Booklet of IVF Adverse Effects and Risks

May 1, 2014

Table of Contents

INTRODUCTION

Reading and understanding this document is part of the process of giving informed consent. We encourage you to read this information carefully. You will be asked to make several decisions before starting your IVF-ET treatment cycle. We hope that this booklet helps you make these important decisions.

As part of our mission, our staff will inform you about your ART procedures and the potential risks associated with it. The following information offers a description of potential adverse effects and risks associated with assisted reproductive technology (ART) procedures offered at the Ottawa Fertility Centre (OFC). You should have received a copy of this booklet and have read this document prior to meeting with your physician to consent for treatment. Prior to the start of treatment, your physician will meet with you to review the most significant potential risks and adverse effects associated with your treatment. You will then be asked to sign the relevant consents and give direction to the OFC on how to use your eggs, sperm and embryos.

Patients are encouraged to ask questions about their procedures so that they fully understand their treatment choices, their chance of success and any potential harmful effects or risks associated with their treatment(s). If you have any questions, please ask any member of our staff.

PRE-TREATMENT RECOMMENDATIONS

During treatment patients getting their eggs retrieved should live a healthy lifestyle in order to optimize their chance of conceiving and having a healthy baby. In addition, the recommendations listed below should be followed.

- Take a prenatal vitamin containing folic acid 1 to 5 mg on a daily basis at least 3 months before your treatment is started to help reduce the chance that your baby will be born with a neural tube defect (spinal bifida).
- Avoid smoking before and during treatment; do not smoke during pregnancy.
- Avoid recreational drugs before or during treatment or when you are pregnant.
- Avoid alcohol during treatment and after pregnancy is established.
- Discuss the use of all prescription and over-the-counter medication (including herbal remedies) with your physician, our nurses or a pharmacist before starting a treatment cycle.
- Ensure that your routine general physical exam, Pap test and vaccination schedules are up to date with your family or OFC doctor.

If a sperm provider is involved in treatment, they should also:

- Avoid smoking before and during treatment.
- Avoid recreational drugs before or during treatment.
- Drink no more than 2 ounces of alcohol twice per week.
- Discuss the use of all prescription and over-the-counter medication (including herbal remedies) with your physician, our nurses or a pharmacist before a treatment cycle.

IN-VITRO FERTILIZATION

In-vitro fertilization (IVF) is a process in which an unfertilized egg is combined with washed semen in a Petri dish to achieve fertilization. The following information discusses relevant steps involved in the IVF process.

Ovarian Stimulation

To improve the chances of pregnancy, the ovaries are usually stimulated to produce multiple follicles (eggs). Various protocols and medications are used to stimulate egg production. Blood tests and ultrasound scans are used to monitor your response to the medications.

The following tables list the medications that may be required during your treatment cycle and some of their possible side effects or complications associated with each.

Any of the medications may be associated with allergic type reactions. Please make sure that you tell the doctor **and** the nurse if you have **any** allergies. Injectable medications may cause local irritation and redness.

From time to time, popular articles suggest that fertility medications may increase the risk of cancer, primarily breast and ovarian cancer. Medical researchers have been unable to prove any increased risk of ovarian or uterine cancer, but there appears to be a small increased risk of breast cancer in some patients who use injectable fertility drugs when they are under age 25. In those who used fertility medication in the past there is an increased risk (0.25%) of borderline ovarian cancer after the age of menopause. If you have any questions about a particular medication, please discuss it with your OFC physician or your pharmacist before you start the medication.

Fertility Medications

Medications	Use	Side Effects
Suprefact/Lupron/ Lupron Depot (GnRH Agonist)	Suprefact is a GnRH agonist used before starting and during actual ovarian stimulation. It is given by sub-cutaneous (SC) injection for Suprefact/Lupron and intra-muscular (IM) injection for Lupron Depot.	May cause hot flashes, mood swings, mild headaches, joint symptoms and altered sleep patterns. It is used to help prevent you from ovulating. Occasionally reddening, itching or swelling may occur at the injection sites. Suprefact contains **latex** which may cause an allergic reaction. Lupron has no latex and will be the replacement.
Cetrotide/Orgalutran (GnRH Antagonist)	This medication is used to prevent spontaneous ovulation, although 1-2% of patients will still ovulate on the drug and may result in a possible cancellation of a cycle. It is given by sub-cutaneous (SC) injection.	May cause headache, fatigue, dizziness and nausea. Transient and mild local reactions (redness, swelling and itching) may occur at the injection sites. Cetrotide is the first choice as it is latex free. Orgalutran contains latex which may cause an allergic reaction in some patients.
Gonadotropins (Gonal-F, Puregon, Repronex, Luveris)	These are fertility hormone injections that are used to recruit, stimulate and grow multiple ovarian follicles. They are given by sub-cutaneous (SC) injection.	May cause headache, fatigue, breast tenderness, abdominal distension, bloating and increase the probability of multiple pregnancies. The most serious complication of gonadotropins is the possibility of ovarian hyper-stimulation syndrome (OHSS) (see below). Mild irritation and swelling are possible at injection sites.

Medications	Use	Side Effects
HCG (Ovidrel, HCG-PPC)	hCG is given in the final phase of ovarian stimulation treatment. This injectable medication causes the final maturation of the eggs in IVF and ovulation in other treatments. It is given by sub-cutaneous (SC) injection.	May cause irritability and restlessness. It also has the same side effects as gonadotropins. HCG can precipitate OHSS.
Estrogen (Estrace, Estradot)	Estrogen orally or by patch may be used to prime the lining of the uterus for implantation of an embryo, to sustain the uterine lining or prevent premature egg maturation	May cause nausea, dizziness, headache, acne and breast tenderness. Estrogen may increase the risks of thromboembolic problems (blood clots, strokes) and long-term use may increase the risk of breast cancer.
Progesterone (Progesterone in Oil, Crinone Prometrium, Endometrin)	Progesterone is used to support an implanted embryo during the early phases of pregnancy.	May cause irritability, fatigue, dizziness and mood swings. Vaginal progesterone may produce vaginal irritation and discharge similar to a yeast infection. Prometrium contains some peanut oil and progesterone in oil may contain sesame oil that may cause allergic reactions in some susceptible individuals.

Other Medications

Medications	Use	Side Effects
Oral Contraceptives (Birth Control Pills)	You may be prescribed the oral contraceptive pill (OCP) to be taken to regulate the cycle before initiating IVF.	There are some studies suggesting that taking the OCP the month prior to your IVF cycle will help with the recruitment of follicles during your IVF cycle. Side effects are headache, nausea, breast tenderness, dizziness, and moodiness. The OCP has been associated with an increased incidence of serious complications such as heart attack, thromboembolism (blood clot) and stroke. You should not take the OCP if you smoke and are over age 35, have liver problems, or have a history of blood clots or migraines with aura.
Antibiotics (Clavulin, Metronidazole, Doxycycline, Ancef, Clindamycin, Cefoxitin, Erythromycin)	The antibiotics are used to prevent infections of the uterus and fallopian tubes before, during or after fertility investigations or treatment.	The primary risk with antibiotic administration is an allergic reaction possibly severe anaphylaxis. Alcohol should be avoided with Metronidazole. Infrequently, antibiotics may affect liver and kidney function or interact with other medications. Rare complications may include clostridium difficile: an infection of the bowels.

Medications	Use	Side Effects
Insulin Sensitizing Agents (Metformin)	Metformin is used as an "off label" medication to treat insulin resistance in those with polycystic ovary syndrome.	Metformin may cause gastrointestinal upset (nausea, diarrhea and vomiting); it may cause a metallic taste in your mouth. It can rarely cause lactic acidosis and should be used with caution in kidney or liver diseases. To date, it has not been shown to cause any congenital problems in babies, but this is being continually monitored.
Anti-estrogen Agents (Clomiphene,Tamoxifen, Letrozole)	Clomiphene and Tamoxifen are indicated in the treatment of patients who do not ovulate. Letrozole is also effective when these drugs fail, but it can only be used after you have signed a medical waiver. All of these drugs help by regulating hormonal secretion and by triggering increased production of your own FSH and LH that result in ovulation. The tablets are usually taken for 5 days of each cycle.	It may cause hot flashes, breast tenderness, headache, dizziness and nausea. Occasionally, temporary visual disturbances and abdominal discomfort/pain may occur.
Dexamethasone 0.5mg (Decadron)	Helps to increase the pool of follicles available to respond to ovarian stimulation. Take the medications with an evening meal.	May cause stomach upset, headache, dizziness, moodiness and agitation. Taken with food or milk will prevent stomach upset.
Medroxyprogesterone (Oral) (Provera)	Induces menstrual bleeding in those who are not pregnant and have not ovulated.	May cause, nausea, bloating, headache, breast tenderness, and moodiness.

Ovarian Hyper-Stimulation Syndrome (OHSS)

Ovarian hyper-stimulation syndrome (OHSS) is an exaggerated response to ovulation induction therapy used in assisted reproduction. It is usually associated with gonadotropin therapy (Puregon, Gonal-F, Menopur, Repronex, Luveris) and is only rarely observed with the use of Clomid/Serophene.

The incidence of moderate to severe OHSS is less than 1% at the Ottawa Fertility Centre.

Risk factors for developing OHSS:

- Young age
- Low body weight
- Polycystic ovarian syndrome (PCOS)
- A high number of developing follicles
- A previous episode of OHSS

Symptoms of OHSS:

OHSS is a self-limiting disorder that usually resolves spontaneously within several days, but may last for a longer period of time, especially when pregnancy occurs. Mild symptoms of OHSS are relatively common and include:

- Occasional lower abdominal discomfort
- Mild nausea

- Vomiting
- Diarrhea
- Abdominal swelling

Onset of symptoms:

Symptoms typically occur soon after ovulation or after oocyte retrieval, but signs and symptoms may be delayed. Progression of illness is recognized when symptoms persist or worsen and may include:

- Rapid weight gain (more than 2 lbs per day)
- Respiratory difficulty (shortness of breath)
- Decreased urinary output (urinating less)
- Abdominal bloating and discomfort

Medical management of OHSS:

Management of mild OHSS can be done on an outpatient basis usually requiring oral analgesics (e.g. Tylenol) and counselling regarding the signs and symptoms of progressing illness. Patients will be assessed by the IVF physician on call at the clinic as required.

Monitoring signs and symptoms of OHSS

The physicians and nurses of the Ottawa Fertility Centre actively monitor symptoms of OHSS in our patients. Patients are asked to call the clinic daily to report on signs and symptoms. Recommendations for the outpatient management of persistent OHSS include:

- Oral fluid intake of no less than 3 litres per day; sports drinks, fruit juices and water
- Strenuous physical activity and intercourse should be avoided
- Limited activity is suggested but strict bed rest is not needed and may increase the risks of blood clot formation in legs and lungs
- Weight should be recorded daily

Culdocentesis

If necessary, patients may require an out-patient procedure called culdocentesis. In this procedure, the physician will drain vaginally the excess fluid from your abdomen - a procedure similar to that of an egg retrieval. Risks associated with a culdocentesis include:

- Allergic reaction to pain medicine or antibiotics
- Complications from insertion of culdocentesis needle such as:
    - Direct needle injury to the blood vessel, bladder or bowel
    - Pelvic infection
- Intra-abdominal bleeding

Hospitalization

Hospitalization is relatively uncommon, but may be required based on the severity of symptoms, analgesic requirements and availability of support at home. There have been case reports of severe OHSS causing blood clots in the veins or lungs, stroke and rarely, death. Pregnant patients are at a higher risk of developing OHSS as the serum level of hCG may aggravate the condition. In an IVF cycle, it may be necessary to freeze all embryos and delay embryo transfer to a later cycle after symptoms have completely gone away. This approach should reduce the risk of developing severe OHSS. If this occurs, the freezing of embryos and later frozen/thawed embryo transfer will be recommended and will be at the patients' expense.

Egg Retrieval

Egg retrieval is a procedure in which a needle is inserted into the ovary to obtain the eggs - this is performed with ultrasound guidance. Patients are given Versed (a Valium-like medication) and an intravenous narcotic (Fentanyl) to make the egg retrieval process as comfortable as possible. Patients are also given an intravenous antibiotic prior to egg retrieval to reduce the risk of infection. Risks of egg retrieval include the following:

- Allergic reaction to pain medicine drugs or antibiotics
- Complications from insertion of egg retrieval needle such as:
  - Direct needle injury to the blood vessel, bladder or bowel
  - Pelvic infection including infection of a fallopian tube or ovary after egg retrieval
- Intra-abdominal bleeding

LABORATORY PROCEDURES

In-vitro Fertilization (IVF) and Intra-Cytoplasmic Sperm Injection (ICSI)

IVF is a process by which the egg is placed in a dish with thousands of washed sperm and natural fertilization takes place. There is, however, a risk that natural fertilization does not take place. IVF allows the natural selection process of fertilization to occur and causes no damage to the egg.

ICSI is a process by which a single sperm is injected into an egg under direct vision using a high-powered microscope. It is ideal for sperm with extremely low counts, abnormal morphology or decreased sperm motility. It can overcome some fertilization problems but does not guarantee that fertilization will occur. Disadvantages include a slightly higher chance of genetic abnormalities (refer to the Genetic Considerations section) and the potential for damage to eggs by the injection procedure.

Under most circumstances, approximately 70% of good eggs fertilize. However, the following risks exist:

- No fertilization due to poor quality sperm and/or eggs
- Abnormal fertilization of some or all of the eggs
- Bacterial contamination of the eggs - the bacteria may be from the semen, the vaginal secretions collected with the eggs, and rarely, from the laboratory products used to support the developing embryo
- Egg loss, due to some unforeseen event, such as equipment failure or loss during handling or manipulation

Embryo Culture

After fertilization, your embryos will develop in an IVF incubator in our laboratory for 2-5 days until they are transferred, frozen or discarded. During this “embryo culture” period, your embryos will receive specifically designed culture media to support their growth and development.

Risks associated with the embryo culture period include:

- Some or all of the embryos may develop abnormally or not at all
- Embryo loss, due to some unforeseen event, such as equipment failure or loss during handling or manipulation
- Bacterial contamination of the embryos for the same reasons as outlined above

Risks associated with culture media include:

- All culture media used for the eggs, embryos and sperm are purchased from reputable manufacturers who abide by all Canadian, U.S. and European practices of good manufacturing. Some of the media may contain small amounts of Human Albumin which is a blood protein.
- Human Albumin has been tested and found negative for HIV, Hepatitis B and C in accordance with current FDA/Health Canada regulations. However, all blood products carry a very low risk of being infectious.

Laser Assisted Hatching (AH)

Laser assisted hatching is a procedure in which a small hole is created in the shell of a developing day 3 embryo to allow easier hatching of the embryo once it has reached the blastocyst stage. It is rarely used. Possible risks of laser assisted hatching include:

- Potential for microorganisms to reach the embryo
- Potential damage to the embryo including loss of cells
- Potential for monozygotic (identical), and rarely, conjoined twins

Pre-Implantation Genetic Diagnostic/Screening (PGD/PGS):

PGD/PGS is a specialized procedure only recommended by physicians under certain circumstances. The information, risks and consent for this procedure are in a separate document.

EMBRYO TRANSFER

The day of your egg retrieval is counted as Day 0. Fertilization of your eggs is confirmed on Day 1 (the day after your retrieval). You will receive a phone call from a nurse confirming the number of fertilized eggs and the anticipated day of your transfer. An *embryo* transfer is typically performed on Day 3, and *blastocyst* transfer occurs on Day 5. Sometimes an embryologist and physician may decide to make your transfer on Day 2 or 4; these circumstances will be explained to you if you encounter this situation. Embryo/blastocyst transfer is a painless procedure not requiring any type of anesthesia, which consists in the placement of the embryo(s) into the uterus by means of a small plastic tube inserted through the cervix into the uterus. Patients are required to have a full bladder prior to transfer. Risks are few but include:

- Pelvic infection
- Multiple pregnancy
- Ectopic pregnancy - implantation of the transferred embryo(s) outside of the uterus (most commonly the fallopian tube)
- Failed catheterization and placement of your embryos. Although rare, difficult embryo transfers do occur. If a transfer is not possible, freezing of all embryos and subsequent re-evaluation of the patient would be necessary.

Blastocyst Transfer

Growing embryos in vitro to Day 5 (blastocyst stage) offers several theoretical advantages over the transfer of cleavage stage embryos (day 3). These include:

- Easier identification of those embryos with the highest chance of producing a pregnancy
- A decrease in the number of embryos transferred when identifying the best embryo
- Better synchronization between the embryo and the endometrium (lining)
- Higher pregnancy rate

Risks of agreeing to a blastocyst transfer include the following:

- Less than 1% chance that there will be no healthy embryo to transfer, despite the fact that there was at least one healthy embryo on day 4
- High multiple pregnancy rate if more than one blastocyst is transferred. Every effort should be made to perform single blastocyst transfer in good prognosis patients
- Fewer embryos to freeze at the blastocyst stage
- An increased risk of monozygotic (identical) twinning, which is a higher risk of multiple pregnancy

BARRIERS TO A SUCCESSFUL PREGNANCY

In addition to advanced egg provider's reproductive age, patients may experience other potential barriers to a successful treatment cycle, including:

- Low or excessive response to fertility medications
- Unable to access ovaries for egg retrieval
- No eggs found at egg retrieval
- Eggs are found to be abnormal at the time of egg retrieval
- The inability of the sperm provider to produce a semen sample or to give a sperm sample of sufficient quality or quantity
- Failure of fertilization
- Abnormal embryo development
- Difficult or failed embryo transfer
- Failure of implantation
- Unforeseen events resulting in unfavourable laboratory conditions. These events may include hazardous or catastrophic weather, equipment malfunction or failure, infection of either partner, contamination of laboratory products or human error.
- Loss or damage to eggs or embryos

PREGNANCY AFTER ASSISTED REPRODUCTION TREATMENT

Spontaneously conceived pregnancies in untreated patients with a history of infertility may be at increased risk for obstetrical complications and perinatal mortality when compared to those with no fertility issues. Similarly, even singleton pregnancies conceived with ovarian stimulation, with or without intrauterine insemination or IVF/ICSI, are at increased risk of obstetrical complications such as high blood pressure, preterm birth, low birth weight and perinatal mortality.

Miscarriage

A spontaneous abortion can occur with any infertility treatment. The risk of miscarriage increases with advancing maternal age. IVF does not increase the risk of miscarriage. Most miscarriages are associated with lower abdominal cramping and bleeding, but do not necessarily require treatment. In some cases, complete removal of the pregnancy tissue must be accomplished by a surgical procedure called a dilatation and curettage (D&C).

Tubal (Ectopic) Pregnancy

An ectopic pregnancy may develop as a result of infertility treatment. The majority of ectopic pregnancies occur in the fallopian tube. If an ectopic pregnancy is diagnosed, you may require surgical treatment that may involve the removal of the involved fallopian tube. Medical treatment with a drug called Methotrexate may be an option in selected cases.

Ovarian Torsion

In less than 1% of cases, a fluid filled cyst(s) in the ovary can cause the ovary to twist on itself. This can decrease the blood supply to the ovary and result in significant lower abdominal pain. Surgery may be required to untwist or possibly remove the ovary.

Genetic Considerations

Couples who suffer from infertility have a higher incidence of congenital birth defects and genetic abnormalities than couples who do not have infertility.

Chromosomal Abnormalities

For some sperm providers, their low sperm count may be due to conditions present since birth such as abnormal chromosomes (47 XXY or microdeletion of some genes in the Y chromosome) or gene mutations (cystic fibrosis). In these circumstances, this may lead to an increased risk of problems associated with certain ART procedures. For example, infants have been born to these individuals with a microdeletion of the Y chromosome following ICSI. These children have the same microdeletion as their parents and may subsequently suffer from infertility.

Chromosomal testing and carrier status testing can be offered to appropriate couples according to the clinical situation, family history or the wishes of the patient(s).

Imprinting Disorders

There is a suggestion that rare genetic conditions may be associated with ART through an abnormal process of gene expression called imprinting. Imprinting disorders can cause rare conditions, examples of which are Beckwith-Wiedemann Syndrome, Angelman Syndrome, retinoblastoma and other childhood cancers. It is estimated that imprinting disorders occur in less than 1 in 1000 ART live births and further studies are needed to determine if there is any association between imprinting-related disorders and ART. Imprinting disorders may be due to the infertility problems of the couple.

Although every effort is made at the Ottawa Fertility Centre to ensure a healthy pregnancy, no guarantees can be made for a normal baby. Patients must understand, similar to any pregnancy, that there is a possibility of giving birth to a child or children with a congenital or genetic abnormality, but that possibility is higher in infertile persons and among those who receive fertility treatment.

Multiple Pregnancies

The chances of a multiple pregnancy are increased with the use of all fertility medications and reproductive procedures (such as super ovulation with IUI and IVF/ICSI). Complications of multiple pregnancies may include but are not limited to the following:

- Complications for the pregnant person: pre-eclampsia (high blood pressure), gestational diabetes, placenta previa (abnormal position of the placenta), placental abruption (separation), post-partum (after delivery) hemorrhage (excessive bleeding), operative deliveries (like a Cesarean Section) and post partum depression. There is also increased parental stress and decreased quality of life.

- Complications for the infants: increased risk of dying before, during or after delivery, fetal growth restriction (reduced growth in the fetus), pre-term birth (consequences may include cerebral bleeding – bleeding into the brain, retinopathy – damage to the eyes, bronchopulmonary dysplasia – severe breathing problems and necrotizing enterocolitis-bowel damage) and cognitive delays – delayed ability to do simple tasks. Following birth, multiples suffer from increased rates of learning difficulties and poor growth in infancy. In addition, blastocyst transfer increases the risk of monozygotic (identical) twinning which is a higher risk type of twin pregnancy with even poorer outcomes than non-identical twins.

It is important to note that the risks to the babies due to multiple pregnancies far exceed the increased risk of genetic or congenital abnormalities outlined previously. Furthermore, this is not only true for triplets and higher-order multiples, but also for twins. At the Ottawa Fertility Centre, every effort is made to reduce the likelihood of multiple pregnancies by offering single embryo transfer when appropriate.

Our goal is to help you build your family – one healthy baby at a time.

The table below lists the **risks to the babies** of a twin pregnancy compared to pregnancy with one baby (singleton).

Risks of Twins Compared to Risk of Singleton Pregnancies			
	Singletons	**Twins**	**Increased risk with twins**
Low birth weight less than 5.5 lbs	5.9 %	53.1 %	9 times ↑ risk
Very low birth weight less than 3.3 lbs	0.7 %	8.2 %	10 times ↑ risk
Prematurity less than 32 weeks	3.1 %	11.0 %	3-4 times ↑ risk
Prematurity less than 28 weeks	0.3 %	3.7 %	10 times ↑ risk
Still birth (death before birth)	0.4 %	1.4 %	3 times ↑ risk
Neonatal death (death in 1st month of life)	0.3 %	2.3 %	8 times ↑ risk
Infant death (death in 1st year of life)	0.9 %	4.9 %	5 times ↑ risk
Malformation rate	2.7 %	3.5 %	1.5 times ↑ risk
Severe handicap rate	2.0 %	3.4 %	1.5 times ↑ risk

The average length of pregnancy in a twin pregnancy is 36 weeks. Full term singleton pregnancies are 40 weeks. Since this is only an average, many twin pregnancies are delivered much earlier than 36 weeks. Because twins are often born prematurely, the risk to the long-term health of these infants is increased. This includes a 7 times increased risk of cerebral palsy. NICU (Intensive Care) hospital care is seen in more than 25% of twins and in more than 75% of triplet pregnancies. Twin pregnancies also pose a **greater risk for the mother** during the pregnancy as shown in the table below. Other risks include premature labour sometimes requiring prolonged bed rest during the pregnancy.

Maternal Risks in Twin Pregnancy	
Hypertension (high blood pressure)	2-3 x higher risk
Heavy bleeding after delivery	3-4.5 x higher risk
Cesarean section	3 x higher risk
Maternal death (rare even with twins)	2-3 x higher risk

CRYOPRESERVATION AND STORAGE OF EMBRYOS

Overview

Approximately thirty percent (30%) of patients will have extra, good quality embryos or blastocysts remaining after their fresh embryo transfer. Freezing extra embryos is a safe procedure that gives some couples the opportunity for another attempt for embryo transfer without the need of ovarian stimulation and egg retrieval. Freezing embryos, however, has some associated risks to it and may bring up an ethical dilemma for some patients as to how to deal with their frozen embryos in the future. Potential risks of freezing embryos include:

- Mechanical failure or other catastrophic event leading to the loss of embryos
- Failure of embryos to survive freezing and thawing
- Psychological effects (dilemma of what to do with extra embryos)
- Theoretical risk of birth defects in the infant (similar to that of fresh embryos)
- Abnormal-appearing or poor quality embryos are not frozen

The Ottawa Fertility Centre uses a cryopreservation method called ***vitrification*** to preserve your extra embryos. Before vitrification, the embryos are placed in a solution that removes some of the water from their cells. Vitrification per se is a specialized freezing technique by which the embryos are cryopreserved using an ultra-rapid cooling technique, turning them into a glassy solid instead of ice, and by doing so avoiding ice-crystal formation which can be very detrimental to their survival. The embryos are then stored at a very low temperature (-196°C). When they are warmed, the embryos are put in a series of different fluid solutions to reverse the dehydration and then they are examined to see if they are suitable for replacement into your uterus. Sometimes embryos will not survive the vitrification or warming.

Benefits and Risks

The benefit of choosing to freeze extra embryos is that, in the future, if you wish to have another embryo implanted, you may do so without the need for drug stimulation (if you ovulate regularly) or another egg retrieval, and the associated inconvenience, cost and risk. Since embryos are preserved, it is also advisable to replace fewer fresh embryos at one time, reducing the risk of a multiple pregnancy, though such a risk may still exist.

The probabilities of establishing an IVF pregnancy through freezing cannot be guaranteed and there are some risks. Approximately 12 percent (12%) of embryos do not survive the freeze/thaw cycle. It is possible that none of your embryos will survive the freezing process and if this is the case, we will not know this until the embryos have been thawed. Another major risk of transferring frozen/thawed embryos is their failure to implant and result in a pregnancy.

The live birth rate per frozen embryo transferred into a patient's uterus has been determined to be approximately equal to the rate for a fresh (not previously frozen) embryo transfer. The risk of genetic defects is equal to fresh embryo transfer.

As with any technique requiring mechanical support systems, laboratory equipment failures can occur, as can unforeseen situations that result in the loss of embryos, despite the best efforts of the staff.

You also understand that the Ottawa Fertility Centre is not obliged to proceed with the transfer of any frozen embryos in the event that the Centre considers the risks associated with doing so outweigh its potential benefits.

Legal Issues affecting Choices

Legal principles and requirements around embryo freezing have not been firmly established.

Ownership of Embryos

Based on the currently accepted principles regarding legal ownership of human embryos, we have been advised that each embryo resulting from the fertilization of the patient's egg shall be considered the property of the person/couple for whom the embryos were created. It is the person/couple's responsibility to seek legal advice where legal ownership may be in question.

Disposition of Embryos

As the owner(s) of any and all such embryos, the consent of the patient (and their partner, if there is one) will be required concerning the disposition of any and all such embryos. Certain uses or dispositions may also require approval by the Ottawa Fertility Centre.

We require that you specifically provide for the disposition of any embryos that are not used for the purpose of attempting to initiate a pregnancy, in case of your death or incapacitation.

You should understand that you (and your partner, if there is one) retain the right to change your decision in this regard at any future time by providing the Ottawa Fertility Centre with written notice to this effect. Refer to the section below on Consent to Use Regulations and Withdraw of Consent.

The ultimate disposition of your marital status or other events interfering with the fulfillment of your present intentions, are subject to applicable law and court decisions (such as a decree of dissolution) and affect the ownership or control of the embryos.

Annual renewal

You (meaning you and your partner, if there is one) understand that a renewal of your decision regarding the disposition of stored embryos must be made annually. Every twelve (12) months from the date of freezing of your embryos, the Ottawa Fertility Centre will contact you by mail to renew your written instructions concerning the disposition of your frozen embryos and the payment of annual storage charges. The Ottawa Fertility Centre will make reasonable attempts to contact you, but it is your responsibility to keep the Ottawa Fertility Centre informed of your current address and telephone number. If you do not reply, your embryos will be discarded unless direction for their use has been provided.

ASSISTED HUMAN REPRODUCTION ACT - SECTION 8 (CONSENT TO USE) REGULATIONS

The information provided in this section is an excerpt from the Assisted Human Reproduction Act Section 8 (Consent to use) Regulations - Guidance Document prepared by Assisted Human Reproduction Canada, 30 October 2007.

The Assisted Human Reproduction Act (AHR Act) seeks to protect the health and safety of Canadians using AHR technologies to help them build their families by regulating AHR activities and related research and prohibiting unacceptable activities such as human cloning. Section 8 of the AHR Act requires that written consent be obtained before using a person's reproductive material (sperm or eggs) to create an embryo or before using an *in vitro* embryo for any purpose. The Regulations also specify that the written consent to use is signed by the donor and attested to by a witness.

Definitions

Donor: In relation to reproductive material, "donor" means the individual from whose body the sperm or eggs were obtained, even if it is for the individual's own reproductive use. In relation to an *in vitro* embryo, "donor" means the individual or couple for whose reproductive use the *in vitro* embryo has been created, regardless of the source of the material used to create the embryos.

Common-law partner: The individual who, at the relevant times, is cohabiting with the donor in a conjugal relationship of at least one year prior to the relevant time.

Third party: In relation to reproductive material, "third party" means an individual or couple other than the donor of the reproductive material or the spouse/common-law partner of the donor. In relation to an *in vitro* embryo, "third party means an individual or couple (spouses or common-law partners) other than the individual or couple from whom the *in vitro* embryo has been created.

Reproductive material: Sperm or eggs obtained for the purpose of creating an embryo (including an *in vitro* embryo).

***In Vitro* embryo:** An embryo that exists outside the body of a human being.

When is consent to use needed?

A donor's consent to use is required before their sperm or eggs can be used to create an embryo, or before an *in vitro* embryo created for them can be used for any purpose, including:

- their own reproductive use;
- the reproductive use of a third party;
- creating an embryo for improving or providing instruction in assisted reproduction procedures, including laboratory and clinical procedures;
- the use of in vitro embryos for research purposes (in which case, the goal of the research project must be stated in the consent to use the embryos);
- the reproductive use of the donor's spouse or common-law partner following the donor's death.

The consent to the use of reproductive material or *in vitro* embryos would normally be provided before or at the time the reproductive material is first obtained or an *in vitro* embryo is to be created. However, such consent to use could be provided later, as long as it is given by the donor before the actual use. For example, an individual or couple whose own reproductive use *in vitro* embryos were created (i.e., the donor(s)) could subsequently decide to donate excess frozen *in vitro* embryos not needed for their own reproductive use to a third party for the third party's reproductive use. In such case, although consent to use the *in vitro* embryos would have previously been provided by the donor(s) for their own reproductive use, consent to the use of the excess *in vitro* embryos for a third party's reproductive use could be given by the donor(s) before or after the *in vitro* embryos were created provided such consent is given by the donor(s) prior to the embryos being used for the third party's reproductive use.

The consent to use the reproductive material or *in vitro* embryos for the purpose(s) stated need only be obtained once. There is no need for a new section 8 consent to use prior to each donation or use at a clinic, physician's office, or another facility. For example, if a donor has given written consent to the use of their sperm for their own reproductive use, provided such consent has not been withdrawn, subsequent donations or use of their sperm for their own reproductive use does not require a new consent to use.

Who must provide consent to use?

It is the donor who must provide consent to use under section 8. In the case of consent to use reproductive material to create an embryo, consent is needed from the person whose body the material was obtained, even if it is for the individual's own reproductive use. In the case of consent to use an *in vitro* embryo for any purpose, consent is needed from the individual or couple for whom the *in vitro* embryo has been created, regardless of the source of the material used to create the embryo. If sperm or eggs are donated by an individual and used to create *in vitro* embryos for the reproductive use of another individual, and there are embryos in excess of the other individual's reproductive needs, the other individual for whom the *in vitro* embryos were created becomes the donor in respect of those excess embryos and their consent to use is required for use of the excess embryos. If they consent to any of the excess embryos being used to provide instruction in AHR, improving AHR procedures or other research, the individual who provided the sperm or eggs to create the *in vitro* embryo (i.e., the donor of the reproductive material) must also have provided consent for such use.

There may be circumstances where an individual may wish to give their consent to the use of their reproductive material after their death. If such sperm or eggs are used to create an *in vitro* embryo for the reproductive use of an individual who, at the time of the death, is the deceased's spouse or common-law partner, then the use of any excess embryos requires the consent to use of the surviving spouse or partner. If the surviving spouse or partner consents to the excess embryos being used to provide instruction in AHR, improving AHR procedures or other research, then the deceased must also have provided consent for such use(s) prior to death.

In situations involving the creation and use of *in vitro* embryos by married couples or common-law partners for their own reproductive use, there must be compatible consent to use from both spouses or partners for the use of those embryos, regardless of the source of the reproductive material used to create the embryos. However, should the couple separate or divorce prior to the use of the *in vitro* embryo and the *in vitro* embryo was created from reproductive material of only one of the individuals in the couple, only that individual needs to have consented to the use being made of the embryo.

Who must obtain the consent to use?

Anyone intending to use sperm or eggs for the purpose of creating an embryo and/or using *in vitro* embryos for any purpose must ensure they have the necessary written consent to use the material or embryo before using it. This includes AHR clinics, physicians and others that:

- provide AHR procedures, such as intrauterine insemination (including with partner's or other known sperm);
- provide AHR services, such as *in vitro* fertilization, (including creating an *in vitro* embryo with a couple's own reproductive material);
- remove sperm or eggs after a person's death for the reproductive use of the deceased's spouse or common-law partner;
- use sperm or eggs to create an embryo for improving AHR procedures or providing instruction in AHR procedures;
- use *in vitro* embryos for any purpose, including research.

It does not matter who actually obtains the consent to use or where the consent to use document is signed and witnessed (for example, at home, a lawyer's office, the location where the donation was originally made or the clinic or physician that will actually be using the reproductive material or *in vitro* embryo), however, the person using the material to create an embryo or using an *in vitro* embryo for any purpose must have received the consent to use prior to the actual use.

What are the requirements for withdrawing consent to use?

- the withdrawal must be in writing;
- the written withdrawal must be provided to the person (i.e., the clinic, physician or researcher) who will be using the reproductive material or *in vitro* embryo. In most cases, donors will submit the written withdrawal to the clinic, physician or researcher where the donation was made, however, such withdrawal does not become effective until such time as it is received by the person intending to use the reproductive material;
- in the case of consent to use reproductive material to create an embryo for one's own reproductive use or that of their spouse or common-law partner, improving AHR procedures or providing instruction in AHR procedures, or to the use of an *in vitro* embryo for the donor's own reproductive use, notice of withdrawal must be provided before the use of the material or *in vitro* embryo;
- in the case of consent to use reproductive material or an *in vitro* embryo for the reproductive use of a third party, a notice of withdrawal must be provided before the third party has acknowledged in writing that the material or embryo has been designated for their reproductive use;
- in the case of consent to use an *in vitro* embryo for improving AHR procedures, providing instruction in AHR procedures or research, the withdrawal must be made before the later of: the person conducting the activity has acknowledged in writing the designation of the *in vitro* embryo for that activity or the person conducting the activity has begun the thawing of the *in vitro* embryo for that activity.

If the donor of an in vitro embryo is a married couple or common-law partner, the consent to use must be compatible and consent to use may be withdrawn by either spouse or common-law partner, regardless of the source of the reproductive material used to create the embryo, in accordance with the requirements noted above. However, if the in vitro embryo was created from reproductive material of only one of the individuals in the couple, should the couple separate or divorce, then only that individual is entitled to withdraw the consent to use.

GENERAL CONSIDERATIONS

Given that you decide to voluntarily participate in the In Vitro Fertilization Program you are still free to withdraw your consent and to discontinue participation at any time without prejudice. However, if pregnancy occurs, follow-up by the OFC is important and will continue from time to time throughout the pregnancy unless you notify the OFC of your objections to the follow-up. Knowing the outcomes of fertility treatment, and any related pregnancy and birth, enable the OFC to make informed practice decisions based on actual outcomes. The OFC is able to better serve you and other patients in terms of what services to provide and how to improve those services. The information may also be used for teaching, research and publication in professional journals. In all those situations, names or other identifying information will not be disclosed.

The references in this document to the Ottawa Fertility Centre shall include such additional qualified physicians or scientists as are added to or assume responsibility for its activities from time to time and any assignee or their successor at the Ottawa Fertility Centre.