Treatments for male infertility

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Literature review current through: Aug 2022. | **This topic last updated:** Feb 28, 2020.

INTRODUCTION

In the United States, infertility in a couple is defined as the inability to achieve conception despite one year of frequent, unprotected intercourse (figure 1) [1]. This topic provides an overview of the treatments of male infertility. The causes and approach to evaluation of male infertility are reviewed separately. (See "Approach to the male with infertility" and "Causes of male infertility".)

OVERVIEW

In studies of untreated couples pursuing pregnancy, 50 percent conceived within three months, 70 percent within six months, and 85 percent within 12 months (figure 1) [1]. Up to 50 percent of young, healthy couples who fail to conceive in the first 12 months will conceive in the next 12 months [2]. Therefore, it might be appropriate to delay invasive reproductive techniques in couples where the female partner has normal menstrual cycles, the male partner has normal semen analyses, and neither partner has an identifiable cause of infertility.

Categories of male infertility — The causes of male infertility can be divided into four main areas (table 1):

- **Endocrine and systemic disorders** (usually related to secondary [hypogonadotropic] hypogonadism) – 2 to 5 percent.

- **Primary testicular defects in spermatogenesis** – 65 to 80 percent, of which the majority have idiopathic dysspermatogenesis, an isolated defect in spermatogenesis without an identifiable cause.

- **Sperm transport disorders** – 5 percent.

- **Idiopathic male infertility** – 10 to 20 percent. Idiopathic male infertility should be distinguished from idiopathic dysspermatogenesis. Idiopathic male infertility describes an infertile man with a normal semen analysis and no apparent cause for infertility, whereas infertile men with idiopathic dysspermatogenesis have abnormal semen analyses.

General principles — Treatment of male infertility should be guided by the following general principles 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 (WHO) 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 [3]. (See "Overview of infertility".)

It is 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, endometriosis, and tubal obstruction, should be simultaneously addressed with or before treatment of the male partner. Treatment of the female partner can often compensate for male factor subfertility and result in pregnancy without treatment of the male. (See "Overview of infertility".)

Documentation of treatment efficacy — Pregnancy often occurs independently from treatment in apparently infertile young couples. 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 large number of initially promising, but ultimately misleading, reports are the use of semen quality, instead of pregnancy, as the criterion of success and the failure to include a control group in the trial [4].

Is the patient hypogonadal? — Assessment of the function of the hypothalamic-pituitary-testicular axis is helpful in determination of the potential role of medical therapy to restore fertility in the small minority of men whose infertility is due to secondary (hypogonadotropic) hypogonadism. Assessment of this axis is also important to identify the subset of men that have combined deficiencies of sperm and testosterone production. Men with testosterone deficiency

may benefit from testosterone replacement therapy, but it is important to recognize that testosterone therapy will **suppress** spermatogenesis. (See "Causes of male infertility" and "Causes of secondary hypogonadism in males" and "Causes of primary hypogonadism in males".)

The distinction between primary (hypergonadotropic) and secondary (hypogonadotropic) hypogonadism is important because medical therapy might be useful in restoring fertility in men with secondary (hypogonadotropic) hypogonadism, but it will not be useful in primary (hypergonadotropic) hypogonadism. Men with primary (hypergonadotropic) hypogonadism generally require assisted reproductive technology (ART) such as surgical testicular sperm extraction (TESE) and intracytoplasmic sperm injection (ICSI) into the female partner's egg in order to conceive children. (See 'Assisted reproductive technologies' below and 'Retrieval of sperm' below.)

Eugonadal, infertile men — Eugonadal, infertile men (with normal serum testosterone, follicle-stimulating hormone [FSH], and luteinizing hormone [LH] concentrations) might have causes that can be treated surgically to enhance or restore fertility (eg, surgical excision of a large varicocele or surgical correction of ejaculatory duct obstruction). However, eugonadal, infertile men, like men with primary (hypergonadotropic) hypogonadism, often must be treated with ART in order to conceive. (See 'Surgical repair of varicocele' below and 'Obstruction of epididymis or ejaculatory duct' below and 'Assisted reproductive technologies' below.)

Use of assisted reproductive technologies — The development of ART has allowed many couples with male factor infertility to conceive. Because ART may be effective in any man with evidence of spermatogenesis (even microscopic nests of sperm visible only on testicular histology, eg, in men with Klinefelter syndrome), ART may useful in the treatment of many causes of male infertility. Thus, we discuss ART in a separate section from categorical causes of male infertility. (See 'Assisted reproductive technologies' below.)

APPROACH BASED UPON DIAGNOSIS

Endocrine and systemic disorders — Most endocrine and systemic disorders that cause male infertility are associated with secondary (hypogonadotropic) hypogonadism. Treatment of the underlying endocrine or systemic disorder may result in eugonadism and improved spermatogenesis and fertility. If treatment of the underlying endocrine or systemic disorder does not normalize serum testosterone and improve spermatogenesis and fertility, then gonadotropin replacement therapy might be beneficial.

For example, if a man with a prolactin-secreting macroadenoma has persistent secondary (hypogonadotropic) hypogonadism and azoospermia 6 to 12 months after appropriate treatment of the prolactin macroadenoma, gonadotropin replacement therapy should be considered if conception is desired. In this example, the underlying pituitary disease has induced hypogonadotropism that is unlikely to resolve. (See 'Hyperprolactinemia' below and "Induction of fertility in men with secondary hypogonadism".)

Secondary (hypogonadotropic) hypogonadism: Induction of spermatogenesis — Specific treatments, including gonadotropin replacement therapy, are available for men whose infertility results from secondary (hypogonadotropic) hypogonadism. Secondary hypogonadism is present if the serum testosterone concentration is low and serum follicle-stimulating hormone (FSH) and luteinizing hormone (LH) concentrations are low or inappropriately normal. (See "Causes of secondary hypogonadism in males".)

Normal spermatogenesis takes approximately three months. As a result, a rise in sperm concentrations, as measured by semen analysis, usually does not occur for at least three and sometimes six months or more with any medical treatment of secondary (hypogonadotropic) hypogonadism. With effective treatment of secondary hypogonadism, time to conception may occur within six months, but may take two or more years. Induction of spermatogenesis in men with secondary hypogonadism is reviewed in detail separately. (See "Induction of fertility in men with secondary hypogonadism".)

Hyperprolactinemia — If secondary (hypogonadotropic) hypogonadism results from hyperprolactinemia, the hypogonadism might 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 or bromocriptine. (See "Management of hyperprolactinemia".)

In some patients who have a prolactin-secreting macroadenoma, secondary (hypogonadotropic) hypogonadism might result from 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 6 to 12 months of the serum prolactin being reduced to normal, gonadotropin replacement treatment should be instituted if fertility is desired. (See

"Management of hyperprolactinemia", section on 'Macroadenomas' and "Induction of fertility in men with secondary hypogonadism".)

Primary testicular defects in sperm production — Primary testicular defects in sperm production with or without testosterone deficiency are the most common causes of male infertility.

Infertility due to primary testicular defects resulting in decreased production of normal sperm can divided into three categories:

- Low serum testosterone and high serum FSH and LH concentrations
- Normal serum testosterone and isolated elevation of serum FSH concentration
- Normal serum testosterone and gonadotropins

Low serum T, elevated FSH and LH — Men with primary (hypergonadotropic) hypogonadism have low serum total testosterone (T) and high luteinizing hormone (LH) and follicle-stimulating hormone (FSH). The seminiferous tubules in these men are severely damaged, so most patients are azoospermic. There are no known effective medical therapies for these men, and success rates with assisted reproductive technology (ART) are low compared with men with other infertility diagnoses. Obtaining testicular tissue for histologic examination helps to determine whether such men can conceive via ART [5,6].

Normal serum T and LH, high FSH — Infertile men with isolated elevation of serum follicle-stimulating hormone (FSH) and normal testosterone (T) and luteinizing hormone (LH) concentrations have variable degrees of dysspermatogenesis, resulting in a spectrum of findings, including:

- Low to low-normal concentrations of sperm in the ejaculate
- Sperm visible only on testicular biopsies
- No sperm on testicular biopsy

Many of these men have sperm present in the ejaculate or in a testicular biopsy that can be used for ART.

Normal serum T, normal LH and FSH

- Most infertile men who have normal serum testosterone (T) concentrations, normal serum gonadotropin (luteinizing hormone [LH] and follicle-stimulating hormone [FSH])

concentrations and a primary defect in spermatogenesis have sperm in the ejaculate, but the numbers of sperm with normal motility and/or normal morphology are low.

- Men with normal serum T and normal LH and FSH who also have azoospermia should be evaluated for ejaculatory duct obstruction. (See 'Obstruction of epididymis or ejaculatory duct' below.)

- For therapeutic purposes, clinicians may consider infertile men with oligozoospermia and normal serum hormones in the same category as men with idiopathic infertility (ie, men with normal semen analyses and normal serum hormones). There is no clearly effective medical therapy for these men. Strategies include continuation of attempts at natural conception or ART. (See 'Assisted reproductive technologies' below.)

Treatment options based upon presence of sperm — Each of the hormone categories described above can be further divided based on whether sperm are seen in the ejaculate or in a testicular biopsy.

Sperm in the ejaculate — When there are sperm in the ejaculate, the options include continued attempts at conception through vaginal intercourse or ART. However, a 2016 Cochrane review found no evidence of an improvement in live birth rate with ART in infertile couples due to male factor infertility (decreased sperm in the ejaculate) [7]. On the other hand, some experts suggest that ART decreases the time to conception and live births for some couples with male factor oligozoospermia due to dysspermatogenesis [8].

Spermatids or mature spermatozoa seen only in testicular biopsies — ART is effective for some men with spermatids or mature spermatozoa seen only in testicular biopsies. Forty to 50 percent of men with primary (hypergonadotropic) hypogonadism and azoospermia on semen analysis have spermatids or mature spermatozoa on testicular biopsies that might be surgically retrievable and used to fertilize the female partner's oocytes using ART (see 'Retrieval of sperm' below). However, there are important genetic implications of using sperm from men with primary (hypergonadotropic) hypogonadism or men with severe oligozoospermia [9]. (See 'Retrieval of sperm' below and 'Genetic counseling and testing' below.)

No sperm seen in testicular biopsies — For men with azoospermia due to a primary testicular defect in spermatogenesis, there is no therapy available to enable conception.

Unproven therapies — Clinicians should be aware of several unproven medical and surgical therapies that are offered as treatments to infertile men with oligozoospermia and normal serum hormones and to men with idiopathic infertility:

Surgical repair of varicocele — We suggest varicocele repair only in infertile men with abnormal semen analyses and large, grade 3 varicoceles. Surgical repair is also reasonable in men (with or without infertility) with large varicoceles causing symptoms [10-12]. We do not recommend varicocele surgery in infertile men with small, nonpalpable varicoceles.

Data on the efficacy of varicocele repair for improving fertility have been conflicting. However, a 2012 meta-analysis of 10 trials in 894 men reported improved pregnancy rates with varicocele repair (surgical ligation or radiological embolization of the internal spermatic vein) when compared with expectant management [12]. The number needed to treat for one additional pregnancy was 17. However, live birth rates were not reported as the primary outcome in any of the trials, and the quality of the evidence was very low.

We also do not recommend repair in men with severe oligozoospermia or azoospermia, high serum FSH concentrations, and small testes, as these men have severe germ cell damage and a lower likelihood of fertility after varicocele repair.

Treatment of leukospermia — We recommend against antibiotic treatment for leukospermia. We also recommend against treatment with nonsteroidal antiinflammatory drugs (NSAIDs) because there are insufficient data that they improve male fertility and there are potential adverse effects (including peptic ulcer diseases and renal injury).

Some infertile men are diagnosed with infections of the urogenital tract based on the presence of increased leukocytes (>1 million per mL) in the semen [13]. 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 [14]. Some experts treat infertile men with leukospermia with antibiotics, but clinical trials have failed to demonstrate a benefit [2,15,16]. Similarly, because inflammation is associated with increased reactive oxidative species, some experts recommend NSAIDs, mast cell blockers, or antioxidants (eg, vitamin E) to improve sperm quality for men with asymptomatic leukospermia [15,17]. Short-term vitamin E therapy has also been tried, but its efficacy is unproven [17].

Medical therapies to increase circulating gonadotropin concentrations — We recommend against using clomiphene, aromatase inhibitors, or gonadotropin therapy for idiopathic dysspermatogenesis or idiopathic male infertility.

Therapies to increase circulating gonadotropins (and maximally stimulate spermatogenesis) include clomiphene citrate, aromatase inhibitors, recombinant human follicle-stimulating hormone (rhFSH). The data for clomiphene do not support its use in the treatment of male fertility, and the data for aromatase inhibitors are restricted to case reports and small, low-quality studies [18-34].

A 2013 Cochrane meta-analysis of six randomized trials of gonadotropin therapy in men with idiopathic infertility reported higher pregnancy rates in the gonadotropin-treated group compared with the placebo group [26]. However, treatment protocols and follow-up periods were variable, and the quality of the evidence was very low. Larger trials are needed before conclusions about the efficacy of this approach can be made.

Lifestyle changes — We suggest healthy lifestyle practices for infertile men. Although there is little evidence that lifestyle changes improve fertility, there is inferential evidence that avoiding tobacco, marijuana, excessive alcohol intake, and obesity might be useful for optimizing spermatogenesis. Although increased scrotal heat may impair spermatogenesis, it is not necessary for men to avoid tight fitting underwear or to avoid saunas or hot baths [27,28,35-37]. (See "Causes of male infertility" and "Approach to the male with infertility".)

Dietary supplements: Fish oil — In addition to adopting healthy lifestyle practices, some men with infertility use fish oil supplements as a treatment strategy. Based upon available evidence, we do not suggest using fish oil as a therapy for male infertility. Placebo-controlled studies of infertile men with fish oil supplements (which contain the omega-3 fatty acids docosahexaenoic acid [DHA] and eicosapentaenoic acid [EPA] have demonstrated inconsistent results on sperm parameters in infertile men [38-40].

Additional data come from a cross-sectional study of healthy, young men presenting for a fitness examination for potential military service [41]. Those who reported fish oil supplement use in the 60 days prior to the examination had slightly higher average testicular volume (+1.5 mL [95% CI 0.2-2.8]) and semen volume (+0.64 mL [95%CI 0.15-1.12] and compared with those who did not use any fish oil supplements. Men taking fish oil supplements tended to have slightly higher average total sperm counts. However, these differences in testicular volume, seminal fluid volume, and total sperm counts were small and minimal clinical significance; average testicular volume, seminal fluid volume, and sperm counts were well within the normal range in men who did not report taking fish oil supplements. Finally, the men who took fish oil supplements self-reported higher levels of health and fewer febrile episodes; it cannot be determined whether fish oil supplements are causally related to these improvements or due to some other confounding factor in this study.

Sperm transport disorders — Decreased sperm transportation to the female partner's vagina include infrequent vaginal sexual intercourse, erectile dysfunction, ejaculatory disorders (eg, retrograde ejaculation), and obstruction of epididymis or ejaculatory duct. All disorders of sperm transportation may be treated with ART, but some can be treated with specific therapies.

Sexual disorders — Fertility may optimized with vaginal intercourse at least twice weekly [42]. Severe erectile dysfunction should be treated. (See "Treatment of male sexual dysfunction", section on 'Erectile dysfunction'.)

Retrograde ejaculation — A 2015 systematic review concluded that oral sympathomimetics improve antegrade ejaculation in many men with complete retrograde ejaculation [43]. However, there are very few data on the effectiveness of medical therapy to increase live birth rates in couples with male factor infertility related to retrograde ejaculation [44]. (See "Treatment of male sexual dysfunction", section on 'Ejaculatory disorders'.)

Obstructive azoospermia — Obstructive azoospermia can be the result of several processes. Most causes of obstructive azoospermia can be treated with surgical correction or with ART. (See "Causes of male infertility".)

Obstruction of epididymis or ejaculatory duct — 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 the vas deferens. The results depend on site of the obstruction and the experience and skill of the operator. Retrospective studies have demonstrated pregnancy rates of 20 to 30 percent after surgical anastomosis [45].

The appearance of spermatozoa after re-anastomosis for vasectomy reversal exceeds 90 percent, with pregnancy in over 50 percent [46,47]. The success rate depends upon the duration between vasectomy and the reversal procedure; in general, the longer after vasectomy, the poorer the pregnancy rate [47,48]. For a man with a history of vasectomy, ART with sperm retrieval with intracytoplasmic sperm injection (ICSI) is also an option. Given the continual improvements in ART, vasectomy reversal and ART should be discussed with the couple with male factor infertility due to vasectomy [49,50]. For example, an older couple that includes a male partner who underwent vasectomy many years ago might opt for ART.

Congenital bilateral absence of the vasa deferentia — For men with congenital bilateral absence of the vas deferentia, the most extreme form of "obstruction" of transportation of sperm, ART with sperm retrieval is the only option for conception. (See 'Assisted reproductive technologies' below and 'Retrieval of sperm' below.)

Because the majority of men with congenital bilateral absence of the vasa deferentia have heritable genetic mutations associated with cystic fibrosis, these men and their partners who are considering ART to achieve pregnancy should be offered genetic screening and counseling. Screening the female partner may be more cost effective than screening the man. If the female partner does not carry a gene mutation associate with cystic fibrosis, the risk that their progeny will have cystic fibrosis or congenital bilateral absence of the vas deferens is less than 1 in 1500

[51]. (See "Causes of male infertility" and "Causes of male infertility", section on 'Sperm transport disorders' and "Approach to the male with infertility", section on 'CFTR gene'.)

ASSISTED REPRODUCTIVE TECHNOLOGIES

Assisted reproductive technologies (ART) are commonly used in the United States and other wealthy or industrialized countries. In the United States, ART was used in approximately 1.6 percent of live births in 2014 [52]. ART with intracytoplasmic injection of sperm (ICSI) that has been retrieved from the ejaculate, epididymis, or testis has allowed some infertile men to conceive (eg, men with azoospermia and men with immotile sperm).

However, ART does not improve rates of live births for all types of male infertility. In a meta-analysis of 10 trials of in vitro fertilization (IVF), ICSI, and intrauterine insemination for couples with male infertility (abnormal sperm parameters), there were no differences in pregnancy or live birth rates between ART and expectant management [7]. Treatment of male factor infertility remains understudied and largely driven by expert opinion and anecdotal experience.

Intrauterine insemination — A 2016 systematic review concluded that the data about the overall effectiveness of intrauterine insemination (IUI) for male infertility are inconclusive [7]. The topic of IUI alone or with gonadotropin stimulation of the female partner is discussed elsewhere (see "Unexplained infertility", section on 'Intrauterine insemination'). Because IVF with ICSI is effective, we do not recommend IUI for most couples with male factor infertility.

IVF with ICSI — We recommend that a couple whose infertility is primarily due to a male factor should seek treatment in an ART center with experience in IVF with ICSI. IVF describes any process where an egg is fertilized by a sperm outside of the human body. IVF with ICSI has revolutionized the treatment of male factor infertility. 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. (See "In vitro fertilization: Overview of clinical issues and questions" and "Intracytoplasmic sperm injection".)

If sperm is retrievable from the male partner, the usual overall fertilization rate of ICSI is approximately 60 percent, and the clinical pregnancy rate per cycle is approximately 20 percent, while the multiple pregnancy rate is approximately 30 to 40 percent [53-55]. The ICSI results are not influenced by the cause of the azoospermia.

In couples with non-male factor infertility, ICSI offers no clinical advantage when compared with conventional IVF. Thus, ICSI should be reserved for those with moderate to severe, male factor infertility. (See "Intracytoplasmic sperm injection".)

Retrieval of sperm — Sperm from the ejaculate or from a urine sample (in men with severe retrograde ejaculation) can be used for ICSI. ICSI can also be performed successfully using spermatozoa that are obtained from testicular aspiration or biopsies. Many men with nonobstructive azoospermia will have isolated regions of spermatogenesis within the testis; sperm can be retrieved in many men with nonobstructive azoospermia, including men with Klinefelter syndrome and men with longstanding azoospermia after chemotherapy [5,55-65].

Men undergoing systemic chemotherapy should be considered for referral for sperm banking and sperm cryopreservation; cryopreservation of ejaculated sperm before initiation of chemotherapy ensures higher-quality sperm for ART and avoids surgical sperm retrieval later [64]. (See "Effects of cytotoxic agents on gonadal function in adult men", section on 'Semen cryopreservation' and "Effects of cytotoxic agents on gonadal function in adult men".)

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 [66,67]. Surgical techniques for retrieval of sperm from the testes include testicular or epididymal aspiration (which can be done with local anesthesia) or multiple open testicular biopsies with testicular sperm extraction (TESE) [68]. TESE is more likely to retrieve sperm for ICSI than testicular aspiration [6]. A modified form of TESE, microTESE, involves microdissection of the testis; using microscopic dissection to identify nests of isolated spermatogenesis to extract with open biopsies is even more effective than TESE for sperm retrieval [6]. (See "Intracytoplasmic sperm injection", section on 'Sperm retrieval'.)

When performed by a surgeon who is experienced in microTESE, sperm may extracted in approximately 50 percent of infertile, azoospermic men [5,6,69]. Serum follicle-stimulating hormone (FSH) concentrations may be useful in determining the choice of testicular extraction technique. Higher serum FSH concentrations and smaller testicular volumes generally correlate with impairment of spermatogenesis, and a high serum FSH concentration in a man with azoospermia predicts low probability of retrieving sperm with testicular aspiration or TESE [70-72]. However, many of these men have testicular nests of spermatogenesis that can be visualized and harvested using microTESE [70].

Pregnancy outcome with ICSI — The success of ICSI to permit men with infertility related to genetic disorders to conceive has raised concerns about an increased risk 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. For example, Klinefelter syndrome is a common genetic cause of male infertility, but the risk of a transmitting man with Klinefelter syndrome having a son with a karyotype associated with

Klinefelter syndrome (eg, XXY karyotype) appears to be low [5,65,73]. These data are discussed in detail elsewhere. (See "Intracytoplasmic sperm injection" and "Assisted reproductive technology: Pregnancy and maternal outcomes".)

Genetic counseling and testing — Although the absolute risk of genetic abnormalities is low for live births after ICSI for male factor infertility, genetic counseling and testing should be offered before ICSI in the following settings: (1) karyotyping for infertile men with sperm concentrations <10 million/mL; (2) testing for Y chromosomal microdeletion for infertile men with sperm concentrations <5 million/mL; (3) screening for gene mutations associated with cystic fibrosis for infertile men with congenital absence of bilateral vasa deferentia [29,74]. (See 'Congenital bilateral absence of the vasa deferentia' above.)

ART with donor semen — The time-tested method of ART with donor semen 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 [75]. This alternative, together with adoption and childlessness, should be offered to all couples with male factor infertility. (See "Donor insemination".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Male infertility or hypogonadism".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a

variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Male infertility (The Basics)")
- Beyond the Basics topics (see "Patient education: Treatment of male infertility (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- We suggest assessment and treatment of the female partner before or concurrent with the male partner of an infertile couple. (See 'Concurrent male and female infertility' above.)
- A small minority of infertile men have medically or surgically reversible causes of infertility. Assisted reproductive technology (ART) is the only potentially effective treatment for most causes of male infertility. (See 'Assisted reproductive technologies' above.)
- We suggest gonadotropin replacement therapy for induction of spermatogenesis in men whose infertility results from secondary (hypogonadotropic) hypogonadism (**Grade 1B**). (See 'Secondary (hypogonadotropic) hypogonadism: Induction of spermatogenesis' above.)
- For men with secondary (hypogonadotropic) hypogonadism due to a prolactin adenoma, we suggest dopamine agonist therapy, usually cabergoline, as this typically restores spermatogenesis and fertility. In men with prolactin macroadenomas, lowering the serum prolactin concentration and shrinking the adenoma may not be sufficient to increase the testosterone concentration and sperm count (because of permanent damage to the gonadotroph cells). In this case, we start gonadotropin therapy for induction of spermatogenesis. (See 'Hyperprolactinemia' above.)
- We suggest against the use of clomiphene citrate, aromatase inhibitors, or gonadotropin therapy for secondary (hypogonadotropic) hypogonadism, idiopathic dysspermatogenesis, or idiopathic male infertility (**Grade 2C**). (See 'Medical therapies to increase circulating gonadotropin concentrations' above.)
- We suggest varicocele repair only in infertile men with abnormal semen analyses and large, grade 3 varicoceles. (**Grade 2C**) Surgical repair is also reasonable in men (with or without infertility) with large varicoceles causing symptoms. We do not recommend varicocele surgery in infertile men with small varicoceles that are not palpable. (See 'Surgical repair of varicocele' above.)

- If sperm are retrievable from testis, epididymis, or ejaculate, we suggest ART as it may result in live births independent of the cause of infertility (**Grade 2B**). (See 'Assisted reproductive technologies' above.)

- Intracytoplasmic injection of spermatozoa (ICSI) into the oocyte is the most effective and common technique used for patients with male factor infertility. (See 'IVF with ICSI' above.)

- Genetic counseling and testing should be offered to many couples with male factor infertility prior to use of ICSI and ART. (See 'Genetic counseling and testing' above.)

ACKNOWLEDGMENTS

The editorial staff at UpToDate would like to acknowledge Ronald Swerdloff, MD, and Christina Wang, MD, who contributed to an earlier version of this topic review.

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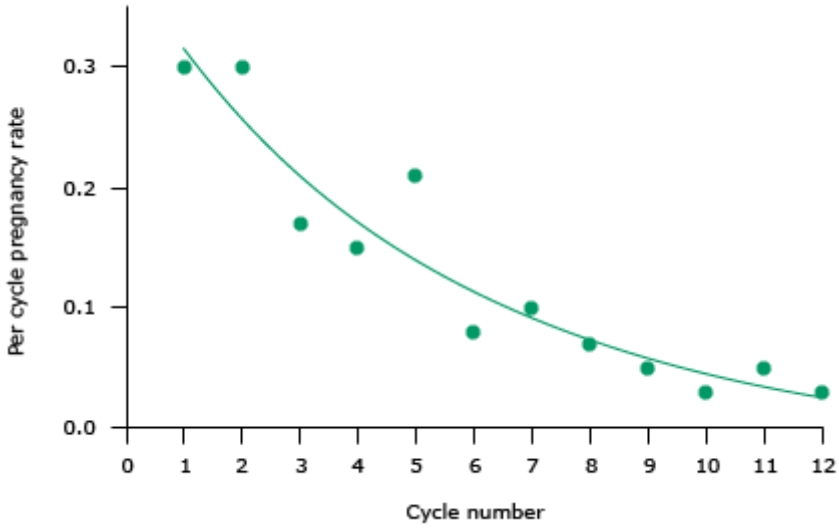
Topic 7452 Version 19.0

GRAPHICS

Fecundability in a cohort of healthy couples attempting to conceive



Data from: Zinaman MJ, Clegg ED, Brown CC, et al. Estimates of human fertility and pregnancy loss. Fertil Steril 1996; 65:503.

Graphic 80057 Version 3.0

Causes of male infertility

Endocrine and systemic disorders (hypogonadotropic hypogonadism)

Congenital disorders

- Congenital GnRH deficiency (Kallmann syndrome)
- Iron overload syndromes
- Multiorgan genetic disorders (Prader-Willi syndrome, Laurence-Moon-Biedl syndrome, familial cerebellar ataxia)

Acquired disorders

- Pituitary and hypothalamic tumors (pituitary macroadenoma, craniopharyngioma)
- Pituitary and hypothalamic infiltrative disorders (sarcoidosis, histiocytosis, tuberculosis, fungal infections)
- Pituitary and hypothalamic lymphocytic infundibulitis or hypophysitis
- Head trauma, intracranial radiation, or surgery
- Vascular (pituitary infarction, aneurysm)
- Hormonal (hyperprolactinemia, androgen excess, estrogen excess, cortisol excess)
- Drugs (exogenous androgens, opioids and psychotropic drugs, GnRH agonists or antagonists)

Systemic disorders

- Severe systemic illness
- Nutritional deficiencies
- Morbid obesity

Primary testicular defects in spermatogenesis

Congenital disorders

- Klinefelter syndrome (XXY) and its variants (XXY/XY, XXXY)
- Cryptorchidism
- Myotonic dystrophy
- Functional prepubertal castrate syndrome (congenital anorchia)
- Androgen insensitivity syndromes
- 5-alpha-reductase deficiency
- Estrogen receptor or synthesis disorders

Acquired disorders

- Varicocele (large, palpable without Valsalva maneuver)
- Infections – Viral orchitis (mumps, echovirus, arbovirus), granulomatous orchitis (leprosy, tuberculosis), epididymo-orchitis (gonorrhea, chlamydia)

- Drugs – Alkylating agents, alcohol, marijuana, antiandrogens, ketoconazole, spironolactone, histamine-2 receptor antagonists, ionizing radiation
- Environmental toxins – Dibromochloropropane, carbon disulfide, cadmium, lead, mercury, environmental estrogens, and phytoestrogens; smoking; hyperthermia
- Immunologic disorders, including polyglandular autoimmune disease and antisperm antibodies
- Trauma
- Testicular torsion

Systemic illness

- Idiopathic dysspermatogenesis
- Renal failure, hepatic cirrhosis, cancer, sickle cell disease, amyloidosis, vasculitis, celiac disease

Genetic causes of dysspermatogenesis

- Y-chromosome microdeletions and related disorders
- Autosomal and X-chromosome defects
- Mutations causing severe defects in sperm morphology

Sperm transport disorders

- Epididymal dysfunction (drugs, infection)
- Abnormalities of the vas deferens (congenital absence, Young syndrome, infection, vasectomy)
- Seminal vesicles and prostate
- Ejaculatory ducts disorders

Sexual dysfunction

- Infrequent vaginal intercourse, erectile dysfunction, and premature ejaculation

Idiopathic male infertility

GnRH: gonadotropin-releasing hormone.

Graphic 54356 Version 5.0

Contributor Disclosures

Bradley D Anawalt, MD No relevant financial relationship(s) with ineligible companies to disclose. **Stephanie T Page, MD, PhD** No relevant financial relationship(s) with ineligible companies to disclose. **Peter J Snyder, MD** Grant/Research/Clinical Trial Support: AbbVie [Hypogonadism]; Crinetics [Acromegaly]; Novartis [Cushing's]; Recordati [Cushing's]. Consultant/Advisory Boards: AbbVie [Hypogonadism]; Novartis [Cushing's]; Pfizer [Acromegaly]; Teva Pharmaceuticals [Cushing's]. All of the relevant financial relationships listed have been mitigated. **Alvin M Matsumoto, MD** Consultant/Advisory Boards: AbbVie [Testosterone];Partnership for Clean Competition [Anabolic steroid doping and testing];US Anti-Doping Agency [Board of Directors, performance enhancing drug doping and testing]. All of the relevant financial relationships listed have been mitigated. **Kathryn A Martin, MD** No relevant financial relationship(s) with ineligible companies to disclose.

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