

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 should be taken daily prior to the start of your treatment. This may reduce the chance that your baby will be born with some birth defects including 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. Optimize any pre-existing medical conditions (such as diabetes, hypertension and hypothyroidism) and normalize extremes of weight.
6. Ensure that your annual general physical exam and Pap test are completed with your family doctor prior to starting treatment. 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 increased risk of complications with oocyte retrieval, including an inability to access the ovaries. Also, obesity is associated with increased risk of adverse obstetrical outcomes including miscarriage, gestational diabetes, hypertension, stillbirth and the increased need for operative delivery. Due to technical challenges, as well as increased medical, anaesthetic and operative risks, patients with a BMI ≥ 40 may not be able to undergo IVF at our facility.

Potential barriers to successful treatment that may be experienced by all patients include, but are not limited to:

- Low or excessive response to fertility medications,
- Inability to access ovaries for egg retrieval,
- 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 it is recommended that he 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, and
- Loss or damage to sperm, 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 through in vitro fertilization, the ovaries are stimulated to produce multiple follicles in which the eggs mature. Various protocols and medications are used to stimulate follicle growth. Frequent 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. Lupron® is a GnRH agonist most commonly 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. Possible side effects include injection site irritation/infection, fatigue, headache and nausea.

Clomiphene Citrate (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 10% incidence of twins, and less commonly (1%), higher order multiple pregnancies (triplets or more).

Letrozole (Femara®)

Letrozole is an oral medication that can also be used to stimulate ovulation, and is also used in IVF protocols, often to reduce the level of circulating estrogen. It is also associated with a risk of multiple pregnancies, similar to clomiphene citrate. Although commonly used in reproductive medicine, Health Canada and the manufacturer state that Letrozole is contraindicated in premenopausal women and may be associated with a risk of birth defects. However, studies have subsequently demonstrated no increased risk of fetal malformations using letrozole for ovulation induction compared to the general population. There may be yet unknown side effects or risks associated with inadvertent exposure to letrozole while pregnant, therefore prior to starting letrozole, women are instructed to take a home pregnancy test.

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

These fertility hormone injections are used to recruit, grow and mature multiple ovarian follicles. They may cause injection site irritation/infection, abdominal distension, bloating fatigue, mood changes, thromboembolism (blood clot), stroke, and increase the probability of multiple pregnancies. Ovarian enlargement may increase the risk of ovarian torsion. The most serious complication of gonadotropins is the possibility of ovarian hyperstimulation syndrome (OHSS) discussed below.

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

These injectable medications cause final maturation of the egg and ovulation. They have the same side effects as the gonadotropins. They 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 clot), stroke 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. Prometrium® may contain small amounts of soy, sunflower and peanut oil and may cause allergic reactions in susceptible individuals.

b. Cancer risk and fertility medication

Although early studies suggested an association between cancer and exposure to fertility medications/ovarian stimulation, several epidemiological studies showed that there does NOT appear to be an increased risk of ovarian or breast cancer in infertile women exposed to fertility medications. However, it must be noted that studies are ongoing. It is known that pregnancy and delivery reduces the risk of ovarian, breast and uterine cancer.

c. 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, have a history of blood clots, migraines with aura, current breast cancer, uncontrolled high blood pressure, diabetes with microvascular complications or coronary artery disease.

Antibiotics

The most common side-effect 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.

Cabergoline (Dostinex®)

Dostinex® is in a class of medications known as dopamine agonists. A limited course at a low dose can be used “off label” to reduce the risk of ovarian hyperstimulation syndrome (see below) in at risk patients. Common side effects include gastrointestinal upset (nausea, constipation, and vomiting), headaches, dizziness and fainting, sometimes caused by a drop in blood pressure. Long-term use of high-dose dopamine

agonists has been associated with an increased risk of heart valve disease (cardiac valvulopathy) in some patient populations.

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.

d. 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 clomiphene citrate/Serophene®.

Factors associated with an increased risk of developing OHSS include but are not limited to:

- Young age,
- Low body weight,
- Polycystic ovarian syndrome (PCOS) or polycystic ovaries,
- High antral follicle count,
- High antimullerian hormone level,
- Higher dose of gonadotropins,
- High level or rapidly rising blood estrogen level, and
- 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 but are not limited to:

- Occasional lower abdominal discomfort and bloating,
- Mild nausea and vomiting,
- Diarrhea, and
- 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 but are not limited to:

- Rapid weight gain,
- Significant abdominal bloating,
- Respiratory difficulty (shortness of breath), and
- Decreased urinary output (urinating less) due to dehydration.

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

Recommendations for the outpatient management of persistent OHSS include but are not limited to:

- Adequate oral fluid intake, including electrolyte containing fluids (such as sports drinks)
- 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.
- Management may also include intravenous (IV) fluids, drainage of effusions/ascites and treatment with blood thinners (thromboprophylaxis).

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 renal failure, 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 are similar compared to fresh cycles, some frozen embryos will not survive when thawed. Nevertheless, this approach reduces the risk for developing severe OHSS.

In some high risk situations, it may be possible to trigger final oocyte maturation prior to egg retrieval with a GnRH agonist (such as Suprefact®) instead of hCG. On rare occasions, this may not be effective and supplemental hCG may be required.

Not all cases of OHSS are predictable, and it may develop in patients at low risk, particularly if pregnancy results from the embryo transfer.

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

Step 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 (rarely through the abdomen) and is done in our procedure rooms. Patients will be given intravenous sedation with midazolam (a Valium®-like medication) and Fentanyl (a narcotic) to make the egg retrieval process as comfortable as possible. Risks of sedation include over-sedation and respiratory depression and allergic reactions. Risks of egg retrieval include:

- Discomfort or pain despite administration of medication,
- Rare complications from insertion of the 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,
- Failure to access ovaries or retrieve eggs, and
- Retrieved eggs are immature or not usable.

Step 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 may 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.

Indications for ICSI include:

- Poor semen parameters (concentration, motility and normal morphology),
- Use of surgically retrieved sperm (from the epididymis or testicle),
- Use of vitrified eggs,
- Presence of significant anti-sperm antibodies,
- Failed fertilization with standard IVF,
- Preimplantation genetic testing (PGT), and possibly
- Low number of oocytes retrieved or unexplained infertility.

ICSI 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 mature eggs fertilize. However, the following risks exist:

- No fertilization due to poor sperm or egg quality,
- Insufficient amount of sperm available to treat all eggs,
- Abnormal fertilization of some or all of the eggs, and
- 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 media to support their growth and development. Risks associated with the embryo culture period include:

- Some or all of the embryos developing abnormally or not at all,
- Egg or embryo loss, due to some unforeseen event, such as equipment failure or loss during handling or manipulation, and
- Bacterial contamination of the embryos for the same reasons as outlined for eggs.

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.

Step 4. EMBRYO TRANSFER

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

- 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,
- Loss of embryo(s), and
- Pelvic infection.

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

A corticosteroid pill (Medrol®) is taken by the woman prior to and after embryo transfer in most cases when assisted hatching is required. Risks of this medication include mood changes headache, dizziness, high blood pressure, water retention, elevated blood sugars, stomach upset and possibly stomach ulcers and bleeding from those ulcers, and masking of infection.

c. Preimplantation genetic testing for aneuploidy (PGT-A)

Preimplantation genetic testing for aneuploidy (PGT-A), formerly known as comprehensive chromosomal screening (CCS) or preimplantation genetic screen (PGS), is a technique to assess all 23 pairs of chromosomes in human embryos for abnormalities. It allows us to identify embryos that are more likely to be chromosomally normal to replace into the uterus. By doing so, the pregnancy rate can be improved and the miscarriage rate can be reduced. It also reduces the chance of chromosomal abnormalities in the fetus.

The most common reason for failure of an in vitro fertilization cycle is that what appears to be a good quality embryo that is transferred is chromosomally abnormal, thus leading to failure of implantation or miscarriage if conception occurs. Embryos are biopsied on day 5 or 6 of embryo development, called the blastocyst stage. Usually, about 5-10 cells are taken from the trophectoderm portion of each blastocyst. The trophectoderm is the part that will form the placenta later. After the biopsy, the blastocysts are then frozen to allow time for the PGT-A testing. The biopsied cells are then sent by courier to the preimplantation genetic testing (PGT) laboratory for analysis. Blastocysts that are found to be chromosomally normal based on the PGT-A test results are subsequently transferred in a frozen embryo transfer cycle. Generally, the embryo survival rate after a freeze and a thaw is very good but there is no guarantee that they survive the process.

This technique may help individuals and couples with recurrent pregnancy loss, repeated IVF implantation failure, or when the female partner is at a higher risk of having eggs with chromosomal abnormalities (an example being a female partner of age greater than 35) by providing chromosomal information about the embryos to help with embryo selection prior to transferring them into the uterus.

It is very important for individuals or couples to understand the limitations of PGT-A before deciding to proceed.

1. PGT-A requires embryos to develop to the blastocyst stage for biopsy. In some cases, embryos may not develop sufficiently for biopsy and the PGT-A attempt may have to be abandoned.
2. PGT-A assesses only chromosomes, not single gene disorders such as cystic fibrosis, hemophilia, thalassemia, Huntington's disease, etc., or multifactorial

- diseases such as autism. Subtle chromosomal abnormalities can still be potentially missed by the technique.
3. The PGT-A result on each embryo is not 100% accurate. The error rate, which is generally not higher than 5%, may be due to a technical aspect of the testing or a phenomenon called chromosomal mosaicism in human embryos. Previous studies have shown that an early human embryo may contain cells of different chromosomal content. This limits the ability of using the biopsied cells to determine the chromosomal content of the rest of the embryo with certainty. Hence, there is a small chance that PGT-A may be erroneous in determining that an embryo is normal when it is not, and vice versa. As a result, the current recommendation is that the standard prenatal genetic testing stays the same after PGT-A has been performed.
 4. There are occasions when PGT-A does not yield results and the chromosomal status of embryos remains undetermined.
 5. Due to the occurrence of chromosomal mosaicism in human embryos, the PGT-A result may indicate possible chromosome mosaicism. Embryos with such PGT-A result likely have a combination of chromosomally normal and abnormal cells. There is a concern that transferring these mosaic embryo is more likely to lead to failure to conceive, increased risk of miscarriages, abnormal placental function and even abnormal livebirths due to the chromosomal mosaicism. Transfer of these embryos should only be considered when there is no alternative and only after further genetic counseling has been done to discuss the clinical implication of the specific type of mosaicism in each of these embryos.
 6. PGT-A does not guarantee pregnancy or normal live birth. Miscarriages and fetal chromosomal abnormalities can still occur after PGT-A although much less frequently.
 7. PGT-A increases the expense of an IVF cycle and requires ICSI to be performed.

PGT-A is a technology for screening all 23 pairs of chromosomes before embryo transfer and may help to improve the pregnancy rate and decrease miscarriage rate. Individuals or couples must, however, consider the potential benefits and limitations of the technology before deciding whether they would like to proceed with this.

Individuals or couples who have more specific genetic concerns, such as a family history or personal medical history of genetic conditions should make arrangements for genetic counseling to assess the genetic risk of them having offspring with specific genetic diseases. Depending on the result of their assessment by Medical Geneticists, they may benefit from a technology called preimplantation genetic testing for monogenic disease (PGT-M) for their specific conditions. Likewise, individuals or couples who have known rearrangement of chromosomes called translocation or inversion should make arrangements to be seen in consultation regarding the option of preimplantation genetic testing for structural rearrangement (PGT-SR).

Please feel free to discuss the above with your physician.

d. Preimplantation Genetic Testing for Monogenic Disease (PGT-M) or for Chromosomal Structural Rearrangement (PGT-SR)

Preimplantation genetic diagnosis (PGT) is a procedure in which genetic testing is performed on embryos produced by in vitro fertilization (IVF) before a clinical pregnancy

is established. Couples who are at higher than usual risk of having offspring with a genetic disorder, e.g. cystic fibrosis, hemophilia, Huntington disease, Fragile X, myotonic dystrophy, thalassemia, Tay Sachs disease, etc. may choose to do preimplantation genetic testing for monogenic disease (PGT-M) to reduce their risk of having a child with the genetic disease. In order for PGT-M to be possible, the genetic abnormalities called a mutation generally needs to be known. Couples who have chromosomal abnormalities and are at higher than usual risk of having offspring with chromosomal abnormalities may also choose to do preimplantation genetic testing for structural rearrangement (PGT-SR). Please contact your physician at the Regional Fertility Program if you think that PGT-M or PGT-SR may apply to your situation and you are interested in it.

Individuals or couples who have genetic concerns, such as a family history or personal medical history of genetic conditions should make arrangements for genetic counseling to assess the genetic risk of them having offspring with specific genetic diseases. Depending on the result of their assessment by the medical genetic specialists, they may consider PGT-M for their specific conditions. Likewise, individuals or couples who have known rearrangement of chromosomes called translocation or inversion should make arrangements to be seen in consultation regarding the option of PGT-SR.

It is very important for individuals or couples to understand the limitations of PGT-M or PGT-SR before deciding to proceed.

1. PGT-M assesses only the specific genetic condition of interest such as a particular single gene disorder e.g. cystic fibrosis, hemophilia, thalassemia, Huntington disease, etc., and PGT-SR only assesses a particular chromosome-related abnormality.
2. The PGT-M or PGT-SR result on each embryo is not 100% accurate. The error rate is generally not higher than 5%. Hence, there is a small chance that PGT-M or PGT-SR may be erroneous in determining that an embryo is normal when it is not, and vice versa. As a result, the current recommendation is that the standard prenatal genetic testing e.g. chorionic villus sampling and amniocentesis should still be done after PGT has been performed to confirm the PGT-M or PGT-SR result.
3. There are occasions when PGT-M or PGT-SR does not yield results and the genetic status of the embryo(s) remains undetermined.
4. PGT-M or PGT-SR does not guarantee pregnancy or normal live birth. Miscarriages and abnormal offspring(s) can still occur after PGT-M or PGT-SR.
5. Some couple may choose to do preimplantation genetic testing for aneuploidy (PGT-A), which is formerly known as comprehensive chromosome screening (CCS) or preimplantation genetic screening (PGS) in conjunction with PGT-M or PGT-SR. Please refer to the PGT-A section of this booklet for further information on this.
6. It is illegal in Canada use PGT for the purpose of social gender selection of embryos.

All patients who are interested in pursuing PGT-M, PGT-SR and/or PGT-A at the Regional Fertility Program Inc. are recommended to attend our PGT and in vitro fertilization information sessions.

Step 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,
- Failure of adequate endometrial development for a frozen embryo transfer attempt, and
- Having excess embryos than a patient’s/couple’s reproductive needs may pose significant psychological, moral or ethical dilemmas.

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. Risk of birth defects in the infant is similar to that of fresh 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 stimulation, 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. Birth Defects

Studies examining the association between IVF +/- ICSI and birth defects have reported varying findings, from no difference compared to natural conception to a doubling of risk associated with assisted reproduction. Overall, there may be a small increase in abnormalities with IVF +/- ICSI, although the increase is only a small proportion of that seen with natural conception.

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 chromosome abnormalities, especially of the X or Y (sex) 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 may 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. This is of particular relevance for most men with congenital obstruction of the reproductive tract resulting in azoospermia.

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 screening including ultrasounds, blood tests, and diagnostic testing such as amniocentesis to check for chromosomal abnormalities.

d. Imprinting Disorders

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, Angelman Syndrome, retinoblastoma and possibly some other childhood cancers. Further studies are needed to determine if there is a true association between these 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. Obstetrical Risks

Singleton pregnancies from fertility treatments, including IVF, are associated with increased obstetrical risks including, but not limited to:

- Pregnancy-induced hypertension,
- Gestational diabetes,
- Placenta previa (abnormal position of the placenta),
- Placental abruption (separation),
- Postpartum haemorrhage (excessive bleeding after delivery), and
- Operative deliveries (like a Caesarean Section).

7. 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:

- All those listed above (6. Obstetrical Risks), but with a greater likelihood of occurrence,
- Postpartum depression, and
- 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, but are not limited to:
 - Cerebral bleeding (bleeding into the brain),
 - Retinopathy (damage to the eyes),
 - Bronchopulmonary dysplasia (severe breathing problems),
 - Necrotizing enterocolitis (bowel damage),
 - Cognitive delays (delayed ability to do simple tasks), and
 - Cerebral Palsy.
- 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) twinning 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 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.