**Treatment of Male Infertility**

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**INTRODUCTION** — Infertility in a couple is defined as the inability to achieve conception despite one year of frequent unprotected intercourse. Use of this time period, while arbitrary, was based upon a study of 5574 English and American women engaging in unprotected coitus who ultimately conceived between 1946 and 1956 [[1](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/1)]. Among these women, 50 percent conceived within three months, 72 percent within six months, and 85 percent within 12 months. Similar estimates were reported in later studies.

There are four main causes of male infertility:

* Hypothalamic/pituitary disease (secondary hypogonadism) – 1 to 2 percent
* Testicular disease (primary spermatogenesis failure and hypogonadism) – 30 to 40 percent
* Post-testicular defects (disorders of sperm transport) – 10 to 20 percent
* Non-classifiable – 40 to 50 percent

The noted frequencies represent an estimate of the approximate proportion of patients in each category presenting to a tertiary referral center with capabilities to diagnose subtle defects including Y chromosome microdeletions [[2](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/2)]. It is likely that some of the non-classifiable causes will be genetic or epigenetic defects that have not yet been identified.

This topic will review the treatment of the different causes of male infertility. The current methods of therapy are divided arbitrarily into the following categories: no available treatment, specific treatment, treatment of uncertain efficacy, empirical treatment, and treatment by assisted reproductive techniques [[2-4](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/2-4)]. The diagnostic approach to the infertile male is discussed separately.

**GENERAL CONSIDERATIONS** — Treatment of male infertility should be guided by the following general considerations, as well as by the specific causes of the infertility:

**Concurrent male and female infertility** — Treatment of male infertility involves the couple. The distribution of male and female causes among infertile couples has not been well defined. In a 1982 to 1985 World Health Organization multicenter study, 20 percent of cases were attributed to male factors, 38 percent to female factors, 27 percent had causal factors identified in both partners, and 15 percent could not be satisfactorily attributed to either partner [[5](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/5)].

It is therefore essential that the female partner be thoroughly investigated and treated while the male partner is being evaluated. Problems in the female partner, such as anovulation or irregular ovulation, hyperprolactinemia, endometriosis, and tubal obstruction, should be treated with medications or laparoscopic surgery simultaneously with or before treatment of the male partner. Treatment of the female partner can often compensate for male factor subfertility due to mild to moderate decreases in semen parameters, resulting in pregnancy without treatment of the male.

**Use of assisted reproductive techniques** — Until lately, management of male factor infertility was a frustrating experience for both clinician and patient because of poor understanding of the pathogenesis of and an inability to treat most cases of male infertility. The development of assisted reproductive techniques (ART) has improved the outlook for many couples with male factor infertility. These techniques, however, are complex, invasive, expensive, and often unsuccessful.

**Documentation of treatment efficacy** — Many medical and surgical procedures have been reported to improve male fertility only to be shown subsequently to be ineffective. The two principal reasons for the initially promising but ultimately misleading reports are the use of semen quality, rather than pregnancy, as the criterion of success, and the failure to include a control group in the trial.

* Pregnancy should be the principal criterion for efficacy in male fertility studies because semen quality is notoriously variable. When the inclusion criteria require certain abnormal semen test results for entry into a study, subjects may be recruited when their semen parameters are at their worst. These parameters tend to improve subsequently because they regress towards the mean; the improvement gives the false impression of resulting from the study treatment. Use of at least three semen specimens over a period of time, eg, six weeks, may diminish this phenomenon, but is still not as good as pregnancy as the principal criterion of fertility.
* Male fertility studies should include a control group because even untreated men who have subnormal semen parameters, unless they are entirely azoospermic, can sometimes impregnate their female partners. As a consequence, pregnancy can occur independent of treatment and false positive results occur in clinical studies that do not use a placebo control group [[6](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/6)].

**LIMITED AVAILABLE TREATMENT** — There are a variety of causes of irreversible infertility for which no therapy is available. As an example, there is no known therapy that will stimulate sperm production when the seminiferous tubules have been severely damaged. Conditions that are often associated with such severe damage are Klinefelter syndrome, microdeletions of the Y-chromosome, Sertoli cell only syndrome, and idiopathic infertility associated with azoospermia.

An exception to this generalization is men with azoospermia previously thought to be untreatable as determined by persistent absence of any sperm in the ejaculate but who do have sperm that can be extracted from the seminiferous tubules of the testes. If mature spermatozoa or spermatids are found in the testicular biopsy, they can be retrieved and used to fertilize oocytes in vitro, resulting in pregnancies in the partner using assisted reproductive techniques (ART) (see below).

In some cases, successful fertility has been achieved in patients with Klinefelter syndrome and Sertoli cell only syndrome using testicular sperm retrieval and intracytoplasmic sperm injection [[7](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/7)]. However, there are important genetic implications of these procedures [[8](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/8)].

Some patients have germ cell arrest, usually at the primary spermatocyte stage. Microinjections of such early germ cells into the cytoplasm of an oocyte have not resulted in viable embryos for transfer in humans. Microinjection of secondary spermatocytes and round spermatid has resulted in viable embryos in mice but not in men [[9](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/9)]. It has been shown that injection of a sperm nucleus can result in viable offspring [[10](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/10)].

Even if a man's infertility cannot be treated, the frequently accompanying hypogonadism can be treated with testosterone. While not enhancing fertility potential, such men will greatly benefit from androgen replacement by improvement in sexual function and mood, and an increase in or maintenance of bone and muscle mass.

**SPECIFIC TREATMENT AVAILABLE** — Specific endocrine treatment is available only for men whose infertility results from hypogonadotropic hypogonadism.

**Hypogonadotropic hypogonadism due to hyperprolactinemia** — If hypogonadotropic hypogonadism results from hyperprolactinemia, the hypogonadism can often be corrected and fertility restored by lowering the serum prolactin concentration.

* If the hyperprolactinemia results from a medication, that medication should be discontinued, if possible.
* If the hyperprolactinemia results from a lactotroph adenoma, the adenoma should be treated with a dopamine agonist, such as [cabergoline](http://www.uptodate.com/contents/cabergoline-drug-information?source=see_link) or [bromocriptine](http://www.uptodate.com/contents/bromocriptine-drug-information?source=see_link).

Normal spermatogenesis takes three months. As a result, restoration of a normal sperm count usually does not occur for at least three and sometimes six months or more after the serum prolactin and testosterone concentrations have returned to normal.

In some patients who have a lactotroph macroadenoma, the hypogonadotropic hypogonadism appears to be the result of permanent damage to the gonadotroph cells by the mass effect of the adenoma. Lowering the serum prolactin concentration and shrinking the adenoma in this setting may not be sufficient to increase the testosterone concentration and sperm count. Thus, if the serum testosterone concentration does not increase to normal within six months of the serum prolactin being reduced to normal, gonadotropin treatment should be instituted if fertility is desired.

**Hypogonadotropic hypogonadism due to other causes** — Men who have hypogonadotropic hypogonadism due to hypothalamic or pituitary diseases can be treated with gonadotropins, but only men who have hypogonadotropic hypogonadism due to hypothalamic disease can be treated with gonadotropin-releasing hormone (GnRH). A complete discussion of the use of gonadotropins can be found elsewhere.

* Gonadotropin therapy – Treatment is initiated with [human chorionic gonadotropin](http://www.uptodate.com/contents/human-chorionic-gonadotropin-drug-information?source=see_link) (hCG), 1500 to 2000 IU three times per week subcutaneously or intramuscularly for at least six months. hCG has the biologic activity of luteinizing hormone. The hCG dose should be adjusted upward according to symptoms of hypogonadism, serum testosterone concentrations, and semen parameters. Some patients with acquired hypogonadotropic states can be stimulated with hCG alone to produce sufficient sperm. If after six to nine months the patient remains azoospermic or severely oligospermic, then human menopausal gonadotropin (hMG) or recombinant follicle-stimulating hormone (FSH) should be added. This topic is discussed in detail elsewhere.
* Pulsatile GnRH treatment – Pulsatile subcutaneous or intravenous treatment with GnRH has also been successfully used to treat gonadotropin deficient patients [[11](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/11)]. GnRH has to be delivered in pulses using a portable pump with an attached catheter and needle for many months or years; most patients find it inconvenient to use GnRH therapy for so long.

**TREATMENT OF UNCERTAIN EFFICACY** — Treatments for the following conditions have a certain rationale, but the evidence for the efficacy of these treatments may not be conclusive ([table 3](http://www.uptodate.com/contents/image?imageKey=ENDO%2F58859&topicKey=ENDO%2F7452&rank=3%7E78&source=see_link&search=Male+Infertility)):

**Genital infections** — Infertile men rarely present with symptoms or signs of acute genital infections or prostatitis, but they are sometimes diagnosed as having infections of the urogenital tract by the presence of increased leukocytes in the semen [[12](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/12)]. These patients are often labeled as having chronic prostatitis, but specific organisms are rarely identified. The effect of chlamydia infections on semen quality and infertility remains controversial [[13](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/13)].

In such situations, it is unclear if the leukospermia plays a pathogenic role in the infertility or is a correlative event. A pathogenic role seems possible because the presence of leukocytes may decrease sperm functional capacity by the release of reactive oxygen species. Seminal fluid cultures should be obtained when there are over one million leukocytes in the semen; however, the yield is usually poor and nondiagnostic.

Despite the absence of symptoms, we typically treat patients who have leukospermia, even if the culture is negative, with at least a 10-day course of antibiotics such as [erythromycin](http://www.uptodate.com/contents/erythromycin-drug-information?source=see_link) or [trimethoprim-sulfamethoxazole](http://www.uptodate.com/contents/trimethoprim-sulfamethoxazole-co-trimoxazole-drug-information?source=see_link) or a quinolone. A second course of therapy is usually given if leukocytes persist in the semen after antibiotics. However, the poor results of this regimen make it difficult to demonstrate a causal relationship between genital infections and male infertility [[14](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/14)]. Exceptions are patients with a past history of genital gonorrhea, tuberculosis, and other specific sexually transmitted diseases which lead to genital tract obstruction at the epididymis and vas deferens [[15](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/15)].

**Sperm autoimmunity** — Sperm autoimmunity is diagnosed by the presence of sperm antibodies on the sperm surface or in the seminal fluid by the immunobead test or mixed antiglobulin reaction [[12](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/12)]. Glucocorticoids have been used in such patients. Continuous or intermittent high doses of [prednisone](http://www.uptodate.com/contents/prednisone-drug-information?source=see_link) (from 40 to 80 mg/day) for up to six months have been shown in placebo-controlled trials to improve cumulative pregnancy significantly in partners of men with sperm autoantibodies [[16](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/16)].

However, many patients cannot tolerate this regimen because of the adverse effects of high-dose corticosteroid therapy. As a result, most couples prefer to try an assisted reproductive technique, such as intracytoplasmic sperm injection (ICSI), as primary treatment for sperm autoimmunity.

**Retrograde ejaculation** — Retrograde ejaculation, as seen in neuropathic disorders, including urogenital tract surgery, sympathetic denervation, and diabetes, can be treated with intrauterine insemination (IUI), using the male partner's spermatozoa collected after alkalinization of the urine and extensive washing of the sperm. Alternatively, the washed spermatozoa can be used for in vitro fertilization (IVF) or ICSI procedures.

**Varicocele** — Although the presence of varicocele can be associated with normal semen parameters and normal fertility, most men with varicocele and presumptive infertility have abnormal semen parameters, including low sperm concentration and abnormal sperm morphology. However, data on the efficacy of varicocele repair for improved fertility are conflicting, and we do not recommend routine varicocele repair in subfertile couples.

In a World Health Organization (WHO) study of over 9000 men who were partners in an infertile couple, a varicocele was much more common in men with abnormal semen (25.4 versus 11.7 percent with normal semen) [[17](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/17)]. The causal relationship between varicocele and male infertility has been ascribed to increased testicular temperature, delayed removal of endogenously derived toxic materials and metabolites, hypoxia, and stasis [[18,19](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/18,19)].

For many years, it has been controversial whether high ligation of varicocele will improve pregnancy rates in the female partner. The WHO conducted a large prospective multicenter clinical trial to compare immediate varicocele ligation with operation deferred for one year; 248 couples participated from 12 countries [[20](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/20)]. The first year cumulative pregnancy rates were 34.8 percent in the immediate operation group and 16.7 percent in the delayed operation group (p<0.003). In addition to the markedly higher pregnancy rate, sperm concentration was significantly improved at 3, 6, 9, and 12 months after surgery (all p<0.001).

These findings suggest that varicocele ligation is approximately 2.5 times more effective than delayed operation. However, there were some flaws in the study design:

* There was considerable loss of follow-up, particularly in the group of men randomized to delayed operation.
* At the beginning of the study, some couples were randomized before formal enrollment in the study.

Other studies [[21,22](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/21,22)] and two systematic meta-analyses [[23,24](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/23,24)] have reported no definitive benefit of varicocele repair. The WHO study was not included in one of the systematic reviews [[23](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/23)], because the results of the trial were never published in full (only in abstract or summary form with different total numbers of subjects and slightly different benefit estimates).

Given this controversy, we do not recommend routine varicocele repair in subfertile couples, although it may be reasonable for men with a large varicocele (grade 3 varicoceles) [[25,26](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/25,26)]. In addition, the response to ligation may be better when the couples are relatively young and the duration of infertility is short. Atrophic testes, elevated serum follicle-stimulating hormone (FSH) concentrations, and/or severe oligospermia or azoospermia indicate severe general epithelial damage and are associated with a lesser likelihood of fertility after varicocele ligation.

In some centers, internal spermatic vein ligation has been replaced with laparoscopic varicocelectomy or vascular catheter embolization of spermatic veins [[27](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/27)]. These procedures should only be performed in centers where the surgeon or radiologist is skilled at this procedure.

An alternative to varicocele ligation or embolization is an assisted reproductive technique. An analysis comparing ICSI to conventional varicocele ligation showed that surgical varicocelectomy may be more cost-effective [[28](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/28)]. This conclusion was confirmed in a later study [[29](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/29)].

**Obstructive azoospermia** — Obstructive azoospermia can be the result of several processes. It is diagnosed by finding testes of normal size, normal serum FSH concentration, azoospermia or severe oligospermia, and normal testicular histology.

Both surgery and assisted reproduction techniques may be beneficial in such patients. As an example, obstruction of the epididymis or ejaculatory duct can be treated surgically. Azoospermia due to obstruction in the epididymis can be treated by microsurgical end-to-end anastomosis of the epididymal duct to epididymal duct or to vas. These procedures may lead to the presence of ejaculated sperm, but the results are variable and depend on site of reanastomosis, the experience and skill of the operator, and the duration of obstruction.

The results are best when obstructive azoospermia is due to vasectomy and not as good with other causes (eg, postinfection and congenital bilateral absence of the vas deferens) [[30](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/30)]. The appearance of spermatozoa after reanastomosis for vasectomy reversal can be over 90 percent, with pregnancy in over 50 percent. The success rate depends upon the duration between vasectomy and the reversal procedure; in general, the longer after vasectomy, the poorer the pregnancy rate [[31](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/31)].

Ejaculatory duct obstruction is characterized by decreased semen volume and azoospermia or severe oligospermia. Transrectal ultrasonography demonstrates dilated seminal vesicles, and aspiration of the seminal vesicles shows spermatozoa, suggesting obstruction. This condition can be treated by transurethral resection of the ejaculatory ducts [[32,33](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/32,33)], with resulting improved semen quality and pregnancy in the partner.

In addition, several assisted reproductive techniques can be combined to use sperm from men who have obstructive azoospermia to fertilize ova of their partners and achieve pregnancy. Spermatozoa obtained by microsurgical aspiration from the epididymis (MESA) [[34](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/34)] or from the testes by biopsy or fine needle aspiration [[35-37](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/35-37)] can be used with eggs aspirated from the female partner for IVF [[34](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/34)] or ICSI [[38,39](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/38,39)]. The fertilization rate of microsurgical sperm aspiration together with ICSI, despite very poor epididymal/testicular sperm quality, is approximately 50 percent, and the pregnancy rate is about 40 percent per cycle and 20 percent per microsurgical aspiration. Thus, men previously classified as sterile can now be fertile.

For obstruction due to vasectomy, surgical reanastomosis appears to be preferable to assisted reproductive techniques. In two separate studies for patients seeking pregnancy after vasectomy, vasectomy reversal was found to be more successful and cost-effective than microsurgical epididymal sperm aspiration followed by IVF or ICSI [[40,41](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/40,41)]. In one analysis based upon expected costs and results in the United States in 1994, the cost of vasectomy reversal was $25,475 with a delivery rate of 47 percent; the respective values for ICSI were $72,521 and 33 percent. In contrast, for obstruction due to other epididymal lesions, the results of surgical anastomosis are not as good as those with sperm retrieval and ICSI. Given the continuous improvements in sperm retrieval and ICSI techniques, surgical reversal versus ART should be discussed with the couple before an informed decision can be made [[42](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/42)].

Because patients who have congenital bilateral absence of the vas deferens may have genetic mutations commonly present in cystic fibrosis, the possibility that they may now have progeny using assisted reproductive techniques means that their offspring might have cystic fibrosis. Thus, such men and their partners who are considering these techniques to achieve pregnancy should have genetic screening and counseling. Screening the female partner may be more cost effective than screening the patient because if she is negative, the risk that their progeny will have cystic fibrosis or congenital bilateral absence of the vas deferens is less than 1 in 1500 [[2](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/2)].

**EMPIRICAL THERAPY** — Many treatments have been used empirically for male infertility, including [clomiphene](http://www.uptodate.com/contents/clomiphene-drug-information?source=see_link) citrate and other hormones, vitamins, and kallikrein [[3,43,44](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/3,43,44)]. However, when placebo-controlled prospective clinical trials have been performed with adequate numbers of subjects in randomized placebo controlled trials, none of these methods, including clomiphene citrate and human recombinant follicle-stimulating hormone (r-hFSH), has been proven clinically effective in idiopathic oligospermia or azoospermia [[45-48](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/45-48)].

A meta-analysis of six randomized controlled trials reported that gonadotropin administration may result in a higher pregnancy rate per couple. However, treatment protocols and follow-up periods were variable. None of the studies included data on miscarriage rates. The authors stated that although the data suggested a beneficial effect of gonadotropin therapy in men with idiopathic infertility, the number of trials and participants was insufficient to draw final conclusions [[49,50](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/49,50)].

Limited data suggest that aromatase inhibitors may improve sperm concentrations in men with severe oligozoospermia or azoospermia prior to sperm retrieval for intracytoplasmic sperm injection (ICSI) [[51,52](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/51,52)]. In one uncontrolled study, [anastrozole](http://www.uptodate.com/contents/anastrozole-drug-information?source=see_link) administration to infertile men with serum low testosterone-to-estradiol ratios resulted in an increased testosterone-to-estradiol ratio and an increase in sperm concentrations [[53](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/53)]. Further data are necessary before recommending this approach.

Another recommendation that has often been made to infertile men is to wear boxer undershorts instead of jockey style and not to take hot showers or baths. The rationale is that increased scrotal temperature can impair spermatogenesis [[54](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/54)]; moderate increases in scrotal temperature have been shown to markedly accelerate germ cell apoptosis in animals [[55](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/55)]. However, a study of men who wore tight athletic supporters lined with polyester for 12 months found a slight rise in scrotal temperature but no impairment in semen quality [[56](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/56)]. The wearing of ordinary brief underwear had no effect on scrotal temperature compared to boxer-style underwear [[57](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/57)]. Similarly, no change in semen parameters was found in men taking frequent saunas or hot baths [[58](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/58)]. Presumably, the degree of intratesticular temperature increase was insufficient to induce the apoptosis seen in experimental animals. We do **not** recommend use of the treatments listed in the table in the treatment of idiopathic male infertility.

**ASSISTED REPRODUCTIVE TECHNIQUES** — Assisted reproductive techniques (ART) are commonly used for the treatment of the female partner of men with moderate or severe oligospermia and azoospermia [[59,60](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/59,60)].

**Intrauterine insemination** — The intrauterine insemination (IUI) procedure consists of washing an ejaculated semen specimen to remove prostaglandins, concentrating the sperm in a small volume of culture media, and injecting the sperm suspension directly into the upper uterine cavity using a small catheter threaded through the cervix. The insemination is timed to take place just prior to ovulation, typically using home urine luteinizing hormone (LH) measurement. A systematic review reported that there is insufficient evidence to recommend one sperm preparation technique over another [[61](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/61)].

In early studies of couples with male infertility, IUI did not appear to be effective [[62,63](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/62,63)]. However, other data suggest that in couples with mild male infertility, IUI does improve pregnancy rates in couples when compared to intracervical insemination or timed natural cycles. The topic of IUI alone or in conjunction with gonadotropin stimulation of the female partner is discussed in detail elsewhere.

**In vitro fertilization** — When in vitro fertilization (IVF) is employed using the ejaculated sperm from a man with moderate oligospermia, the pregnancy rates are very low. Before the advent of intracytoplasmic sperm injection (ICSI), IVF was used for the treatment of male infertility in patients with moderate oligospermia. However, when the sperm concentration was below five million/mL and sperm motility was poor, the fertilization rate of the oocytes was much less than when the sperm count was normal. The result was an unacceptably low pregnancy and take-home baby rate (less than 10 percent).

Other micromanipulation techniques, such as partial zona dissection and subzonal insertion of spermatozoa from severely oligospermic men, are also associated with low fertilization rate or polyspermic fertilization. They do not significantly improve the chance of pregnancy.

**Intracytoplasmic sperm injection** — Intracytoplasmic sperm injection (ICSI) has revolutionized the treatment and improved the prognosis for fertility of men with very severe oligospermia, asthenospermia (low sperm motility), teratospermia (a higher rate of abnormal sperm morphology), and even azoospermia. This technique involves the direct injection of a single spermatozoon into the cytoplasm of a human oocyte, usually obtained from follicles produced under controlled ovarian hyperstimulation.

The efficacy of ICSI using spermatozoa from infertile men who had severe oligospermia or who had failed IVF was documented in a series of studies from Belgium [[64-66](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/64-66)]. This technique has also been successful in men with nonmosaic Klinefelter syndrome [[67-69](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/67-69)], where spermatozoa are obtained from testicular biopsies.

ICSI has been adopted by most IVF centers throughout the world. The overall fertilization rate is about 60 percent and the clinical pregnancy rate per cycle is about 20 percent while the multiple pregnancy rate is about 29 to 38 percent [[59,70,71](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/59,70,71)]. The ICSI results are not influenced by either the cause of the azoospermia or the origin of the spermatozoa. This rate is similar to that of IVF in patients with tubal infertility and compares favorably with the 30 percent per cycle chance of successful pregnancy in a couple following natural intercourse. One long-term study reported that the cumulative pregnancy and cumulative live birth rates are comparable between ICSI-IVF and natural pregnancy [[72](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/72)]. As a result, we recommend that a couple whose infertility is mostly due to a male factor should seek ART treatment only in a center in which ICSI is available.

In couples with non-male-factor infertility, ICSI offers no clinical advantage when compared with conventional IVF [[73](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/73)]. Thus, ICSI should be reserved for those with moderate to severe male-factor infertility.

When there are no sperm in the ejaculate but there are germ cells in the testes, ICSI can be performed with spermatozoa isolated from testicular biopsies or fine needle aspirates [[74,75](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/74,75)]. ICSI success is dependent on retrieving adequate numbers of spermatozoa or spermatids from the biopsies. Successful pregnancy has been reported even with injection of fresh or cryopreserved immature sperm cells, such as elongated and round spermatids, but not with spermatocytes [[76,77](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/76,77)]. The ability of testicular spermatozoa to fertilize human oocytes has been reported in azoospermic men with maturation arrest [[78](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/78)], defective spermiogenesis [[79](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/79)], deletion of the DAZ gene [[80](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/80)], Klinefelter syndrome [[81](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/81)], and in men with long-standing azoospermia after chemotherapy [[82-84](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/82-84)].

**Pregnancy outcome** — The ability of spermatozoa from men with severe sperm abnormality and genetic disorders to fertilize human oocytes raises the concern over the frequency of chromosomal abnormalities and congenital malformations in live births following ICSI. Children conceived by IVF and/or ICSI are at increased risk for birth defects, but the absolute risk is very low, and there is no risk difference between children conceived by IVF and/or ICSI. These data are discussed in detail elsewhere.

Most men with NOA will have isolated regions of spermatogenesis within the testis; studies have illustrated that sperm can be retrieved in most men with NOA, including Klinefelter's syndrome (KS). In addition to congenital abnormalities, there is concern that use of sperm from subfertile men and the ICSI procedure itself may increase the risk of chromosomal and gene abnormalities in children conceived by ART. Subfertile men (and women) are more likely than fertile individuals to have chromosomal abnormalities (eg, aneuploidies, structural abnormalities, gene mutations, microdeletions) that may contribute to their subfertility and may be passed to their offspring. Y chromosome microsome deletions will be transmitted to the offspring from their subfertile father. Data from men with nonmosaic Klinefelter syndrome are reassuring and suggest that the risk of transmitting genetic abnormalities by ICSI is very low in the other genetics conditions.

Couples selecting ICSI as the method of treatment should be counseled about the potential risk of congenital abnormalities and of transmitting sex-chromosome aberrations and fertility problems to their offspring. In men with Klinefelter syndrome and those with Y microdeletions, including those with deletions of the gene, their offspring might carry the same gene or have an increased risk of sex chromosome aneuploidy, and the infertility might not be detected unless special genetic studies are performed.

**Retrieval of sperm from the testis** — New surgical techniques have been introduced to retrieve spermatozoa from patients with nonobstructive azoospermia [[85](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/85)]. A technique called microdissection of the testis to extract sperm (TESE) from the seminiferous tubules has been successful in obtaining sperm in over 50 percent of patients with nonobstructive azoospermia, including patients with Klinefelter syndrome [[7,86](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/7,86)].

This technique is also used in men who become azoospermic post-chemotherapy. Ideally, men who will be undergoing chemotherapy should be referred for sperm banking. However, only 50 percent are offered this option and even fewer result in cryopreserved sperm [[87](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/87)], in spite of current guidelines from the American Society of Clinical Oncology [[88](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/88)]. In the past, men who developed azoospermia after chemotherapy were considered to be sterile. Now, many of these men (approximately 37 percent in one study) are able to undergo successful testicular sperm extraction and intracytoplasmic sperm injection [[89](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/89)].

**Klinefelter syndrome** — Sperm retrieval rates are higher in Klinefelter syndrome patients with serum testosterone near the reference range (>250 ng/dL) [[52](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/52)]. Testicular sperm extraction (TESE) should only be performed in a center where the urologist has been trained and is skillful in these procedures.

There have been reports of successful pregnancies and healthy children after TESE and intracytoplasmic sperm injection (ICSI) in men with nonmosaic Klinefelter syndrome. In one series, adequate sperm was retrieved for IVF/ICSI in 29 of 39 procedures [[7](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/7)]. Of the 39 cycles with sperm retrieved, 33 had embryos for transfer; there were 18 clinical pregnancies resulting in 21 live births (18 of 29 = 46 percent). All children had a normal karyotype.

In a second series, spermatozoa were retrieved from 15 of 38 azoospermic patients with nonmosaic Klinefelter syndrome and 26 ICSI cycles were performed. There were 15 pregnancies, with 16 live births; all were normal, healthy babies [[90](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/90)].

**Artificial insemination with donor semen** — The alternative to ART for many couples, including those who fail ART, is artificial insemination with donor sperm. This time-tested method has a very high success rate in apparently normal female recipients: 50 percent pregnancy rate with six cycles of insemination. Children born from pregnancies resulting from donor insemination grow and develop normally, both physically and psychologically [[91](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/91)]. This alternative, together with adoption and childlessness, must be offered to all couples with male factor infertility.

**POTENTIAL TREATMENTS IN THE FUTURE** — Mammalian (mouse) germ cells undergo self-renewal, can be maintained in vitro for several hours, can initiate organized, normal spermatogenesis when transplanted to mice depleted of germ cells due to genetic mutation or after chemotherapy, and can result in normal progeny after successful mating with females [[92,93](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/92,93)]. Successful germ cell transplants can be achieved from mouse to mouse, rat to rat, and rat to immune-compromised mouse [[94](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/94)]. Recently, successful ectopic xenografts of testis from a number of species including primates into mice have allowed studies of drugs and toxicants on spermatogenesis without having to administer the agent to the species [[95](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/95)].

These observations suggest that germ cell transplantation or cultured testicular stem cells may become a treatment for male infertility and for genetic diseases in men that can be corrected and eradicated in germ cell lines. This possibility raises serious ethical, social, and moral issues [[96-98](http://www.uptodate.com/contents/treatment-of-male-infertility/abstract/96-98)].

Other possible future developments include methods of early diagnosis of the underlying causes of male infertility, preventing infertility with early diagnosis and treatment of sexually transmitted genital infections, and identification and avoidance of environmental toxins and medications that may adversely affect reproductive function.

**SUMMARY AND RECOMMENDATIONS**

* Assessment and treatment of the female partner must be initiated for the infertile couple.
* Specific treatment for male infertility includes dopamine agonists for prolactin-secreting pituitary tumors, and for men with hypogonadotropic hypogonadism, exogenous LH to increase serum and intra-testicular testosterone and, in some cases, exogenous follicle-stimulating hormone (FSH) to enhance spermatogenesis.
* Data on the efficacy of varicocele ligation are conflicting. However, it may be useful for young patients with large varicocele and no testicular atrophy.
* Assisted reproductive technology is used for the treatment of male infertility in most patients.
* Intracytoplasmic injection of spermatozoa (ICSI) into the oocyte is the most common technique used for patients with male factor infertility. Pregnancy and live birth rates are similar to natural conception. In non-obstructive azoospermia, testicular sperm extraction (TESE) may harvest adequate number of spermatozoa to achieve fertilization of the oocyte and subsequent pregnancy, even in patients with Klinefelter’s syndrome previously considered to be sterile.
* Infants born after assisted reproductive technology may have low birth weight.
* For couples with chromosomal aneuploidy and Y chromosome microdeletions considering ICSI, we suggest pretreatment counseling on the potential risk of transmitting sex-chromosome aberrations and fertility problems to their offspring ([**Grade 2C**](http://www.uptodate.com/contents/grade/6?title=Grade%202C&topicKey=ENDO/7452)).

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