IVF:The Way We Do It

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Efficient approach

IVF:The Way We Do It. We believe you should consistently be able to get an advice / recommendation for a fertility treatment, handcrafted to your special reproductive potential and egg reserve. *Your ovarian stimulation protocol will most certainly not be suited for the next woman*. We think carefully and for quite sometime about the best adjuvant and stimulation medication protocol, after obtaining adequate information about you and your partner. Moreover, attention to details during stimulation avoids pitfalls and optimize the quality of oocytes through selecting the most appropriate size to trigger final egg maturation. We then present the regimen to you in a simplified and chronological presentation that is easy to follow.

We believe that you should be able to understand all the intricate details of treatment and train on medications within one to two visits (supplemented with phone calls and e mails). You and your reproductive endocrinologist can reach a treatment decision and even train you on execution parts of that decision in the second visit even if you did not do any fertility tests before. This is how we efficiently do it.

IVF : The Way We Do It

I. Initial visit ultrasound, labs and prior records

Basic information about you and your partner are collected through detailed history, exam and vaginal ultrasound.The main aim is to identify any specific fertility factor as well as

estimate ovarian reserve. In addition we order fertility labs and preconception tests. We then discuss in details treatment options, including expected pregnancy rates, multiple pregnancy rates and potential complications.

We obtain and interpret lab results in few days and are discuss them with you especially genetic risk assessment, in person, via secure e mail or phone.

Reproductive endocrinologists should want to care for their patients to help them acheive a healthy baby, not just go through the motions and dynamics of treatment, that has minimal or no chance of working. This is an absolute guiding and ethical principal. Its related to the biological possibilities detected on initial fertility testing and its also related to their physician skills and expertise. At the end of the day infertility specialists need to be ***clearly convinced*** *that a particular woman has a reasonable chance of get pregnant before initiating a proposed fertility treatment. Fertility specialists then should take that woman to her maximum potential.*

II. Second Visit: Saline sonography, trial transfer, medication teach, stimulation protocol.

Checking the cavity of the uterus is essential to exclude factors that prevent implantation. Passing a catheter into the uterus helps anticipating difficulty in embryo transfer. Both are simple office procedures.

Ovarian stimulation Protocol Selection: we think deeply when assigning stimulation protocols in relation to dose and type of protocol (agonist or antagonist) and adjuvant use of medications before and during stimulation. Reviewing prior stimulation can help in improving the current protocol in terms of egg yield and quality. The physician that saw you first will conduct all day to day monitoring as well as all procedures. Attention to details during monitoring is

paramount in determining the dose and length of stimulation and time for egg retrieval.

Additional procedures that we perform during an IVF cycle include sex selection, PGD, number of embryos for transfer, egg and embryo freezing are all available to you. I explain those in details.

Medication teach: a hands on exercise on using the medicine. Now You are ready to start.

III. IVF: monitoring, retrieval, embryology lab procedures.

We always strive to deliver compassionate day to day Guidance, tailored around you comfort and convenience. We want you to waste minimal time waiting because you have the rest of your life and work to attend to.

Cycle conduct: we meticulously interpret the response to stimulation through ultrasound and blood work, with each visit and modify the dose of medications to improve response in the ovaries and minimize complications. The same physician perform monitoring and daily instructions as well as all other procedures. He or she knows your story and you never have to repeat yourself to a new person each time.

Embryology procedures: egg retrieval and embryo transfer done by the same reproductive endocrinologist. Excellent embryologists attend to your reproductive tissue.

Embryo selection for transfer: aiming at transfer of the smallest number of embryos that do the job. Up to age 39 we champion single embryo transfer to minimize twin pregnancy. Sometimes, when appropriate, we employ PGS / PGD to select the best embryo for transfer

IV. Pregnancy Follow up

10-12 days later you will get a blood pregnancy test, then early pregnancy ultrasounds. The aim is to confirm viability, position and health of the embryo. I then discuss nutrition in early pregnancy. I also explain different options in prenatal screening of chromosomal abnormalities in details. These include quad screen, nuchal translucency, Non Invasive Prenatal Test. Amniocentesis and CVS.

In addition, I describe options on multiple pregnancy and fetal reduction in details. We generally transfer a single blastocyst up to age 39 to the majority of women, minimizing the risk for twins.

The years of discomfort, time wasted, untoward effects and long waiting should all be behind us. You should be able to get pregnant in few weeks, safely without loosing any work time. Fertility treatment can be successful while attending to all other aspects of your life. We want to make sure that you are not dealt a false hope but if there a small hope will go fight for it together till we realize it together.

Male Factor Infertility: Azospermia

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Male Factor Infertility: Azospermia means no sperm are found in the ejaculate. Azospermia requires careful evaluation and treatment so that the couple has the best chance to conceive with IVF. The evaluation should be methodical and

compassionate to guide the couple through such a multifaceted process to pregnancy and delivery of a healthy child.

Four Things Have to Happen at Initial Evaluation for Azospermia

a. Is it truly azospermia? sometimes repeat sperm analysis together with spinning of the ejaculate multiple times may yield few sperm. This has to be performed by a diligent andrologist and in a facility that can freeze sperm immediately if found. In some azospermic men, repeat analysis and freezing can avoid a surgical procedure to retrieve sperm.

b. A genetic cause for azospermia should be excluded. Specifically three known genetic problems should be excluded because they can be passed to offspring and because they can predict the success of surgical sperm retrieval. A chromosome analysis should be done to exclude sex chromosome abnormalities e.g klinefelter Syndrome (47XXY). Y chromosome microdeletion study should be conducted to exclude a deletion of the part of Y chromosome related to sperm production. Cystic fibrosis carrier screening should also be run to detect defect in the CF gene that may be associated with absence of the ducts conducting the sperm outside of the testes.

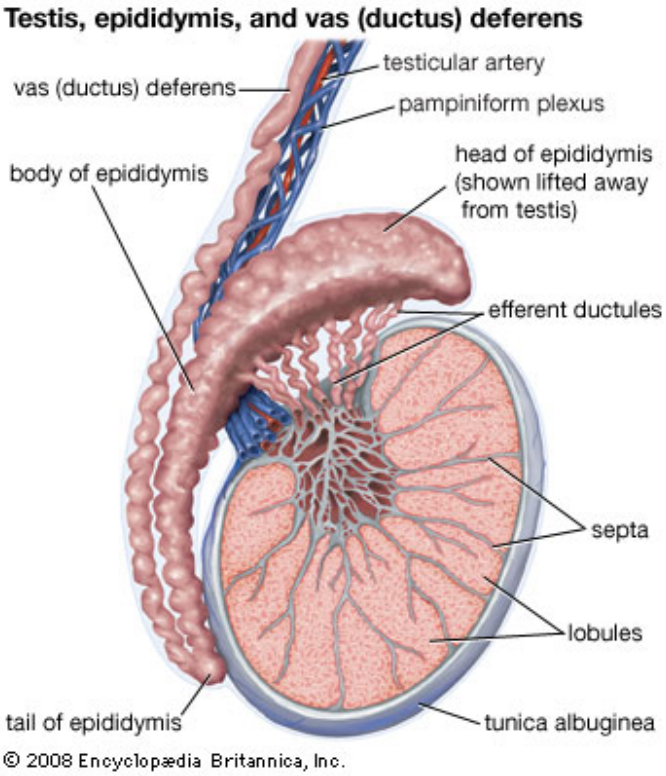
c. Evaluation of Ovarian Reserve for Female Partner. If ovarian reserve evident by day 3 FSH, AMH levels and antral follicle count seen on vaginal ultrasound is not diminished, this predicts reasonable chance for success with IVF-ICSI if sperm are found. Extremely low ovarian reserve or advanced female age may preclude surgical sperm retrieval, unless an donor eggs are acceptable.

d. Urological evaluation. This has to be the last step in evaluation. Male urologists are the physicians specializing in evaluating the chance for successful sperm retrieval (TESE) as well perform these procedures. Before referral by a reproductive endocrinologist and infertility specialist, there

should be every reason to think that if sperm were obtained there is a reasonable chance for conception after IVF-ICSI. The urologist should be a specialist in male reproduction and well versed in the techniques of sperm retrieval. You actually need to ask your urologist two questions: what are my personalized chance for finding sperm when surgery (TESE) is performed? What the technique used to obtain sperm? Authorities generally agree that the technique for TESE markedly affect the chance for finding sperm.

Moreover, every workup should end with an important question; would you accept donor sperm if no sperm were obtained after surgery?

How is TESE Performed?



Testes and ducts

Testicular sperm extraction is a surgical procedure that entails sampling of multiple areas of the testes aiming at finding sperm to be used for IVF-ICSI. The tested is delivered outside the scrotum, bisected and multiple biopsies obtained

from several areas of the testes. The tissue is examined for the presence of sperm. If no sperm were found, more biopsies are obtained till sperm are found. There are generally two types of azospermia: obstructive azospermia (due to obstruction of the ducts of the testes while sperm production is intact). Sperm is obtained in close to 100% of these cases. Non-obstructive azospermia (NOA) where is a defect in sperm production, approximately 60 to 70% of the procedures yield sperm.

Blind biopsy from one area of the testes has no place in modern treatment of azospermia. Asking your urologist about the technique of TESE is of paramount importance. The first surgical attempt carries the highest chance for success.

Recently, Doppler ultrasound mapping of the testes can help localize the areas of that should be biopsies because they yield a higher chance for finding sperm.

Why is IVF-ICSI Required after Sperm Retrieval?

The number of sperm obtained after TESE is small in the magnitude of tens to hundreds of sperm, too small to use the sperm for IUI. ICSI is absolutely required for all cases of surgical retrieval of sperm. The sperm can be used in one of two ways

a. Frozen TESE sperm: The sperm are frozen to be thawed at a later date, on the day of egg retrieval for the female partner. This method saves the cost of IVF if no sperm were retrieved and donor sperm use is unacceptable.

b. Fresh TESE sperm: Ovarian stimulation is started and TESE is performed on the day of egg retrieval or the day before. Fresh sperm are used for ICSI. Donor sperm (if acceptable) is obtained as a backup. Though suggested, there no concrete evidence that fresh TESE sperm is superior to frozen TESE

sperm.

In addition in some caes with associated genetic problems, preimplantation genetic diagnosis (PGD) can be performed followed by the transfer of normal embryos.

Can the Chance for Pregnancy be predicted in Male Factor Infertility: Azospermia ?

There are several predictive factors for pregnancy in female partners of men with azospermia. These can be categorized into:

i. Successful sperm retrieval is related to whether the procedure is the first one or a repeat procedure, the volume of the testes, medical treatment before surgery, the technique used and the cause for azospermia. Some causes are associated to minimal chance for obtaining sperm.

ii. Pregnancy after sperm retrieval is related to the female partner age and her ovarian reserve. Younger women have a very good chance of conceiving if sperm are obtained. This is the most important factor once sperm are retrieved.

iii. Obstructive azospermia has a higher chance for sperm retrieval than non-obstructive azospermia.

iv. Moving sperm at the time of ICSI has a higher chance to yield a pregnancy than non moving sperm

v. Men with higher testosterone levels and lower LH levels has higher chance of sperm retrieval

vi. The effect of using of frozen TESE sperm is controversial. Some authorities think that using a fresh TESE sperm is better than frozen sperm.

vii. Use of Doppler: recent work indicates that the use of Doppler study of the testes before the procedure may help

localize the areas that should be biopsies and yield a higher chance for sperm harvest.

> *Male Factor Infertility: Azospermia requires a multidisciplinary approach; first consultation with a reproductive endocrinologist (female age is still the most important factor) followed by a consultation with a reproductive urologist for the TESE procedure for successful sperm harvest and pregnancy*

Anatomy of Ovarian Stimulation Protocol for IVF

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Understanding the anatomy of ovarian stimulation Protocol for IVF or how is the ovary stimulated to produce multiple eggs, helps you understand different medications you are administering prior to IVF. Understanding the endocrine make up of a woman is essential before selecting and optimizing a protocol including

i. ovarian reserve (and predicting before starting treatment if she is a high, average or low responder)

ii. Age and what is a reasonable response for a pregnancy to ensues

iii. Differentiating between PCOS, hypothalamic amenorrhea and normal ovulatory women.

iv. Other gynecologic problems e.g endometriosis

v. other factors that may lower the response : prior ovarian surgery, medical disorders, chemotherapy exposure ..

vi. What are the specific aims of IVF in addition to pregnancy e.g PGD..

After evaluating these factors for each woman, different options are selected for stimulation prior to IVF. There is o place for one protocol fits all. Its a diligent thinking of what works best, one patient at a time.

Adjuvants

These are medications given prior to menses or during the cycle to improve response to gonadotropins

Estradiol: oral or vaginal to synchronize the follicles, so that they are equal before starting stimulation so that they end the cycle close to each other at the time of egg retrieval

Antagonist: to prevent a premature growth of follicles prior to starting stimulation so that we obtain a synchronized group of follicle.

Oral contraceptive pills: we do not use birth control for timing of the cycle most of the time but sometimes to obtain a regular group of follicles before starting stimulation

Testosterone: testosterone gel for 2-3 weeks has been shown in randomized clinical trials likely because of of sensitizing the ovary to the effects of stimulation medication. No other androgen preparation has been demonstrated to improve pregnancy outcome including DHEA.

Clomid or letrozole: these oral medications may improve response through release of internal FSH from the master gland.

Other medications suggested to improve response with week evidence that they actually improve the pregnancy rates e.g Growth Hormone

Prevention of premature ovulation

One landmark improvement in stimulation protocols is the addition of medicine that prevents the master gland in the brain from triggering ovulation prematurely. Two options are available agonist or antagonist

Agonist in a short protocol (flare lupron) or long protocol

Antagonist starts during the cycle when the largest follicle reach 14mm and estardiol level 300pg/mL

Each have its advantages and merits and they are generally used for women with different endocrine environmwnt. Antagonist protocols gained more dominance in the past decade.

Gonadotropins

Two main types of gonadotropins exist in the US; Pure FSH and a mixed FSH + LH preparation. FSH is the main stimulating medicine but in some women the addition of LH improves the response. Many women receive mixed FSH and LH ptotcols.

The dose of such medicine starts at the highest dose then is drops gradually, the step down protocol. The initial dose depends on egg reserve, weight and expected response. Usually the maximum starting dose is a total of 450 units.

Some reproductive endocrinologists recommend Minimal stimulation IVF in select patients. There is no proof that the concept one healthy egg is correct. As a matter of fact many women produce many healthy eggs in the same cycle. There is no evidence that cycle for cycle they produce comparable pregnancy rate. Proponents of multiple stimulation recommend multiple cycles to produce multiple embryos.

Ovulation Trigger

When your reproductive endocrinologist perceive that the eggs are close to maturity, she or he employs a triggering agent to finalize follicle maturity and prepare the eggs for retrieval. Two agents age available

hCG given in muscle or under the skin. Its associated with higher incidence of ovarin hyperstimultion.

Agonist (Lupron) trigger given under the skin and has a short duration of action. It prevents ovarian hyperstimulation syndrome.

The Length of Stimuation

In general, shorter the stimulation the better the outcome. The earlier the the trigger shot is administered the better the quality of the eggs. Longer stimulation increases the exposure of eggs to gonadotropins and likely lower the quality of eggs.

Luteal phase Support

Every woman stimulated for IVF require luteal phase support as progesterone production after retrieval is defective. Two preparations exist

Progesterone in the muscle. This is the classic way of supplementing progesterone. Its very stable but require injections and also can cause allergy.

Vaginal progesterone. Recently introduced, used twice a day using an applicator in the vagina.

> *Many aspects of stimulation protocol need to be considered in each patient to ensure optimal stimulation of the ovaries, best possible egg yield and subsequently the highest number of good quality embryos and highest pregnancy rate. Sometimes changing the protocol is better for women than to continue*

with a protocol that is less productive and associated with low pregnancy rate. The talent, care and experience of reproductive endocrinologist is central to selection appropriate stimulation regimen

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Androgens: Improving Response to Ovarian Stimulation prior to IVF

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Ovarian stimulation is the most significant improvement in IVF. Response to stimulation together with age are the most important determinants of successful outcome. Women with prior low response to stimulation and women with expected low response (diminished ovarian reserve) are at higher risk for cycle cancellation and produce a smaller number of mature eggs and embryos. Many approaches were suggested to improve response in low responders including

Increasing the dose of gonadotropins (injection medications)

Use of antagonist protocol

Use of flare lupron protocol

Use of oral medications e.g clomid or letrozole

Synchronization of follicles prior to stimulation using

estrogens

Minimal stimulation IVF

Adjutant use of growth hormone

Use of androgens.

Androgen may Improve Ovarian response to stimulation

Testosterone is known to increase the sensitivity of the ovary to FSH (the hormone that stimulate recruitment and development of follicles in the ovary). Testosterone increases the number of FSH receptors in the follicle and thus its response to stimulation. Women that naturally have high androgens e.g polycystic ovary syndrome (PCOS) show an strong response to FSH. Androgen stimulation increase growth of early follicles and expand the number of follicles available for stimulation. Agonists (lupron) and antagonists (ganirelex) used in ovarian stimulation suppresses testosterone levels in some women.

Androgen Preparations

Two major preparations are available to deliver androgens prior to starting stimulation

Testosterone gel 10 to 12.5 mg applied to skin per day for 21 days or

DHEA oral tablets 75 mg for variable period 4 weeks to 4 months

Transdermal Testosterone

There were three randomized clinical trials (generally the best type of studies in biological sciences) investigating the use of transdermal testosterone prior to IVF. Of the 221 patients included in these studies. Women receiving testosterone required less fertility medications, had

significantly more eggs retrieved and less cycles were cancelled due to low response. There were no side effects in all studies. There was a two fold increase in pregnancy and live birth rates in women that used transdermal testosterone. *There is evidence that transdermal testosterone prior to stimulation improves IVF outcomes.*

Oral DHEA

The mechanism of action of DHEA is not well understood. There were many studies on DHEA but only one was randomized clinical trial. When all the studies with control group were considered, they demonstrated a significantly lower number of oocytes retrieved in DHEA treated women when compared to the controls. There was no significant difference in the clinical pregnancy rate between women pre-treated with DHEA compared to those without DHEA pre-treatment. It is possible that DHEA can improve embryo quality, but this dud not translate into higher pregnancy rate. It is suggested that DHEA should be used for 2-4 months prior to IVF which delays treatment start.

The conclusions related to the use of androgens prior to IVF require more confirmation in larger studies. However, if andregens are used, transdermal testosterone is the preferred androgen pre-treatment prior to ovarian stimulation and IVF.

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.

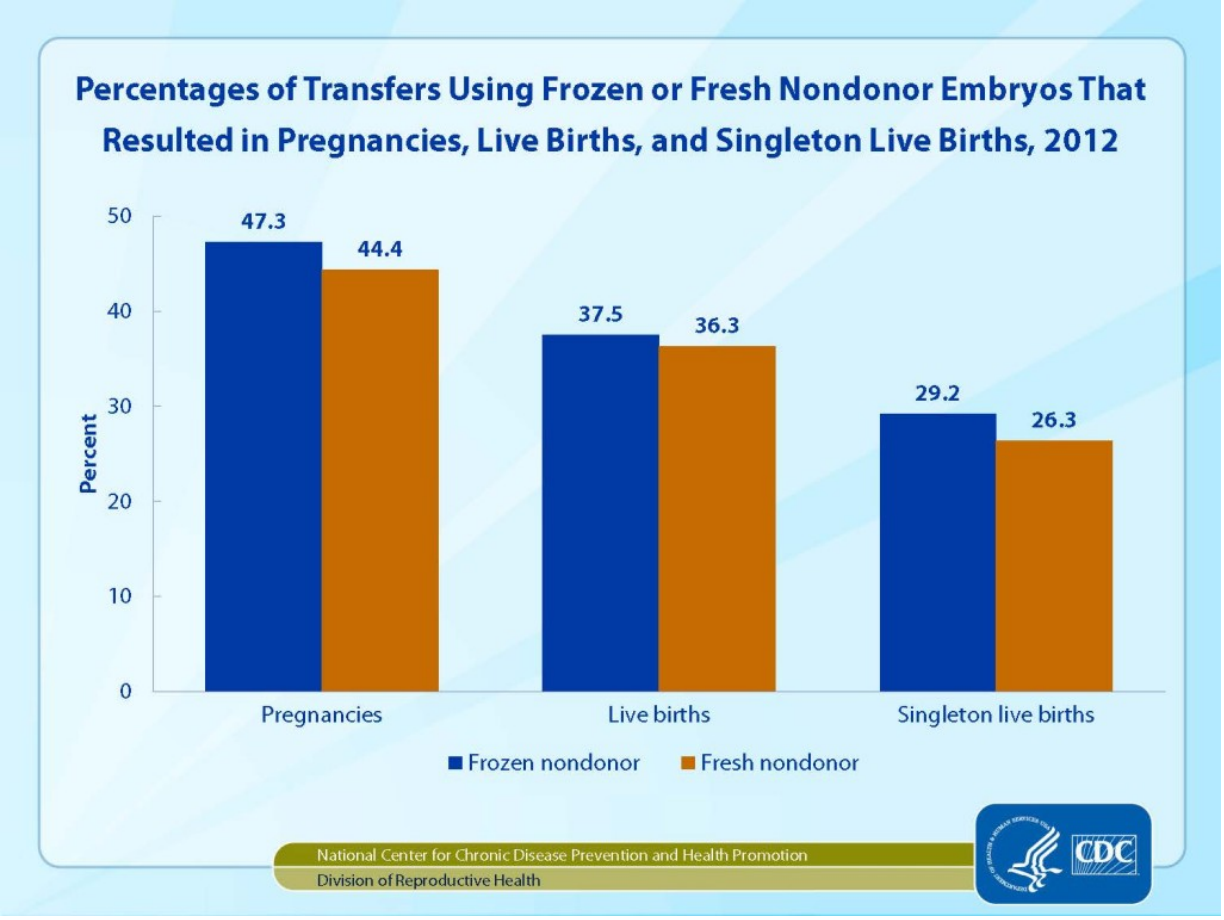
The aim here is to discuss the merits for and against *elective* embryo freezing to transfer the embryo or embryos in a thaw cycle. A thaw cycle involves preparation of the uterine lining, embryo thaw and embryo transfer (no stimulation or egg retrieval). Preparation of the lining of the uterus can be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

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Embryo Selection after IVF

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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

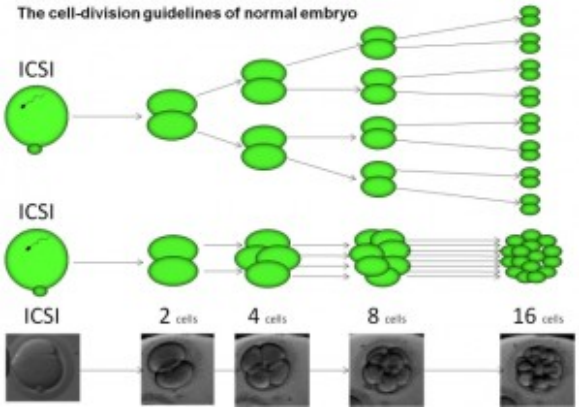
Embryo Morphology and Female Age

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)

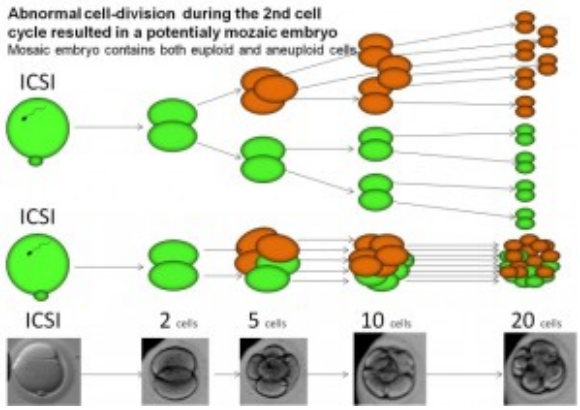
Keeping day 3 embryos in culture may give these embryos may time to develop to blastocysts. Presumably, the better embryos progress to blastocysts or do so faster than less healthy embryos, thus they are preferentially selected for transfer.

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)

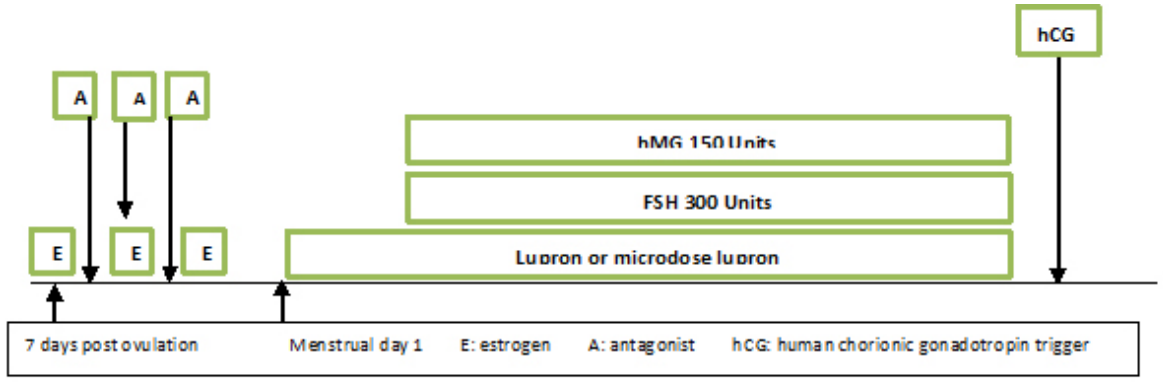
New forms of PGS (performing biopsy at the blastocyst stage) and more accurate platforms for analyzing the biopsied cells are available. However, the concept that better selection will lead to improved IVF results is far from certain.

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.*

Ovarian stimulation protocols for Low Responders prior to IVF



Flare lupron protocol with luteal priming (synchronization) for Low Responders prior to IVF

Ovarian Stimulation Protocols for Low Responders prior to IVF

Low response to controlled **ovarian stimulation** represent a significant fraction of IVF population presenting for fertility treatment. Low responders may represent 30% or more of women seeking IVF. The proportion may be larger in some areas due to delay in childbearing as a lifestyle choice. Low response to ovarian stimulation is commonly defined as producing 5 eggs or less after stimulation. While may factors may contribute to low response e.g smoking, prior surgery of the ovary, exposure to chemotherapy, the vast majority of are age related. Sometimes low response happens in younger women

e.g 30 year old. Young low responders has a better chance of conceiving because their eggs, though few, are healthier (chromosomally normal) than older e.g >38 low responders.

Few strategies can increase egg yield and possibly egg quality in low responders, usually employing one or a combination of

i. increasing the dose of gonadotropins,

ii. avoiding long lupron suppression before start of stimulation,

iii. adding an oral agent (clomid or letrozole),

iv. synchronizing follicles prior to start injections,

v. using androgen prior to cycle start and sometimes

vi. adding growth hormone.

There is no clear evidence to one protocol over the other. Increasing the dose above a total of 450 units per day does not seem to further increase egg yield in low responders. Some patients respond to one ovarian stimulation protocol over another. One example of low responder protocol is illustrated above. Estradiol and antagonist are used to synchronize the follicles before menses so that they are uniform in growth when stimulation starts. Short lupron is used (flare or microflare) to induce the release of internal gonadotropins. This is followed two days later by high dose of fertility medication (total 450 units per day).

There is some evidence that pre-treatment with androgens (testosterone) may improve egg yield. The evidence for the use of DHEA (dehydroepiandrosterone) is limited. There is also week evidence that the use of growth hormone may improve egg quality.

Embryological procedures are also sometimes suggested as ICSI of all available eggs to maximize fertilization and assisted

hatching of the egg shell (zona pellucida). Pre-implantation genetic screening is unlikely to be helpful as few embryos are available for testing.

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

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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.

Fertility Treatment Options

Fertility Treatment Options: What Are Infertility Treatments?

Following detailed fertility investigation of the male tubal and ovarian factors, patient and her reproductive endocrinologist decide together on the optimal **fertility treatment options**.

Factors to consider in selecting the best **fertility treatment options** include:

Sperm source

1. Is there a male partner: if so what is the ejaculate volume, sperm concentration, motility and shape? if >10 million moving sperm then pregnancy through intercourse or IUI is possible. Lower numbers indicates **IVF** or ICSI. If azospermia (no sperm in the ejaculate) then surgical sperm retrieval may be needed (TESE) or donor sperm can be used.
2. If there is no male partner: anonymous or known donor sperm is used

Tubal Factor

1. Open fallopian tubes allow for natural conception or IUI.
2. Blocked fallopian tubes require IVF. Sometimes tubes can be fixed using tubal surgery.
3. Blocked and dilated fallopian tubes (Hydrosalpinx) require surgical removal of the dilated tubes followed by IVF. Dilated tubes are very difficult to fix and can leak fluid into the uterine cavity and prevent implantation of the embryo.

Ovarian Factor

1. Women who do not ovulate due to polycystic ovary syndrome (PCOS): ovulation can be induced using oral medications (clomid or letrozole) or injection medications (gonadotropins). This is usually combined with IUI.
2. Women who do not ovulate due to defect in the master gland in the brain (Hypothalamic amenorrhea): ovulation can be induced using injection medications (gonadotropins). This is usually combined with IUI.
3. Women diminished ovarian reserve and unexplained (idiopathic) infertility commonly have lower quality eggs and may benefit from inducing multiple ovulation

followed by IUI or IVF, to increase the chance that one of the eggs is healthy (chromosomally normal).

Donor Eggs

1. Donor eggs are needed in women with low egg reserve that fail multiple IVF cycles after menopause or those who carry some genetic abnormalities.
2. Donor eggs can enable same sex male couples parent a child (together with a gestational carrier).

Gestational carriers

1. Gestational carriers enable women to parent a child if the uterus is absent or was removed due to a disease e.g endometrial cancer or if the lining of the uterus is damaged e.g intrauterine scarring due to prior scrapping.
2. Gestational carrier enable women who cannot get pregnant to parent a child e.g history of breast cancer
3. Gestational carriers enable same sex male couples to parent a child.

Genetic analysis of the eggs or embryos (PGD)

1. Women and men with risk of conceiving a child with a specific genetic disorder e.g cystic fibrosis, sickle cell anemia should consider testing their embryos before transfer into the uterus (PGD)
2. PGD can also be used for selecting the sex of the baby for family balancing.
3. PGD can be used to test the chromosomes of the embryo to increase the chance for pregnancy in women select women but its efficacy for that purpose is still being investigated.

Fertility Preservation

1. Women at risk for diminished fertility due to a medical problem or treatment e.g breast cancer can freeze their

eggs or embryos to use later
2. Men at risk for azospermia due to genetic factors, cancer and cancer treatment can freeze sperm for use later
3. Many other techniques for fertility preservation can also be applied to adults and children to preserve reproductive organs and tissue.

Many **fertility treatment choices** exist to help women and men conceive a child. One or more of these methods can be tailored to each

i. individual circumstances:

singles women or men,

heterosexual couples or

same sex couples.

ii. reproductive aim:

wants to get pregnant now versus later,

wants one child only or accepts twins,

wants to conceive a child of certain sex,

will use own uterus or a gestational carrier,

will use own gametes- sperm or egg or donor gametes.

To learn more about fertility treatment options please visit nycivf.org

Idiopathic Infertility Treatment: what do you need to know

Idiopathic Infertility Treatment: what do you need to know

Idiopathic infertility (**unexplained infertility**) is defined as inability to conceive after trying for 6 months in women 35y or older and one year for women younger than 35, with no tubal, ovarian or male factor infertility. This diagnosis of idiopathic infertility is established after open fallopian tubes are detected in HSG or laparoscopy, regular ovulation is detected from history, lab tests and ultrasound and sperm is near normal on sperm analysis. These fertility tests can be performed within few days. Note that good health and physical fitness..etc are not factors here. Many women with terrible general health do conceive. On the other hand, many women in excellent physical fitness and sound health have extreme difficulty conceiving even with fertility treatment. Having difficulty getting pregnant without an apparent cause applies to a large category of the sub-fertile population and is puzzling to couples trying to conceive. The consensus of opinion among reproductive endocrinologist can divide the underlying factors for unexplained infertility into

1. Chromosomal abnormalities in the egg (low egg quality)

Abnormal eggs are present in every woman, albeit to a varying

degree. Older women has more abnormal eggs. In addition, the fewer eggs you have the higher the proportion of abnormal eggs. There is no *non-invasive test* for egg quality and history, age, blood tests for ovarian reserve and antral follicle count detected on vaginal ultrasound are the most used methods.

Factors that point to low egg quality

1. Advanced maternal age,
2. Diminished ovarian reserve (e.g high FSH, low AMH), also prior surgery in the ovaries, smoking, family history of early menopause and exposure to chemotherapy
3. Early pregnancy loss before a fetal heart activity is detected (chemical pregnancy, blighted ovum),
4. Abnormal chromosomes of the products of conception and
5. Abnormal chromosome configuration of male or female partner e.g chromosome translocation. Less than 5% of couples miscarry due to a translocation in the male or female partner.

2. Other factors: may be more prevalent in younger patient and include mild endometriosis, immunological factors as anti-sperm antibodies, abnormality in cervical mucus, abnormalities in the cavity of the uterus and endometrial lining. Generally, these are not considered major factors in idiopathic infertility. Mostly oral medication produce few or only one follicles, thus they do not increase te chance that one or more eggs are healthy leading to a pregnancy.

Treatment Options for Idiopathic Infertility

Oral medication – IUI or expectant treatment (intercourse)

Oral medications are either clomid (clomiphen citrate) or an aromatase inhibitor (mostly letrozole) are used. This is

followed by intercourse or intrauterine insemination (IUI). The pregnancy rate is about 5% to 7% per treatment cycle. There is no evidence that oral medications followed by IUI are superior to just intercourse in treatment of unexplained infertility. The risk for multiple pregnancy is about 8%. However, because oral medication (clomid) widespread use, mostly without ultrasound monitoring, they are probably responsible for more multiple pregnancy than any other fertility treatment.

Injection medications – IUI

This **treatment** should probably be avoided in the majority of couples because of a. No added benefit: Pregnancy rate is not significantly higher than Clomid-IUI cycles; 9% pregnancy rate per treatment cycle and drops to 5% in women >38y. b. Risks: notably multiple pregnancy (two or more babies; 30%) and higher order multiple pregnancy (three or more babies; 3 to 8%). Multiple pregnancy has significant risks to the mother and babies. Preterm delivery can be associated with permanent neurological and intellectual defects in the babies. This risk can be minimized with careful stimulation under supervision of a reproductive endocrinologist, but cannot be completely prevented.

In Vitro Fertilization (IVF)

a. The pregnancy rate per an IVF treatment cycle is approximately 30% on average, three times that of IUI. The specific pregnancy rate is dependent on female age. The time to conception is also shorter than any other fertility treatment modality. The higher success rate can be further extended through the use of frozen embryos in couples that have good quality embryos available for freezing. The cumulative pregnancies resulting from fresh transfer and subsequent frozen-thaw embryo transfer can result in a very high odds for pregnancy. Frozen embryos can be used years after their creation, when ovarian reserve has considerably

diminished. The contribution of IVF to treatment success becomes more pronounced in older women >38 years as the success of ovarian stimulation – IUI drops considerably. b. The risk for twins and higher order multiple pregnancy can be greatly minimized through single embryo transfer (1% twins and no higher order multiple pregnancy). In other words *if you want to get pregnant faster, with one baby and at higher chance for success per treatment cycle strongly consider IVF with single embryo transfer.*

Infertility Treatment Strategy for Idiopathic Infertility

Conventional **fertility treatment**: "expectant management → clomid / letrozole- IUI x2 to 3 cycles → gonadotropin – IUI x3 cycles → IVF " is the old method of treatment for unexplained infertility Modern treatment of Unexplained infertility: " expectant management or oral medication – IUI → IVF preferably with single embryo transfer ". Women 38 years and older modern treatment strategy suggests Immediate IVF as the initial fertility treatment. The modern paradigm for fertility treatment will lead to pregnancy faster, is more successful, minimize multiple pregnancy and is more cost effective (lower dollar cost per baby). The majority of women (>70%) with unexplained infertility especially women with normal ovarian reserve will succeed in delivering a baby.