Medications that impair male fertility

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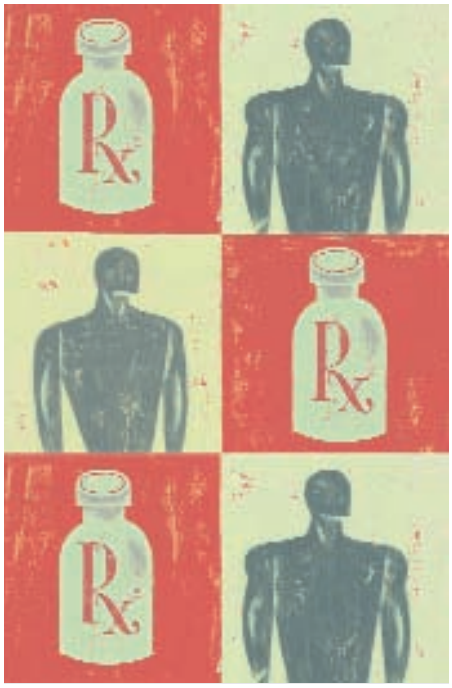
Pharmacologically mediated male infertility can be an unintended effect of medical treatment or an unanticipated consequence of dietary supplementation or recreational drug use. Cases of the former may be minimized when clinicians select agents that are unlikely to impair fertility. For the latter, patient education about the deleterious effects of these drugs and supplements is necessary and interventions to help them end their use may be appropriate.

A male patient's desire for future fertility should be assessed when considering a course of treatment that includes any of the agents described below. Additionally, for a patient who reports that he and his partner have been unable to conceive after 1 year of unprotected intercourse, semen analysis and a medical history that includes specific questioning about these medications, drugs, and supplements are the first steps.



Mechanisms of fertility impairment

Fertility is impaired through any of 4 basic mechanisms: direct gonadotoxic effects, alteration of the hypothalamic-pituitary-gonadal (HPG) axis, direct effects on ejaculation and/or erectile function, and direct effects on libido.[1] Gonadotoxins damage germ cells in the testis or inhibit the supporting Sertoli cells, thus impairing spermatogenesis.[1,2] HPG axis feedback mechanisms can be altered by hormonal therapies, anabolic steroids, and some psychiatric medications causing abnormal concentrations of gonadotropins or testosterone.[1,2] Drugs that cause retrograde ejaculation, block spinal reflexes, or inhibit ejaculate emission will directly impair ejaculation.[1,2] Any drug that interferes with the neurologic or vascular-mediated events necessary for normal erectile function can lead to erectile dysfunction.[1] Finally, there are several drugs that may disrupt male libido by acting on the central nervous system,[1] thus decreasing sexual drive and perhaps adversely affecting fertility.

Assessment challenges of medication-induced infertility

Patients often do not realize that nutritional supplements can have a deleterious effect on fertility, and they should be advised about the importance of full disclosure. Many men may not volunteer information about their use of body building supplements or anabolic steroids and should be questioned specifically about these agents. Similarly, men who abuse illicit substances are likely to be reluctant to discuss their use.

Additional elements of an initial screening include details regarding sexual practices, duration of infertility, childhood

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and other illnesses, developmental and sexual history, and exposure to gonadotoxins, including heat.[3] Detailed sources providing recommended methods for evaluation and management of male infertility are available.[3-7]

Management of medication-induced male infertility

The key question when determining a course of treatment for male infertility due to a medication is whether the patient should discontinue or change the drug. It may be possible to cycle the use of medications, particularly in the case of agents that cause ejaculatory dysfunction or depression of libido. However, spermatogenesis depressants may require months off treatment for effects to be ameliorated.

KEY POINT

Cycling the use of agents that cause ejaculatory dysfunction or depression of libido may help to resolve infertility.

Sources of information

One of the greatest challenges in understanding and avoiding medication-related male infertility is that evidence of an agent's fertility effects is often anecdotal or minimal. Additionally, effects may be highly dependent on dose and length of exposure. This review will provide a brief

TABLE

Agents Proposed to Adversely Affect Male Fertility

Medication	Gonadotoxic	Altered HPG Axis	Decreased Libido	Erectile Dysfunction	Fertilization Potential
Recreational/Illicit drugs					
Alcohol	+	+	+	+	-
Cigarettes	+	-	-	+	-
Marijuana	+	+	-	-	-
Opiates	-	+	+	-	-
Cocaine	+	-	-	+	-
Antihypertensives					
Thiazide diuretics	-	-	-	+	-
Spironolactone	-	+	+	+	-
Beta-blockers	-	-	+	+	-
Calcium channel blockers	-	-	-	-	+
Alpha-adrenergic blockers	-	-	-	+	-
Psychotherapeutic agents					
Antipsychotics	-	+	+	+	-
Tricyclic antidepressants	-	+	+	+	-
MAOIs	-	-	-	+	-
Phenothiazines	-	+	-	-	-
Lithium	-	-	+	+	-
Chemotherapeutic agents					
Alkylating agents	+	-	-	-	-
Antimetabolites	+	-	-	-	-
Vinca alkaloids	+	-	-	-	-
Hormones					
Anabolic steroids	-	+	-	+	-
Testosterone	-	+	-	+	-
Antiandrogens	-	+	+	-	-
Progesterone derivatives	-	+	+	+	-
Estrogens	-	+	+	+	-
Antibiotics					
Nitrofurantoin	+	+	-	-	-
Erythromycin	+	-	-	-	-
Tetracyclines	-	-	-	-	+
Gentamycin	+	-	-	-	-
Miscellaneous medications					
Cimetidine	-	+	-	-	-
Cyclosporine	-	+	-	-	-
Colchicine	-	-	-	-	+
Allopurinol	-	-	-	-	+
Sulfasalazine	+	+	-	-	-

HPG, hypothalamic-pituitary-gonadal; MAOIs, monoamine oxidase inhibitors.
Modified from Nudell DM, et al. *Urol Clin North Am.* 2002;29:965-973.

summary by drug class of agents that may adversely affect male fertility (TABLE).

Detailed information to help evaluate the human reproductive risks of a particular drug is available in the *Physician's Desk Reference* and in a number of databases. Thomson Micromedex, and particularly the REPRORISK® System (www.micromedex.com/products/reprorisk/), is a comprehensive source of drug information from 4 databases, including REPROTOX®, REPROTEXT®, TERIS, and Shepard's Catalog.

Recreational and illicit substances

Heavy marijuana use has been associated with gynecomastia, decreased serum testosterone levels, decreased sperm concentration, and pyospermia (white cells in the semen indicating possible infection).[8-10] Patients experience variable sensitivity to marijuana, and it may take 2 to 3 months for symptoms to improve.

Oligospermia (abnormally low sperm concentration in the ejaculate) and defects in sperm morphology and motility have been reported in users of cocaine.[11,12] Opiates have also been shown to decrease libido and erectile function through induction of hypogonadotropic hypogonadism.[1,13] This also is important to note when prescribing opioids for pain. Chronic opioid use, whether oral or intrathecal, may lead to sexual dysfunction.[14]

Cumulative evidence suggests that cigarette smoking may have a deleterious effect on male fertility by reducing sperm production, motility, and morphology.[1,15,16] Cigarette smoking may also lead to development of pyospermia, decreased sperm penetration,[10] and hormonal alterations.[1]

Long-term abuse of alcohol has detrimental effects in the HPG axis.[1,2] Alcoholics exhibit significant decreases in semen volume, sperm count, motility, and number of morphologically normal sperm.[17] They also show signs of pyospermia.[10] Alcohol in excess can thus exert profound deleterious effects on all aspects of the male reproductive system.[18] However, there is no evidence that moderate alcohol intake impairs male fertility.

Antihypertensives

Although most men who are treated for hypertension are older, the recent focus on the importance of blood pressure control has led to greater numbers of younger patients on antihypertensives.[1,2] Many of these medications are commonly associated with erectile dysfunction but most do not directly affect fertility. One exception is spironolactone, which acts as an antiandrogen and has been associated with impaired semen quality.[1,19]

Calcium channel blockers have been reported to cause reversible functional defects in sperm, impairing their ability to fertilize eggs without affecting sperm production or standard semen analysis parameters[20,21]; however, not all investigators report these types of effects.[22] Diuretics can affect function by decreasing penile blood flow, and beta-blockers may affect libido and erectile function.[1]

Although alpha-adrenergic blockers decrease hypertension, they are more commonly prescribed for benign prostatic hyperplasia (BPH) and are addressed below.

Hormones

Diethylstilbestrol (DES) was given to pregnant women in the 1950s, and reports of epididymal cysts and cryptorchidism (undescended testes) in males with prenatal DES exposure have raised concerns about fertility[23]; however, follow-up studies on adult men with prenatal DES exposure have revealed no adverse effects on fertility.[24]

Exogenous androgens are well known to induce hypogonadotropic hypogonadism. This may be induced directly by testosterone supplementation or by use of synthetic anabolic steroids, leading to azoospermia. This hypogonadism is usually reversible but may take 3 to 6 months, and some patients do not recover pituitary function.

It is important to remember that testosterone replacement therapy in younger men may lead to infertility. Dehydroepiandrosterone (DHEA) is a natural steroid prohormone precursor of androsterone, testosterone, and estrogen. DHEA is commonly taken and easily available over the counter; however, there are no human male fertility data available and rat studies have demonstrated no effect on spermatogenesis.[25] Antiandrogens and estrogens can adversely affect fertility by altering the HPG axis or decreasing libido or erectile function, while progesterones act by decreasing libido or erectile function.[1]

KEY POINT

Cigarette smoking reduces sperm production, motility, and morphology and, therefore, may impair fertility.

KEY POINT

Antidepressants elevate serum prolactin levels, leading to significant but reversible suppression of spermatogenesis.

BPH medications

The alpha-blockers used to treat BPH may cause decreased ejaculate volume or anejaculation and may be worse with tamsulosin compared with other alpha-blockers.[26] Saw palmetto is a commonly used over-the-counter medication for prostate problems; however, there currently are no human male fertility data available. Finasteride and dutasteride are antiandrogens that act by inhibiting 5-alpha-reductase. Finasteride has also been used to treat male-pattern baldness. These drugs increase the risk of low ejaculate volumes and libido, as well as cause erectile and ejaculatory dysfunction[26]; however, men taking low doses of finasteride for hair loss have shown no changes in semen parameters.[27]

Antibiotics

Many antibiotics have been reported to exert adverse effects on male fertility[28]; however, there are few human data on the majority of these medications. High doses of nitrofurantoin have been reported to cause early maturation arrest at the primary spermatocyte stage[1,29] but the more common short-term low-dose therapy is not likely detrimental. While in vitro data on erythromycin, tetracycline, and gentamycin suggest the potential for adverse effects on fertility, documentation of an in vivo effect in humans is lacking.[30]

Sulfasalazine, used in the treatment of ulcerative colitis, is well known to cause defects in human sperm concentration and motility.[31,32] These are reversible, and patients with concerns about fertility should take 5-amino salicylic acid, which does not affect semen parameters.[33]

Psychotherapeutic agents

Many psychotherapeutic agents affect male fertility by suppressing the HPG axis and decreasing erectile function and libido. Indeed, one of the most significant side effects of the antidepressants is elevation of serum prolactin, leading to significant but reversible suppression of spermatogenesis.[1,2]

Psychotherapeutic agents include antipsychotics, tricyclic and selective serotonin reuptake inhibitor (SSRI) or selective norepinephrine reuptake inhibitor (SNRI) antidepressants, monoamine oxidase inhibitors (MAOIs), phenothiazines, and lithium. There are now large numbers of patients taking SSRI or SNRI medications, many of which have significant effects. In a study of 610 women and 412 men, the incidence of sexual dysfunction with SSRIs and the SNRI venlafaxine was high, ranging from 58% to 73%, as compared with the serotonin-2 (5-HT2) blockers (nefazodone and mirtazapine), the MAOI moclobemide, and the tricyclic amineptine.[34]

It is important to remember that the psychological benefits of many of these drugs often outweigh any fertility issues; however, if possible, switching to another class of medication may ameliorate infertility symptoms.

Chemotherapeutic agents

Chemotherapy for the treatment of cancer can have devastating effects on male fertility through the impairment of spermatogenesis[35]; indeed, alkylating agents, antimetabolites, and the vinca alkaloids are all gonadotoxins. In patients with testicular cancer, the cumulative dose of cisplatin determines whether spermatogenesis is impaired irreversibly.[36] Most patients will become azoospermic, with the majority recovering spermatogenesis within 4 years.[37] The majority of Hodgkin's disease or leukemia patients become azoospermic after chemotherapy; this may or may not lead to permanent sterility. After treatment with VOVP (mitoxantrone, vincristine, vinblastine, prednisone) combination therapy plus abdominal radiotherapy for Hodgkin's disease, sperm counts and motility were restored to pretreatment levels in most patients.[38] Nonmyeloablative bone marrow transplantation (BMT) has been associated with germ and Leydig cell damage leading to infertility.[39]

Finally, although some men who receive chemotherapy and full body radiation therapy (XRT) prior to BMT may not be permanently sterile, incorporating XRT often does lead to sterility.[40,41] For young male cancer patients who are concerned about fertility, offering semen cryopreservation as soon as possible after diagnosis and prior to any treatment may be an important step.

Miscellaneous medications

Cimetidine has been reported to have antiandrogenic effects that induce gynecomastia and decreases in sperm count.[1] Ranitidine has not been shown to have any effect on the testes.[42]

Immune modulators are commonly used but, unfortunately, clear human data regarding male fertility for interferon or the immunosuppressant mycophenolate mofetil are lacking. Although cyclosporine has been found to induce impaired fertility in rats,[43] there are no human data available.

Colchicine has been reported to induce oligospermia; however, this was demonstrated in a study of patients with Behçet's disease with long-term exposure. Short-term use in healthy males induced no effect on semen parameters and it is unclear if spermatogenic defects are due to the long-term use or underlying disease.[44,45]

Cholesterol-lowering drugs such as hydroxyl-methyl-glutaryl coenzyme A reductase inhibitors have been of concern because of potential effects on cell membranes. While there are no human data indicating adverse effects, rat data have suggested no effect on fertility.[46]

Epilepsy has been associated with decreased testosterone levels and increased estrogen levels leading to reductions in libido and to erectile dysfunction. Medications used to treat epilepsy (eg, valproate, oxcarbazepine, and carbamazepine) may worsen hormonal abnormalities and have been associated with some sperm morphologic defects.[47-49] One report suggested that switching from valproate to phenytoin may improve oligoasthenozoospermia (low sperm count with abnormal sperm motility).[50]

Conclusions

Approximately 15% of couples cannot conceive a child after 1 year of unprotected intercourse.[3] Infertility present solely in the male partner occurs in about 20% of these couples, and male infertility is a contributory factor in another 30% to 40% of cases.[16]

Awareness of a male patient's desire for future fertility may help to avoid medication-induced infertility, and patients who are given agents that impair fertility should be advised of this effect. A number of sources are available to the clinician to help evaluate the reproductive risks of drugs and other agents. ■

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KEY POINT

Infertility present solely in the male partner occurs in about 20% of infertile couples.

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