

Specialists In Reproductive Medicine & Surgery, P.A.

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Excellence, Experience & Ethics



Patient Information Summary Oocyte Cryopreservation

Historical Perspective:

The British team of Dr. Steptoe and Dr. Edwards, using an unstimulated cycle, were able to accomplish fertilization in a “test tube” (i.e., In Vitro Fertilization: IVF), replace the embryo back into the uterus and have implantation occur. This first “test-tube baby”, Louise Brown, was born in the United Kingdom on July 25, 1978.

There have been numerous advances made over the decades since Louise Brown. While sperm and embryos have been cryopreserved for many years leading to the creation of healthy offspring, the ability to freeze the human oocyte has been more difficult. The human oocyte is the largest cell in the body containing a comparatively large amount of water, which can cause cellular damage if not cryopreserved properly. Additionally, the DNA within the oocyte was positioned for fertilization and early division and it was important that it not be significantly disturbed. Eventually, the first human offspring born from a thawed oocyte took place in 1986 (Chen C, The Lancet, 1986).

Two additional techniques were needed to make oocyte cryopreservation (OC) a reasonable, although still considered an experimental, option for women. The first concerned the freezing technique itself. Vitrification involved a very rapid freezing of the oocyte and seemed to result in a higher rate of survival post thaw. The second technique that was needed was the ability to consistently fertilize the thawed oocyte. Apparently, during the freezing and thawing process, the outer covering of the oocyte hardened making it difficult for sperm to penetrate normally. Through direct intra-cytoplasmic sperm injection (ICSI), fertilization rates vastly improved, thereby significantly improving the chances for conception.

Summary Of The Oocyte Cryopreservation Process

General Indications for Oocyte Cryopreservation:

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|-------------------------------|--|
| Lack of Sperm: | Following an IVF procedure wherein the partner is unable to provide a semen specimen or there aren't enough sperm to fertilize the number of oocytes available, OC would be indicated. |
| Cancer: | Prior to new/recurrent cancer treatment including surgery, chemotherapy and radiation. |
| Delaying reproduction: | A woman may prefer to freeze her oocytes now for use at a later date when her reproductive capabilities may be compromised. |

Patient Information Summary, Oocyte Cryopreservation (*cont.*)

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| Destructive pelvic disease: | Prior to pelvic surgery for benign disease if the surgery may place her at risk for reduced fertility. |
| Prior to medical treatment: | Prior to medical treatment that may impair fertility. |
| Do not want excess cryopreserved embryos: | Due to ethical or religious reasons, some patients do not want to freeze excess embryos during IVF, so the alternative would be to freeze excess oocytes. |
| Quarantine: | Although not mandated at this time, some programs quarantine oocytes prior to Egg Donation. |
| At risk for premature menopause: | There may be a family history or genetic reasons why a woman may be at risk of entering menopause earlier so she may want to freeze her oocytes before this occurs. |
| Egg donation | A number of facilities offer egg donation procedures using cryopreserved oocytes in locations where egg donor availability is often limited |

The indications for OC include the above, but should not necessarily be limited to the above, as the list continues to be expanded frequently. This procedure has tremendous potential with more than 1,000 children born worldwide through OC. (Rodriguez-Wallberg KA, Oktay K. Best Pract Res Clin Obstet Gynaecol 2012) In addition, the American Society for Reproductive Medicine no longer considers OC experimental. (Mature Oocyte Cryopreservation: a guideline. Fertil Steril 2012)

General Evaluation:

A number of criteria need to be met before you are accepted into the OC program. All final determinations are made by the ART team, which consists of medical, nursing and laboratory staff.

Phase 1: Review Of The Medical Records, History & Physical Exam

All pertinent medical record, X-ray studies and laboratory results will be reviewed and summarized. A history and physical exam will then be performed. Alternatives to OC will be briefly discussed so you will be able to make an informed decision. Detailed written information will be provided.

Phase 2: The Updating Of Laboratory Studies

The following is a summary of the common tests and procedures that are routinely examined to be included into the OC program:

| General Blood Work: | Sexually Transmitted Diseases: | Procedures: | At no charge to the patient: |
|------------------------------|---------------------------------------|--------------------|-------------------------------------|
| Cycle Day 21-23 Progesterone | HIV I/II | PAP Smear | Urine drug testing |
| Cycle Day 2-5 FSH level | Syphilis (RPR) | Pelvic Ultrasound | Cytomegalovirus (CMV) |
| CBC | Hepatitis B (HBsAg) | | |
| Electrolytes | Hepatitis B (anti-HBc IgG) | | |
| Blood Type | Hepatitis C (HCsAb) | | |
| Antibody Screen | Gonorrhea/Chlamydia | | |

Urine drug and CMV testing will be needed should you decide at a later date to donate your cryopreserved oocytes rather than use them yourself. These will be done at no charge to you.

Genetic testing appropriate for your ancestry (i.e, Afro-Americans are screened for sickle cell carrier state) will be requested. Most of the laboratory tests are good for two years but Pap Smears and Pelvic ultrasounds are generally repeated every year.

Phase 3: Final Evaluation

Once all screening studies are completed, the ART team will determine if you are accepted into the OC program. They will also decide which specific ovarian stimulation protocol will be used. Such variables including the age of the woman, accessibility of the ovaries, previous attempts at ART as well as patient wishes will all be used to deciding which stimulation protocol will be best for you.

Once the protocol is decided upon, legal contracts, study consents (if applicable) and financial arrangements will be completed. The IVF Nurse Coordinator will guide you through these steps.

Optional Evaluation:

It has been suggested that mental health counseling be provided to patients undergoing OC. This is certainly *offered* but will not routinely be mandated. In comparison, men who provide sperm for cryopreservation (i.e., fertility preservation) are not mandated to have counseling, so a “double-standard” seems to exist. That stated, if the team here at SRMS feel psychological counseling is mandatory, refusal to undergo counseling may be grounds for exclusion from the OC program.

Information Particular to Oocyte Cryopreservation

There are issues particular to OC that the patient needs to be made aware:

1. Depending upon the number of oocytes retrieved, it may be recommended that you undergo a second procedure fairly soon after the first to potentially double the number of cryopreserved oocytes. It is entirely uncertain how many oocytes need to be frozen to produce one viable offspring but recent estimates provide a very wide range from 5 to 25. This is probably dependent on the age of the patient with more oocytes needed as the patient ages. ***A 20% reduction on charges billed by SRMS for a second or third cycle will be offered (outside laboratory and anesthesia expenses are excluded).***
2. We (and many others) believe that vitrification (rapid freeze) rather than the conventional slow freeze process yields higher survival rates of the oocytes.
3. There are fees involved for yearly storage of your oocytes. This is covered in the [Price List](#).
4. Because the outer covering of the oocytes seems to harden following freezing and thawing, the oocytes will need to be fertilized using Intra-Cytoplasmic Sperm Injection (ICSI). A separate fee will apply.
5. There is a reasonable likelihood that you may never use your cryopreserved oocytes.
6. It is important that you are careful in assuming that by cryopreserving your oocytes you have a risk free reproductive insurance policy. Making major life decisions (i.e., delaying marriage and/or childbearing) due to career demands, financial issues or waiting for the right person, for example, increases the risks for a successful result. On the other hand, oocyte cryopreservation can offer you a solution to your choice to delay reproduction until such a time as you feel you are ready, instead of feeling pressured into making marriage/reproductive decisions in haste.
7. However unlikely, your oocytes may be lost due to laboratory accidents, closure of the facility (We've been here since 1991!), hurricanes and/or other “acts of god”.

Financial Arrangements:

OC is a complex and relatively expensive process. The costs of maintaining the advanced laboratory equipment and the employment and continued education of the highly trained staff are high. Because

Patient Information Summary, Oocyte Cryopreservation (*cont.*)

of the high costs involved in maintaining a successful ART program, we will ask that all procedures be paid for in full prior to initiating the ovarian stimulation process.

SRMS has been quite careful in accurately estimating the costs for the OC process. These estimates can be reviewed in the enclosed Price List. The front office staff will be available to answer additional financial and insurance questions upon request.

Women needing OC with a diagnosis of cancer may qualify for Financial Assistance through Sharing Hope and/or Verna's Purse through ReproTech, Ltd (See **Long Term Storage** information below).

SRMS is a proud member of LIVESTRONG's Sharing Hope Program. As a participating center in the Sharing Hope Program, SRMS works with LIVESTRONG to increase access to fertility preservation services for cancer patients. To apply or for more information about Sharing Hope, please visit www.livestrong.org/fertilityapplication

To apply or for more information about Verna's Purse, please visit:

http://reprotech.com/images/docs/vp_fa_application_oocyte_ovarian_tissue.pdf

[Verna's Purse Financial Assistance Application - Oocyte/Ovarian Tissue](#)

Ferring Pharmaceuticals also offers free medications through their Heartbeat Program to women with a cancer diagnosis needing OC. To apply or for more information about Ferring's Heartbeat program, please visit: www.heartbeatprogram.com.

The Potential To Donate Your Cryopreserved Oocytes:

Should you decide to not use your oocytes and are less than or equal to 33 years of age at the time of the OC procedure, it might be ideal that you donate them to needy women/couples. To do so, you will eventually need to complete consents and additional paperwork. While this may change in the future, you will not be reimbursed for donating your cryopreserved oocytes.

Ovulation Induction:

Regardless of the stimulation protocol, all patients will be placed on hormonal contraception in a continuous fashion for at least three weeks prior to the initiation of stimulation hormones. This is done to control your menstrual cycle and allows us to control the date of initiation of the ART cycle. Approximately three days after the contraception is stopped, a **baseline** transvaginal ultrasound will be performed. The ovarian stimulation protocol will be initiated if there are no significant ovarian cysts, which may otherwise confuse the later ultrasounds. A "**Negative-Baseline**" is desired which means no problems were seen. Your bladder needs to be empty to perform all pelvic US procedures, so don't load up on fluids.

Injectable medications, with or without additional oral medications, which mimic the body's natural hormones, will be given to stimulate the ovaries increasing the number of eggs available for use.

In general, there are two protocols used to stimulate the ovaries. The protocols involve either the use of Gonadotropin Releasing Hormone Analogs (GnRH-a) or Gonadotropin Releasing Hormone Antagonists (GnRH-Ant), hormones that inhibit the pituitary gland from releasing the eggs too early in the stimulation cycle. The first protocol, which is called the “**Meldrum**” or “**Down-Regulated**” protocol, uses the GnRH-a. This medication starts in the later half of the prior cycle. The “**Letrozole Protocol**”, however, uses a GnRH-Ant, which is not started until ovarian follicles have reached 12-14 mm in size during the month of stimulation. Each basic protocol has its advantages and disadvantages and will be chosen by the ART Team. Please rest assured that they will choose the protocol that is best for you.

The overall length of ovarian stimulation varies but usually ranges from 7-10 days. One to two injections each day may be needed to accomplish the stimulation. You will learn how to give these injections.

Follicular Monitoring:

Periodic ultrasound measurements and blood tests should be expected during the stimulation process. As the follicles grow, they release estrogen, specifically estradiol (E2). The E2 levels will be monitored along with the ultrasound evaluations. We are well aware of the distances many of our patients travel and will make every attempt to minimize their travel to SRMS.

We will watch the follicles grow to about 17 – 18 mm and then ask you to administer an injectable medicine called human chorionic gonadotropin (HCG) to initiate the final stages of oocyte maturation. The eggs will then be retrieved approximately 36 hours later.

Approximately 8% of the patients will be canceled due to inadequate ovarian stimulation. Cancellation of a cycle is disappointing to everyone; however, it may be preferable to modify the protocol and restart the stimulation in a future cycle.

Retrieval:

If you have a complicated medical or anesthesia history and would like to meet the anesthesiologist or nurse anesthetist ahead of time, a meeting may be scheduled in advance of the procedure upon request.

It is important that you not have anything by mouth (except for a few sips of water) for eight hours prior to the retrieval. As with any outpatient surgical procedure, the patient meets the Certified Registered Nurse Anesthetist (CRNA) or Anesthesiologist prior to the procedure and consents are reviewed and signed. Under intravenous (IV) sedation (you are asleep and breathing on your own), the eggs are retrieved using a slender needle placed through the walls of the vagina and into the ovaries under ultrasound guidance. The complications of the egg retrieval process here at SRMS are less than 1%.

The entire egg retrieval process usually takes about 30-45 minutes. A family member or friend is encouraged to attend the retrieval and may be allowed in the retrieval room itself. Recovery will last for about 30-60 minutes. It will be necessary that someone drive you home after the procedure. Pelvic cramping is expected following the procedure.

After the eggs have been retrieved, each one will be stripped of the outer cells/tissue and examined carefully. Oocytes that have released their first polar body are considered mature and will be chosen for cryopreservation. Those oocytes that are immature will most likely be discarded, although the lab is occasionally able to coax a minority of them into maturity, wherein they too will be cryopreserved.

Oocyte Cryopreservation:

If there are viable mature oocytes, they will be cryopreserved in liquid nitrogen for future use. The oocytes can be thawed at a later date should the patient desire to conceive. Members of the ART team will choose the method for cryopreservation and the storage container.

Any study protocols will be examined separately from this summary.

The process of freezing and thawing may apply a great deal of physiologic stress on the oocytes such that some may not survive. In general, about 25% of the oocytes will not survive the freeze/thaw process although this percent can vary tremendously. In general, the younger the patient, the more likely they are to survive. Likewise, oocytes that degenerate following thaw may have been genetically abnormal from the start and were not going to result in viable pregnancies. Because there is a drop in the number of oocytes available after thaw, it is sometimes suggested to perform two separate retrievals (within a couple of months of each other) to provide enough viable oocytes that will result in at least one successful pregnancy.

Procedure Risks & Discomforts:

The ovarian down regulation medications and protocols, monitoring and procedure for egg retrieval for the oocyte cryopreservation are identical to those used in routine IVF treatment. Therefore, there are no increased physical risks to the patients participating in OC other than those associated with routine ovarian stimulation for IVF, including ovarian hyper stimulation. There is no additional discomfort expected other than that associated with routine egg retrieval, which commonly results in pelvic cramping.

Risks Associated With the Childbearing Potential:

Cryopreserved eggs may not survive the freezing and/or thawing procedures, or may occasionally be rendered unsuitable for fertilization. The feasibility of establishing a pregnancy declines with increasing maternal age. While there is no clear-cut scientific data available to indicate an increase incidence of birth defects or chromosomal abnormalities in children born from cryopreserved oocytes, more investigations are needed to confirm this claim. Thus far, data is encouraging and the children are seemingly no different than those conceived naturally (Tao T, et al. *Curr Opin Obstet Gynecol*, 2009; Winslow KL, et al. *Fertil Steril* 2001; and Cobo RC, et al. *Fertil Steril*, 2009).

Oocyte Cryopreservation Success Rates:

Expect to be somewhat confused in comparing various statistical results between different therapies and programs. One of the most important factors to remember is that different patients may have different procedures and that different programs often have different admission criteria. One must

always remember that the chance of becoming pregnant using natural techniques in the normal fertile population is about 20% each month. All of the ART statistics should be compared to this natural fecundity rate. Overall, recent studies indicate that live birth rates using thawed oocytes are likely similar to live birth rates with IVF using fresh oocytes (Grifo J and Noyes N, Fertil Steril 2010 and Hodes-Wertz B, et al. Reprod Biomed Online 2011)

As previously written, the percentage of oocytes that are genetically abnormal increases as a woman ages. This is extraordinarily important to understand, as the OC process doesn't eradicate this problem. If nothing else, the OC highlights the issue in that abnormal oocytes may not survive the thaw, may not fertilize normally, may not grow normally, may never implant after transfer or will be miscarried after implantation. ***It is not in the control of the ART team to produce healthy oocytes where none exist.*** Essentially, if the oocyte is normal, the chances for success can be excellent.

Whenever possible, clinic specific data should be provided to the patient. This will be posted on the www.DreamABaby.com website when available.

Long Term Storage:

SRMS uses ReproTech, Ltd. (RTL) as our long-term storage facility for oocytes. RTL is a licensed clinical laboratory whose main focus is long-term storage of reproductive cells. RTL has been providing safe and secure long-term off-site reproductive tissue storage since 1990. RTL adheres closely to Federal and American Society for Reproductive Medicine guidelines regarding the cryopreservation of reproductive tissue as well as a host of other regulatory agencies. RTL has three facilities with the closest being in Coconut Creek, Florida. \

Below is a link to the RTL documents for those patients who will need long-term storage facilities. Please download and complete all the **Oocyte** Forms and the **All Tissues - Transfer TO RTL** Form.

<http://forms.reprotech.com/srms.html>

SRMS will require that all of these materials be completed and we will forward them to RTL with your oocytes.

Frequent Questions

What general restrictions are necessary during the month of stimulation?

We ask that you check before taking **any** additional medications other than regular or extra strength Tylenol. Smoking, herbal medications, over-the counter medications, recreational drug use and alcohol must be eliminated. If another physician prescribes you a medication, please have the physician contact us and we will clear the use of the desired medication or provide alternative treatments.

May I exercise during the month of stimulation?

Strenuous activity is to be avoided and new activities should not be initiated. We ask our patients to use good common sense. When deciding what is strenuous and what is not, please discuss the "grey" areas with the IVF coordinator. Once again, please use good common sense.

Do I really need to buy or borrow an answering machine?

It is **imperative** that our patients be available by home phone, cell phone or some sort of message recording device to receive instructions regarding medications and appointments for monitoring. The inability to contact you may result in the cancellation of your cycle. Please clearly identify yourself on any devices that we will use to contact you.

Why is my stimulation so different from others in the group?

Each person's response to therapy is individual, so your lab values and stimulation protocol may be very different from others in the group. A different protocol simply means the protocol has been tailored to fit your specific needs.

Is it all right to discuss the stimulation with others in the group?

Please be sensitive to the fact that some of the individuals going through the program have not even discussed the process with any of their family members or close friends. Therefore, please do not be offended if they are reluctant to discuss the information with relative strangers. At the same time, patients often benefit from mutual support. We simply ask that you be sensitive to the other patient's potential desire for privacy.

May I have intercourse just prior to the retrieval?

We ask that our couples not have intercourse for at least two to three days prior to the retrieval. Your pelvis may be somewhat tender due to the enlargement of your ovaries. If you do not want to become pregnant, it is imperative that you use barrier contraception (usually condoms and spermicide) for at least one week prior to retrieval and a few days following as an occasional oocyte may be left behind and be fertilized on the month of the oocyte retrieval.

Will my children be normal if conceived through Oocyte Cryopreservation?

The medications used in the ovarian stimulation process and during egg retrieval are used universally around the country and the world. There is no human data that indicates that the medications are harmful to you.

There have been some studies which indicate the average ART pregnancy will deliver somewhat earlier with a smaller-for-gestational-age baby compared to those conceived through natural means. This is probably due to the fact that the patients are simply at higher risk for problems due to the issues that made them subfertile in the first place. We do not know if this is true for OC.

ART conceptions are **not** more prone to significant abnormalities. We offer no guarantee that the child will be normal, but tens of thousands of children have been created by the IVF process and the children are generally as healthy as those conceived in the more natural settings.

How long can my oocytes stay frozen?

We really do not know the limit of the cryopreservation therapy. Animal research has shown that offspring are possible after many years of cryopreservation. The cryopreserved oocytes may last for years, decades and perhaps even longer. One study in humans has confirmed no differences in live birth rates between oocytes thawed and transferred after 48 months compared to those thawed earlier. (Parmegiani L, et al. *Reprod Biomed Online* 2009)

This Packet Of Information And Additional Legal Documents:

Patient Information Summary, Oocyte Cryopreservation (*cont.*)

SRMS has done the best they can to simplify the cryopreservation process. Even so, there are a number of complexities that must be reviewed.

It is essential that you read this entire packet and understand all of the material. ***Be sure, however, to read all materials thoroughly before making the appointment.***

SRMS staff will provide you with all the documents required by RTL. SRMS will require that all of these materials be completed and we will forward them to RTL with your oocytes.

Additional In formation:

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| Specialist In Reproductive Medicine & Surgery, P.A. 12611 World Plaza Lane Fort Myers, FL 33907 Phone: (239) 275-8118 Fax: (239) 275-5914 | ReproTech, Ltd. 4661 Johnson Rd., Suite 2 Coconut Creek, FL 33073 Phone: 1-888-953-9669 Fax: 954-570-7693 infofl@reprotech.com |
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Summary:

ART and oocyte cryopreservation are very exciting fields. This area of medicine demands more from the participants over a shorter period of time than most other areas of medicine. This information packet may need to be reviewed on more than one occasion. Feel free to ask any questions of the IVF Coordinator, the Embryologist or the Physician.

We welcome you to our practice and look forward to providing you with the very best of medical care.