Freezing embryos and the replacement of embryos

fertility NEW ZEALAND

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Why freeze embryos?

The vast majority of in vitro fertilisation cycles (including ICSI) use fertility drugs to stimulate oocyte (egg) production. This means there are often more embryos available than can be replaced in that cycle. Providing those 'spare' embryos have developed to the appropriate stage within a certain time they can be preserved by freezing and replaced at a later date, without the need for further ovarian stimulation. This increases the overall chance of pregnancy from each oocyte pick-up. Embryo freezing is also an important way to preserve embryos in cycles where fresh replacement is inadvisable, for example, where the woman is considered at risk of developing Ovarian Hyperstimulation Syndrome (OHSS).

At what stage can embryos be frozen?

Embryos can be frozen at any stage from single cell on day one to blastocyst on day five or six. The stage at which freezing takes place may depend on the planned day of the embryo replacement, usually two to five days following the oocyte pick-up.

Once the 'best' or now less often, the 'best two' embryos are chosen to replace fresh, the developmental stage and quality of the 'spares' will determine their suitability for freezing. For an embryo to be regarded as a good candidate for freezing (and surviving thawing) it should have reached the appropriate cell number for its age and have shown reasonable evenness of development.

Even then, embryos not regarded as suitable for freezing at day two or day three can be kept in culture to see if they become blastocysts, and be frozen at that stage.

There is an increasing tendency to freeze as blastocysts on day 5 or 6 because of better embryo survival and a higher chance of pregnancy per embryo.

How are embryos frozen?

Embryos may be frozen in two different ways. One is known as slow cooling and the other, vitrification. With both methods, embryos to be frozen are placed in a solution of cryoprotectant (anti-freeze) medium which allows the cells to survive freezing and thawing. The cryoprotectant draws water out of the embryo, reducing the chance of lethal ice crystal formation within the cells upon cooling. With slow cooling, embryos are then loaded into plastic straws labeled with patient identification information. Once loaded, the straws are placed within a special freezing machine which cools them very slowly to -35˚C.

Once the freezing machine has completed its programme the straws are immediately plunged in liquid nitrogen (at a temperature of -196˚C).

With vitrification, embryos are placed on a special straw in a tiny volume of cryoprotectant, and 'snap-cooled' straight to -196˚C. With both methods straws are then placed within plastic goblets, also labeled with patient identification details, then those goblets are placed in a liquid nitrogen bank for storage.

Thawing embryos for use

For women with reasonably regular cycles, frozen/thawed embryos can be successfully replaced in a natural cycle, preventing the need for any drug administration. The woman would normally inform the clinic within a day or two of the start of her period and the clinic would arrange a plan to track the cycle to pinpoint ovulation. Tracking is normally by blood tests. Tracking establishes the day of ovulation during that cycle and that becomes day zero. The embryos are then thawed in synchrony with the cycle. For instance, embryos frozen on day one following oocyte pick-up will be thawed on day one post ovulation of the natural cycle. This synchronisation ensures that the developing embryo is ready to implant when the uterine lining is at its most receptive.

Women who do not cycle or have very irregular cycles can have their embryos replaced in an artificial cycle. Different clinics have different strategies for mimicking a natural cycle with medication, but all have two essential steps. Firstly the uterine lining is stimulated to grow (usually with estrogen tablets or patches). Once the lining has reached a certain thickness, it is primed with progesterone to become receptive to an implanting embryo. Artificial cycles are becoming popular because then people can plan the exact day for embryo transfer.

Straws containing the embryos are removed from the liquid nitrogen bank and allowed to warm rapidly. The straw seals are then cut and the embryos recovered.

The embryos are then passed through a series of solutions which slowly draws the cryoprotectant out of the cells. It is only when the embryos have come out of the final thawing solution and been placed in culture medium that survival of most embryos can be fully assessed.

In cleavage stage embryos (those frozen on day two or day three of development) we can evaluate how many cells have survived. If 50% or more cells have survived the embryo is regarded as viable and can be considered for replacement. The chance of an embryo which has been frozen on day 1 to day 3 surviving completely intact is 50–70% but can vary between individual couples and even between different cycles for the same couple. With blastocysts, embryo survival is around 90–95%.

If embryos have been frozen at day 1 (pronuclear), or day 2 (four-cell), they would often be cultured overnight before replacement. During that time the thawed embryo would be expected to continue cleaving. With embryos frozen on day 3 (eight-cell) or day 5 (blastocyst) resumption of development is not usually seen as embryos are usually replaced on the same day as the thaw.

Embryo replacement

You would normally have been asked to call the clinic beforehand to check embryo survival. Often this would be on the same day as the intended embryo replacement. The embryo replacement procedure is the same as that used for replacing fresh IVF or ICSI embryos. Women having their embryos replaced in an artificial cycle will need to carry on progesterone support until the time of a pregnancy test (and beyond, if they do become pregnant). Pregnancy testing is around fourteen days after 'ovulation' for both types of cycle.

The chance of success

As with all fertility treatments, the chance of success depends on several factors, such as the woman's age. The chance of pregnancy following the replacement of frozen/thawed embryos tends to be slightly lower than that achieved replacing fresh embryos. There are several reasons why this should be.

In theory, frozen embryos can be stored for hundreds of years, but the HART Act in New Zealand imposes a time limit for storage of ten years.

- During a cycle of IVF (including ICSI), several embryos are cultured to the day of replacement. The 'best' developing embryos are selected for fresh replacement, leaving the 'second best' for freezing.
- Frozen/thawed embryos can lose up to 50% of their cells and still be regarded as viable and therefore can be replaced. Fresh embryos are almost always totally intact.

Further considerations

Immersed in liquid nitrogen at -196˚C, all biological activity ceases within stored embryos. This means that, in theory, they can be stored for hundreds of years without degrading, but in practice, embryos are rarely stored for more than a few years and the HART Act in New Zealand imposes a time limit for storage of ten years. Even so, quite a lot can happen to a couple over that time!

All clinics will want to know the wishes of the couple on what they want done with stored embryos should the couple separate or should one partner die, and these difficult decisions have to be made before any embryos are stored. As clinics continually improve chances of success with all treatments, it is likely that many couples may be in a position where they have decided that their families are complete, but embryos remain in storage.

The options open to the couple at this stage are to remove the embryos from storage and allow them to perish or to donate the embryos to another infertile couple. Embryo donation is a complex process that requires ethics committee approval.

Perhaps the most important point to remember is that you, the couple, are responsible for informing the clinic at which your embryos are stored if you move or your circumstances change. It may come as a surprise to know that embryo storage banks all over the world, including New Zealand, contain embryos belonging to untraceable couples. Eventually, at the end of the legal storage period, these embryos are removed from the banks and disposed of, without the couples ever being able to be informed. If you move, let the clinic know! If you move to a long way from the clinic, or even overseas, it is possible to ship frozen embryos to another more convenient clinic.

While almost all couples choose to freeze 'spare' embryos, you should think about the implications before you make this choice. ■

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