Investigational Oocyte Cryopreservation for Medical and Non Medical Indications

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Introduction

Oocyte cryopreservation is a procedure offered currently by commercial facilities 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. To this end, the Ethics Committees of the American Society for Reproductive Medicine (ASRM; 2005) and Committee on Gynecologic Practice of the American College of Obstetricians and Gynecologists (ACOG; 2008) have 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 (IRB).

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 the termination of gonadal function. 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 (Chen, 1986). Historically, post-thaw recovery of cryopreserved oocytes with subsequent fertilization and embryo transfer led to disappointing results (Porcu et al., 1999; Marina & Marina, 2003). An assessment of egg quality and an understanding on how it may be impacted based on demographics such as age and various chemotherapeutics is an essential next step in offering the technology.

Hundreds of babies have now been born worldwide following oocyte cryopreservation with reportedly no apparent increase in birth anomalies and the technique holds clinical and practical promise for many patient populations (Noyes, 2009). Consequently, it is appropriate to offer this emerging technology as an investigational procedure with appropriate informed consent, in a research setting and with the oversight of an institutional review board (IRB). Patients who are candidates for this investigational procedure are young women at risk of potential fertility loss due to medical reasons, such as chronic disease and / or treatments using radiation or chemotherapy, or a genetic disposition to infertility, and non medical reasons; unforeseen necessity to halt an IVF treatment cycle (adverse reactions to hormonal hyperstimulation, inappropriate endometrial receptivity or inability of the partner to produce a viable sperm sample), patients concerned with ethical and legal issues related to embryo cryopreservation, and women who fear their childbearing may be deferred to an advanced age.

We believe that the process of undergoing a fertility preservation consultation and/or undergoing an oocyte harvest in itself has a potential therapeutic benefit. Focusing on, “after” a patient’s cancer diagnosis has been suggested to have a positive effect on a

patient's psychosocial state. We wish to explore this theory with implementation of a follow-up interview and the validated Ferti-Qol questionnaire to assess a patient's quality of life. (Boivin et al, 2011) We also plan to assess egg quality in all of our patients to determine the impact of patient demographics and various chemotherapeutics.

Purpose & Objective

Purpose: This investigational study will permit patients to cryopreserve their oocytes, after first obtaining full written informed consent, for the purpose of potential future use under the oversight of the institutional review board, as specified by ASRM and ACOG current guidelines. The data obtained will also contribute to the knowledge base surrounding quality of life issues and fertility preservation in general, and oocyte cryopreservation in particular.

Objective: To determine the long term benefits, in particular impact on patient quality of life and clinical outcomes associated with the use of oocyte cryopreservation as an investigational option for women who wish to preserve their fertility, to assess egg quality and determine how patient demographics and various chemotherapeutics may affect it.

Hypothesis: Oocyte cryopreservation, which is currently investigational and requires IRB oversight, may be an effective and safe method of fertility preservation for women who may be facing the loss of future fertility due to medical or non medical reasons, with resulting future successful pregnancies. The process of fertility preservation will have a perceived improvement on patient quality of life. Egg quality will be impacted by patient age and alkylating chemotherapy but not other agents or demographic characteristics.

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 (Zeltzer, 1993). 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 (Patrizio et al., 2005). Women may also be at risk of experiencing fertility loss due to many non-oncological conditions such as endometriosis, diminished ovarian reserve / premature ovarian failure, chromosomal abnormalities (for example Turner's syndrome) and autoimmune disorders that may require treatment with gonadotoxic agents which can lead to premature ovarian failure. Women whose childbearing may be delayed may also desire fertility preservation. Finally, patients who are undergoing in vitro fertilization to treat infertility may experience situations that result in a halt in their treatment cycle due to problems such as adverse reactions to hormonal hyperstimulation, inappropriate endometrial receptivity or inability of the partner to produce a viable sperm sample on the day of their egg retrieval (e.g. partner unexpectedly out of town, unable to collect sample), or

who do not wish to inseminate all the oocytes collected that may result in the production of an excessive number of embryos, or who wish not to cryopreserve embryos for ethical reasons can utilize oocyte cryopreservation so that their retrieved oocytes are not wasted.

Chen reported the first successful attempt at cryopreserving and thawing a human oocyte – a twin pregnancy resulted after *in vitro* fertilization and embryo transfer (Chen, 1986). Progress in the field moved slowly for the next decade after murine data suggested that cryopreserved oocytes showed higher levels of chromosomal anomalies when compared with fresh oocytes (Johnson & Pickering, 1987). 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 (Gook et al., 1994). By 2004, 100 human babies had been born from cryopreserved oocytes. However, these infants were produced with great inefficiency (Stachecki & Cohen, 2004). For instance, Marina & Marina (2003) reported a 4% live birth rate from 99 frozen oocytes and results with larger sample sizes were even less impressive; 16 pregnancies from 1502 thawed oocytes (Porcu et al., 1999). Breakthroughs made by Italian researchers in optimizing freezing and thawing methods greatly improved pregnancy rates with mature human oocytes yielding pregnancy rates per thaw cycle of 10% which compares favorably with the natural fecundity rate of 20% per cycle (Coticchio et al., 2006; Paynter et al., 2005; Fabbri et al., 2001; Bianchi et al., 2007; Borini et al., 2004; Borini et al., 2006; Grifo and Noyes, 2009; Nagy et al., 2009). However, these results are still well below the pregnancy rates for fresh IVF cycles in women under the age of 37 years (45-55% live-birth rate).

There is little doubt that oocyte cryopreservation offers a reasonable fertility preservation option for cancer patients. However, it is imperative that follow-up data regarding the actual efficacy of this approach and the health of infants born following its use be prospectively generated, notwithstanding the difficulties inherent in the time frame over which patients might need to be followed.

The ASRM and ACOG practice guidelines stating that oocyte cryopreservation is still considered investigational and may only be offered with appropriate informed consent in a research setting with IRB oversight necessitate more rigorous investigation into the methods and consequences of oocyte cryopreservation in order for it to evolve from an experimental to a standard procedure,. 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. During our investigation we will explore egg quality and quality of life measures.

Lastly, the implementation of fertility preservation counseling and obtaining of oocytes for future use is believed to have a positive impact on a cancer patient's quality of life. We will obtain a structured fertility focused quality of life questionnaire and survey to assess one year after harvest the impact of the process. We will compare cancer patients to those patients undergoing oocyte cryopreservation for non-medical reasons.

Study Design

Research Design & 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 a potential medical or non medical risk of loss of fertility. Women wishing to preserve their oocytes using cryopreservation will be informed of the risk and limitations of the procedures involved in ovarian hyperstimulation, oocyte recovery, cryopreservation and subsequent viability after warming. Women who consent to the procedure will undergo standard controlled ovarian hyperstimulation (COH) and oocyte retrieval procedures currently in use for IVF. Following harvest all eggs obtained will be evaluated for degree of fragmentation and maturation status. The oocytes will be cryopreserved using kits of media and devices currently approved for use in the vitrification of fertilized eggs and embryos, and the cryopreserved oocytes will be stored for future patient use in a long term storage facility in Minnesota (Reprotech Ltd.). Patients with stored oocytes will be contacted annually to determine the outcome of any oocyte warming procedures (oocyte thawing, fertilization and embryo transfer).
We will obtain a structured fertility focused quality of life questionnaire (FertiQol) and survey to assess one year after harvest the impact of the process. We will compare cancer patients to those patients undergoing oocyte cryopreservation for non-medical reasons. FertiQol is scored based on the standards of the assessment tool in a quantitative manner. The structured interview will be assessed in a qualitative manner.
Duration: Until the completion of our investigational study and the patient outcome follow-up one year following oocyte harvest.

Location: Female patients will be identified and consented and all study procedures will be conducted through the Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, University of Illinois at Chicago (UIC).

Participant Selection and Enrollment

This study will enroll up to 50 women of reproductive age over 5 years at UIC, 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 who experience unforeseen events that halt the treatment cycle, such as adverse reactions to hormonal hyperstimulation, inappropriate endometrial receptivity, inability of the partner 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 discarded, as is standard procedure currently.(e.g., failed testicular sperm aspirations, inability to collect or unexpected need to be out of town or patients with ethical objections to freezing of embryos).

3. Women seeking oocyte cryopreservation for non medical reasons such as deferred 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 aged ≥18 and ≤ 40years.
- Women able to defer definitive cancer therapy for 21 to 30 days.
- Women 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.
- Women undergoing standard In Vitro Fertilization to treat infertility who experience unforeseen events that halts the treatment cycle.
- Women seeking oocyte cryopreservation for non medical reasons, such as deferred childbearing.
- Women who are carriers of BRCA mutations predisposing them to cancer.
- 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 ≥ 10 mIU/ml for patients having egg freezing for a medical indication
- Serum FSH ≥ 10 mIU/ml for patients having egg freezing for social reasons
- Women who upon undergoing psychological assessment are found to be unable to provide informed consent or are expected to be unable to cope with the rigor of the study)
- Patients with extensive disease whose therapy is deemed palliative by the medical oncologist.

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 non-covered 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 University of Illinois at Chicago Medical Center. Payment for this treatment will be the subject's responsibility.

Study Procedures

Following selection, potential subjects must be informed fully about the process involved and clinical outcomes that can be reasonably expected. Counseling by a qualified mental health professional will also be required. After obtaining informed consent, enrolled subjects will participate in the following:

Standard Oocyte Harvesting Procedure: Subjects will undergo controlled ovarian hyperstimulation according to established clinical protocols utilized in the In Vitro Fertilization Program at UIC. Briefly, they will be treated with variable dosages of injectable gonadotrophins over a period of 8 to 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 20 minutes 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.

Investigational Oocyte Cryopreservation: Oocyte cryopreservation will be carried out using the technique of vitrification, which has resulted in high oocyte survival, fertilization, pregnancy and implantation rates in case series reported in the literature (Oktay et al, 2006; Fadini et al, 2009; Cao et al, 2009, Smith et al, 2010). Oocytes will be cryopreserved using modifications of vitrification techniques described by Cao et al, 2009, Griffo and Noyes, 2009, Nagy et al, 2009 and Smith et al, 2010. **Prior to cryopreservation, when eggs are being evaluated by the embryologist; fragmentation score and maturation status will be formally evaluated and recorded.**

Standard Oocyte Storage: All cryopreserved oocytes will be transferred to Reprotech, Ltd. (RTL) in St. Paul, MN for storage and subsequent release. Reprotech, Ltd. is an FDA-compliant and American Association of Tissue Banks (AATB)-accredited long term storage facility for reproductive tissues. Patients will execute a separate storage agreement with Reprotech, Ltd which defines the length of storage, shipping requirements, infectious

disease screening and testing and disposition of the tissues in the event of the patient's death.

Standard Infectious Disease Screening and Testing: Banking and subsequent use of oocytes is regulated by the Food and Drug Administration (FDA). In order to be prepared for any future requirement, patients will be tested and screened for a number of infectious diseases prior to banking their oocytes. 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 a standard questionnaire for reproductive tissue donors. The testing that will be performed is mandated for donors of reproductive tissues and must be performed within 30 days of oocyte retrieval. The testing will be performed by LifeSource Blood Services, IL and Viromed Laboratories, MN. This way, the tissue could potentially be used by the patient herself, but it could also be suitable for future use in another individual (such as a gestational surrogate) if indicated by the patient's medical condition (e.g., 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 oocytes at Reprotech Ltd., St. Paul, MN, to permit any future testing requirements 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..

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.

Quality of Life Assessment
Specifically, they will agree to notify the investigators of any changes in their contact information. Study participants will be contacted on an annual basis using the "Investigational Oocyte Cropreservation Follow-up Call Script" to determine any subsequent attempts to utilize the stored oocytes for the purpose of initiating a pregnancy, along with the outcome of the attempt. An additional follow up email script will also be added to this research. In addition, patients will complete the Ferti-Qol questionnaire at the one year time point. 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 ten years following storage, whichever comes first. Patients will be assigned a research number and data will be de-identified. All de-identified data and the master code list will be stored in a locked file cabinet in a locked office and in a password-protected computer in a locked office by the PI and only the co-investigators and the PI will have access to the data.

The subject's participation in this study may involve the following risks;

Standard 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. In patients facing a cancer diagnosis, the use of fertility medication will cause a significant increase in two ovarian hormones, estrogen and progesterone, which could potentially worsen the prognosis for the cancer. However, in the case of most cancers the use of fertility drugs does not appear to worsen the chances for cure. Nevertheless, patients will need to discuss with their medical oncologist the pro's and con's of fertility drug use prior to undertaking oocyte cyropreservation.

Standard 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 1/1000. 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.

Standard 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 1/1000 cases.

Investigational Cryopreservation: Although care will be taken, damage to the retrieved 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 cancer treatments 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 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. 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 and co-investigators 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 & Monitoring: The principal investigator and co-investigators will monitor the subject records every 6 months for completeness and to determine whether any new information has become available, which may impact continuation of this study. Any adverse events or complaints will be reported to the IRB with the appropriate notification form.

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 the University of Illinois at Chicago's IRB.

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 University of Illinois at Chicago's 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 as well as those fearing loss of fertility due to deferred childbearing. 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. The psychosocial impacts of fertility preservation and oocyte harvest are not well established. At the conclusion of the study, we hope to have sufficient data to assess the long term benefits and outcomes of oocyte cryopreservation, including information regarding the future use of cryopreserved oocytes, their survival and viability, pregnancy and live birth outcomes, as well as quality of life assessment, so as to confidently offer the procedure as a safe and effective method of fertility preservation. We also hope to build on the current understanding of the factors that impact egg quality; another key aspect of success and thus patient consultation.

Anticipated Results & 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).

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