Frozen Embryo Transfer Vs Fresh Embryo Transfer after IVF

Frozen Embryo Transfer Vs Fresh Embryo Transfer after IVF

After embryos are created with in vitro fertilization, should you have your embryos transfer 3 to 5 days later or should embryos be frozen and transferred later in frozen-thaw cycle (FET)? This question became viable after improvement in freezing technology (vitrification) to the extent that the vast majority of embryos (>95%) frozen in The US survive thaw and has high implantation potential.

There are indications to freeze all embryos after IVF i. avoiding ovarian hyperstimulation syndrome,ii. unfavorable uterine lining (thin, fluid..) iii. allow more time for PGD / PGS, iv.personal reasons related to patients.

The aim here is to discuss the merits for and against *elective* embryo freezing to transfer the embryo or embryos in a thaw cycle. A thaw cycle involves preparation of the uterine lining, embryo thaw and embryo transfer (no stimulation or egg retrieval). Preparation of the lining of the uterus can be accomplished through one of two main methods

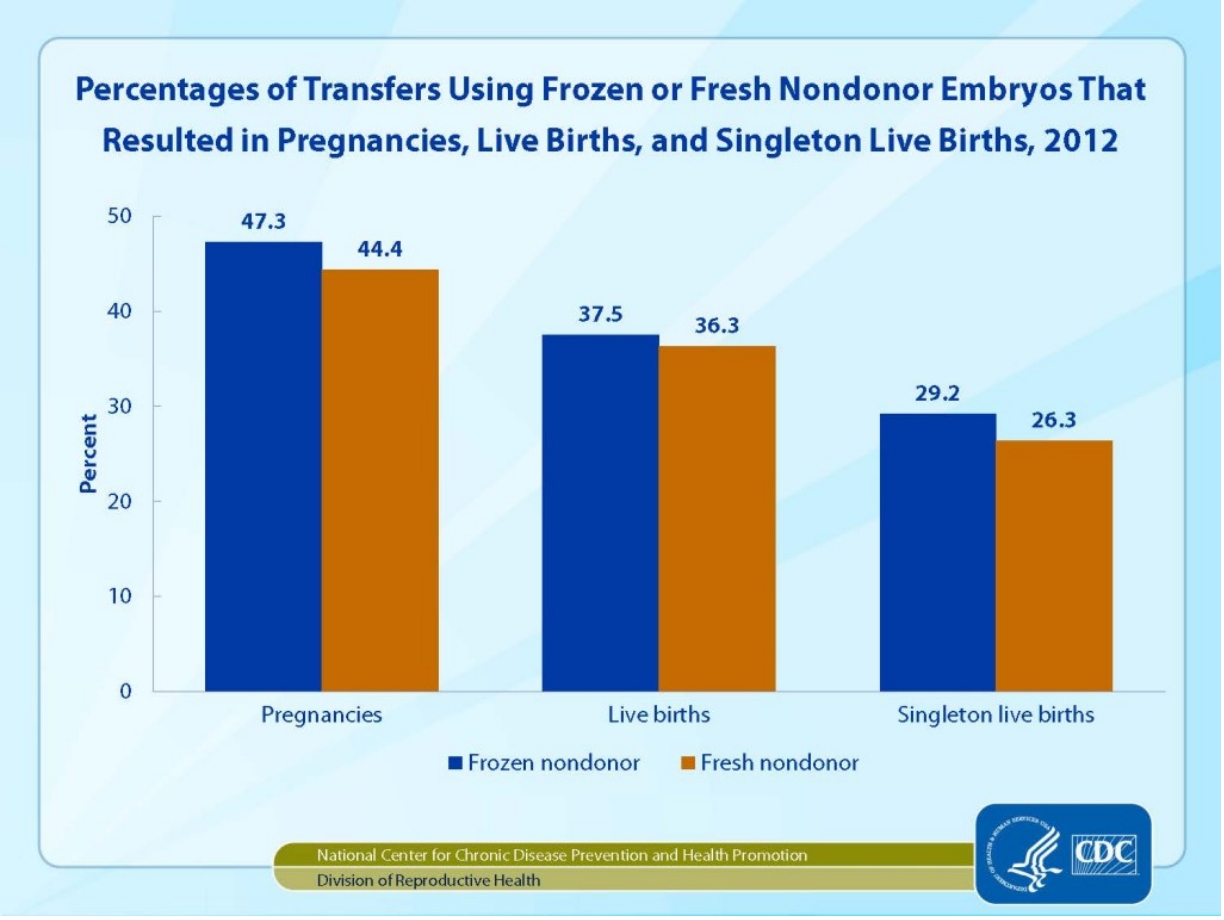
a. Natural Cycle FET : Natural ovulation is monitored using ultrasound and blood work. The time of ovulation need to be accurately defined. Embryos are thawed 3 or 5 days later and transferred. It requires minimal medications but require regular ovulation.

b. Synthetic Cycle FET : Estrogen is administered (patches, pills..etc) till the lining of the uterus reach the desired

thickness and pattern. Progesterone is then administered (injections, vaginal tablets) and embryos are thawed and transferred few days later. It does not require ovulation and allows more flexibility in timing of embryo transfer.

There is some evidence that both methods are equivalent with regards to implantation and pregnancy.

On The Advantages of Elective Frozen Embryo transfer



Fresh embryos vs Frozen Embryos

In the US frozen cycles result in equivalent number of pregnancies and deliveries as fresh embryos.

Should Elective Frozen Embryo Transfer be Recommended to The General Fertility Population

Undergoing IVF?

In other words, do we have enough data to recommend freezing all embryos created after IVF and transfer later?

The possible advantages cited for performing frozen embryos transfer originates from two sources

1. Physiological information: excessive exposure of the lining of the uterus to estrogen may lead to abnormal development of the placenta and

2. Observational studies: when compared to fresh embryo transfer, pregnancies resulting from frozen transfer are less affected by bleeding and are associated with heavier babies with lower odds for low birth weight.

Conclusions resulting from non controlled studies and physiologic interpretation are not always accurate due to differences between the two groups and cannot be relied upon for definitive conclusions. A definitive study will need to be prospective and patients can be randomly allocated to fresh transfer or elective frozen transfer. This study does not exist at this time

Can Elective Frozen Embryo Transfer Improve Pregnancy & Delivery Rates?

Three studies showed a trend to improve in pregnancy rates following frozen transfer when compared to fresh IVF transfer. The studies should be interpreted with caution as it included young high or normal responders and not low responders and older women. The studies did show an improve in delivery rate, did not track perinatal outcomes and did not include economic analysis of cost and benefits. So a larger and more comprehensive study is still needed.

New Ideas in reproductive medicine, though exciting, still require the scientific rigorous study to ensure that the

conclusions are correct and define which group will benefit most from freeze all strategy before its general application to women undergoing IVF.

If you need to freeze your embryos after IVF to avoid ovarian hyperstimulation syndrome, because of unfavorable uterine lining or other reasons, please do so especially if the clinic has a robust freezing program. Freezing of embryos (especially with vitrification) is unlikely to affect your chance to get pregnant. On the other hand if you want to freeze all your embryos to improve your chance of getting pregnant, know that this strategy is debatable and not backed by solid scientific evidence.

When undergoing a frozen transfer cycle and if you have regular ovulation and a favorable lining, consider natural cycle FET over synthetic (medicated) cycle as there is evidence that they are equivalent. Natural cycle avoid external medications and excessive exposure to estrogen

---

Embryo Selection after IVF

Embryo Selection after IVF

Many of human embryos produced after in vitro fertilization carry abnormal chromosomes. Placing a chromosomally normal embryo (s) into a normal uterus has a very high chance of achieving a pregnancy. Your eggs have been retrieved and the mature eggs were fertilized. Now You and your reproductive endocrinologist are faced with the critical task of how many and which embryo to transfer to the uterus or which ones to freeze.

Why do we Need Embryo Selection?

Selection of the most appropriate embryo(s) for transfer aim at i. Maximizing the chance for pregnancy and ii. Minimizing the risk of twins and other multiple pregnancies. Casual inspection of the embryo does not yield accurate information about its chromosome makeup. One can follow an indiscriminate approach where all embryos are transferred. The problem is this approach yields high unacceptable multiple pregnancy rates. On the other hand one can transfer one embryo at a time. This is a much safer approach in terms of markedly minimizing twin rates but may lower the chance for getting pregnant. In addition it also require a robust freezing program so that frozen embryos can survive thawing. Right now in The US the survival of frozen embryos exceed 95% and the chance for pregnancy with a thawed embryo is approximately equal to a fresh embryo.

Measure of Success: time to conceive or cumulative chance for pregnancy?

One major issue related to fertility treatment especially IVF is how to measure success? specifically consider this question: if you have three embryos and decided to transfer them one at a time and got pregnant after the third transfer with a singleton, how does that compare to transferring all embryos in the fresh cycle and getting pregnant in twins? before answering it is important to know that twin gestation is associated with higher risk for pre-term delivery, ICU admissions and long term consequences for the babies.

In other words should you consider success as pregnancy taking place after one retrieval (cumulative chance from fresh and frozen embryos) or pregnancy taking place in the fresh cycle only (fresh embryos)? In other words would you like to shorten the time to conceive at the expense of higher risk for multiple pregnancy? Within *reason*, this is a question for you and your reproductive endocrinologist to answer based on your

preferences and his practice

You have a Voice: How should you use your embryos after IVF?

You need to have a voice in the number of embryos transferred to your uterus. Although your fertility specialist can discuss numbers and chances and other technical details as well as long term risks for multiple pregnancy, there are questions that cannot be answered by anyone but you.

- How do you feel about twins? triplets and quads?
- Would you accept fetal reduction (removal of one or more sacs from the uterus and leaving only one or two)?
- Do you have the social support system to take care of twins?

For these and many other reasons your input in the number of embryos to transfer is paramount.

Methods of Embryo Selection after IVF

Embryo Morphology and Female Age

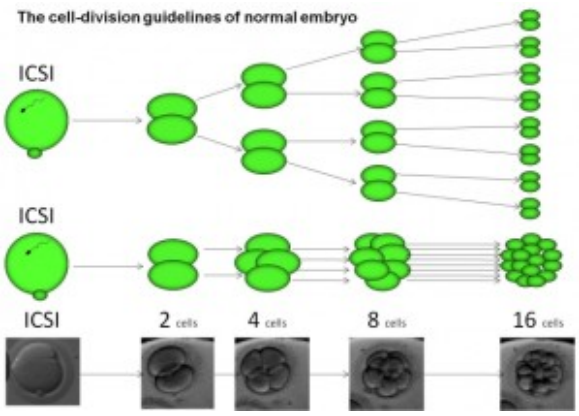
Age is, by far, the strongest predictor of the health of the embryos. Younger women produce more chromosomally normal embryos than older women. An embryo from a woman at age 30 commonly implants 40% of the time as opposed to 5% or less in a woman age 40. For any given cohort, embryos are graded based on specific morphological criteria from the best looking to the worst. These criteria are technical and followed by all embryologists. Embryos are prioritized for transfer based on their shape. Morphology, however is may be 50 to 60% predictive of pregnancy, far from ideal. The combined use of morphology of embryos, stage of development (day 3 or blastocyst) and age is the standard selection method for which embryo is transferred first and how many. This method has the advantage of being sheep, quick and non-invasive. All other methods must prove superior to morphology + age before

adoption.

Extended Culture to Blastocyst Stage (Day 5 Embryo)

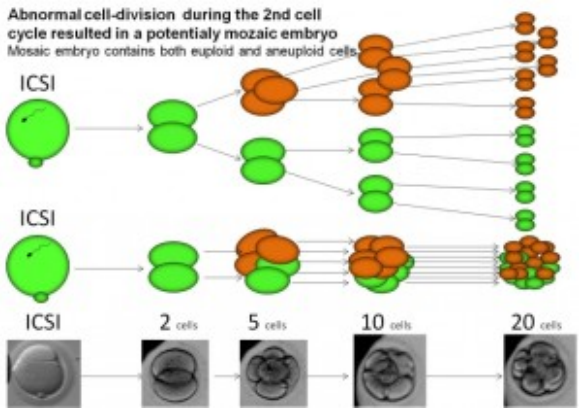
Keeping day 3 embryos in culture may give these embryos may time to develop to blastocysts. Presumably, the better embryos progress to blastocysts or do so faster than less healthy embryos, thus they are preferentially selected for transfer.

Time Lapse Imaging of Embryos



time lapse embryo imaging- normal embryo division

Embryos are placed in a specific incubator in a specific plate and is observed at predetermined time



time lapse embryo imaging- abnormal embryo division

points using time lapse microscopy / photography. Photos are analyzed manually or through a computer and embryos are graded based on timely division of blastmeres (component cells). There is no evidence so far that pregnancy rate is improved above using morphology. There is extra cost associated with the use of the special plate and is also limited by the number of special incubators available.

PGS (Embryo Chromosome testing)

New forms of PGS (performing biopsy at the blastocyst stage) and more accurate platforms for analyzing the biopsied cells are available. However, the concept that better selection will lead to improved IVF results is far from certain.

It success of an IVF cycle is measured after transfer of fresh then frozen embryos till pregnancy ensues (cumulative success) ad patients are will to be patient for 1-2 more months, then any form of embryo selection, PGS or otherwise, will not improve the live birth rates. Moreover, PGS can be harmeful as it may misdiagnose the health of the embryos (see this article on PGS for details). PGS increases the expense of treatment $4000 to 6000

Embryo selection is maybe be able to improve the time to pregnancy, if embryos with the highest implantation potential are transferred first.

> *Based on the available evidence, judicious selection of embryos based on patient age, morphology and the use of extended culture to blastocysts are the standard of care in embryo selection after IVF. Two additional factors to consider is how robust is the freezing program of that specific lab (generally excellent all over the US) and the acceptability of fetal reduction by the couple. Liberal use of single embryo transfer when appropriate should be strongly considered. 'New' ideas should be subjected to rigorous scientific evaluations 'fertility clinical trials' before*

they are ready for routine use. Thus far, based on published evidence, embryo time lapse imaging and PGS should remain investigational.

Pre-implantation Genetic Screening (PGS): What are we really talking about?

Pre-implantation Genetic Screening (PGS): What are we really talking about?

The tenant behind **pre-implantation genetic screening (PGS)** is to biopsy one or few cells from each embryo after creation, analyze the chromosomes for each embryo and transfer the ones that has normal chromosomes back into the uterus to boost IVF success and increase the live birth rate.

Central to this idea is that abnormal chromosomes in the embryos is the main reason why an embryo does not yield a newborn. It is logic then that **PGS** should allow the selection for the best embryo (preferably one only) for transfer into the uterus ending into one singleton newborn.

If this premise is accepted then the following assumptions should also be generally accepted

a. All or the majority of embryos reached the appropriate stage of development and expansion to allow biopsy.

b. Biopsy of the embryo does not harm its ability to implant

c. The cell or few cells obtained represent the rest of the embryo (has identical chromosomes to all the other cells in the embryo)

d. The platform used to analyze the embryo chromosomes is close to 100% accurate (otherwise some embryos will be wasted because they are abnormal according to the test, while they are actually normal). The platform reports only the chromosomes of the embryo and is not accountable for other elements of implantation i.e. the endometrium.

e. The delay (one or more days) needed to finish the testing does not affect embryo implantation

f. Freezing and then thawing of a biopsied embryo does not affect its implantation potential

g. Patients and physicians have agreed on how to calculate success: how many live births one would obtain from all embryos resulting from a single IVF cycle (all fresh and frozen embryos) i.e. total potential of one IVF cycle versus fresh embryo transfer only.

h. The added cost of biopsy and testing of embryos, potential increases the delivery rate and reduces the incidence of multiple pregnancy and miscarriage is cost-effective from the viewpoint of individual and a modern society.

The initial attempt to perform **Preimplantation genetic diagnosis** using an old technology called FISH that tested 7 to 9 chromosomes proved harmful few years ago and that its wide adoption at that time was a form of medical illiteracy : because it depends on logic not actual well conducted study. When the studies were conducted, they all showed that women universally achieved lower pregnancy rates after PGS.

New platforms are now available to test for all the

chromosomes (array cGH and SNP array) and using cells (trophoectoderm) obtained from more advanced stages of the embryo (blastocyst). The question in hand is should we adopt these techniques, not as a research tool, but as the standard of care that should be offered to the majority of women undergoing IVF?

How Effective is PGS? The case for Logic

Applying logical thinking to modern pre-implantation genetic screening (PGS) methods indicates:

a. Not all embryos will reach the blastocyst stage (day 5) to be suitable for biopsy. Not all physicians and patients push their embryos to the blastocyst stage especially if few embryos exist in culture on day 3. Moreover, some normal embryos may not survive extended culture to blastocyst.

b. There are no conclusive evidence that biopsy of the trophoectoderm (the part that makes the placenta) of an embryo does not harm the embryo.

c. Mosaicism ; when one or few cells are different in chromosomes than the rest of the cells, is known to take place in embryos. The cells in the trophoectoderm maybe abnormal while the cells in the embryo maybe normal. Interestingly the embryo can later get rid of the abnormal cells in the trophoectoderm. This can lead in misdiagnosis of the embryo as abnormal while the embryo itself has the potential to implant and yield a healthy baby.

d. The platform used to analyze the embryo chromosomes is not 100% accurate either because of the accuracy of the test itself or because of mosaicism. The accuracy reported by labs administering the test is 97%. This means some normal embryos will be discarded and some abnormal embryos will be

transferred. Actually the accuracy was not validated by many labs, only very few worldwide. Clinically some physicians have experienced much lower accuracy (80 or 90%). The platform reports only the chromosomes of the embryo and is not accountable for other elements of implantation i.e. the endometrium. So it is possible that the lower accuracy is due to other elements on embryo gentics (other than the number of chromosomes) or the lining of the uterus.

e. Currently the transfer of embryos into the uterus has to be delayed for one day (day 6) or several weeks (embryo has to be frozen then thawed back after results are obtained). This delay may reduce implantation of the embryo because it will not match the window of implantation in the lining of the uterus. This is a controversial point as some researchers found no difference in implantation between day 5 and day 6. This research, however, is not widely replicated.

f. After PGS some 'normal' embryos will be frozen. The survival of thawed and biopsied embryos is maybe reduced, potentially leading to loss of normal embryos. No large studies on survival of biopsied embryos after thaw exist.

g. Patients and physicians have agreed on how to calculate success: if success is calculated based on how many live births one would obtain from all embryos resulting from a single IVF cycle (fresh and frozen) i.e. total potential of one IVF cycle, then PGD has no value as it will not make an abnormal embryo normal or vice versa. If the success is based on what happens in the fresh cycle only with no regard to frozen embryos then PGS may improve the success rate of IVF. All assuming an excellent embryo freezing program.

For exampe If you are a young woman <38, with a good number of available embryo on day 5, say 4 blastocysts that are suitable for biopsy, you may elect to

i. transfer one embryo in the fresh cycle and freeze 3

embryos. If you are not pregnant, then transfer one embryo in each subsequent frozen cycle. If you are destined to get pregnant you will do that within a maximum of 3 months after your initial IVF and the risk for multiple pregnancy is minimized to 1% or less. If you were not destined to get pregnant no testing would have helped you or

ii. Alternatively, you may elect to test all your embryos in the fresh cycle, transfer one normal embryo, if any and freeze any normal embryo remaining. The potential benefit is getting pregnant in the fresh cycle instead of getting pregnant 1-3 months later. Also you will reduce the risk of miscarriage because abnormal embryos will likely be eliminated. The potential risks are misdiagnosis by PGS (not 100% accurate), loss of a thawed embryo (did not survive biopsy and freeze) and lower implantation potential of a normal embryo due to biopsy and delayed transfer.

h. A cost-effective analysis for PGS is not available at this time. The added costs are biopsy and testing of embryos. The potential benefits are increase in the delivery rate and reduction in multiple pregnancy and miscarriage. In the scenario above you either pay for i. frozen embryo transfer(s) if you do not get pregnant in the fresh cycle or ii. pay for ICSI (required for PGS by the majority of programs), biopsy and testing in the fresh cycle and frozen embryo transfer(s) if you do not get pregnant in the fresh cycle. In terms of multiple pregnancy, it can be minimized in either pathways if your physician is transfers one embryo anyway, tested or not. Things are not that simple, the payer will also make a difference: PGS is completely out of a patient pocket as it is not covered by any insurance while frozen embryo transfer may or may not be covered.

How Effective is PGS? The case for

Published Studies

In general decision making in biological sciences is not amenable to logic, but determined by well designed ad well conducted studies. So far, three studies were published using the new platforms for embryo chromosome analysis, aiming at increasing IVF success. The studies were criticized because of

1. Restricted to young women (median age 31 to 32) so results cannot be generalized to the general IVF population: 2 studies

2. Did not account for frozen embryos: all studies

3. The studies did not demonstrate superiority of PGS to transfer best embryos based on morphology (shape): one study. Specifically a transfer of a tested embryo in the fresh cycle was not inferior to transfer of two untested embryos. Non inferiority does not mean superiority. Noninferiority study design is not suitable for a PGS study as patients and physicians are only interested in such an expensive treatment that can harm their embryos only if it promises superior results for their infertility treatment. Moreover, treatment could actually be inferior because a limit is placed that will make the outcome non inferior, in that study 20%. So if the difference is less than 20% PGS is considered not inferior.

4. End point should be live birth or ongoing pregnancy. Surrogate or intermediate endpoints as pregnancy, implantation (short of a baby in hand or at least pregnancy beyond 20 weeks) are not ideal outcomes.

Randomized studies related to **pre-implantation genetic testing** using newer platforms were independently analyzed. So far no study showed that PGS is superior to the strategy of transferring the best embryo based on morphology (the standard of care). Moreover due to factors related to the biology of reproduction and that the accuracy of the test is unlikely to reach 100% accuracy soon, it is unlikely that PGS will prove

beneficial to women undergoing IVF for fertility treatment. PGS may only shorten the time to pregnancy but will not be able to improve the pregnancy rate and due to inaccuracies may even reduce it.

Alternatives to PGS are being studied. One alternative is time lapse photography of the embryos to observe the cell division of the embryo cells and select the best embryo for transfer. It is noninvasive but further studies are required before its ready for general use. Another alternative is polar body biopsy of oocytes but results of ongoing studies are not available yet.

It is possible that factors in this article could be interpreted differently in a specific situation by patients and their physicians, in conjunction with the number of mature eggs produced, but it does not appear that PGS is ready for generalized application in the majority of IVF population.