
where those options are available.

Charges for infectious disease testing will be your responsibility since this test-
ing is only required for your use of your own tissue (approximately $220) and is not
part of the research project. We will bill this insurance carrier and any portion that
is not covered will be your responsibility.

There will be no charge for the freezing of your tissue, the first year of storage,
or the initial shipping of your tissue to [name of storage facility]. After the first year,
you will be responsible for the annual storage fee (approximately $300) and any
other charges accrued (e.g., shipping to another institution, at your request). [Name
of storage facility] has a financial assistance program in place for those who qualify.
You will enter into a separate storage agreement with [name of storage facility] to
cover the storage and disposition of your tissue.

If there is insufficient ovarian tissue to use for both research and your own
use, then you will indicate what should be done with your tissue: all frozen for your
own use or all donated to research. If there is not sufficient tissue for both your own
use and for research, please initial the option you would choose:

________ My ovarian tissue should all be frozen for my own use in the future at
my expense. I understand that some costs for fertility preservation will be my
responsibility.

There will be no charge for the freezing of your ovarian tissue. However, shipment to long-
term storage (approximately $175) and an annual storage charge (approximately $300/year)
will be at your expense. Your tissue is for your own use and will remain under your control;
expenses associated with any future use of that tissue are your responsibility. Charges for
infectious disease testing are your responsibility since this testing is only required for your
use of your own tissue (approximately $180). Insurance usually covers the infectious dis-
ease testing. Costs of surgery not covered by insurance will be my responsibility.

________ My ovarian tissue should all be donated to research. I understand that
none will be frozen or available for my own use and that there will be no charges or
compensation for this donation.
What if I want my ovarian tissue frozen for my own use and do not want to donate any portion to research?

Your ovarian tissue can be frozen for your own use only and you can decide not to donate any to the research effort but to participate in the long-term follow-up on how you use this tissue. All expenses not covered by your insurance (including your surgery) will be your responsibility. There will be a charge for the freezing of your ovarian tissue ($1,000) and shipment to long-term storage (approximately $175) and an annual storage charge (approximately $300/year) will be at your expense. Your tissue is for your own use will remain under your control; expenses associated with any future use of that tissue are your responsibility. Charges for infectious disease testing are your responsibility since this testing is only required for your use of your own tissue (approximately $180). Insurance usually covers the infectious disease testing. As part of your participation in this study, you will be updated on new options that are available for the use of your tissue and where those options are available.

Please indicate that you want to exercise this option by initialing before the statement; if this statement does not reflect your wishes, please cross it out:

_______ I do not wish to donate any of my tissue to research and request that my ovarian tissue be frozen for my own use only regardless of the amount of tissue available. I will participate in the long-term follow-up on my use of this tissue as described. I understand and agree to the financial responsibilities described above.

What should I do if I am injured as a result of being in this study?

In the event of injury or illness as a result of study medications or study procedures, you should seek medical treatment through your physician or treatment center of choice. You should promptly notify the study doctor in event of any illness or injury. Payment for this treatment will be your responsibility.

If I have questions or concerns about this research study, whom can I call?

You can call us with your questions or concerns. Dr. Ralph Kazer at (312) 695–7269 is the person in charge of this research study. You can also call Kristin Smith, Patient Navigator for the Oncofertility Consortium at 312-503-3378 with questions about this research study. In the event of an injury or illness as a result of the study, you should contact Dr. Ralph Kazer at (312) 695–7269.
What are my rights as a research subject?

If you choose to be in this study, you have the right to be treated with respect, including respect for your decision whether or not you wish to continue or stop being in the study. You are free to choose to stop being in the study at any time. Choosing not to be in this study or to stop being in this study will not result in any penalty to you or loss of benefit to which you are entitled. Specifically, your choice not to be in this study will not negatively affect your right to any present or future medical treatment for which you are otherwise entitled.

Any new findings developed during the course of this research that may affect your willingness to continue in this study will be shared with you.

If you want to speak with someone who is not directly involved in this research, or have questions about your rights as a research subject, please contact the Office for the Protection of Research Subjects. You can call them at 312-503-9338.

What about my confidentiality and privacy rights?

We are committed to respect your privacy and to keep your personal information confidential.

When choosing to take part in this study, you are giving us the permission to use your personal health information that includes health information in your medical records and information that can identify you. For example, personal health information may include your name, address, phone number, or social security number.

Your health information we may collect and use for this research includes:

- All information in a medical record
- Results of physical examinations
- Medical history
- Lab tests

The study doctor must report positive HIV tests to the Illinois Department of Public Health (IDPH). The IDPH keeps track of all persons in the state with positive HIV tests. The database that keeps track of this information is coded so that your name does not appear with your HIV status. You are given a unique identification number. This helps keep your name private.

You are also giving permission to the following groups of people to give information about you (described above) to the researchers for this study:

All current and previous health-care providers, including but not limited to [name of institution] and [name of storage facility].
Once we have the health information listed above, we may share some of this information with the following people. Please note that any research information shared with people outside of [name of institution] will not contain your name, address, telephone or social security number, or any other direct personal identifier unless disclosure of the direct identifier is required by law [except that such information may be viewed by the Study sponsor and its partners or contractors at the Principal Investigators’ office].

- Authorized members of the [name of institution] workforce, who may need to see your information, such as administrative staff members from the Office of Research, and members of the Institutional Review Board (a committee which is responsible for the ethical oversight of the study)
- Government agencies and public health authorities, such as the Food and Drug Administration (FDA) and the Department of Health and Human Services (DHHS)

Those persons who get your health information may not be required by Federal privacy laws (such as the Privacy Rule) to protect it. Some of those persons may be able to share your information with others without your separate permission.

The results of this study may also be used for teaching, publications, or presentations at scientific meetings. No personal identifiers will be used in any publication or presentation.

**Please note that:**

- You do not have to sign this consent form. If you do not, it will not affect your treatment by health-care providers, or the payment or enrollment in any health plans, or affect your eligibility for benefits. However, you will not be allowed to take part in this research study.
- You may change your mind and revoke (“take back”) this consent at any time. Even if you revoke this consent, the principal investigator may still use or share health information that was obtained about you before you revoked your consent as needed for the purpose of this study. To revoke your consent for the use of your health information, you must do so in writing to: [contact name and information].
- Unless you revoke your consent, it will not expire.
- If you revoke (“take back”) your consent to use any blood or tissue taken for the study, the principal investigator will make sure that the research specimens are destroyed (the tissue that is for your own use will not be destroyed, unless you request that separately in writing) or will make sure that all information that could identify you is removed from these samples. You will not be contacted for follow-up.
Consent Summary:

I have read this form and the research study has been explained to me. I have been given the opportunity to ask questions and my questions have been answered to my satisfaction. If I have additional questions, I have been told who to contact. I agree to participate in the research study described above and will receive a copy of this consent form. I will receive a copy of this consent form after I sign it. I have initialed the sections as indicated above on page 8.

__________________________________________________
Subject’s Printed Name

__________________________________________________
Subject’s Signature Date

__________________________________________________
Printed Name of Person Obtaining Consent

__________________________________________________
Signature of Person Obtaining Consent Date

__________________________________________________
Investigator’s Signature Date
Appendix C
Sample IRB Protocol: Oocyte Banking for Fertility Preservation in Women Facing a Fertility Threatening Medical Diagnosis or Treatment Regimen

Introduction

The technical ability to cryopreserve gametes for future use provides important options for patients who wish to preserve their childbearing potential before facing therapy that is anticipated to result in infertility or gonadal failure. Most commonly, the desire for fertility preservation is seen in individuals who are about to undergo either chemotherapy or radiation therapy for various malignancies. It has been possible to successfully freeze and thaw semen samples for many years; more recently, it has become feasible for couples to cryopreserve zygotes. Until very recently, however, for a variety of technical reasons, successful cryopreservation of mature oocytes has been problematic.

Mature oocytes can be retrieved following hormonal stimulation identical to that used for in vitro fertilization and cryopreservation [7]. Historically, post-thaw recovery of cryopreserved oocytes with subsequent fertilization and embryo transfer led to disappointing results [14, 17]. However, due to the ban in Italy on freezing embryos, investigators were compelled to reexplore the practicality of mature oocyte cryopreservation. These political and legal limitations thus facilitated improvements in both freezing and thawing techniques for human oocytes and have led to acceptable pregnancy rates [3, 5, 6, 9, 10, 16]. Hundreds of babies have now been born worldwide following oocyte cryopreservation. Consequently, it is appropriate to offer this emerging technology to young women at risk for losing ovarian function following cancer treatment.

Purpose and Objective

*Purpose:* This study will contribute to the knowledge base surrounding oocyte cryopreservation so as to provide cancer patients and women who wish to delay childbearing scientifically sound options for fertility preservation.
Objective: To determine the long-term benefits and outcomes associated with the use of oocyte cryopreservation as an option for women who wish to preserve their fertility, regardless of disease status.

Hypothesis: Oocyte cryopreservation will be an effective and safe method of fertility preservation for cancer patients and women who wish to delay childbearing, resulting in future and successful pregnancies.

Rationale: Fertility preservation is an important quality-of-life issue for cancer patients. For instance, when considering the long-term sequelae of cancer therapy, infertility surfaces as a primary concern, particularly among female survivors [19]. Unlike other late effects of cancer treatment, such as complications in cardiovascular or liver function, female infertility has biological and psychosocial implications that cannot be narrowly defined, nor easily addressed given the number of ethical and legal questions surrounding fertility preservation [15]. Women who wish to delay childbearing may also desire fertility preservation. Finally, patients who are undergoing in vitro fertilization to treat infertility but where a sperm sample is unavailable on the day of their egg retrieval (e.g., partner unexpectedly out of town, unable to collect sample, etc.) can utilize oocyte cryopreservation so that their eggs are not wasted following the egg retrieval.

In 1986, Chen reported the first successful attempt at cryopreserving and thawing a human oocyte—a twin pregnancy resulted after in vitro fertilization and embryo transfer. Progress in the field moved slowly for the next decade after murine data suggested that cryopreservation showed higher levels of chromosomal anomalies when compared with fresh eggs [12]. However, work in the early 1990s by Gook et al. demonstrated that cryopreservation was not as detrimental as originally thought, leading to renewed research interest in human oocyte cryopreservation [11].

By 2004, 100 human babies had been born from cryopreserved oocytes. However, these infants were produced with great inefficiency [20]. For instance, Marina and Marina [14] reported a 4% live birth rate from 99 frozen oocytes. Results with larger sample sizes were even less impressive. In fact, Porcu’s [17] research group reported only 16 pregnancies from 1,502 thawed oocytes (slightly more than 1%). Fortunately, breakthroughs made by Italian researchers in optimizing freezing and thawing methods greatly improved pregnancy rates with mature human oocytes [3, 5, 6, 9, 10, 16], yielding pregnancy rates per thaw cycle of 19% and 22% per cycle which compares favorably with the natural fecundity rate of 20% per cycle.

There is little doubt that oocyte cryopreservation is now a reasonable alternative for cancer patients. The procedure is now being offered commercially throughout the United States not only to cancer patients, but also to healthy women who wish to delay childbearing. Nevertheless, little follow-up data regarding the actual efficacy of this approach or the health of infants born following its use are available. It is imperative that such data be prospectively generated, notwithstanding the difficulties inherent in the time frame over which patients might need to be followed.
The Ethics Committee of the American Society for Reproductive Medicine [2] and Committee on Gynecologic Practice of the American College of Obstetricians and Gynecologists [1] both stated that while oocyte cryopreservation holds significant promise for fertility preservation, the procedure is still considered investigational and may only be offered with appropriate informed consent in a research setting and with the oversight of an institutional review board. This practice guideline necessitates that in order to transform oocyte cryopreservation from an experimental to a standard procedure, more rigorous investigation into the methods and consequences of oocyte cryopreservation must be conducted. To this end, this protocol has been designed to identify suitable candidates for oocyte cryopreservation and to systematically follow them in order to assess the long-term benefits and outcomes associated with its use.

**Study Design**

**Research Design and Methodology:** We will conduct a prospective study to assess the long-term benefits and outcomes of the existing oocyte cryopreservation methods for fertility preservation in women with cancer diagnoses.

**Duration:** Until the American Society of Reproductive Medicine determines that this procedure is no longer experimental and need not be done under IRB supervision.

**Location:** Female patients will be identified and consented and all study procedures will be conducted [institution name].

**Participant Selection**

This study will enroll women of reproductive age in three different categories:

1. Women of reproductive age who are diagnosed with cancer or any disease whose treatment or its progression may impair their reproductive potential.
2. Women undergoing standard in vitro fertilization to treat infertility whose partner is unable to provide a semen sample on the day of the egg retrieval so that the eggs can be cryopreserved and not lost for use. (For example, failed testicular sperm aspirations, inability to collect or unexpected need to be out of town).
3. Women seeking oocyte cryopreservation for social (lifestyle) issues such as delaying childbearing.

Women seeking fertility preservation are referred for a comprehensive consultation with a reproductive endocrinologist to discuss the range of treatment options.
available to her. Only patients who choose oocyte cryopreservation as their method of fertility preservation will be enrolled in the study.

**Informed Consent Procedure**: Participation in this study is entirely voluntary. Choosing to not participate will not impact the care received at this institution. Following selection and counseling as outlined above, all subjects will be required to provide informed consent for participation in the study. All potential subjects will be informed of the risks of the procedure. Information about oocyte retrieval and cryopreservation will be provided and the experimental nature of oocyte cryopreservation will be emphasized. They will be informed of the extent to which they may benefit from the study. The subject will be granted time to read the informed consent document, and all questions will be answered to her satisfaction.

**Inclusion Criteria**

- Women of reproductive age who are diagnosed with cancer or any disease whose treatment or its progression may impair their reproductive potential (this would include but not be limited to cancer patients requiring treatment with chemotherapy or radiation; patients with rheumatologic diseases such as lupus, rheumatoid arthritis, and ulcerative colitis; and patients with genetic predisposition to cancers).
  - Age 16–41.
  - Girls under the age of 18 must have reached menarche and must, in the estimation of their physician and parents (and with their assent) be able to tolerate the entire procedure including vaginal ultrasounds and retrieval.

- Women over the age of 18, undergoing standard in vitro fertilization to treat infertility whose partner is unable to provide a semen sample on the day of the egg retrieval or who are unable to consent to freezing of embryos so that the eggs can be cryopreserved and not lost to use. (For example, failed testicular sperm aspirations, inability to collect or unexpected need to be out of town, or patients with religious objects to freezing of embryos).

- Women seeking oocyte cryopreservation for social (lifestyle) issues such as delaying childbearing.
  - Age 18–39

- Patients who are carriers of BRCA mutations predisposing them to cancer.
  - Age 18–39

- Otherwise healthy females

- Ability and willingness to comply with study protocol

- Informed written consent, prior to any study-related procedure not part of normal care, with the understanding that the subject may withdraw consent at any time without prejudice to their future medical care

**Exclusion Criteria**

- Current pregnancy
- Serum FSH >15 for patients having egg freezing for a medical indication
- Serum FSH >11 for patients having egg freezing for social reasons
Compensation to Subjects for Participation

Subjects will not receive compensation for participation in the study. No direct reimbursement will be made to the subjects or to their families. All costs will be billed to the subject or subject’s insurance. All noncovered services are the subject’s responsibility.

In the event of injury or illness resulting from the research procedures, medical treatment for injuries or illness is available through the [institution name]. Payment for this treatment will be the subject’s responsibility.

Study Procedures

After selecting and counseling potential subjects, and obtaining informed consent, enrolled subjects will participate in the following:

Oocyte Harvesting and Cryopreservation: Subjects will undergo controlled ovarian hyperstimulation according to established clinical protocols utilized in the In Vitro Fertilization Program at NMFF. Briefly, they will be treated with variable dosages of injectable gonadotrophins over a period of 8–12 days. Response will be monitored using vaginal ultrasound and serum estradiol levels. When appropriate follicle maturation has been achieved, a single dose of human chorionic gonadotropin (hCG) will be administered to induce final oocyte maturation. Thirty-six hours after hCG administration, the subject will undergo standard transvaginal oocyte retrieval under ultrasound guidance. The procedure takes approximately 15 min and is carried out under conscious sedation with fentanyl and versed. The oocytes are immediately handed off to the embryology technicians in the IVF laboratory.

Oocyte Cryopreservation

Oocyte cryopreservation will be carried out using one of the following two techniques:

Slow Freezing: This slow freezing protocol will be a modification of the techniques of Fabbri et al. [10] and Porcu et al. (2004) [18]. The technique may be modified as needed.

Vitrification: This method that used will be that of Bagchi et al. [4], Chian et al. [8] and kuwayama et al. [13]. These methods will be modified as needed as new studies are published in peer-reviewed literature.
Oocyte Storage

For cancer patients seeking fertility preservation and for women pursuing oocyte cryopreservation for lifestyle choices:

All cryopreserved oocytes will be transferred to [insert name and location of storage facility]. [Insert name of storage facility] is an FDA-compliant and American Association of Tissue Banks accredited long-term storage facility for reproductive tissues. Patients can store their oocytes as long as they wish and ship them to a fertility treatment center of their choice at the time of use. The patient can determine how her oocytes will be used as technology changes and based on her unique circumstances. [Insert name of storage facility] does not perform fertility treatments and is not affiliated with any fertility center, so there is no potential conflict of interest. Patients will enter a separate storage agreement with [insert name of storage facility], which defines the length of storage, shipping requirements, infectious disease, screening, and disposition of the oocytes in the event of their death.

Patients and/or their insurance carrier will be responsible for costs associated with the shipping of their oocytes (approximately $195) and an annual storage fee ($300). There is financial assistance available for those who qualify. Patients will enter into a separate storage agreement with [insert name of storage facility]. Patient samples will be stored at an institutional laboratory for a short time prior to shipping to [insert name of storage facility] and the storage agreement that is signed with [insert name of storage facility] will determine the disposition of the oocytes if the patient dies while they are still in storage at our institution (the oocytes will be shipped to [insert name of storage facility]).

For IVF patients whose partner is unable to provide a semen sample on the day of egg retrieval:

Oocytes will be stored at [insert name of storage facility] and patients will be charged an annual storage fee (approximately $500) (this is the same fee currently charged infertility patients for embryo storage). Maximum storage period at [insert name of storage facility]: X years (if applicable). Patients have the option, at any time, to transfer their oocytes to another facility for storage or use or to request that they be discarded.

Utilization and Final Disposition of Stored Oocytes: Subjects will have access to their oocytes for the purpose of initiating a pregnancy at any point in time following their initial storage. Subjects will also have the option of having their oocytes discarded or earmarked for any appropriate research studies at any point. If the subject chooses to donate their oocytes for research studies, no such studies would involve a fertilization step. All stored oocytes will be considered the property of the subjects and will not be made available to anyone other than the subject without her approval. If the oocytes are stored at [insert name of noninstitutional storage facility], the separate [insert name of storage facility] storage agreement signed by the patient will determine the disposition of the oocytes if the patient fails to pay the annual storage fee or dies while they are still in storage. If the oocytes are stored at our institution,
the patient will designate in her signed consent the disposition of the oocytes if she dies, abandons them, or fails to pay her storage fee. Oocytes will be stored at our institution for a maximum of 3 years. At the end of 3 years, if oocytes are still available, subjects will be asked to choose between utilizing the oocytes, disposing of them, or transferring the oocytes to a commercial long-term storage facility.

Establishment and Maintenance of the Outcome Data: Subjects in the study will agree to maintain contact with the investigators, as outlined in the consent form. Specifically, they will agree to notify the investigators of any changes in their contact information. Any subsequent attempts to utilize the stored oocytes for the purpose of initiating a pregnancy will be recorded, along with the outcome of the attempt. All other dispositions of the oocytes will also be recorded. Individual files will be kept active until all oocytes have been utilized, disposed of in some other way, or 10 years following storage, whichever comes first. Patients will be assigned a research number and data follow-up will include the use of the research number. All research data will be stored in a locked file cabinet and only the research coordinator and the PI will have access to the database.

The subject’s participation in this study may involve the following risks.

Ovarian Stimulation: The ovarian stimulation step often causes a sense of fullness or bloating, which usually goes away within a few days after the retrieval. In about 1% cases, patients will develop ovarian hyperstimulation syndrome (OHSS) a serious complication resulting in the accumulation of fluid in the abdominal cavity. This complication is self-limited, but severe cases may require several days of hospitalization for fluid management.

Oocyte Retrieval: Risks of oocyte retrieval include infection, damage to internal organs, or bleeding problems as a result of the insertion or manipulation of the needle used to recover the oocytes. The chance hospitalization or more extensive surgery for the management of such complications is about 1/1,000. Such complication(s) may necessitate a delay in further chemotherapy or radiation therapy treatments for the subject’s disease. Minor complications, such as temporary abdominal pain or cramping, are common.

Conscious Sedation: The sedation step is very safe and rarely results in complications. In unusual cases, sedation may result in cessation of breathing efforts (apnea), and medications to counteract the sedating drugs may need to be administered. This complication occurs in about 1/1,000 cases.

Cryopreservation: Although care will be taken, damage to the removed oocytes may occur during any part of the cryopreservation (freezing) or storage process. The effects of cryopreservation and long-term storage on human oocytes are not known and possible damage to the oocytes may occur. The risk of birth defect(s) and/or genetic damage to any child who may be born following such a procedure is also unknown. Thousands of children have been born worldwide from frozen embryos and there has been no report of increased risk of birth defects in these children. Hundreds of children have been born worldwide from the use of frozen eggs and
there does not appear to be an increased incidence of birth defects but more data must be collected. The oocytes removed may not yield usable eggs, or pregnancy may not result when the eggs are ultimately used. Oocytes could be lost or made unusable due to equipment failure, or unforeseeable natural disasters beyond the control of this program.

Emotional Risks: Participation in this study may subject the participant to additional emotional risks beyond those directly related to her planned treatment.

Risk/Benefit Ratio: The oocytes stored for the patients’ own use can eventually be used successfully to initiate a pregnancy. Participation in this research study may indirectly help other women who could benefit from information about the efficacy and safety of oocyte cryopreservation, long-term oocyte storage, and use of frozen oocytes. The risks are small in comparison to the benefit and are the same as those encountered by all infertility patients undergoing routine in vitro fertilization (IVF) procedures in our Division.

Alternatives: The subject has the alternative to choose not to participate in this study.

If the subject is undergoing medical treatments (such as for cancer) she may receive chemotherapy or radiation therapy without undergoing retrieval and storage of oocytes. If she has a partner, she has the option of undergoing treatment with in vitro fertilization in order to cryopreserve (freeze) embryos for future use. She also has the alternative of undergoing therapy GnRH agonists prior to her cancer treatment. There is some evidence that such treatment reduces the risk of damage to the ovaries by either chemotherapy or radiation therapy. This treatment is still considered experimental. It is not approved for this use at this time. She also has the option of undergoing ovarian tissue cryopreservation which is also an experimental procedure.

If the subject is undergoing IVF, has had eggs retrieved but the sperm sample needed to fertilize the oocytes is not available or she is unable to give consent for freezing of embryos, the eggs can be discarded.

If the subject is freezing eggs for social reasons, she can decide not to do that.

Protection of Subjects: The principal investigator, coinvestigators, and other members of the investigative team will only access data collected as part of this study. All information will be kept confidential and will not be shared except as may be required by law. No information by which the subject can be identified will be released or published in connection with this study. All data will be stored in a confidential database.

Information will only be used for the purpose of this study. The following groups of people may have access to the research information: the research team, the Hospital’s ethics committee (Institutional Review Board), and the Food and Drug Administration and the Center for Disease Control as required by federal law.

Data Safety and Monitoring: The principal investigator and clinical coordinator will monitor the subject records periodically for completeness.
Appendix C

Criteria for Terminating the Study: Once the risk/benefit ratio of the protocol becomes unfavorable, where the subject is exposed to greater harm than potential benefit, the study will be terminated. Notice of study termination will be submitted to [institution name] IRB. If ASRM determines that oocyte cryopreservation is no longer investigational, the study will be terminated.

Procedures for Reporting Deviations from the Original Plan: Any deviations from the original protocol that take place during the course of the study will be reported in a timely fashion to [institution name] IRB in the form of a revision or safety/other submission.

Conclusion

Fertility preservation ranks as one of the greatest concerns for women diagnosed with cancer. Therefore, establishing the effectiveness and safety of oocyte cryopreservation as a fertility preservation option would greatly impact the reproductive destinies of women undergoing fertility-threatening treatment. At the conclusion of the study, we hope to have sufficient data to assess the long-term benefits and outcomes of oocyte cryopreservation so as to confidently offer the procedure as a safe and effective method of fertility preservation.

Anticipated Results and Potential Pitfalls: It is anticipated that oocyte cryopreservation will provide a scientifically sound fertility preservation option for cancer patients and for women who wish to delay child bearing. While the cryopreservation procedure is still experimental, early findings have demonstrated promising results. The findings from this study will contribute to the existing knowledge base by providing valuable evidence about how to perfect the cryopreservation process and increase pregnancy rates in women whose oocytes have been frozen and thawed and to document the long-term outcomes from the use of these oocytes (pregnancy rates and rate of birth defects).

References

3. Bianchi V, Coticchio G, Distratis V, DiGuisto N, Flamigni C, Borini A. Differential sucrose concentration during dehydration (0.2 mol/l) and rehydration (0.3 mol/l) increases the implantation rate of frozen human oocytes. RBM OnLine. 2007;14:64–71.
Appendix D
Sample Consent Form: Oocyte Banking for Fertility Preservation in Women Facing a Fertility Threatening Medical Diagnosis or Treatment Regimen

CONSENT FORM AND AUTHORIZATION FOR RESEARCH

Title: Oocyte Banking For Fertility Preservation In Women Facing A Fertility Threatening Medical Diagnosis Or Treatment Regimen

Principal Investigator:

Supported by [or Funded by]:

You are being asked to take part in a research study. This document has important information about the reason for the study and what you will do if you choose to be in this research study.

What is the reason for doing this study?

You are being asked to participate in this research study because you are a woman of reproductive age who wishes to cryopreserve (freeze) your eggs (oocytes) and store (bank) them and you fall into one of the following categories:

1. You will be undergoing chemotherapy or radiation therapy treatments to treat a medical condition (such as cancer or rheumatologic diseases). Although not all chemotherapy and/or radiation treatments affect fertility (the ability to become pregnant), the treatments you will receive may affect your ovaries and may cause you to become sterile (unable to become pregnant) after therapy is finished. Egg banking must take place before your treatment begins.

2. You are a woman who is undergoing in vitro fertilization (IVF) to treat infertility but the sperm sample required to fertilize your eggs is not available (e.g., your partner is unavailable, unable to collect a sample or frozen samples, did not arrive in time for your procedure) or you are unable to consent to freezing of embryos.

3. You are a woman who wishes to freeze your eggs for social (lifestyle) reasons.
Published studies indicate that mature oocytes (eggs) can successfully be removed from the ovaries of women, frozen, and subsequently thawed and fertilized with sperm using a technique called in vitro fertilization (IVF). Such fertilized eggs (embryos) have been transferred to the uterus of women who have stored their eggs in this way, and pregnancies have resulted. Early results indicate that the babies resulting from these pregnancies are no more likely to have birth defects than babies conceived naturally, but more time will be required to assess this concern accurately.

The principal goal of this study is to provide long-term follow-up with women who wish to store their oocytes for future attempts to become pregnant. This will make it possible to learn more about the long-term effectiveness of this approach as well as the health of the children who are born following its use. You have been identified as a woman who might benefit from this approach.

If you choose to participate in this experimental study, you will undergo oocyte (egg) retrieval and your eggs will then be frozen and stored. The procedures for freezing the eggs in this study are still considered experimental. The stored eggs will be available to you at any time after the storage procedure if you wish to try to become pregnant. You may also, at any time, elect to have the eggs discarded or donated for research purposes. Any such research will not involve fertilizing the eggs with sperm.

What will you do if you choose to be in this study?

Pre-operative assessment: Prior to enrollment in the study, you will be evaluated to confirm that the retrieval process will not represent an increased risk to you by virtue of your disease or your general state of health. You will also require a blood test (serum FSH) to confirm that your ovaries are likely to yield a sufficient number of healthy eggs to justify doing the retrieval. You will also be assessed by your oncologist (if applicable), a reproductive endocrinologist, and will have the option to meet with a clinical psychologist. The purpose of this screening is to confirm that you are eligible for this study and specifically, to ensure that the risk you will incur by enrolling is acceptably low (particularly if you have a medical condition that will require chemotherapy and/or radiation). This will require one or two additional office visits, each lasting between 30 and 60 min.

Ovarian stimulation: In order to permit the recovery of as many oocytes as possible, you will be treated with a series of hormone injections (gonadotrophins) to stimulate your ovaries to develop a number of mature follicles (and eggs) simultaneously. Ordinarily, in a natural menstrual cycle, only one follicle develops, and it releases only one oocyte (egg). The injections are given under the skin on a daily or twice-daily basis for about 10 days. Your response to the medication will be monitored by blood tests and ultrasound examinations, and your daily dosage may be changed during the course of this part of your treatment. When the follicles appear to be mature, you will administer a single injection of human chorionic gonadotropin (hCG) to trigger ovulation roughly 36 h later.
Oocyte retrieval: Oocyte retrieval is an outpatient procedure performed under conscious sedation about 35 h after the HCG injection. The retrieval involves the intravenous administration of pain medication and relaxants (including but not limited to fentanyl, versed, propofol, and/or diazepam) designed to keep you comfortable during the procedure, which usually takes 10–15 min. These medications will usually cause patients to doze off from time to time, but should not prevent communication between patients and the individuals performing the procedure. The retrievals are done in a procedure room adjacent to the IVF Laboratory in the Galter Pavilion.

Once sedation has been established, your ovaries will be visualized using an ultrasound probe inserted into your vagina. Under ultrasound guidance, a needle will be passed into the ovaries and the follicles. Each follicle contains an oocyte, which will be emptied one by one with the needle. Once all of the follicles have been emptied, the procedure will be terminated. The effects of the sedation should be gone by the following day.

Oocyte cryopreservation and storage:

If you are a cancer patient seeking fertility preservation or a woman pursuing oocyte cryopreservation for lifestyle purposes:

Your recovered oocytes will be stored for your future use at an accredited long-term storage facility at [storage facility]. You will be asked to sign a separate storage agreement with [storage facility] that addresses the ownership, storage, shipping, and future disposition of your samples. You and/or your insurance carrier will be responsible for costs associated with the shipping (approximately $195) and storage ($300/year) of your oocytes. There is no limit as to how long your samples may be stored at [storage facility], provided your storage fees are paid annually. [Storage facility] has a financial assistance program in place for those who qualify.

When you are ready to use your oocytes, your oocytes will be transferred by [storage facility] to the facility of your choice at your request and at your expense. All stored oocytes will be considered your property and will not be made available to anyone other than you without your approval. Your oocytes will be stored at an [institution name] laboratory for a short period of time prior to transfer to [storage facility] and the storage agreement that you sign with [storage facility] will determine the disposition of your oocytes if something were to happen to you.

If you are an IVF patient whose partner is unable to provide a semen sample on the day of egg retrieval:

Your oocytes will be passed directly into the IVF laboratory, where they will undergo the cryopreservation (freezing) process. Your oocytes will be stored for you at [institution name] for a period of up to 3 years (from the date of freezing), provided your applicable annual storage fees are paid. You will have access to your
oocytes for the purpose of initiating a pregnancy at any point in time following their initial storage. You will also have the option of having your oocytes discarded or donated for any appropriate research studies at any point. If you choose to donate your oocytes for research studies, no such studies will involve a fertilization step.

Abandonment of Eggs in Storage: There are fees associated with keeping embryos in storage. You must remain in contact with [institution name] on at least an annual basis in order to inform [institution name] of your wishes in regard to these eggs and to pay fees associated with the storage of these eggs (approximately $500). In situations where there is no contact with [institution name] for a period of 2 years or annual fees associated with egg storage have not been paid for a period of 2 years and [institution name] is unable to contact you after reasonable efforts have been made, the eggs will be considered to be abandoned and may be destroyed by [institution name] in accordance with normal laboratory procedures and applicable law. Reasonable efforts may include phone calls and registered mail to the most recent phone numbers/address in your chart. At the end of 2 years, if you do not notify us of what you wish to do with your oocytes on an ongoing basis (utilizing the oocytes, disposing of them, or transferring them to a long-term storage facility at your expense) they will be discarded. If your oocytes are sent to [storage facility] for storage, the separate storage agreement that you sign with [storage facility] describes the disposition of your oocytes if you fail to pay your storage fees, abandon the oocytes, or die while they are in storage.

**Maintain contact:** By signing this consent form and enrolling in the study, you agree to maintain contact with the investigators and notify them of any changes in your contact information.

**Infectious Disease Testing:** Banking and subsequent use of your eggs is regulated by the Food and Drug Administration (FDA). In order to comply with current tissue banking regulations and to be prepared for any future changes in regulations while your eggs are in storage, you may be tested and screened for a number of infectious diseases prior to banking your eggs particularly if you are a patient who is banking eggs for medical reasons (such as before chemotherapy or radiation) where carrying a pregnancy in the future is not possible or safe.

These tests will include but not be limited to testing for HIV, hepatitis B and C based on current federal regulations. The screening and tests that will be performed are the same that would be performed on an anonymous reproductive tissue donor and will include a physical examination and questions about possible high-risk behaviors as well as blood tests. In this way, the eggs could potentially be used by you or would be suitable for use in another individual (such as a gestational carrier/surrogate) in the future, if this is necessary. Your eggs will be stored with eggs of the same infectious disease status. This blood must be drawn within 30 days of your egg retrieval.

In addition, a sample of your blood plasma will be stored with your eggs if you are a patient who is banking eggs for medical reasons (such as before chemotherapy or radiation) to permit any additional future infectious testing required under federal tissue banking regulations. Current FDA regulations about required infectious
disease testing for those storing tissues are specific and must be performed on a plasma sample that is obtained within 30 days of the egg retrieval. If additional tests are required by the FDA in the future, this stored plasma might be used to perform those tests. However, in spite of storing blood plasma, the plasma sample may be inadequate to perform required testing under any new regulations and you may not be able to use your eggs in the future, if a gestational carrier were needed.

**Long Term Follow-up:** You will be contacted annually to determine if you chose to use your eggs, if you became pregnant and the pregnancy outcome. These contacts will be made by phone and will take about 10 min. You will continue to be contacted until you use your eggs, you notify us that you no longer wish to be in the study, or the American Society for Reproductive Medicine determines that egg freezing is no longer investigational.

**What are some of the risks and discomforts that may happen to people who are in this study?**

**Ovarian stimulation:** The ovarian stimulation step often causes a sense of fullness or bloating, which usually goes away within a few days after the retrieval. About 1% of the time, patients will develop ovarian hyperstimulation syndrome (OHSS) which is a serious complication resulting in the accumulation of fluid in the abdominal cavity. This complication is self-limited, but severe cases may require several days of hospitalization for fluid management.

**Oocyte retrieval:** Risks of this procedure include infection, damage to your internal organs, or bleeding problems as a result of the insertion or manipulation of the needle used to recover the oocytes. The chance of you requiring hospitalization or more extensive surgery for the management of such complications is about 1/1,000. Such complication(s) may necessitate a delay in further chemotherapy or radiation therapy treatments for your disease. Minor complications, such as temporary abdominal pain or cramping, are common.

**Conscious sedation:** The sedation step is very safe and rarely results in complications. In unusual cases, the sedation may result in a cessation of breathing efforts (apnea) and medications to counteract the sedating drugs may need to be administered. This occurs in about 1/1,000 cases.

**Cryopreservation (freezing):** Although care will be taken, damage to your oocytes may occur during any part of the cryopreservation (freezing) and storage process. The long-term effects of cryopreservation and storage on human oocytes are not known and possible damage to the oocyte may occur. The risk of birth defect(s) and/or genetic damage to any child who may be born following such a procedure is also unknown.
Oocyte freezing has resulted in the births of hundreds of babies worldwide. The technique is still considered experimental because long-term studies of the children born are still underway.

The oocytes removed may not survive the freezing and thawing process, or pregnancy may not result when the eggs are ultimately used. If you have reached menopause at the time you use these eggs and they do not produce a pregnancy, you will not be able to have a child that is biologically your own.

It is possible that medications you have taken may have some damaging effect on your egg quality. There are many medications whose effects on the ovary or egg quality are not yet known or have not yet been determined.

While pregnancy rates using frozen/thawed oocytes have increased dramatically in the past few years, the technique is still considered experimental because more information must be collected from a broader and larger group of centers worldwide. While freezing of embryos has been available for decades, it is impossible to know at the present time how freezing of oocytes will compare to freezing of embryos in terms of pregnancy rates. Preliminary results look promising but it is possible that women who choose to freeze unfertilized eggs may have a reduced pregnancy rate when compared to women who freeze fertilized eggs.

All women should keep in mind that pregnancy rates with both frozen eggs and frozen embryos decrease with the age of the woman at the time of freezing.

Oocytes could be lost or made unusable due to equipment failure, or unforeseeable natural disasters beyond the control of this program.

**Emotional Risks:** Your participation in this study may subject you to additional emotional risks beyond those directly related to your planned treatment.

**What are some of the benefits that are likely to come from my being in this study?**

The possible benefits to you from this study include having the opportunity to become pregnant using your stored oocytes at some point after your treatment is complete. Your participation may also advance our understanding of how to successfully freeze oocytes in a manner that permits subsequent use by patients at some point in the future.

**What other procedures or courses of treatment might be available to me?**

You do not have to take part in this research study.

If you are woman undergoing medical treatments, you may receive chemotherapy or radiation therapy without undergoing retrieval and storage of your oocytes.
However, in addition to being in this research study involving egg freezing and storage the following treatment choices are available for your condition:

You have the alternative of undergoing therapy with a type of medication called GnRH agonist (a protein which suppresses hormonal stimulation of your ovaries) prior to your cancer treatment. There is some evidence that such treatment reduces the risk of damage to the ovaries by either chemotherapy or radiation therapy. This treatment is still considered experimental. It is not approved for this use at this time. You also have the option of undergoing ovarian tissue cryopreservation which is also an experimental procedure.

If you have a partner, you have the option of undergoing treatment with in vitro fertilization in order to cryopreserve (freeze) embryos for future use.

If you are undergoing IVF, have had eggs retrieved but the sperm sample needed to fertilize your oocytes is not available, your eggs can be discarded.

If you are freezing eggs for social reasons, you can decide not to do that.

Are there any financial costs to being in this study?

You will not receive compensation for your participation in this study. All aspects of this study as described above, including the oocyte stimulation, retrieval, freezing, and storage, will be billed to you or to your insurance carrier. The approximate costs associated with oocyte cryopreservation are as follows: oocyte stimulation, monitoring, and retrieval, laboratory charges: $6,000; medications: $3,000; shipping: $195; annual storage fee: $300–$500/year; infectious disease testing: $500. The costs involved in having the eggs thawed, fertilized, and transferred to your uterus at a later date are not included in these costs and are currently approximately $2,000. How much you have to pay depends on whether or not you have health insurance and what costs your insurer will cover. If you have any questions concerning your insurance coverage, you should speak to your health-care insurance carrier.

What should I do if I am injured as a result of being in this study?

In the event of injury or illness resulting from the research procedures, medical treatment for injuries or illness is available through the [institution name]. Payment for this treatment will be your own responsibility.

The Office for the Protection of Research Subjects of [institution name], at [telephone number], can provide further information about your rights as a research subject and is where any research-related injury should be reported. Further information regarding this study may be obtained from the principal investigator, [investigator name], at [telephone number], including evenings and weekends.
If I have questions or concerns about this research study, whom can I call?

You can call us with your questions or concerns. [Investigator name] is the person in charge of this study and can be reached at [telephone number], including evenings and weekends.

If you have any illness or injury during your time on this study, you should contact [investigator name] as soon as possible. You can call him at telephone number [telephone number], including evenings and weekends.

What are my rights as a research subject?

If you choose to be in this study, you have the right to be treated with respect, including respect for your decision whether or not you wish to continue or stop being in the study. You are free to choose to stop being in the study at any time.

Choosing not to be in this study or to stop being in this study will not result in any penalty to you or loss of benefit to which you are entitled. Specifically, your choice not to be in this study will not negatively affect your right to any present or future medical treatment or present or future employment to which you are otherwise entitled.

Any new findings developed during the course of this research that may affect your willingness to continue in this study will be shared with you.

If you want to speak with someone who is not directly involved in this research, or have questions about your rights as a research subject, please contact the Office for the Protection of Research Subjects. You can call them at 312-503-9338.

What about my confidentiality?

We are committed to respect your privacy and to keep your personal information confidential.

When choosing to take part in this study, you are giving us the permission to use your personal health information that includes health information in your medical records and information that can identify you. For example, personal health information may include your name, address, phone number, or social security number.

Your health information we may collect and use for this research includes:

- All information in a medical record
- Results of physical examinations
- Medical history
- Lab tests
You will be tested for HIV. HIV is the term used for the virus that produces HIV infection and may ultimately lead to AIDS. Your blood will be taken to test for HIV.

The study doctor must report positive HIV tests to the Illinois Department of Public Health (IDPH). The IDPH keeps track of all persons in the state with positive HIV tests. The database that keeps track of this information is coded so that your name does not appear with your HIV status. You are given a unique identification number. This helps keep your name private.

You are also giving permission to the following groups of people to give information about you (described above) to the researchers for this study:

All current and previous health-care providers, including but not limited to [institution name].

Once we have the health information listed above, we may share some of this information with the following people. Please note that any research information shared with people outside of [institution name] will not contain your name, address, telephone or social security number, or any other direct personal identifier unless disclosure of the direct identifier is required by law [except that such information may be viewed by the Study sponsor and its partners or contractors at the Principal Investigators’ office].

- Authorized members of the [institution name] workforce, who may need to see your information, such as administrative staff members from the Office of Research, and members of the Institutional Review Board (a committee which is responsible for the ethical oversight of the study)
- Government agencies and public health authorities, such as the Food and Drug Administration (FDA), Center for Disease Control and the Department of Health and Human Services (DHHS)

Those persons who get your health information may not be required by Federal privacy laws (such as the Privacy Rule) to protect it. Some of those persons may be able to share your information with others without your separate permission.

The results of this study may also be used for teaching, publications, or presentations at scientific meetings. No personal identifiers will be used in any publication or presentation.

Please note that:

- You do not have to sign this consent form. If you do not, it will not affect your treatment by health-care providers, or the payment or enrollment in any health plans, or affect your eligibility for benefits. However, you will not be allowed to take part in this research study.
- You may change your mind and revoke (“take back”) this consent at any time. Even if you revoke this consent, the principal investigator may still use or share health information that was obtained about you before you revoked your consent as needed for the purpose of this study. To revoke your consent for the use of your health information, you must do so in writing to [investigator name and contact information].
- Unless you revoke your consent, it will not expire.
- If you revoke (“take back”) your consent, you will not be contacted for follow-up but your oocytes will be discarded.
In the Event of your Death (complete only if you are storing your oocytes at [institution name]): As a participant in this study, we must also ask you for your instructions about what to with your eggs if you were to die while we have your eggs in storage at our facility. Please place your initials next to option you would choose:

_______ If I die while my eggs are in storage at [institution name], please discard them.

_______ If I die while my eggs are in storage at [institution name], please donate them for an IRB-approved research project that does not include adding sperm to them (fertilization). I understand that if no such study can be found at that time, the oocytes (eggs) will be discarded.

_______ If I die while my eggs are in storage at [institution name], the individual named below can use these eggs for the purpose of producing a pregnancy in themselves or their partner but may not assign them to other individuals.

Name _____________________________________________________________
Address ___________________________________________________________
Phone Number: _____________________________________________________

Consent Summary:

I have read this consent form and the research study has been explained to me. I have been given time to ask questions, and have been told whom to contact if I have more questions. I agree to be in the research study described above.

A copy of this consent form will be provided to me after I sign it.

__________________________________________________ __________
Subject’s Name (printed) and Signature Date

__________________________________________________ __________
Name (printed) and Signature of Person Obtaining Consent Date
Appendix E
Letter Template: Provider Letter of Medical Necessity for Fertility Preservation Procedures

[Center Letterhead]
[Date]
[Insurance Provider] Review Unit
By fax: (999) 999–9999
Attn: Appeals

RE: Doe, Jane
D.O.B: 9-30-1984
[Insurance Provider] ID #: 9999999999
Group #: 99999

To Whom It May Concern:

[Insert patient name] is a 35-year-old with stage 4 colon cancer diagnosed in January 2009. The patient’s plan of care for this diagnosis includes chemotherapy and likely subsequent radiation. Many of these therapies that so effectively help increase survival have side effects that may cause the loss of fertility. The patient is not currently infertile but may be rendered sterile by the cancer treatment (a covered benefit under her plan).

In preparation for these treatments, the patient saw me in consultation to review fertility preservation options as per American Society of Clinical Oncology (ASCO) and American Society for Reproductive Medicine Guidelines (Attached).

After discussing the probable impact of the proposed cancer treatment on her fertility, we reviewed the range of options available.

(Include the appropriate paragraph)

1. After discussing the range of options available, based on my cancer treatment, age, diagnosis, and time available to the start of my cancer treatment, the decision was made to bank embryos. Embryo banking is the standard of care for fertility preservation for someone in my circumstance.
2. After discussing the range of options available, based on my cancer treatment, age, diagnosis, and time available to the start of my cancer treatment, the decision was made to bank eggs. Egg banking is the standard of care for fertility preservation for someone in my circumstance.

3. After discussing the range of options available, based on my cancer treatment, age, diagnosis, and time available to the start of my cancer treatment, the decision was made to perform a fertility sparing unilateral salpingo-oophorectomy and ovarian cryopreservation prior to beginning her treatment. Surgical intervention is the standard of care for obtaining ovarian tissue for cryopreservation.

**Note on Male Patients:** This can be customized to include a description of the male diagnosis if the male is the patient. Use of sperm banking, donor sperm, and/or assisted reproductive technologies to treat couples where the man has been rendered infertile by cancer treatment is NOT the same as infertility from other causes and often covered.

Therefore, we request that this treatment as well as related procedures and testing, which have been previously denied, be reconsidered for coverage for this patient.

As noted, the patient did not present with infertility but this fertility preservation treatment is essential to preserving fertility prior to beginning cancer treatment.

If you have any questions or need further information, please do not hesitate to contact me.

Sincerely,

[Physician name]
[Title]
[Institution]

**References**

Appendix F
Letter Template: Patient Letter of Appeal for Fertility Preservation Procedures Template

[Patient name]
[Patient Address]
[Date]
[Insurance Provider] Review Unit
By fax: (999) 999–9999
Attn: Appeals

RE: Doe, Jane
D.O.B: 9-30-1984
[Insurance Provider] ID #: 9999999999
Group #: 99999

To Whom It May Concern:

I am a 35-year-old with stage 4 colon cancer diagnosed in January 2009. My plan of care for this diagnosis includes chemotherapy and likely subsequent radiation. Many of the therapies that so effectively help increase survival have side effects that may cause the loss of fertility. I am not currently infertile but may be rendered sterile by the cancer treatment (a covered benefit under their plan).

In preparation for these treatments, I met with Dr. John Smith in consultation to review the possible impact of my cancer treatment on my fertility and my options for fertility preservation options as per American Society of Clinical Oncology (ASCO) and American Society for Reproductive Medicine Guidelines (see below). (Include the appropriate paragraph)

1. After discussing the range of options available, based on my cancer treatment, age, diagnosis, and time available to the start of my cancer treatment, the decision was made to bank embryos. Embryo banking is the standard of care for fertility preservation for someone in my circumstance.
2. After discussing the range of options available, based on my cancer treatment, age, diagnosis, and time available to the start of my cancer treatment, the decision was made to bank eggs. Egg banking is the standard of care for fertility preservation for someone in my circumstance.
3. After discussing the range of options available, based on my cancer treatment, age, diagnosis, and time available to the start of my cancer treatment, the decision was made to perform a fertility sparing unilateral salpingo-oophorectomy and ovarian cryopreservation prior to beginning her treatment. Surgical intervention is the standard of care for obtaining ovarian tissue for cryopreservation.

**Note on Male Patients:** This can be customized to include a description of the male diagnosis if the male is the patient. Use of sperm banking, donor sperm, and/or assisted reproductive technologies to treat couples where the man has been rendered infertile by cancer treatment is NOT the same as infertility from other causes and often covered.

Therefore, we request that this procedure as well as related procedures and testing previously denied for coverage be reconsidered.

As noted, I do not have infertility but this treatment was essential to preserving my fertility before my cancer treatment could begin.

If you have any questions or need further information, please do not hesitate to contact me or [insert physician name] at [insert treatment institution].

Sincerely,

[Patient name]

**References**

Appendix G

National Physicians Cooperative of the Oncofertility Consortium®

Section 4. FDA Registration: *Updating or Establishing your Registration*

Background:

1. All centers that are involved in processing or storing donor tissue or cells must register initially with FDA and update that registration every December.
2. We are treating the cryopreserved ovarian tissue as though it is from an anonymous donor of leukocyte tissue, in case the patient must use a gestational surrogate or other method to establish a pregnancy.
3. Therefore, all NPC centers performing ovarian tissue freezing must register with the FDA.
4. If you are already registered with the FDA, you must update your registration to include ovarian tissue.
5. If you already process donor tissues or cells such as donor eggs or embryos, bone marrow, etc., you should already be registered with the FDA and so you must just update that status.
6. Under FDA regulations, you must do this NO LATER than 5 days after beginning to freeze ovarian tissue.
7. You must update this registration every year in December.
How to Update/Establish your FDA Registration:

1. Locate your current FDA registration form, you will need the identification numbers on it. If you usually update this form online, you will also need your user name and password.

2. Go to http://www.fda.gov/Cber/tissue/tisreg.htm and login.
   - If you do not already have a user name and password, you can create a new account on this page.
   - If you already have an account but have forgotten your username and password, you can retrieve it on this page.
   - If you have never registered with the FDA, this is the place to do that too.

3. Once you have logged in you should go to Tissue Establishment Registration (Form FDA 3356). Your current form will be visible if you have one.

4. Update your FDA Registration to include ovarian tissue.
   - Insert ovarian tissue on one of the blank lines that begins on Line J.
   - You do not have to differentiate SIP, etc.
   - Check off all columns EXCEPT “test” (according to the definitions of these terms, you will not be testing; testing means that your lab is performing the serology itself). For definitions, refer to: http://www.access.gpo.gov/nara/cfr/waisidx_07/21cfr1271_07.html.

5. Registration must be established or updated NO LATER than 5 days after beginning to freeze ovarian tissues. If you have already missed this time frame, do it immediately.

6. Update this registration every year in December.
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