Frozen Embryo Transfer

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Frozen embryos is a term used to refer to those embryos that are not transferred during in vitro fertilization cycles and are subsequently cryopreserved. A frozen embryo transfer can be used to produce a viable pregnancy by first thawing the frozen embryo, and transferring it into an appropriately prepared uterus. Other names for this process such as embryo freezing or embryo cryopreservation have been commonly used. The treatment to establish a pregnancy using frozen embryos has been called a thaw cycle or a frozen embryo transfer cycle or simply an FET cycle.

Pretesting for a frozen embryo transfer

In order to maximize the chances for success using frozen embryos, a woman should have a normal uterine cavity. There are three tests that can be used to assess the uterine cavity:

- Hysterosonogram – In which saline is injected into the uterus and the cavity is viewed with ultrasound
- HSG in which x-ray dye is injected into the uterus and the cavity is viewed with x-rays.
- Hysteroscopy – In which a fiberoptic telescope is introduced into the uterus and the cavity is viewed directly.

If abnormalities of the uterine cavity are discovered, they should be corrected surgically before proceeding with a frozen embryo transfer.

Protocols for frozen embryos transfer
Hormone preparation for FET

Using hormones to prepare the uterus is the most common way in which a frozen embryo transfer is performed. The first step is to suppress the pituitary gland. This is necessary to reduce the chances of ovulation occurring unexpectedly. Typically, Lupron is used for pituitary suppression. For most women, this will require approximately two weeks of daily Lupron injections.

The second step in a frozen embryo transfer cycle is to use hormones to duplicate the changes that normally occur in the uterus during a regular menstrual cycle. This requires the use of two hormone medications: estrogen and progesterone.

Estrogen preparation for FET

During a normal menstrual cycle, estrogen is produced by the developing follicle. This estrogen acts on the uterus to thicken and mature the uterine lining. Estrogen is given in a FET cycle for the same reason. There are many different ways that estrogen can be given in a frozen embryo transfer cycle:

- Estrogen pills – Estrace, Premarin
- Estrogen patches – Estraderm, Climera
- Estrogen injections – Delestrogen (estradiol valerate), Depogen (estradiol cypionate)
- Vaginal estrogen – Vagifem, Femring

There is no data that any one method works better than another and a method is usually chosen based on physician

preference. We like to use estrogen pills since it is easy to do, inexpensive and very well tolerated.

During the time when estrogen is given, the woman will come to the office periodically to be monitored. A transvaginal ultrasound is performed to determine the thickness of the uterine lining and a blood test is performed to look at the level of estrogen in the blood. On occasion, if the lining is not thickening as it should, the dose or type of estrogen must be increased or prolonged. The length of time the estrogen can be given is very flexible. During this phase, for example, the duration of estrogen may be prolonged to delay the day of embryo transfer to accommodate the patient’s schedule.

The monitoring in a thaw cycle is very flexible. Unlike a fresh IVF cycle during which the required days for monitoring are determined by the growth of the follicles in the ovary, in an FET cycle, the days can be adjusted at any time. Thus, a frozen embryo transfer cycle is much less stressful on the patient.

Progesterone in an FET cycle

Once the uterine lining has been thickened sufficiently, progesterone is added. Once the progesterone is added, the Lupron may be stopped. Progesterone matures the uterine lining and makes it receptive to an embryo to implant. Once the progesterone is begun, there is a certain “window of implantation” during which the embryo must be transferred. The stage of the embryo must match the stage of development of the uterus. Therefore, the only factor that locks the patient into performing the transfer on a certain day is starting the progesterone. Once the progesterone is begun, if the embryo transfer is not performed on a certain day, the cycle must be cancelled and a new preparation with hormones must be begun after allowing a period to occur.

There are many different types of progesterone that can be used in a frozen embryo transfer cycle. Some of the more common methods include:

- Progesterone pills – Prometrium
- Progesterone injections
- Progesterone vaginal suppositories
- Progesterone vaginal gels – Crinone, Procheive

There is considerable uncertainty in the medical literature concerning which type of progesterone is the best for FET cycles. Again, the choice of progesterone for an FET cycle is up to the discretion of the physician. A few things, however, most experts would agree on. Progesterone given by mouth is unreliable due to variable absorption and subsequent metabolism in the liver.

In our practice, we give progesterone as intramuscular injections and with a vaginal gel. In this way, we can ensure that we have used whatever method of progesterone is ultimately determined to be the best.

Once the uterine lining is adequately thickened with estrogen, the progesterone is usually started on a particular day to allow for scheduling of the embryo thaw and embryo transfer for a time that is convenient for the in vitro fertilization laboratory staff.

In our practice, we commonly freeze embryos at the blastocyst stage. This is an embryo that has developed for five days in the laboratory. It must be placed into a uterus that has been exposed to progesterone for five days. Our protocol is to start progesterone on a Sunday and then thaw and transfer the blastocysts on a Thursday, in the afternoon. This allows my laboratory staff to be able to prepare ahead of time for all of the frozen embryo transfer cycles on one day. The afternoon transfer allows them to thaw the embryos in the morning, assess for viability during the day, thaw additional embryos if necessary and still have the transfer the same day.

FET during a natural cycle

If a woman has regular, ovulatory menstrual cycles, a frozen embryo transfer can be performed without the use of hormone preparation. Several studies have shown that the pregnancy rates in natural FET cycles are equivalent to that of hormone prepared cycles. In practice however, these cycles are much more difficult logistically to perform.

In the section above, it was stated that there is a precise window of implantation for transferring frozen embryos. This must be maintained in a natural FET cycle as well. This requires precise determination of the time of ovulation. This can be done by using a home ovulation predictor kit. However, as anyone who has ever used these kits knows, it is sometimes difficult to read them accurately. Although the instructions accompanying the ovulation kits usually recommended that women test the urine once each morning, for FET cycles we recommend testing in the morning and evening. It is also possible to monitor natural cycles using blood tests and ultrasounds just as we do for a hormone prepared frozen embryo cycle.

Unfortunately, during a natural cycle, we cannot control the day of ovulation. If the day of embryo thaw and transfer falls regularly on a Sunday or holiday, the laboratory staff will become very unhappy.

Stage of cryopreservation for frozen embryos transfer

After an egg is fertilized, it can be grown in the laboratory for up to five or six days. Cryopreservation of the embryos has been accomplished at all stages of embryo development. There is no universal agreement as to which stage of embryo development is the best for cryopreservation.

If an embryo is frozen immediately after it has been fertilized (pronuclear stage), the survival of the embryo after thawing appears to be high. However, since the embryo was not cultured in the laboratory first, its potential viability is unknown. Therefore, after the embryo is thawed, it must then be cultured in the laboratory in the same way it would have been if it had not been frozen. It is impossible to predict how many of the thawed embryos will reach the stage of development desired by the physician for transfer. Therefore, a higher number of embryos must be thawed. If a large number of embryos does reach that stage of development, then there is a dilemma. Either a larger number of embryos must be

transferred (which increases the risk of multiple pregnancy) or the extra embryos must be discarded or refrozen. There is very little data about the safety or success of refreezing embryos so it is not recommended.

An embryo can also be frozen after two to three days of embryo development. This is called the cleavage stage. Cleavage stage cryopreservation allows for some limited assessment of the development of the embryos. Some embryos, for example, will not have developed or look abnormal and thus would not be frozen. On the downside, the survival of cleavage stage embryos is lower. As with the case of embryos frozen at the pronuclear stage, cleavage stage embryos can also be cultured after thawing to further help determine the best embryos for transfer.

We freeze embryos at the blastocyst stage. Since the embryos have been cultured for five to six days, this enables the best assessment for viability and thus fewer non-viable embryos will be frozen at this stage. In the past, survival of the embryo after thawing has not been very good. In recent years, however, techniques for freezing blastocysts have improved and in selected centers the survival rate is very good. Blastocyst cryopreservation allows for the thaw and transfer of embryos on the same day.

Pregnancy rates using frozen embryos

There is much confusion about the ability of frozen embryos to produce pregnancy. On initial inspection, the chance for pregnancy using frozen embryos appears to be lower than the transfer of fresh embryos. On closer analysis, however, this may not be true. Find out more about frozen embryo transfer success rates on the follow up page.

How long can frozen embryos remain viable ?

In 2006, researchers from New Jersey compared the pregnancy rates obtained when embryos were frozen for different lengths of time. The data showed that no difference in the chance for pregnancy was evident even when embryos were frozen for more than ten years.

Is embryo freezing safe for the baby?