Egg freezing at the Victoria Fertility Centre.

Introduction

Oocyte cryopreservation has been a new area of clinical ART (assisted reproductive technologies) practice leading to promising options for women to store their gametes for future fertility needs . For many years women facing potentially sterilizing treatments for oncology related health concerns have had no alternative for the possible preservation of their future fertility. Oocyte preservation may now also offer hope to single women wanting to delay childbearing for social and professional reasons avoiding the only choice of embryo cryopreservation with the use of a sperm donor perhaps leading to even more social challenges.

Women facing scenarios of diminished ovarian reserve or with oocytes of very poor quality are known to have a decreased potential for a positive outcome using their own oocytes. Oocyte donation has been a solution for couples where access to a young oocyte donor is possible. A successful oocyte cryopreservation program could lead to greater access for women to work towards their family building options.

For decades men have been able to successfully preserve their fertility by the cryopreservation of sperm. This option however has not been that easy for women. Since the 1980s embryos at various stages of development have been successfully cryopreserved, however it is only more recently through improved laboratory techniques such as vitrification that oocyte cryopreservation has become more of a clinical reality. One of the major hurdles to successful preservation of human tissue is preventing ice crystal formation and cellular damage. The use of cryo protectorants to replace water and thereby limit ice crystal formation and subsequent damage has been successful in slow freezing techniques for sperm, zygotes, and cleavage stage embryos however has been more challenging for successfully cryopreserving oocytes and blastocysts.

Oocytes being the largest cell in the human body contain a large volume of water and are thereby very susceptible to ice crystal damage. Secondly the oocyte membrane is relatively impermeable to some of the clinically used cryo-protectorants which have a large molecular weight. This means that the oocytes need to be exposed to the cryo-protectorants for a relatively long period of time before there is satisfactory water replacement. The cryo- protectorants are cytotoxic and of course the longer the exposure at room temperature prior to freezing the more significant the damage that can be done. Studies on oocyte freezing in the 1990s in Italy suggested possible induced genetic damage and as a result of this there was for many years a voluntary international moratorium on the clinical use of this technology in humans.

Vitrification is a novel labortatory technique allowing the protection of oocytes and blastocysts from harmful consequences commonly seen with the slow freezing methodologies. Vitirication involves a rapid cooling rate in the presence of higher concentrations of cryo-protectorants. Studies have shown improved survival rates with

this new method and pregnancy rates nearing those seen with fresh cycles (Kim et al, 2010).

We believe there is room to increase access to care for our patients through fertility preservation.

The clinical application of oocyte cryopreservation at the Victoria Fertility Center

1. For fertility preservation in younger patients undergoing potentially toxic therapies for cancer treatments
2. To overcome some of the ethical dilemmas related to embryo freezing and disposition of surplus and unwanted embryos.
3. For fertility preservation in women concerned about advancing age, and also for single women who may wish to delay motherhood for personal, professional and financial reasons
4. For fertility preservation in women requiring surgery for control of conditions such as endometriosis and benign or malignant ovarian pathology
5. Donor oocyte cryopreservation would allow for an easier clinical application and more responsible quarantine period prior to clinical use. This would avoid the necessity for synchronization of cycles and exclude or at least minimize some of the extra costs related to fresh cycle egg donation.

Safety

The use of higher levels of cryoprotectorants is a known factor leading to potential cytoxicity (Yoon,et al, 2000), however limiting oocyte exposure and the fast rate of cooling have led to high survival and pregnancy rates when compared to other methods. Since the late 1990s the number of reported live births resulting from oocyte cryopreservation has increased dramatically.In 2009 Noyes et al published a review (Reprod Biomed Online 2009,18:769 -777) of 936 live births resulting from cryopreserved oocytes. Compared with congenital abnormalities occurring in 30 conceived babies there was no difference noted (Chian et al Repromed Biomed online 2008. 16: 608 – 610).

In summary therefore, at this stage, previously frozen oocytes by vitrification, subsequently warmed and used for assisted reproduction (IVF) , result in pregnancies and babies with no higher risks than with routine IVF.

When it comes to discussing the risks of birth defects, it is important to remember that all babies born naturally have an approximately 4% risk of being born with a birth defect. Birth defects may be minor or major and may include such things as hernias, clubfoot, cleft lip and palate, hypospadias, kidney and heart defects and many more. Some are minor and some are major.

It has been found that the risk of birth defects in babies born after in vitro fertilization is slightly higher at around 6% with an increased propensity for renal and cardiac defects. It is not known what aspect of the IVF process causes the risk.
It has also been shown that couples experiencing infertility may have an increased risk of having a child with a birth defect whether they eventually conceive on their own or through IVF.

Another risk associated with in vitro fertilization is related to epigenetics. This is related to all in vitro fertilization and not specifically to egg freezing. The study of genes and chromosomes and referred to as "genetics" is highly complicated. Genes are literally the biological software that program and run our bodies. Certain genes when exposed to altered environments may undergo a chemically induced change which alters their function. This may result in certain illnesses referred to as "imprinting disorders", and secondly may increase the risk of certain genetically orientated cancers. Although these risks are very small, our patients need to be aware of them.

The experience at the Victoria Fertility Center

VFC introduced vitrification in January 2010. We have seen dramatic improvement in pregnancy rates for vitrified embryos as compared to slow frozen embryos. In fact our pregnancy rates now from embryos that have been vitrified and warmed are close to pregnancy rates for fresh embryo transfers. Personally I feel that vitrification is the single most important change in assisted reproductive technologies in the past 10 years.

Although our experience is quite new, we have now frozen eggs for a number of patients in different circumstances and have confirmed deliveries and many ongoing pregnancies from these previously vitrified eggs. We have therefore confirmed that the applied technology in our laboratory, as reported by numerous other centers, is effective.

We feel at this stage that we can therefore offer egg freezing by vitrification to our patients.

Expectations

It is important to realize that only a percentage of eggs that are surgically from the ovary will actually result in a baby. Data published from the USA through the Centers for Disease Control which monitors all assisted reproductive technologies in the U.S. a few years ago found that less than 10% of eggs surgically retrieved for IVF actually result in a baby. This data does however include eggs from women of all ages.
The reasons for this are as follows………..

1. Only a percentage of eggs retrieved are genetically normal. As a woman gets older so the percentage of genetically normal eggs goes down. For instance of 10 eggs retrieved from a woman age 30 approximately 7 are genetically

normal, and from 10 eggs retrieved from a woman age 40, approximately 4 or 5 may be genetically normal.

2. Not all eggs retrieved are mature. There may be some that are postmature or immature.
3. Not all eggs will fertilize normally
4. Not all fertilized eggs develop into a normal embryo
5. Not every normal embryo will implant in the uterus
6. Not every pregnancy results in a live birth. Miscarriage rates are determined by maternal age – with the miscarriage rate in a woman aged 30 years being 10 – 15 %, and for a woman aged 42 years, over 50 %.
7. Not all the eggs that are frozen will survive the warming process.

Retrieving the eggs for freezing

During a normal regular monthly menstrual cycle only one egg is released at the time of ovulation. To make the process more efficient, we stimulate the ovaries using a combination of fertility drugs known as gonadotropins. (Commercially these are commonly known as Gonal F, Puregon, Luveris, Bravelle, Menopur and Repronex) these drugs are given by daily subcutaneous injections. We normally recommend that these injections are given into the tummy around the belly button area.
The eggs grow in small capsules of fluid called follicular cysts (follicles). Although we cannot see the eggs which are a microscopic, by ultrasound we can monitor the growth of the follicles and using this information as well as blood levels of estrogen (estradiol) to determine the time to retrieve the eggs.
It normally requires around 14 days of daily injections before the eggs are mature. During these 14 days the ovaries will be monitored every few days by ultrasound and blood tests are done to measure estrogen levels.
The egg retrieval is performed transvaginally. A fine needle is passed through the vagina into the ovaries and the fluid in the follicles is aspirated. Because this procedure can be uncomfortable it is done under light anesthesia known as conscious sedation. An intravenous line is established and medication is given intravenously for the sedation and pain control. The retrieval itself only takes 5-10 minutes and most patients have minor discomfort only.
An hour or so after retrieval, the patient will be allowed to go home but must be accompanied by an adult and not be left alone for 24 hours. There is a small risk of internal bleeding after the egg retrieval so it is imperative that the patient have somebody to assist her if necessary.

The fluid retrieved from the ovaries is carefully examined by an embryologist and the eggs are identified and separated. A few hours later the cells around the eggs are stripped off and the eggs then vitrified. Each egg is vitrified (frozen) individually.

Preparing a woman's uterus for embryo transfer

Once a woman is ready to use her frozen eggs, her uterus is first prepared hormonally. This requires that she take estrogen for about 2 weeks, and then later progesterone as well. The estrogen tablets are taken orally and the progesterone tablets intravaginally.
After the eggs have been warmed and fertilized, the fertilized eggs develop into embryos and are cultured to either day 3, or preferably day 5 if possible, before the best quality embryo/s are selected for transfer to the uterus.
Extra good quality embryos may be frozen for later use.

Commonly asked questions

How many eggs would I need to freeze to guarantee me a chance of having a successful pregnancy when I choose to warm and fertilize my eggs.?

There are NO guarantees.
Although unlikely, no eggs may survive the thaw, or the eggs may not fertilize, or the embryos may not develop normally – so there is always a chance that from all the eggs frozen, there may not even be an embryo transfer. Although this is unlikely it is possible.
The success rates (for a pregnancy) from warming previously frozen eggs, fertilizing them, and transferring the embryos to a uterus are dependent on a number of factors which include…. The age of the egg donor (at the time the eggs were frozen) , the quality of sperm used to fertilize the eggs, the quality and stage of embryo development and the health of the uterus at the time of embryo transfer.

The results are very age dependent.
For a woman aged 30 years ,if a good quality embryo is created in vitro and the embryo transferred to her uterus, the chance of becoming pregnant is about 55 %, and if pregnant the risk of miscarriage about 10 - 15%
For a woman aged 42 years,. if a good quality embryo is created in vitro and the embryo transferred to her uterus, the chance of becoming pregnant is about 20 %, and if pregnant the risk of miscarriage over 50 %.

How are the eggs fertilized after they have been thawed ?

When an egg is retrieved from the ovary it is covered by a layer of cells called the cumulus. In order to freeze an egg, these cells need to be stripped off the egg first. When the egg is thawed it is therefore devoid of these cells. This means that the sperm would not be able to fertilize the egg on their own. The eggs have to be fertilized using a technology of micromanipulation known as intracytoplasmic sperm injection (ICSI) This involves injecting a single sperm into each egg - using very sophisticated equipment. Our patients are encouraged to read up about ICSI. The information on ICSI is available on the VFC website. There are some risks related to performing ICSI - specifically a chance that an abnormal sperm may be injected into

an egg. Children born from ICSI cycles have a 1% risk of a chromosome abnormality related to the process. Special testing can be done during a pregnancy to check the baby's chromosomes. All pregnant women have a risk of having a baby with a chromosome abnormality, however ICSI raises the risk by another 1%.

Are there any risks related to ovulation induction and egg retrieval ?

One of the potential risks of ovulation induction is of a condition called OHSS (ovarian hyperstimulation syndrome) This is a condition directly caused by the fertility drugs – and tends to occur in young women who over respond to the fertility drugs resulting in numerous eggs and high levels of estradiol in their blood. The condition is fueled by pregnancy hormones – so does not tend to occur in women unless they become pregnant. In other words the risk of OHSS related to ovulation induction for egg freezing is very low.
The egg retrieval itself is a surgical process and the potential risks include infection, bleeding and damage to internal pelvic organs. The truth is that the risks are very small.
As far as we know there on no long-term risks from using the fertility drugs for this purpose. There has been speculation that the use of fertility drugs may pose a long-term risk of cancer however this has never been substantiated.
Retrieving a bunch of eggs from the ovaries makes no difference regarding age of menopause. These are eggs that would be lost during a natural cycle anyway.

Costs.

Initial consultation. If you have a referral from your family physician for an initial fertility consultation, and you are seen in person at the Victoria fertility center, the cost of the initial consultation will be covered by the medical services plan. If you have a telephone consultation or if you are from out of province or if you are self-referred, the cost of the initial consultation is: $300.00

The IVF/Egg freezing cycle itself.

For ovulation induction, egg retrieval, and freezing the eggs	$5500.00
For annual storage of eggs (per year)	$200.00
Drugs costs (on average) for ovulation induction	$3-4000.00
For warming the eggs,fertilizing by ICSI and embryo transfer	$1000.00
For storage of any frozen extra embryos per year	$200.00

Please make sure you understand the information provided – before you sign any consent forms.