

Testosterone Therapy-Male Infertility

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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.

Practical Approach to Male Infertility

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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. It 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 indication 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.

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

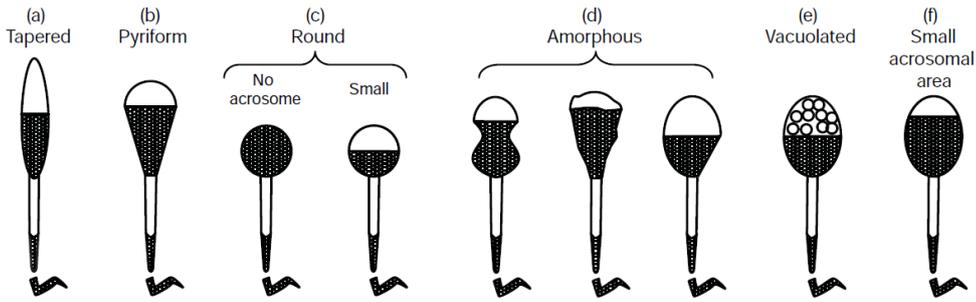
Sperm volume: the total amount of fluid produced. Commonly 1.5 mL or more.

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

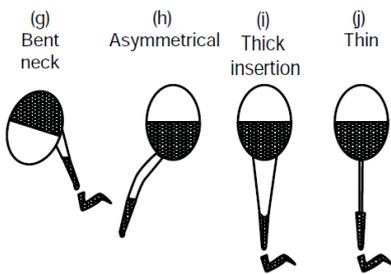
Sperm motility: % of sperm with vigorous or moderate movement. Total motile sperm count=volume x concentration x %motility

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

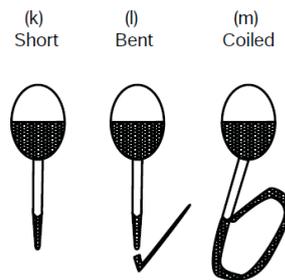
A. Head defects



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

Fertility in Men Diagnosed with Cancer

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Who needs to consider preservation of Fertility?

a. The American Cancer Society estimates that 760,000 men will be diagnosed with cancer in 2009. Cancer itself (before treatment) is sometimes associated with less sperm production in men. This is specially the case in Hodgkin's lymphoma, testicular cancer, prostate cancer, leukemias and colon cancer. The most harmful factor, however, is cancer treatment. Chemotherapy and radiation significantly impair sperm production. The effect of chemotherapy depends on age, drug used, dose and duration. Cyclophosphamide appears to be the most harmful agent. Radiation also impairs sperm production especially at doses of 1200cGy or more.

Sperm count sometimes recover to a variable extent years after cancer treatment. This depends on the type of cancer and treatment used. For example 90% of men diagnosed with Hodgkin's lymphoma, treated with MOPP chemotherapy regimen, do not have any sperm in the ejaculate after one year.

b. Bone marrow transplantation for cancer of nonmalignant diseases usually require prior irradiation and chemotherapy. This is associated with high risk (85%) of complete failure of sperm production.

c. Connective tissue / autoimmune diseases as lupus and

rheumatoid arthritis requiring treatment with chemotherapy.

d. Genetic abnormalities associated with rapid loss of male germ cells e.g. Klinefelter syndrome, Y chromosome microdeletion (AZFc).

Methods used for Fertility Preservation

Methods used to preserve fertility in men are generally divided into two categories:

Protection of the testes from damage caused by cancer treatment:

1. Shielding the testes from radiation field.
2. Protection of the testes from the effect of chemotherapy.

GnRH agonists are a group of medications that suppress the master gland in the brain, preventing the release of the hormones that stimulate sperm production in the testes. Although suggested, there is no proof that they actually increase the odds for pregnancy after the use of chemotherapy. Actually, there is no effective protective medication available for use in men or women.

Low Temperature Storage of Sperm and Testicular Tissue:

a. Sperm Cryopreservation. This is the standard method for preservation of fertility in men. A sperm sample is obtained by masturbation and frozen for later use. If feasible multiple samples are obtained. In the future, sperm sample are used for intrauterine insemination or IVF / intracytoplasmic sperm injection (ICSI). Banking sperm was found to offer not only a chance to father children in the future but also encouragement and improved morale during disease treatment especially if it was initiated by the patient own initiative.

Lack of information and counseling is the most important reason why men diagnosed with cancer do not bank their sperm.

Although freezing may reduce the quality of sperm especially if it was not optimal before freezing, modern reproductive medicine can handle the majority of compromised specimens yielding excellent pregnancy rates, similar to those of fresh sperm.

b. Testicular Sperm Extraction (TESE). This surgical procedure retrieves sperm from inside the testes if no sperm was found in the ejaculate. If this procedure is used before cancer treatment, sperm are retrieved in over 50% of cases. Sperm or testicular biopsies are frozen for later use. ICSI is used for fertilization. In case of testicular cancer, sperm retrieval can be performed at the same time of surgery for cancer.

c. Testicular Tissue or Germ Cell Freezing. This is an experimental technique. Immature germ cells or testicular pieces are frozen for later transplantation. No pregnancy was achieved using this method so far.

In conclusion, fertility-sparing strategy is readily available to the majority of men at risk for diminished fertility through sperm cryopreservation. Men interested in fathering children in the future should be counseled about this option.