### <u>Varicocele and Male Factor</u> <u>Infertility</u>

### Varicocele and Male Factor Infertility

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 <u>male</u> <u>infertility</u> 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:

- Varicocele was large enough to be felt on examination (not ultrasound).
- 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, nonpalpable 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 Varicocele is a dilatation men: (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 <u>female factor infertility</u> 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

### **IVF: The Way We Do It**

### IVF : The Way We Do It

### 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.

### <u>Endometriosis will not Lower</u> <u>IVF Success</u>

Endometriosis will not Lower IVF

### Success

Effects of <u>endometriosis</u> 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.

# AgeRelatedFertilityPreservation:ShouldyouConsiderMultipleEggFreezingCycles?

### 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 <u>history</u>, <u>antral follicle count and AMH</u> <u>level</u>.

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.

### <u>Anatomy of Ovarian</u> <u>Stimulation Protocol for IVF</u>

### Anatomy of Ovarian stimulation Protocol for IVF

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

### <u>Medically + Economically You</u> <u>Should Avoid IUI at Age 38</u>

### Medically + Economically You Should Avoid IUI at Age 38

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 (<u>asrm.org</u>).

### 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  $\geq$  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.

**FORTT** 

### What if You Have Dual <u>Infertility Factor</u>

#### What if You Have Dual Infertility Factor

Many Times You Do

Infertility factors are generally classified into tubal factor (blocked fallopian tubes), male factor (abnormal sperm concentration, movement or shape) and ovarian factor (no ovulation). In the majority of situations though multiple factors exist. If you partner has low sperm count, you also may have a blocked tube. Women who do not ovulate can also have endometriosis. Some men think that their female partners are infertile due to a female factor while they also have subtle sperm abnormality that prevents fertilization. Women sometimes think their male partners sperm is abnormal while they also have low egg reserve and low egg quality. *Couples potentially have a dual infertility factor, most of the time*. Most notably, low egg number and quality should be considered in any couple seeking fertility evaluation and treatment. Even young women with good egg reserve have abnormal eggs.

Irrespective of infertility factors, consideration of other general factors e.g genetic screening results can have a significant impact on choice of fertility treatment modality. If both partners are carriers for cystic fibrosis, they may require embryo testing (PGD) in the setting of IVF as opposed tosimilar couples without this genetic risk factor.

### Do not Accept Treatment Before a Complete Workup. Do not Accept Empiric Treatments

For that reason, no assumptions about fertility factors and treatment should be made before a completed workup for sperm, ovulation, ovarian reserve, Fallopian tubes and general

factors (genetic and preconception screening). This careful and deliberate testing is unfortunately not always followed. In many cases, couples are treated with empiric treatments. Here are two very common empiric treatments commonly prescribed

a. <u>Clomid used for everyone</u>. Clomiphene is suitable as initial treatment for women who do not ovulate due to polycystic ovary syndrome (PCOS), have open tubes and normal sperm analysis. In modern reproductive medicine, clomid should not be used without testing of male and tubal factor. Clomid also should not be used in older women that ovulate regularly. The majority of these women are older and do not get pregnant because of lower egg quality. They require superovulation (more than one eggs) to compensate for lower egg quality.

b. Progesterone supplementation. Low progesterone can cause early miscarriage (not infertility) in a small percentage of women. Women that yield low progesterone after ovulation do so because of abnormal development of follicles. They are better served by induction of ovulation to produce better follicles, rather than progesterone supplementation. During fertility treatment, progesterone levels are monitored and maybe supplemented if low. Progesterone treatment in itself is not a treatment for any form of infertility.

c. Laparoscopic surgery for endometriosis. The magnitude of benefit for surgical treatment of infertility associated with endometriosis is limited and maybe harmful. Laparoscopic surgery for severe endometriosis is risky e.g bowel injury. Resection of endometrioma can reduce ovarian reserve. IVF is a better than laparoscopic surgery in treating infertility due to moderate and severe endometriosis . The increase in pregnancy rate after excision of mild endometriosis is limited (probably 30 surgeries are needed to produce one newborn).

d. <u>Varicocele repair for male factor infertility</u>. Although sperm parameters may improve after varicocele repair, there is

no conclusive evidence that it will translate into higher odds of pregnancy in female partners. There is a limited indication for varicocele repair aiming at improving fertility in males.

Many of these empiric treatments and prescribed with no or limited scientific basis and represent bias and expertise of the prescriber.

### <u>How to Select an Egg Donor</u>

### How to Select an Egg Donor

Egg donation entails the fertilization of eggs of a young woman and transfer of the resulting embryo or embryos into the intended mother uterus. In the majority of cases, women are interested in egg donation when their ovarian reserve is diminished in quantity and quality, commonly after multiple unsuccessful IVF cycles. The eggs of young women are usually high in quality making the chance for pregnancy and delivery very high. Women can select an egg donor from one of two pools



Egg Donors

### Eggs from a Live Donor

An young woman is selected for donation, her ovaries are stimulated then eggs are retrieved. Two types of egg donors exist:

#### i. Known Egg donor

The egg donor is known to the intended mother. The donor could be a related e.g. sister or not a relative but agreed to open identity egg donation.

#### ii. Anonymous Egg donor

The egg donor is not known to the recipient. The majority of eggs donated are contributed by anonymous donors. If you select a closed identity donor you will still be able to know a great deal about her as age, ethnicity, religion, education, medical and family history, prior donations, physical features, childhood or even adult photo. Anonymous egg donors are usually recruited by a third party: IVF clinic or an egg donation agency. Shared Donor cycle: Sometimes the eggs from one donor are shared between two recipients to reduce cost. Sharing however may yield lower chance for pregnancy per couple.

### Donor Egg Bank

An egg bank will recruit the donors, stimulate their ovaries and freeze them. Recipient select from an already frozen inventory. The advantage is that they do not need to wait for a donor to be found, tested and her eggs harvested. In addition it is cheaper because only some of the eggs resulting from stimulation are obtained and no expenses incurred for donor travel and accommodation. On the other hand, it may yield lower chance for pregnancy (eggs are frozen and fewer of them are available). Donor selection is also restricted to available inventory of eggs that were already donated at an earlier time.

### Results of Donor Egg Cycles Based on Donor Selection

Based on hundreds of thousands of donor egg cycles some general expectations of pregnancy and live birth rates can be made:

a. Anonymous cycles usually yields a higher pregnancy rates than known donors. Anonymous donors are selected on pure medical grounds first. They tend to have better ovarian reserve and are commonly younger than known donors. Many times known donors are based on other grounds e.g sister donor or a friend that will donate without compensation

b. Donor egg cycles distributed to one recipient are more successful than those shared between two recipients due to more eggs and embryos being available for selection and transfer.

c. Fresh eggs from live donors produce more babies than frozen donor eggs. A study of 11,148 egg donation cycles performed in 380 U.S. clinics in 2013, including 2,227 that used frozen eggs indicated that

for each IVF cycle the live birth rates were 50% with fresh eggs, and 43% with frozen eggs and

for each embryo transfer, 56% of embryos created with fresh eggs resulted in a live birth, compared to 47% of embryos created with frozen eggs.

#### The Process of Selecting an Egg Donor

The process of selecting an egg donor is complex that involves you, your partner, your reproductive endocrinologist and sometimes other parties. The guiding principals for selecting a donor are

a. Selecting a donor with good ovarian reserve b. Protecting the mother from the transmission of infectious

diseases c. Protecting the babies from the transmission of genetic diseases d. Protection of the egg donor from potential complications of IVF e. Partners preferences.

Ovarian reserve: an egg donor should have an excellent ovarian reserve. This predicts excellent response to treatment with fertility medications and the collection of large number of mature goo quality eggs. Egg reserve is assessed through history taking, vaginal ultrasound estimation of antral follicle count, day 3 FSH and estradiol assay and AMH levels. Donors should be younger than 32 years and preferably younger than 30.

Infectious disease screening: donor are screened using first a thorough history and examination. Donor practicing in high risk behavior and those that lived in certain geographical areas are excluded. Lab tests are obtained for hepatitis B, hepatitis C, HIV I/II, Syphilis, gonorrhea and chlamydia. Other tests for infectious diseases could include testing for human T lymphocyte virus I/II, West Nile virus and South American trypanosomiasis. Tests are run at initial encounter then repeated in specialized labs within 30 days of retrieval to minimize the possibility of acquiring any of these infections at a later time.

Genetic screening: Extensive genetic and family history is first obtained from the donor. This is followed by screening for at minimal cystic fibrosis and any genetic disease related to donor ethnicity e.g hemoglobin abnormalities in African, Asian and Meditranean donors-Ashkenazi pannel in Jewish donors. Spinal muscular atrophy and fragile X syndromes are commonly also screened. More recently a universal genetic test that include 100 most common genetic diseases is routinely used. If an abnormality is found, a genetic counselor is consulted.

Donor related precautions: Egg donors should have the ability and intelligence to understand the process. This is evaluated by a trained psychologist. egg donors are counseled that the process does not impair their ability to conceive children of her own. Stimulation is tailored to avoid excessive stimulation and ovarian hyperstimulation syndrome. Donor are followed up after the procedure to monitor for any complications form retrieval and that the ovaries regained their normal size after stimulation.

Partners preference: Partners are offered a session with a psychologist to express their feelings about the process and to discuss some of the early and long term aspects of the process inducing legal issues an disclosure to children when they reach maturity. Partners may prefer certain race or ethnicity e.g Asian, Jewish...Some agencies specialize in recruiting donors of specific demographics. Physical features are also strongly considered and discussed with couples.

Other considerations: Male partner sperm analysis and labs are obtained. The mother is assessed for any medical disorder and the ability to carry a pregnancy safely. The uterine cavity is evaluated using hysteroscopy or saline sonography. The endometrium is evaluated for its response to hormones. The cervix is mapped to avoid difficult embryo transfer.

The process of egg donation is commonly satisfying to recipients, donors and physicians and is flexible to allow for safe selection of an egg donor and still consider your preferences and aspirations.

### **Testosterone Therapy-Male**

### **Infertility**

### **Testosterone Therapy-Male Infertility**

Many men are prescribed testosterone for a variety of reasons. Low testosterone levels (Low T) with no symptoms, general symptoms of low energy and feeling tiered and sexual symptoms, among others. Approximately 2.5 million men are prescribed testosterone each year in The US, mostly with no proper testing. Testosterone is only approved by FDA for low testosterone associated with specific diseases affecting testicular function. The FDA recently issued a <u>safety</u> <u>communication</u> cautioning the use of testosterone replacement for low testosterone levels and requiring labeling change to inform men of a possible increase in side effects.

From the fertility standpoint, there is no role for testosterone treatment, that could be detrimental. There is also no *proven* role for other medical treatment as clomid, letrozole, nolvadex, hCG and others in enhancing fertility in the vast majority of men

### Effects of testosterone on male fertility

When men are prescribed testosterone, sperm production slows down significantly and may completely stop. Many of them, no sperm can be found in the ejaculate (azospermia). Testosterone therapy can markedly lower the ability of men to father children. Testosterone inhibits a key master gland hormone (FSH) that is required to stimulate spermatogenesis (making sperm). The specific effects of testosterone on sperm count are unpredictable. In some men sperm count drops to zero even after a short use of testosterone.

Interestingly, when testosterone is stopped some men but definitely not all of them recover sperm production, commonly in one to six months. The extent of the recovery of sperm count is also unpredictable. The recovery of sperm count maybe limited requiring fertility treatment for conception to take place. A short course of testosterone can lead to a low sperm count for a very long time.

What can be done about low sperm count related to testosterone treatment

In addition to evaluation of female factors especially ovarian reserve, always a priority, men on testosterone and showing low sperm count should be advised to

1. Stop testosterone administration immediately

2. Repeat sperm analysis in 2 months. Sperm analysis should be performed in a facility that can perform diligent search for even very few sperm and can freeze sperm. If sperm is found in the ejaculate it should be cryopreserved immediately. If no sperm is found then sperm analysis should be repeated in another 2 months. The wait for recovery cannot be indefinite because of further deterioration of ovarian reserve in female partner with time.

3. Depending on the extent of recovery sperm can be utilized to promote conception. If sperm count recover close to 10 million moving sperm, natural conception can take place. Also sperm can be used for IUI, if needed. If the number of motile sperm is significantly lower, IVF is required, sometimes with intracytoplasmic sperm injection (ICSI).

4. If still no sperm were found after repeat analysis, TESE (testicular sperm extraction) can be attempted. A male reproductive urologist can perform diligent search for areas of spermatogenesis in the testes through repeat minute biopsy and searching under the microscope.

From the preventive aspect, avoid testosterone treatment if you intend to father children in the future. Know that there are very few solid indications for testosterone. If testosterone treatment is inevitable, consider pretreatment sperm freezing. Use gel preparation preferential to injection as they are not stored for a long time in the body.

Testosterone treatment is a preventable cause for infertility in males and could be detrimental to future fertility.

### Why are You Afraid of Infertility Treatment (and generally should not)

### Why are You Afraid of Infertility Treatment (and generally should not)

When have been trying to conceive for a while, women and men often are reluctant to seek help from a fertility specialist. What if they told me you cannot conceive? what if they find a major problem with my fertility? what if I need extensive treatment? All are viable questions. One deviation at that point is to consult with a specialist in your immediate circle but in another discipline: gynecologist or internist. This deprives you from valuable resources and tend to underestimate any issues you may have. This is a very common reaction in general use of supplements instead of medicine, go to a holistic specialist instead of a physician..

### Why are you afraid of Fertility Consultation

When you consult with a reproductive endocrinologist you may anxious about a discovery of one or more fertility issues, that may require treatment. Fertility problems are very private, maybe more than any other medical problems. They are certainly more private, though less risky, than heart disease or intestinal problems. You are also worried about the treatment of such factors and the required time and financial resources. One evidence of evidence of such fear is reluctance to seek consultation for years sometimes.

### Why are you afraid of fertility treatment

Once you start a consultation with a fertility specialist and treatment is recommended, couples are worried about the treatment process: complications and results.

#### Possible Complications of Fertility Treatment

All the complications of fertility can be classified into proven complications and unproven complications

#### Proven Complications

i. Multiple Pregnancy



Multiple pregnancy

Twins and higher order multiple pregnancy is an established complication of fertility treatment. It is directly related to the type of treatment (IUI or IVF), age and the number of embryos (IVF) transferred or follicles observed (IUI). The general incidence of twins is 1% after natural conception, 30% after IUI or two or more embryo transfer and 1% after single embryo transfer. The general incidence of triplets or higher is less than 0.1% after natural conception and 3% following fertility treatment.

ii. Ovarian Hyperstimulation Syndrome

Also an established complication of ovarian stimulation. It is more common in younger patients with large number of antral follicles seen in the ovary and high AMH levels. Women with PCOS are particularly at risk. The incidence of sever forms is 0.5 to 1%. In its severe forms it may lead to accumulation of fluid in the abdomen, blood clotting and may require hospital admission.

iii. Complications from egg retrieval

Egg retrieval is associated with very low level of comlications <1/1000, including bleeding, infection and anesthetic complication.

iv. Pregnancy Complications

Like any pregnancy there is a risk for miscarriage (15%) and ectopic pregnancy (3%) (e.g pregnancy in the fallopian tubes).

Unproven Complications

Cancer

There is no conclusive evidence that ovarian stimulation or any fertility treatment, in itself, increases the risk of cancer (any type). It is true that women who delay conceiving are at an increased risk for some types of cancer e.g breast cancer, ovarian cancer...There is however no proof that there is an increased risk of cancer *due to treatment*. For example, the risk for breast cancer in women living in the US is 1 in 8. This risk is slightly increased for women who deliver their first child after age 30. If a woman decided to undergo fertility treatment, her risk for breast cancer is not increased say to 1 in 6 because of that above her baseline risk

Congenital abnormalities

is also no conclusive evidence that congenital There abnormalities in babies conceived after fertility treatment is significantly increased after fertility treatment, for the vast majority of couples. In any population in the world, the incidence of birth defects after natural conception is 3-4% (not zero). This is the baseline risk. If a couple undergo fertility treatment, there no proof that that incidence is increased, say to 5%, compared to couples that declined fertility treatment. Many women seeking fertility treatment are older and are at increased risk for chromosomal abnormalities. Also infertility itself appear to be a risk for factor for slight increase in birth defects. But there is no evidence that medical procedures themselves increases the risk for congenital abnormalities. There are some special situations e.g severe male factor that even associated with further increase in risk of abnormalites, so a couple specific should be discussed with your reproductive risk endocrinologist. Note also that becoming pregnant at a younger age (with or without fertility treatment) reduces your risk for chromosomal abnormalities.

#### Results

You are certainly worried about the result of fertility treatment. That may make some women fearful of proceeding with treatment. Do confront this heads on. Ask your reproductive endocrinologist to give you a customized chance for pregnancy and delivery. Generally, fertility treatment is ultimately very successful. Over 60% of women seeking treatment ultimately deliver a baby or more after fertility intervention. There are many factors that indicate high chance for success, prior to starting treatment: age, ovarian reserve markers, the order of the cycle (first and second cycles are more successful)..

#### Long Term Effects

Outcomes of babies and young adults conceived after ovarian stimulation and IVF are definitely a long term concern. The first baby conceived at delivered following IVF was in 1978. Since then, approximately 1% of the world population are born after IVF. The scientific community have long term follow up data on babies born after fresh and frozen embryo transfer. There is even data on the third generation of babies (children of women who were conceived after IVF).

Egg freezing recently gained ground into as a procedure that broadens reproductive options for women. There are no long term data, nor a large number of babies (millions) conceived after egg thawing.

### Why you should not be afraid of fertility consultation and fertility treatment

#### Fertility Consultation

The majority of women undergoing a fertility consultation turns out to have no specific fertility factors and simply regular intercourse is advised. A fertility consultation is crucial in identifying risk factors (e.g genetic, multiple pregnancy) and to estimate odds for a healthy baby without or with treatment. Here is an example. A Caucasian couple are seeking fertility treatment. No fertility factors found, female partner is young. The only abnormality found is that they are both carrier for cystic fibrosis gene mutation (risk of transmission to baby is 25%). Same example apply to an African American couple in the case of sickle cell anemia. Would you want to know this? Another example, you are young but on fertility testing it was found that both of your fallopian tubes are blocked and you may need help conceiving. Is this an important information for you to know? Knowledge is very important, even if you decide not act upon.

#### Fertility Treatment Complications

Multiple pregnancy: is definitely the most dreaded complication of fertility treatment. There are many steps in evaluation and treatment that can minimize the risk of multiple pregnancy to a rate close to natural conception. Avoiding ovarian stimulation and IUI in favour of IVF with single embryo transfer appears to be the most important treatment decision that can minimize multiple pregnancy. IUI appears more conservative but actually that is not true. IVF with a single embryo transfer is more conservative due to lower risk for multiple pregnancy. Acceptability of fetal reduction is also another issue that should be discussed before starting treatment. The indiscriminate use of clomid appears to contribute the largest magnitude of risk for multiple pregnancy due to its widespread use without monitoring.

Ovarian Hyperstimulation Syndrome: is largely preventable complication through judicious use of fertility medication and avoiding the use of hCG as a trigger shot in favor of using lupron. An astute reproductive endocrinologist is able to keep this complication to a bear minimum.

#### Fertility Treatment Results

From one aspect the success rate of fertility treatment (per treatment cycle) is a factor of female medical factors and quality of fertility treatment she receives, if needed. On the other hand, the majority of courageous women who persevere, do get pregnant with fertility treatment. Those who are very unlikely to conceive are identified early on during evaluation and are should counseled accordingly. Women who do get pregnant do not write about it in lay media. Because the chance for conception is personal, you should seek to know your own chance for conceiving fertility treatment success, paying no attention to what your peers say or what you read. They cannot in any way reflect your own odds for success.

#### Long term effects of fertility treatment

Data on long term outcomes of young adult conceived with fertility treatment are reassuring of normal development and no significant abnormalities. In relation to egg freezing, there are reports of about a 1000 babies followed for short interval. They appear to show no increase in abnormalities. There are no long term follow up studies of babies conceived from thawed eggs.

The anxiousness about fertility treatment is natural, considering its intimate relationship to our life. Input from lay media and peer anecdotal stories is skewed and not readily applicable to anyone else. Irrespective of the decisions you make, knowing the facts about fertility treatment, personalized to your own personal medical reality is probably empowering and can prevent harm even if you decide not to pursue fertility treatment.