Varicocele and Male Factor Infertility

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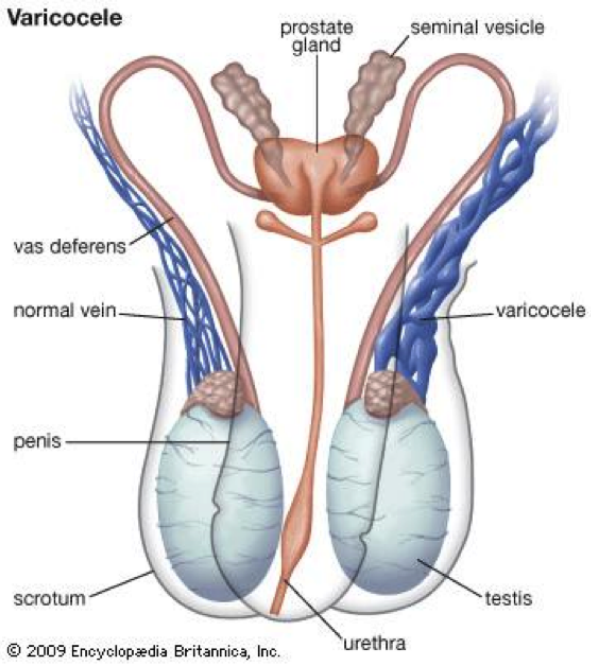
Varicocele and male factor infertility: Many men (40%) with low sperm count, low movement and high abnormal sperm shape have dilated veins around the testes. On the other hand, many men (15%) with varicoceles have normal sperm parameters and fertility. Only large varicoceles than can be felt by a physician are associated with lower fertility in men. Varicoceles are found during physical examination and can be confirmed with Doppler ultrasound of the testes. How dilated veins – varicoceles may cause abnormal sperm and male infertility is still unknown for sure (pressure, heat, toxin accumulation, oxidative stress).



varicocele surgery

Does surgical treatment of varicocele increase the chance of pregnancy in female partners?

Some urologists recommends surgical treatment of varicoceles in adult men to improve the chance for spontaneous conception

This recommendation should at least be issued if and only if:

1. Varicocele was large enough to be felt on examination (not ultrasound).
2. The couple had documented infertility or desire future fertility.
3. The female partner had normal fertility (especially normal egg reserve) or correctable infertility.
4. The male partner had one or more abnormal semen parameters.

The rationale is that repair may restore normal sperm parameters and spontaneous conception. *Varicocele repair is definitely not indicated in the presence of female factor requiring IVF* e.g blocked fallopian tubes, as improved sperm parameters will not achieve a pregnancy. Some studies reported improved sperm parameters and sometimes fertility after surgical treatment of varicocele but many of them were low quality studies (no control group, not randomized, non-palpable varicocleles).

Good quality studies: randomized (one group of men underwent surgery for large varicoceles and another group did not)

Ten randomized studies were published (including 894 men). Some studies indicated improve in sperm parameters after surgery. Most of the studies indicated that the chance for live birth is not increased after varicocele repair. There is no conclusive evidence that varicocele repair increases the chance for pregnancy and delivery in female partners of men

diagnosed with varicoclele (summary below).

Surgery or embolization for varicoceles in subfertile men: Varicocele is a dilatation (enlargement) of the veins along the spermatic cord (the cord suspending the testis) in the scrotum. Dilatation occurs when valves within the veins along the spermatic cord fail and allow retrograde blood flow, causing a backup of blood. The mechanisms by which varicocele might affect fertility have not yet been explained, and neither have the mechanisms by which surgical treatment of the varicocele might restore fertility. This review analysed 10 studies (894 participants) and found evidence (combined odds ratio was 1.47 (95% CI 1.05 to 2.05) to suggest an increase in pregnancy rates after varicocele treatment compared to no treatment in subfertile couples, in whom, apart from poor sperm quality, varicocele in the man was the only abnormal finding. This means that 17 men would need to be treated to achieve one additional pregnancy. However, findings were inconclusive as the quality of the available evidence was very low and more research is needed with live birth or pregnancy rate as the primary outcome (Kroese 2012).

Surgical repair of varicocele should only be considered in carefully selected subfertile couples. There is no conclusive evidence that repair increases the chance for delivery in female partners. Data supporting surgical repair of varicocele are controversial and results or surgery is certainly inferior to IVF-ICSI.

A consultation with reproductive endocrinologist & fertility specialist is very important before deciding on varicocele surgery to study female factor infertility and discuss potential benefits and harm from surgery in achieving the final goal which is conceiving not just improving sperm count and motility.

varicocele and Male Factor Infertility

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

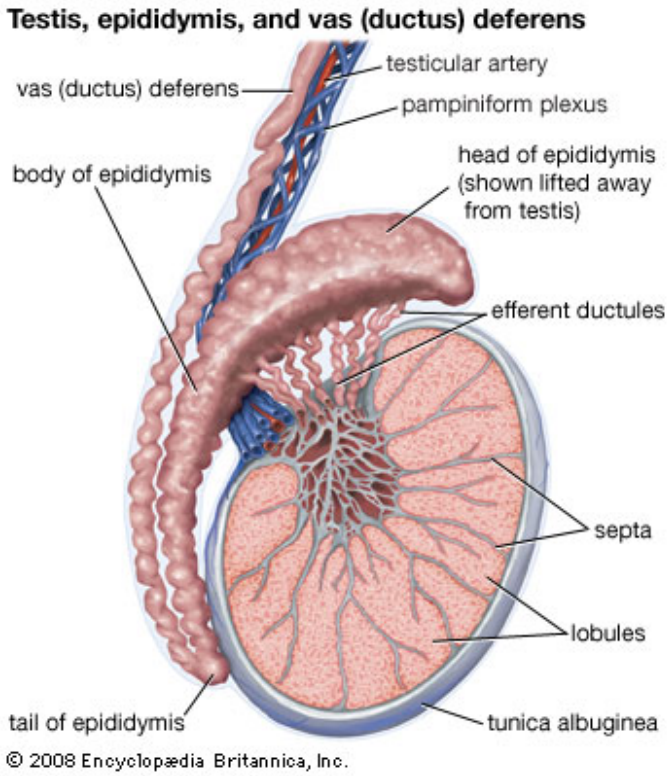
the ducts conducting the sperm outside of the testes.

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*

Endometriosis will not Lower IVF Success

Endometriosis will not Lower IVF Success

Effects of endometriosis on fertility treatment success has always been a controversy. When a woman is diagnosed with endometriosis, she receives multiple contradicting advises from multiple sources. It is very difficult for women to sort through these recommendations and pick the ***one that are suitable for her symptoms and reproductive plans***. Indeed reproductive plans and symptoms are by far more important than the nature of the problem, anatomically, as well as what one reproductive surgeon or a fertility specialist think you should do.

Reproductive Plans in women diagnosed with endometriosis

Simply do you want to fave a baby or did you complete your family?. If you want to have a baby, then an initial infertility evaluation is required: testing for ovulation, ovarian reserve, male factor and Fallopian tube patency is required. Sometimes other forms of pelvic imaging e.g MRI is needed to test for ovarian cysts or endometriomas…Endometriosis itself may require laparoscopy and biopsy for accurate diagnosis.

Women are then categorized according to findings: endometriosis only, endometriosis with other factor or endometriosis with low egg reserve. That will facilitate further advice.

One very important indicator that you are not talking to the right person if he or she did not complete the evaluation for male factor and egg reserve. These are essential tenets of fertility and failure to test them will have impact on success. It would be absurd to do surgery for endometriosis for example to discover later that you have a severe male factor that require IVF -ICSI.

If you desire future fertility, reproductive endocrinologists should taylor their advice to preserve reproductive tissues and minimize surgery. There is a strong evidence that surgery in the ovary reduces ovarian reserve, irrespective of technique used.

Pain in women diagnosed with endometriosis

If the main symptom is pain, in different forms, then medical or surgical treatment can be employed. in women who completed their families. Medical treatment e.g non cyclic oral contraceptive pills of GnRH agonists (depot lupron) prevent pregnancy. From a practical stand point, surgery im many cases may not promote pregnancy in women with with mild and severe endometriosis.

> ***Women diagnosed with endometriosis and report pelvic pain should focus on getting pregnant. Pregnancy can suppress endometriosis for a long time after delivery***

Fertility Treatment in Women Diagnosed with Endometriosis

Absolutely avoid doing surgery in the ovaries in women interested in pregnancy. This is crucial. Opening endometriomas and tripping their walls leads to significant loss of egg reserve. The only indication to remove endometriomas if they are complicated e.g rupture or suspicion

of malignancy. There are many reports of finding eggs in the wall of endometriomas after removal and reduction in egg reserve markers after surgery. Bilateral surgery for endometioma can lead to menopause, irrespective of the skill of the surgeon.

In minimal and mild endometriosis with reasonable egg reserve, normal sperm analysis and open fallopian tubes, ovarian stimulation and IUI can be entertained in young women (38 years).

In women with moderate or severe endometriosis e.g endometriomas, blocked tubes.. or those with associated male factor infertility or low egg reserve, IVF yields a much higher pregnancy rate.

IVF Success in Women with Endometriosis

Recent analysis of IVF cycles performed in women with endometriosis with or without other factors (tubal, male, unexplained infertility) indicates that

Isolated endometriosis is associated with similar IVF success and live birth to other infertility factors, though the number of eggs retrieved may be smaller.

Endometriosis when associated with other factors e.g male or tubal factor may have lower success rates. The live birth rate is still excellent 35 to 45% per cycle.

Endometriosis-and-IVF

Treatment of Endometriosis related pain

Both medical treatment and surgery are effective for treatment of pain. Endometriomas do not respond to medical treatment. Endometriosis on the peitoneum and and other organs respond to medical and surgical treatment. Adenomyosis (endometriosis of

the uterus) is a surgical disease and respond only to surgery.

In general medical treatment is successful but requires patience and can be used for a longer period of time with add back therapy.

If you are diagnosed with endometriosis there is wide range of treatment options. Treatment should be personalized to your reproductive goals and symptoms not to physician expertise and bias. There is really little controversy about what need to be done in each situation. Women just need to be specific about what they want: get rid of pain or have another baby. IVF success is not impaired in women with endometriosis.

Age Related Fertility Preservation: Should you Consider Multiple Egg Freezing Cycles?

Age Related fertility Preservation:

Should you Consider Multiple Egg Freezing Cycles?

All what we really know for sure about reproductive competence (ability of eggs and sperm to produce a baby) is thatembryos that has the correct number of chromosomes has a very high chance of implanting and produce healthy babies. In the

majority of cases, the egg is the source of abnormal chromosome material: extra or missing chromosomes.

Female age is the most important fertility factor. As age advances, the number of eggs in the ovary decline and the proportion of abnormal eggs increase. This fact underline the need for modern women think about ***reproductive planning*** as early as possible, say age 25 to 30. When do you want to get pregnant for the first time? Is it socially feasible to start now? Do you have enough support around you to have a baby now? how large of a family do you want? do you care about the sex of the baby?

In general the following are available options

Try to get pregnant on your own as early as possibly can

Consider Embryo freezing with partner for later use

Consider using donor sperm to create embryos for storage

Egg freezing is a viable option for fertility extension

Egg Freezing

The ovaries are stimulated to produce multiple eggs. Eggs are retrieved using a simple procedure. Mature eggs are frozen using flash freezing (vitrification). The eggs are stored in a special device in liquid nitrogen, indefinitely. The main aim here is to freeze multiple mature eggs at a younger age that can be used at a later female age when eggs are fewer and less healthy.

The most critical part of counseling women here about ultimate chance of conception using egg freezing is accurate estimation of egg reserve via history, antral follicle count and AMH level.

In general women <38years that produce >8 eggs has a very good chance of conceiving and delivering at least one baby from an

egg freezing cycle.

Egg-freezing-study

Women who are older or produce less eggs then would ask do I need more eggs?

Multiple Egg Freezing Cycles

Should you Consider Multiple Egg Freezing Cycles? If you do not produce enough eggs in the first round of egg freezing you can consider another egg freezing cycle. But you now have the advantage of knowing how did you respond the first round. You know a bit more about the quality and maturity of the eggs. You know if the stimulation protocol worked for you and you can discuss with your reproductive endocrinologist methods of improving response. If increasing the number of frozen mature eggs is possible with another cycle of egg freezing, then another cycle should be considered.

On the other hand if the prior response is low, egg quality is low and age is 40 or more, women should consider conceiving as soon as possible.

Medically + Economically You Should Avoid IUI at Age 38

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Medically and Economically you should void IUI at age 38 or older. Couples facing difficulty conceiving and after completing a fertility workup, they have three general

fertility treatment options. Regular intercourse, ovarian stimulation with oral medications (clomid or letrozole) or injection medications followed by IUI (COH-IUI) or IVF.

The chance for pregnancy is very low with COH-IUI that you may as well just try with intercourse. The likely cause is production of a small number of eggs with these stimulation protocols, lowering the chance of encountering a chromosomally normal eggs. IUI in itself slightly increases the pregnancy rate but the main benefit in fertility treatment is produced through ovarian stimulation and recruitment of multiple eggs.

On the other hand, IVF carries a very good chance for getting pregnant. If not ready for fertility treatment just have regular intercourse. If ready, proceed directly to IVF as you will realize much higher success rate and save also on treatment with minimal yield (IUI). Here is a synopsis of published studies (asrm.org).

Traditional egg reserve tests

Women who initiated infertility treatment with FSH of 10 to 15 mIU/mL and E >40 pg/mL on day 3 testing were unlikely to achieve live birth after COH-IUI treatment. In two well designed studies on 603 patients contributing 2,717 total cycles, no live births occurred during COH-IUI. IVF still afforded these patients a reasonable chance of success (6/18 couples, 6/40 cycles, 33.3% live-birth rate per couple).

Female Age

Age ≥ 38 to 42y:

The *cumulative clinical pregnancy rates per couple after the first two cycles of CC/IUI, FSH/IUI, or immediate IVF were 21.6%, 17.3%, and 49.0%*, respectively. After all treatments, 110 (71.4%) of 154 couples had conceived a clinically recognized pregnancy, and 46.1% had delivered at least one

live-born baby; 84.2% of all live-born infants resulting from treatment were achieved via IVF. There were 36% fewer treatment cycles in the IVF arm compared with either COH/IUI arm. Also couples conceived a pregnancy leading to a live birth after fewer treatment cycles.

Age 21-39:
Per cycle pregnancy rates for CC/IUI, FSH/IUI, and IVF were **7.6%, 9.8%, and 30.7%**, respectively. Average charges per delivery were $9,800 lower ($25,100 lower to $3,900 higher) in the accelerated arm (IVF) compared to conventional treatment (IUI).

Other Fertility and Social Factors to consider

There are other factors to consider: moderate to severe male factor and blocked tubes makes IUI and intercourse not an option. Absolute cost and insurance coverage are maybe important (although its by far more cost effective). Risk of multiple pregnancy should always be considered especially with Injection +IUI cycles. Some couples have personal ” resistance” to adopting IVF as difficult, uncomfortable, risky or unnatural, and that autonomy has to be both respected and embraced but also discussed. Their sentiment has to be balanced against a 7% per cycle pregnancy rate if you do Clomid-IUI, 9% per cycle injection -IUI (both become zero if egg reserve tests are abnormal) *versus* 35%pregnancy rate with IVF.
Knowing the expected rate of success is an integral part of fertility counseling.

Medically + Economically you should avoid IUI at age 38

> *All being equal, for modern couples, the most humane approach is to get them pregnant before the short favorable window of reasonable number and quality of eggs wane. No to do so means letting them enter the into the more difficult phase of final reproductive years. Treatment ssuccess drops in late*

reproductive years to a single digit and they jeopardize their chance of having a baby.

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Ovarian Reserve Revisited-Do You Have Enough Good Eggs?

Ovarian Reserve Revisited-Do You Have Enough Good Eggs?

Trying to conceive over age 35 is generally not easy

I know because I tried for years to have a baby without success. While there are many factors which impact conception, one of the first concerns for women over 35 is if they have enough healthy eggs to get pregnant. Research has shown that women carry a reserve of eggs throughout their lives and that reserve diminishes over time. There are several tests which help to determine ovarian reserve including antral follicle testing, the clomid challenge and the AMH test which is relatively new.

The antral follicle test

Uses vaginal ultrasound to count and measure the small follicles, antral follicles, on the ovary. The higher the number of antral follicles, the better ovarian reserve and better odds for conception.

The AMH Test

Anti-mullerian hormone test, measures the levels of AMH in a woman's blood. Since this hormone remains relatively constant over the menstrual cycle, it can be tested at any point in the month. Women with higher AMH levels tend to have a better ovarian reserve and a better chance at conception.

When I decided to try to conceive one last time at age 44

My reproductive endocrinologist began by ordering the *Clomid Challenge Test*. For the test, I took clomid, a fertility drug used to induce ovulation, for 5 days. Generally speaking, the procedure works like this:

- On Day 3 of your menstrual cycle, a blood test is given to measure your FSH, LH, and estradiol levels.
- On Day 5 of your cycle, you begin to take a 5-day supply of clomiphene citrate, 100 mg of clomiphene each day for five days.
- On Day 10, you will have another blood draw to check FSH, LH, and estradiol levels again.

Normal results include low FSH values on both Day 3 and Day 10, and low estradiol values on Day 3. Results are abnormal if your FSH values are elevated. Your doctor may decide to re-test if your results are abnormal.

My results were normal but that is a fraction of the total conception story and half of the ovarian reserve story. Ovarian reserve consists not only of the quantity of eggs but also the quality of eggs. Research tells us that while tests like the clomid challenge check for the quantity of eggs, the quality of eggs is generally determined better by age. This is an unfortunate fact for those of us over 35.

According to Dr. James Toner in his paper "Ovarian Reserve,

Female Age and the Chance for Successful Pregnancy", once women reach their mid thirties, specifically 37, their egg quantity begins to diminish at a faster rate. Tonor also reports that even if egg quantity is good, chances of a viable pregnancy drop due to the diminishing quality of eggs as women age.

Based on the research, it is clear that the averages do not look promising for women over age 35 trying to have a baby. There is, however, other information to consider. Let's take a look at the bell curve. Basically, about 2/3 of the cases for a given situation fall in the fat part of the curve meaning that averages generally apply to most people. However, there are still one third of the people who fall outside of the fat part of the bell curve and averages do not generally apply to them. As you look at your individual situation, it is your lab work, anatomy and physiology that matter. I am a classic example of defying the odds. My ovarian reserve quantity was good but that wasn't what was preventing me from conceiving a child. It took many more tests to determine that a badly placed uterine tumor was most likely preventing implantation. At age 44, the research showed that an average woman in my situation had only a 3% chance of having a healthy baby. Yet, I was able to conceive in two of 4 IUI treatments and gave birth to a healthy little girl 9 months ago at the age of 45.

There are many components to conceiving a child

Ovarian reserve is one of them. There are also many medical interventions to boost the odds of conception. Medical research provides us with excellent information about infertility and age including work on ovarian reserve. While the research tells us that the odds of getting pregnant in late 30's and 40's diminishes, one needs to remember that each woman is unique and she needs to work with her doctor to

explore all options in her quest for pregnancy.

About the Author: Deborah Lynn is the creator/owner of Over 35 New Moms and a former corporate vice president. She holds degrees in Education, Kinesiology and pursued doctoral study in Physiology. She spent over 17 years working in the corporate environment and now focuses her time on raising her daughter and helping other women over 35 in their journey to have a baby. For more information, visit The Resource Guide for Pregnancy over 40 at http://www.selfgrowth.com

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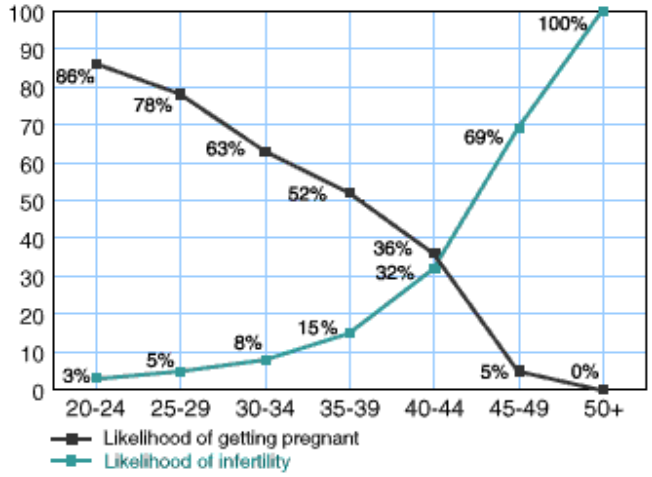
Fertility Options for Single Women

Fertility Options for Single Women

Single women may face some challenges regarding fertility options: understanding them then picking one or more options, suitable for your reproductive plans. Clearly, a woman cannot delay pregnancy indefinitely, as the number of good quality eggs decline quickly in her 30s and older.



Decline in Fertility with age

Modern reproductive medicine enables single women to be mothers now and in the future. As with anything in reproduction, the younger you are, the more successful your efforts will ultimately be, irrespective of your choices. In addition, think of what would you accept: donor sperm? are you ready to get pregnant now or do you want do that in the future?

Are you ready to Start a Family without a Partner?

This could be a difficult question considering the time, financial and emotional commitment of raising children without a male partner. A psychologist with expertise in reproductive issues can help women tackle issues as readiness and commitment, disclosure to children when mature, capitalizing on family resources, legal issues and many more. Some anonymous donors accept open identity in the future.

Starting a family without a male partner requires a selection of sperm donor. The sperm donor could be anonymous (from a sperm bank) or known (friend). In either cases, the donor is screened for infectious diseases (hepatitis B, hepatitis C, HIV, Syphilis, Gonorrhea and Chlamydia) and common genetic abnormalities. The sperm is quarantined then the donor is retested for infectious diseases. Tests are done in a

specialized high accuracy labs.

How to use donor sperm to achieve a pregnancy?

This is a question related to female ovarian reserve and other fertility factors. If the fallopian tubes are open, as indicated by HSG (hysterosalpingogram, X-ray of the tubes) then IUI (intrauterine insemination) is possible. Age is also an important factor. Women 38 or older have much higher chance of conceiving with IVF than IUI using frozen sperm. This issue require thorough evaluation by a reproductive endocrinologist.

On Starting a Family with a Partner in the Future

If the use of donor sperm is not acceptable, egg freezing is a viable option for women with reasonable ovarian reserve and younger than 40. Evaluation of antral follicle count using vaginal ultrasound and antimullerian hormone levels (AMH) can predict response to fertility medications and ultimate egg yield from the cycle. Age reflects well how many of these eggs are chromosomally normal. The ovaries are stimulated using injection medications. Eggs are retrieved under vaginal ultrasound guidance which is a minor procedure. Mature eggs are frozen 4 hours later using vitrification. Immature eggs are cultured for <24 hours and frozen if mature. The eggs can be stored for years to come.

If the number of eggs retrieved is low another egg freezing cycle can be attempted to freeze more eggs.

When pregnancy is desired the eggs are thawed and fertilized via ICSI (direct injection of the sperm into the egg) and the resulting embryos are transferred into the uterus after preparation of its lining. The pregnancy rate after egg freezing is close to fresh eggs and is age dependent.

These options allow single women achieve their reproductive goals while respecting their values and preferences.

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

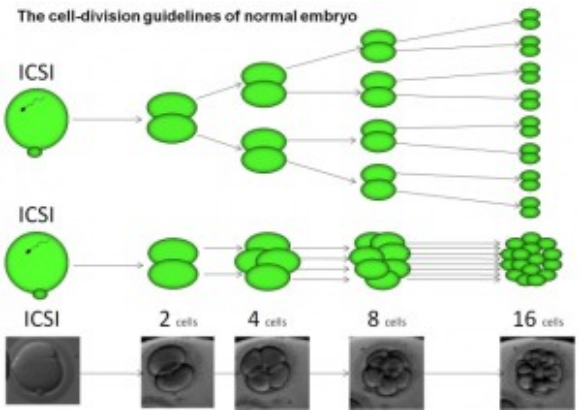
Embryo Morphology and Female Age

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)

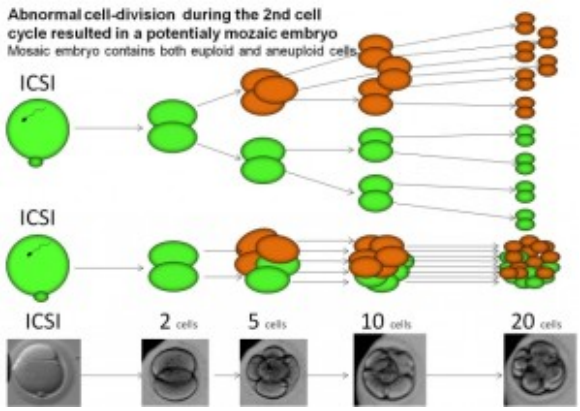
Keeping day 3 embryos in culture may give these embryos may time to develop to blastocysts. Presumably, the better embryos progress to blastocysts or do so faster than less healthy embryos, thus they are preferentially selected for transfer.

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

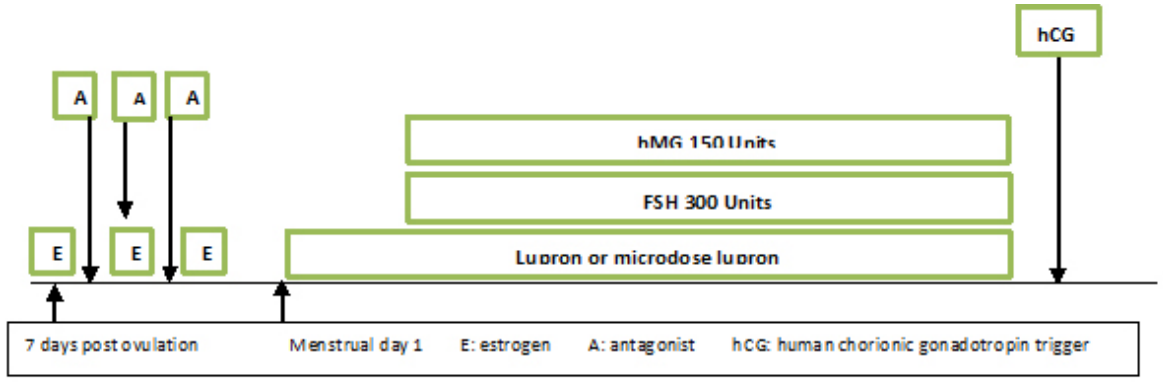
are available. However, the concept that better selection will lead to improved IVF results is far from certain.

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.*

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?

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.