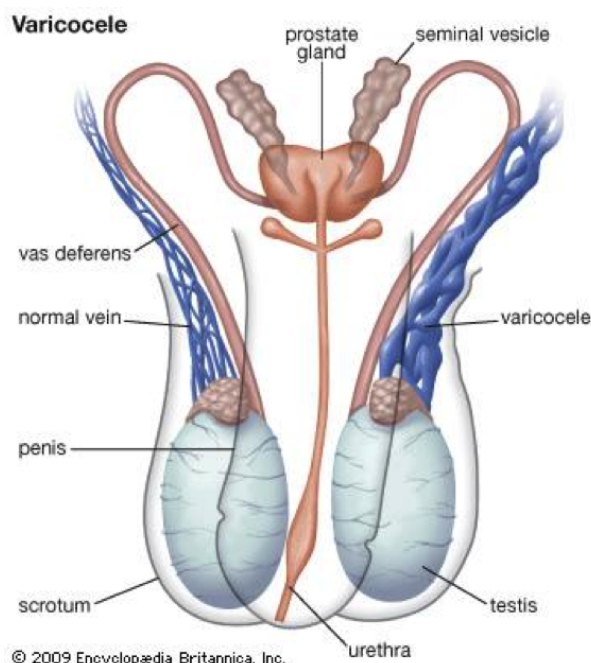


# Varicocele and Male Factor Infertility

## 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 that 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 varicocele (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 of 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](#)

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# Male Factor Infertility: Azospemia

## **Male Factor Infertility: Azospemia**

Male Factor Infertility: Azospemia means no sperm are found in the ejaculate. Azospemia 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 Azospemia**

a. Is it truly azospemia? 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 azospemic men, repeat analysis and freezing can avoid a surgical procedure to retrieve sperm.

b. A genetic cause for azospemia 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.

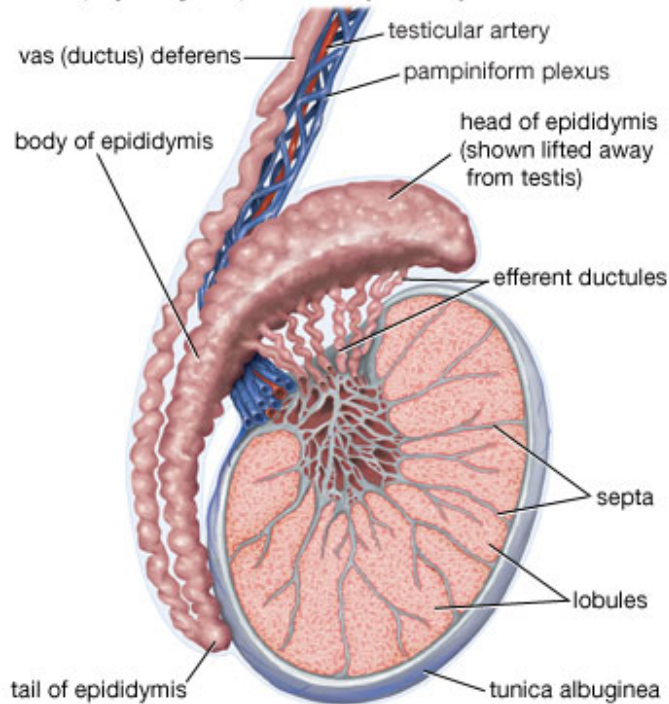
c. Evaluation of Ovarian Reserve for Female Partner. If ovarian reserve evident by day 3 FSH, AMH levels and antral follicle count seen on vaginal ultrasound is not diminished, this predicts reasonable chance for success with IVF-ICSI if sperm are found. Extremely low ovarian reserve or advanced female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

### Testis, epididymis, and vas (ductus) deferens



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### 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 testis 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 there 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 biopsied 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 is no concrete evidence that fresh TESE sperm is superior to frozen TESE sperm.

In addition in some cases 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*

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# 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 tired 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 [safety communication](#) 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.

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## Practical Approach to Male Infertility

### **Practical Approach to Male Infertility**

Male factor infertility is present in approximately 40% of couples having difficulty to conceive. In most cases, however, it is seldom one factor. A basic element that is encountered in every case is the number and quality of eggs. Other factors in also include sexual factor and other female factors (e.g blocked fallopian tubes). Hence, evaluation of female factors is integral to evaluation and successful treatment of male factor.

Evaluation of female factors includes testing for [ovarian reserve](#) and testing of the fallopian tubes for patency. In addition to evaluation of medical, obstetric and genetic risks of getting pregnant.

# Evaluation of Male Factor

Reproductive ability in males is initially evaluated through i. Detailed history of male partner and ii. sperm analysis. History can indicate many factors that may reduce the ability to conceive: social habits, erectile dysfunction, childhood infections (mumps), medical disorders, genetic diseases (chromosomal abnormalities, specific genetic diseases as cystic fibrosis), occupational exposure..etc. Unfortunately in the majority of cases history may not predict abnormalities in male factor

## *Sperm Analysis*

Accurate interpretation of [sperm analysis](#) (volume, concentration, movement and shape) is the most important step in evaluation. It is important to take in consideration each factor separately and then in combination. Normal parameters are volume >2mL, concentration 15million/mL, motility 40% and normal shape 4% using strict morphological criteria (Kruger).

Repeat sperm analysis is commonly recommended when abnormalities are detected. There is no strong evidence to repeating the sperm analysis. If the sperm analysis is to be repeated this should be done at least 2 months later as it would take that long for new sperm to be 'manufactured'.

Generally 10 million moving sperm sperm per ejaculate (volume x concentration x % motility) is required for successful reproduction with intercourse and IUI. Approximately 2 million motile sperm are adequate for IVF. Lower parameters especially if low morphology <2% require IVF with intracytoplasmic sperm morphology (ICSI).

## *Other Tests*

Genetic screening for chromosome analysis and Y chromosome micro-deletion is required in low sperm concentration (<10 million /mL) and [azospermia](#) is required. Abnormalities are

found in 5-10% of men and can be transmitted to children. Genetic screening for cystic fibrosis and its congenital absence of the vas deferens is also required if azospermia (obstructive) is present.

Other sperm tests as pH, fructose and sometimes hormone analysis are sometimes helpful.

Tests for sperm DNA fragmentation is still being evaluated but are not part of routine fertility workup.

## **Treatment of Male factor Infertility**

Improvement in sperm analysis is not the main aim of treatment. The main aim is conception and delivery of a healthy child. Sperm analysis improvement is a surrogate outcome not a final goal. In most cases, the improvement in sperm parameters (count, movement and shape) does not translate into a higher chance for conception. In addition, in the majority of cases there is no specific cause identified for male factor abnormalities. The two practical strategies left are to wait (within what is allowed by female ovarian reserve) for sperm analysis to improve and conception to occur or to use the small / abnormal sperm available for assisted reproduction (ICSI) which is a very efficient strategy.

### ***Four Important Considerations before Treating Male Infertility***

a. Female age and ovarian reserve: any treatment for male factor should be guided with the number of eggs in the ovary and their quality (age related). In women with low egg reserve and 35 or older consideration to ovarian stimulation (to increase mature egg production) followed by IUI or ICSI should be exercised.

b. Sperm Freezing: In men with moderate to severe male factor one should consider freezing one or more sperm samples. The future sperm parameters cannot be predicted and can deteriorate even to a complete absence of sperm in ejaculates.

Sperm freezing is cheap, non invasive and can save men from the need for surgical retrieval of sperm. Men undergoing vasectomy can also consider sperm freezing, prior to procedure, in case they decide to father children in the future

c. Genetic screening: there are two main values to screening males with moderate to severe sperm abnormalities to chromosomes, Y micro-deletion and cystic fibrosis. To avoid transmission to children and to counsel the couple about the chance of successful surgical sperm retrieval (TESE). In some cases the chance for finding sperm is extremely low that TESE is not indicated.

b. Urological consultation: After female and initial male evaluation is complete, evaluation by a male urologist is very useful. A urologist well versed in male infertility can counsel the couple about the chance for success of surgical sperm retrieval and following correct of obstruction.

#### *Four Treatment Options to Consider*

Surgical sperm retrieval: in obstructive and non-obstructive azospermia sperm can be retrieved directly from the testes by a male urologist. Micro-TESE involves dissecting one or both testes and obtaining multiple tiny biopsies from many areas. In real time each biopsy is examined under a microscope. The process is repeated till sperm are obtained. The best chance

Surgical treatment for obstructive azospermia: in men that underwent vasectomy before vasectomy reversal can, if successful, restore fertility. Other areas of obstruction can also be restored by urological surgery.

IUI: in few cases of mild male infertility (producing close to 10 million motile sperm) or mild shape abnormalities, ovarian stimulation and IUI is an aoption for 3 cycles. IUI using donor sperm is also an option.

IVF-ICSI: assisted reproductive technology is very robust and can address the majority of male infertility: low sperm count, low motility, abnormal sperm shape, prior fertilization failure. Its is very efficient that it can achieve a conception with very few available fresh or frozen sperm. It can be synchronized with surgical sperm retrieval so that fresh sperm are used for ICSI. Once sperm are available, the success of IVF is dependent on female age and ovarian reserve.

### *Interventions to Avoid or Consider Cautiously*

Surgical treatment of varicocele: Varicocele is a common finding in infertile males and can be associated with low concentration and motility and higher abnormal shape of sperm. Varicocele surgery does improve sperm parameters. The problem with varicocele surgery is that it is not proven to increase the odds of delivering a child by female partner. Varicocele surgery should be cautiously considered due to lack of solid evidence of its benefits.

Medical treatment: The use of medications (e.g clomid, nolvadex, anastrozole) should be avoided as there is no evidence that they will improve the chance of pregnancy and improvement in sperm parameters. The use of injection medications should only be employed in men with a specific indications related to deficiency of such hormones

Supplements: so far there is NO supplement or 'vitamin' proven to increase the chance for successful reproduction in male with sperm abnormalities.

*A practical approach to male infertility requires initial evaluation of sperm analysis, ovarian reserve and genetic risk factors followed by a treatment plan oriented with the ultimate goal: conceiving healthy child not intermediate issues as cause of male infertility and improving sperm analysis.*

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# Sperm Analysis in Natural and Assisted Conception

Sperm analysis is the initial test for evaluation of male fertility. Components of **sperm analysis** include volume, count (concentration), movement and shape of sperm cells.

## Normal Sperm Analysis

Sperm volume: the total amount of fluid produced. Commonly 1.5 mL or more.

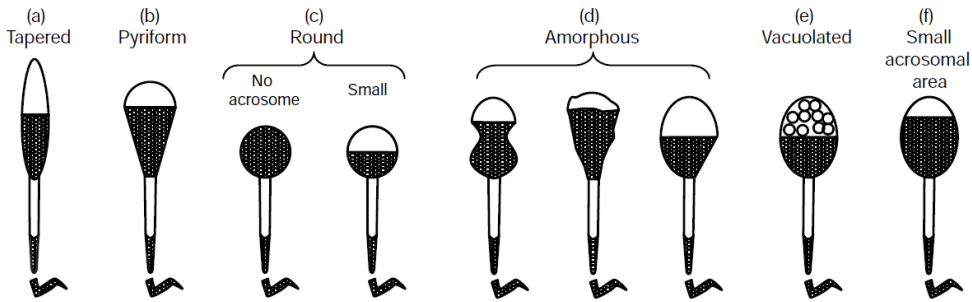
Sperm count: number of sperm in each mL of fluid. Normal concentration is 15 to 20million per mL. Total count= volume x concentration (count).

Sperm motility: % of sperm with vigorous or moderate movement. Total motile sperm count=volume x concentration x %motility

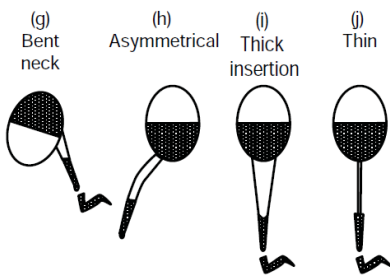
Sperm morphology: Shape of sperm using strict (Tygerberg, Kruger) criteria 4% normal or more



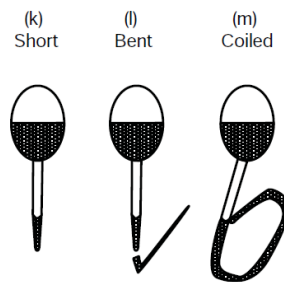
#### A. Head defects



#### B. Neck and midpiece defects



#### C. Tail defects



#### D. Excess residual cytoplasm



### Strict Sperm Morphology

Lower reference limits for men whose partner conceived within 12 months after stopping use of contraception had the following parameters (WHO manual , 5th ed.) are:  
Semen volume (ml) 1.5 (1.4–1.7)

Total sperm number ( $10^6$  per ejaculate) 39 (33–46)

Sperm concentration ( $10^6$  per ml) 15 (12–16)

Total motility (PR + NP, %) 40 (38–42)

Progressive motility (PR, %) 32 (31–34)

Vitality (live spermatozoa, %) 58 (55–63)

Sperm morphology (normal forms, %) 4 (3.0–4.0)

All parameters should be interpreted in conjunction with clinical information. If abnormal it can be repeated in 2 to 3 months.

## How much sperm is enough?

Evaluation of male fertility through sperm analysis is complex. Clinical factors in history and examination should be considered. Total sperm count in the specimen is an important

factor e.g low sperm morphology in specimen of 200 million sperm may have a different effect than low morphology in a specimen of 30 million sperm. Although there are notable variations in a sperm sample of the same man over time, there is no evidence that repeat evaluation of semen is helpful in managing infertility in a female partner.

Since we have very limited tools (medications, supplements, surgery) to meaningfully improve sperm parameters and fertility, a practical management of fertility due to male factor is:

>10 million motile sperm: suitable for natural conception and IUI

2-10 million motile sperm: suitable for IVF

<2million motile sperm or strict morphology <2% suitable for IVF with ICSI (intracytoplasmic sperm injection)

IVF + ICSI is indicated if surgical sperm harvest is needed and some cases of retrograde ejaculation and anti-sperm antibodies.

## **Can the sperm analysis be improved?**

The count, motility and morphology can sometimes be improved (lifestyle modifications, medicine, surgery). Two important tips to consider though

a. In the majority of cases, there is no evidence that this improvement increases the odds of a pregnancy in female partner

b. The delay in treatment is sometimes critical for women with low egg reserve while they wait for their partners to improve their sperm parameters