INTRODUCTION

The following information offers a description for potential adverse effects and risks of In Vitro Fertilization (IVF) offered at the Regional Fertility Program. Our staff will educate you about your IVF procedures and the potential risks associated with it. Patients are encouraged to ask questions about their procedures so that they fully understand their treatment choices, their chance of success and any potentially harmful effects or risks associated with their treatment(s).

Pre-treatment Recommendations

During treatment a woman should avoid those activities, behaviours, and medications that could reduce her chance of conceiving and having a healthy baby. In addition, the recommendations listed below should be followed.

1. A prenatal vitamin containing folic acid 1 to 5 mg should be taken daily for 6 weeks prior to when your treatment is started. This will reduce the chance that your baby will be born with a particular type of birth defect called neural tube defect (spinal bifida).
2. Smoking must be avoided before and during treatment. You should not smoke during pregnancy.
3. Recreational drugs and alcohol should be avoided before and during treatment, and when you are pregnant.
4. The use of all prescription and over-the-counter medications (including herbal remedies) should be discussed with your physician or our pharmacist before starting a treatment cycle.
5. Ensure that your annual general physical exam and Pap test are completed with your family doctor prior to starting treatment. Also be sure that your vaccination schedules are up to date.

Barriers to Successful Pregnancy

Maternal age has a profound effect on the chances of a successful pregnancy. As a woman becomes older, her chance of pregnancy decreases and her chance of miscarriage increases. With a woman’s advancing age, there is an associated increased risk of genetically abnormal children in general, but particularly with Trisomy 21 (Down Syndrome).

Obesity is also associated with a poorer outcome after IVF. Patients with elevated body mass index (BMI) may experience reduced response to fertility medications, difficulty with follicular monitoring and an inability to access the ovaries for oocyte retrieval. Also, obesity is associated with increased risk of adverse obstetrical outcomes including gestational diabetes, hypertension, stillbirth and the need for operative delivery. Due to technical challenges, as well as increased medical, anaesthetic and operative risks, patients with a BMI \( \geq 40 \) are generally not able to undergo IVF at our facility.

The following are potential barriers to successful treatment that may be experienced by all patients:

- Low or excessive response to fertility medications
- Inability to access ovaries for egg retrieval
Risks associated with IVF

• No eggs or only abnormal eggs are found at egg retrieval
• Inability of the male partner to produce a semen sample or to produce a sperm sample of sufficient quality or quantity for use – if the male partner is concerned he cannot produce a semen sample on the day of egg retrieval he may choose to freeze a sample prior to initiation of the IVF cycle.
• Failure of fertilization
• Abnormal embryo development
• 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

IN VITRO FERTILIZATION (IVF)

In vitro fertilization is a process where unfertilized eggs are retrieved from the female partner and combined with washed semen in a small dish to achieve fertilization. It is divided into several steps and potential risks will be discussed for each step.

Step 1. OVARIAN STIMULATION

To improve chances of pregnancy, the ovaries are stimulated to produce multiple follicles in which the eggs mature. Various protocols and medications are used to stimulate follicle growth. Blood tests and ultrasounds are used to monitor your response to the medications. Response to medications may be inadequate or excessive, necessitating cancellation of the IVF cycle prior to egg retrieval. Even normal ultrasounds and blood tests do not guarantee that eggs will be retrieved.

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

a. Fertility Medications

Suprefact®/Lupron® (GnRH Agonist)

Suprefact® is a GnRH agonist used before starting actual ovarian stimulation. It is used to help prevent you from ovulating. It is given by nasal spray and may cause nasal irritation, hot flashes, mood swings, mild headaches, joint symptoms and altered sleep patterns. It is occasionally given by injection.

Orgalutron®/Cetrotide® (GnRH Antagonist)

This medication is also used to prevent spontaneous ovulation, although 1-2% of patients will still ovulate resulting in a possible cancellation of a cycle. It is given by injection.
Risks associated with IVF

Clomiphene Citrate (Clomid/Serophene®)

Clomiphene citrate is an oral medication used to stimulate ovulation and is taken early in the cycle. It may be associated with headaches, nausea, hot flashes or breast discomfort. More significant, but rare side effects include visual disturbance, liver problems, ovarian cyst formation or ovarian hyperstimulation syndrome. Clomiphene is associated with a 5-7% incidence of twins, and less commonly (1%), higher order multiple pregnancies (triplets or more).

Letrazole (Femara®)

Letrazole is an oral medication used in the treatment of some breast cancers. However, it is also commonly used in the treatment of infertility and particularly in women with breast cancer undergoing ovarian stimulation for IVF. In 2005, the manufacturer of letrazole stated that letrazole should not be used in women trying to conceive due to risk of fetal malformations. This statement was based on a report of 150 babies born to women using letrazole. Since then many large, good-quality studies have demonstrated that there is no increase risk of fetal malformations with letrazole compared to the general population. In 2008, MotherRisk, a program based at Sick Kids Hospital which monitors drug safety in pregnancy, issued the following statement: “Based on the aforementioned findings, the use of letrazole to induce ovulation does not appear to be associated with an apparent increased risk of major congenital malformations in humans.” Side effects include bloating, moodiness, dizziness, fatigue, headache and occasionally, hot flashes and visual disturbances. Rarely, letrazole may cause significant ovarian enlargement and ovarian hyperstimulation syndrome. Letrazole is associated with a 5-7% incidence of multiples (mostly twins), and less commonly, higher order multiples.

Gonadotropins (Puregon®, Gonal-F®, Menopur®, Luveris®)

These fertility hormone injections are used to recruit, grow and mature multiple ovarian follicles. They may cause abdominal distension, bloating and increase the probability of multiple pregnancies. The most serious complication of gonadotropins is the possibility of ovarian hyperstimulation syndrome (OHSS) discussed below.

Human chorionic gonadotropin (hCG, Ovidrel®, Pregnyl®)

This injectable medication causes final maturation of the egg and ovulation. It has the same side effects as the gonadotropins. It may also be used to help support pregnancy and may increase the risk of OHSS when used in this manner.

Estrogen (Estrace®/Estradot®)

Estrogen by patch or orally/vaginally may be used to prime the lining of the uterus for implantation of an embryo. Estrogen may increase the risks of thromboembolism (blood clots, strokes) and long-term use may increase the risk of breast cancer.

Progesterone (Prometrium®, Endometrin®, Crinone®, Progesterone in oil)

Progesterone is used to support the uterine lining to facilitate implantation of an embryo. Vaginal progesterone may produce vaginal irritation and discharge similar to a yeast infection.
Risks associated with IVF

Prometrium® may contain small amounts of soy, sunflower and peanut oil and may cause allergic reactions in susceptible individuals.

b. Other Medications

Oral Contraceptives (Birth Control Pills)

You may be prescribed the oral contraceptive pill (OCP) to be taken the cycle before initiating IVF. There are some studies suggesting that taking the OCP the month prior to your IVF cycle will help with recruitment of follicles during your IVF cycle. 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, and have a history of blood clots or migraines with aura.

Antibiotics

The primary risk with antibiotic administration is stomach upset, nausea and diarrhea. Allergic reactions, including anaphylaxis, are possible. Infrequently, antibiotics may affect liver and kidney function or interact with other medications. Rare complications may include clostridium difficile, an infection of the bowel, and fatal cardiac arrhythmia with azithromycin.

Insulin Sensitizing Agents (Metformin®)

Metformin® is used as an “off label” medication to treat insulin resistance in some women with polycystic ovaries. It may cause gastrointestinal upset (nausea, diarrhea and vomiting). 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 birth defects in babies.

Corticosteroid (Medrol®)

Medrol® is taken by the woman prior to and after embryo transfer when assisted hatching is required. Risks of this medication include stomach upset and possibly stomach ulcers and bleeding from those ulcers. Blood sugar levels are often increased.

All of the above 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, news articles in the popular press 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 invasive ovarian or uterine cancer or breast cancer, but there appears to be a small increased risk of borderline ovarian tumors in some women who use fertility medications.
Risks associated with IVF

c. Ovarian Hyperstimulation Syndrome (OHSS)

Ovarian hyperstimulation syndrome (OHSS) is an exaggerated response to ovarian stimulation medication. It is usually associated with injectable fertility medication (Puregon® Gonal-F®, Menopur®, Luveris®) and is only rarely observed with the use of Clomid/Serophene®.

The following factors increase the risk for developing OHSS:

- Young age
- Low body weight
- Polycystic ovarian syndrome (PCOS) or polycystic ovaries
- High antral follicle count
- Higher dose of gonadotropins
- High level or rapidly rising blood estrogen level
- Previous episode of OHSS

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

- Occasional lower abdominal discomfort and bloating
- Mild nausea and vomiting
- Diarrhea
- Abdominal swelling

Onset of symptoms typically occurs soon after egg retrieval but signs and symptoms may be delayed up to two weeks. Progression of illness is usually associated with pregnancy and becomes evident when symptoms persist or worsen and may include:

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

Management of mild OHSS is usually performed on an outpatient basis, and generally consists of taking Gravol® for nausea, oral pain killers (Tylenol®) and careful observation.

Recommendations for the outpatient management of persistent OHSS include:

- Adequate oral fluid intake; Sports drinks or fruit juices are preferable to other beverages.
- Avoidance of strenuous physical activity and intercourse.
- Limitation of activity is suggested but strict bed rest is not needed and in fact may increase the risks of blood clots.
- Weight should be recorded daily.
Risks associated with IVF

Hospitalization is relatively uncommon but may be required depending 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 very rarely, death.

Pregnant patients are at a higher risk of developing OHSS as the presence of hCG from the pregnancy aggravates and prolongs symptoms.

In patients at high risk of OHSS, it may be necessary to consider freezing all embryos and thereby delaying the embryo transfer to allow symptoms to resolve and reduce the risk of OHSS. Although pregnancy rates in frozen embryo transfer cycles may be lower than in fresh cycles, this approach reduces the risk for developing severe OHSS.

The incidence of severe OHSS is less than 3% of all patients undergoing IVF at the Regional Fertility Program.

2. EGG RETRIEVAL

The majority of egg retrievals that occur at the Regional Fertility Program follow ovarian stimulation with fertility medications. This short operative procedure involves placing a needle into the ovaries via the top of the vagina and is done in our operating rooms. Patients will be given intravenous Versed® (a Valium®-like medication) and Fentanyl (a narcotic) to make the egg retrieval process as comfortable as possible. Risks of egg retrieval include the following:

- Discomfort or pain despite administration of medication
- Allergic reaction to the medications used during the surgery
- Rare complications from insertion of egg retrieval needle including:
  - Direct needle injury to blood vessel, bladder, bowel, ovary, uterus or other internal organ
  - Pelvic infection including infection of a fallopian tube or ovary after egg retrieval.
  - Intra-abdominal bleeding

3. FERTILIZATION OF OOCYTES AND EMBRYO CULTURE

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

b. Intracytoplasmic sperm injection (ICSI) is a procedure by which a single sperm is injected into an egg under direct visualization using a high-powered microscope. It is ideal for men with an extremely low sperm counts, abnormal looking sperm and for those with decreased sperm motility. It does overcome some fertilization problems but does not guarantee that fertilization will occur. Disadvantages include a slightly higher chance of genetic abnormalities in men with very low sperm counts (refer to genetic risks) 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 sperm or egg quality
Risks associated with IVF

- Insufficient amount of sperm available to treat all eggs
- Abnormal fertilization of some or all of the eggs
- Bacterial contamination of the eggs. The bacteria may be from the semen, the vaginal secretion collected with the eggs, and rarely, from the laboratory products used to support the developing embryo.

c. Embryo Culture: Your embryos will develop in an IVF incubator until they are transferred, frozen or discarded. During this “embryo culture” period, your embryos are cultured in 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
- Egg or 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

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 a human protein called Albumin. The product has been tested and found negative for HIV, Hepatitis B and C, in accordance with current FDA/Health Canada regulations. However, all human-derived products carry a minimal risk of being infectious.

4. EMBRYO TRANSFER

Embryo transfer is performed 2-5 days following your egg retrieval procedure. Embryo transfer is a painless procedure that does not require any type of anesthesia. Patients are required to have a full bladder at the time of embryo transfer. Risks are few but include:

- Pelvic infection
- Multiple pregnancy
- Ectopic pregnancy. Implantation of the transferred embryo(s) may occur outside of the uterus (most commonly the fallopian tube)
- Failed catheterization and placement of your embryos. Although rare, difficult embryo transfers may occur. If a transfer is not possible, freezing of all embryos until surgery has been done to correct the problem may be necessary.

a. Blastocyst Transfer
Growing embryos in culture for 5 or 6 days (blastocyst stage) offers several theoretical advantages over the transfer of cleavage stage embryos (day 2 or 3). These include:

- Easier identification of embryos with the highest chance of producing a pregnancy.
- A decrease in the number of embryos that are required to be transferred while maintaining an excellent chance of pregnancy
- Better synchronization between the embryo and the endometrium (lining) of the uterus where implantation of the embryo occurs.
Risks associated with IVF

- A reduction of twins and higher order pregnancies which makes pregnancy safer for both the mother and infant

Risks of blastocyst transfer include the following:

- A risk of multiple pregnancy if more than one blastocyst is transferred. Every effort should be made to perform single blastocyst transfers in good prognosis patients
- Fewer embryos to freeze as not all embryos have the ability to develop in culture to day 5 or 6 blastocysts
- An increased risk of monozygotic (identical) twinning

b. 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 help it break out of the shell prior to implantation. Possible risks of laser assisted hatching include:

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

A corticosteroid pill (Medrol®) is taken by the woman prior to and after embryo transfer when assisted hatching is required. Risks of this medication include stomach upset and possibly stomach ulcers and bleeding from those ulcers.

5. CRYOPRESERVATION (FREEZING) OF EMBRYOS

Many patients will have extra, good quality embryos or blastocysts remaining after their fresh embryo transfer that may be cryopreserved. Freezing extra embryos is a safe procedure that gives some couples the opportunity for additional embryo transfers without the need of ovarian stimulation medication and egg retrieval. Freezing embryos, however, has some potential associated risks and may also pose 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 catastrophic event leading to the death of an embryo
- Failure of embryos to survive freezing and thawing
- Psychological and ethical considerations including the dilemma of what to do with extra embryos
- Risk of birth defects in the infant is similar to that of fresh embryos

Note that abnormal-appearing and poor quality embryos are not frozen as they are unable to produce a pregnancy in the future. Also, there is no guarantee of a successful pregnancy after transfer of frozen-thawed embryos.

D. PREGNANCY AFTER ASSISTED REPRODUCTIVE TECHNIQUES

Spontaneously conceived pregnancies in untreated women with a history of infertility may be at an increased risk for obstetrical complications and perinatal problems when compared to women with no fertility issues. Similarly, pregnancies conceived with ovarian simulation, with or
without IVF/ICSI, are at increased risks for obstetrical complications including high blood pressure, preterm birth, low birth weight and perinatal mortality. The following adverse pregnancy outcomes may occur after IVF:

1. Miscarriage
The risk of miscarriage increases with advancing maternal age. 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 either by taking a medication or having a surgical procedure called a dilatation and curettage (D&C). A miscarriage may also occur after a naturally conceived pregnancy.

2. Tubal Pregnancy (ectopic pregnancy)
The majority of ectopic pregnancies occur in the fallopian tube. If an ectopic pregnancy is diagnosed, surgical treatment may be required and may involve removal of the involved fallopian tube. Medical treatment with a drug called Methotrexate may be an option in selected cases. An ectopic pregnancy may also occur after a naturally conceived pregnancy.

3. Ovarian Torsion
Rarely the fluid filled follicles that are present after IVF 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.

4. Genetic Considerations
Children born through IVF or ICSI may be at an increased risk for genetic abnormalities. At the Regional Fertility Program, the rate of congenital defects has been similar to that of the general infertile population.

a. Chromosomal Abnormalities after Intracytoplasmic Sperm Injection (ICSI) may occur in infants from fathers with very low sperm counts. This is likely caused by abnormalities in the genetic makeup of the injected sperm. Pregnancies conceived by ICSI have an increased risk of abnormalities of the X or Y (sex) chromosome and other chromosomes.

b. Male infants that have been fathered by men with microdeletions of the Y chromosome will likely have the same microdeletion as their father and subsequently suffer from infertility as well.

c. Children born to parents that carry the genes for cystic fibrosis (CF) are at risk for inheriting those genes as well. Patients in whom CF genes have been identified will receive counselling regarding the risks to their children prior to treatment.

Genetic and carrier status testing may be offered to pregnant couples when indicated according to the clinical situation, family history or the wishes of the patient(s). Couples achieving pregnancy through ICSI may choose to have prenatal testing including ultrasounds, blood tests and amniocentesis/chorionic villous sampling to check for chromosomal abnormalities.

d. Imprinting Disorders
There is the possibility that some very rare genetic conditions may be associated with ART procedures through an abnormal process of gene expression called imprinting. Examples of imprinting disorders include Beckwith-Wiedemann Syndrome, Silver-Russell Syndrome,
Risks associated with IVF

Angelman Syndrome, retinoblastoma and possibly some other childhood cancers. Although they are seen more often after IVF, further studies are needed to determine if there is a true association between imprinting-related disorders and ART procedures.

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

5. Preterm Delivery and Low Birth Weight
Singletons born from fertility treatments, including IVF, are at increased risk of preterm delivery (less than 37 weeks) when compared to spontaneously conceived pregnancies. Similarly, rates of low birth rate (less than 2500g) and very low birth rate (less than 1500g) are also higher in singletons born from fertility treatments.

6. Multiple Pregnancies
The chances of a multiple pregnancy are increased with the use of all fertility medications and fertility treatments. Complications of multiple pregnancies may include but are not limited to the following:

Complications for the mother:
- Pre-eclampsia (high blood pressure)
- Gestational diabetes
- Placenta previa (abnormal position of the placenta)
- Placental abruption (separation)
- Post partum haemorrhage (excessive bleeding after delivery)
- Operative deliveries (like a Caesarean Section)
- Post partum depression.
- 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),
  - Necrotizing enterocolitis (bowel damage) and
  - Cognitive delays (delayed ability to do simple tasks).
- Following birth, children born from multiple pregnancy may suffer from increased rates of learning difficulties and poor growth in infancy.
- Blastocyst transfer increases the risk of monozygotic (identical) twining which is a higher risk type of twin pregnancy than non-identical twins.

It is important to note that the risks to babies born from multiple pregnancies far exceed those of singleton pregnancies. This includes twin and higher order multiples. At the Regional Fertility
Risks associated with IVF

Program, every effort is made to reduce the likelihood of multiple pregnancies by performing single embryo transfers in good-prognosis patients. This is consistent with the current Canadian Fertility and Andrology Society’s clinical practice guideline for embryo transfer.

E. ACKNOWLEDGMENT OF INFORMED CONSENT AND AUTHORIZATION

Patients undergoing IVF at the Regional Fertility Program are required to have read and understand the contents this document prior to initiating treatment and signing consents.

Medical information concerning patients’ IVF treatment may be analyzed and used anonymously for quality assurance purposes and/or scientific publications.

Patients acknowledge that:

- While the purpose of those procedures is to establish a viable pregnancy, there is no guarantee of success
- Every conceived pregnancy has a chance of resulting in a fetus that is abnormal
- If more than one embryo is transferred into the uterus at the same time, the outcome could be a multiple pregnancy, such as twins, triplets or more.
- At present there are unknown long-term risks of these treatments including those that could occur in subsequent generations
- We are free to withdraw from treatments or procedures at any stage. If we choose to withdraw, we will let the Regional Fertility Program know our wishes in writing.
- By participating in the Regional Fertility Program IVF program, patients accept the responsibilities, conditions and risks set out in this document and as explained by their physician and/or other staff at the Regional Fertility Program.