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What's New in Male Contraception?

Learning Objective: At the conclusion of this continuing medical education activity, the participant will be able to define options for male contraception. Specific to vasectomy, the participant will be able to appropriately counsel a patient considering vasectomy, describe acceptable vasectomy techniques and define successful sterility. In addition, the participant will be able to describe the efficacy and safety of novel hormonal and non-hormonal male contraceptive options.

This AUA Update aligns with the American Board of Urology Module on Impotence, Infertility, Infection and Andrology. Additional information on this topic can be found in the AUA Core Curriculum section on Sexual Medicine.

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INTRODUCTION

Male contraceptives date back to 40 A.D., when Dioscorides described the use of hemp seeds and rue in *De Materia Medica*.[1] Surveys demonstrate that nearly 80% of men believe contraception is a shared responsibility,[2] and the most commonly practiced forms of male contraception include the withdrawal method, barrier devices such as condoms, and surgical sterilization with vasectomy. The most commonly used contraceptive methods among couples in the U.S. are condoms (29.5%), female oral contraceptives (25.6%), tubal ligation (8.1%) and vasectomy (5.7%).[3] The most updated data on married couples from the National Survey of Family Growth showed condom use at 15.3%, female sterilization at 31.2%, male sterilization at 17.1% and female oral contraceptives at 18.6%.[4]

Methods to prevent pregnancy involving only male physiology are few and relatively underused. This Update will review the currently available forms of male contraception, including advantages, disadvantages, risks and outcomes, as well as examine novel forms of male contraception currently under investigation.

CONDOMS

Condoms are made of a thin latex polyisoprene or polyurethane material. They are inexpensive and easily accessible. Condoms are the most commonly utilized method for contraception. In the United States, 20% of couples and 47% of single men report using condoms as their primary method of contraception. Although condoms provide protection against sexually transmitted infections, they carry a 13% typical use failure rate with respect to pregnancy, can reduce the spontaneity and sensitivity of sexual intercourse, and present problems of storage and disposal. The high failure rate can be attributed to not using condoms throughout sexual intercourse, not leaving space at the tip, not using only water-based lubricants, incorrect placement of condom and incorrect withdrawal. When used correctly and consistently, failure rates drop to 2%. There is a trend toward technological improvement in condoms to increase effectiveness and acceptability. This includes better heat transference between partners, thinner dimensions to improve sensitivity, diminished breakage, improved fit and being easier to put on (one has an applicator). To improve marketing to consumer preferences, different appearance, flavors, shape, texture, increased and decreased sensation, and substances added to condoms aim to improve consistent use and effectiveness.[5] Couples should be counseled regarding methods to optimize effectiveness of condom use. Centers for Disease Control and Prevention guidelines on proper use of condoms can be found at https://www.cdc.gov/condomeffectiveness/male-condom-use.html.

VASECTOMY

Vasectomy is one of the most common procedures performed by urologists in the United States, with over 500,000 vasectomies performed annually.[6] Compared to tubal ligation, an alternative permanent contraception, vasectomy is more effective at preventing pregnancy, less invasive, more cost-effective and requires less recovery with fewer complications.[7] Couples with higher numbers of children, higher educational levels, and non-Hispanic white ethnicity are more likely to choose vasectomy.[8] The American Urological Association published the Vasectomy Guideline in 2012, and it was most recently updated in 2015.

Consultation. **Vasectomy consultation should comprise a review of medical history including bleeding disorders or anticoagulation, reproductive history and a physical examination, preferably in person, although consultation by telephone or electronic communication is an acceptable alternative.** Patients should understand that vasectomy is intended to be a permanent form of contraception and that some states require a delay between signing the consent form and procedure date. Patient selection is variable and up to the performing surgeon. Patients who are interested in sperm banking prior to vasectomy should discuss this with their surgeon, but it is not routinely recommended to do so. Vasectomy does not confer immediate sterility, and use of contraception is encouraged until sterility is confirmed with post-vasectomy semen analysis. **The risk of vasectomy failure (not achieving sterility and requiring repeat procedure) is less than 1%.[9] Rates of surgical complications such as symptomatic hematoma and infection are 1%–2%,[10] and risk for clinically significant chronic scrotal pain is 1%–2%.[11]**

Procedure. While there are a variety of vasectomy techniques, the following apply to all procedures. **Prophylactic antibiotics are not indicated for vasectomy unless patient comorbidities are associated with a particularly high risk of infection.[12]** The vast majority of vasectomies can be performed with local anesthesia to the skin and vasal nerve block with or without oral anxiolytic. Topical anesthesia has shown inconsistent results in reducing discomfort in addition to standard local injection of anesthetic.[13] A pneumatic injector, also known as a jet or no-needle device, delivers anesthetic transcutaneously and may be useful in men who would prefer not to use needles.[14]

Vasectomy techniques. Isolation of the Vas: Minimally invasive vasectomy, including no-scalpel vasectomy, incorporates small (<1 cm) openings in the scrotal skin and minimal dissection of the vas using a vas dissector and vas ring clamp. These minimally invasive techniques decrease procedure time, can reduce pain, result in fewer hematomas and infections, and leave a much smaller wound than conventional methods.[15] Regarding skin opening, single midline or bilateral scrotal openings are acceptable and based on surgeon preference. Minimally invasive vasectomy skin opening(s) <1 cm may be closed with a suture or left open at the end of the procedure.

Vas Separation and Occlusion: Vasectomy techniques involve complete division of the vas and may or may not include excision of a segment of vas. For excision, a 1.0 cm segment is an adequate length to minimize risk of recanalization while also minimizing the risk of surgical complications and facilitating vasectomy reversal if needed. Routine histological examination of the excised vas segments is not required. Vas occlusion

ABBREVIATIONS: FSH= follicle-stimulating hormone, GnRH=gonadotropin-releasing hormone, LH=luteinizing hormone, PVSA=post-vasectomy semen analysis

is accomplished by separation and/or occlusion of the divided ends. Separation with fascial interposition involves placing a layer of the internal spermatic fascia between the 2 divided ends of the vas using suture or clips. Techniques for occlusion include the following: ligation, clips or mucosal cautery that is applied to the cut ends of the vas to create a plug of scar tissue, which occludes the vas lumen. The open-ended technique involves leaving the testicular end of the divided vas un-occluded while occluding the abdominal end. This technique aims to prevent or reduce post-vasectomy pain by decreasing back pressure in the epididymis.[16]

The ends of the vas should be occluded by one of following methods (fig. 1):

1) Mucosal cautery with fascial interposition
2) Mucosal cautery alone
3) Open-ended vasectomy—leaving the testicular end of the vas unconcluded, using mucosal cautery on the abdominal end and fascial interposition

These techniques have all been shown to have a vas occlusion failure rate as low as ≤1%; however, ligation or clips are also acceptable procedures if the failure rate is low for the individual surgeon (table 1).

Post-vasectomy follow-up. Post-Vasectomy Semen Analysis: There are varying practices around post-vasectomy semen analysis, including timing, sample and analysis technique. The aim of a PVSA is to confirm occlusive effectiveness and to advise a patient that he can safely rely on his vasectomy for contraceptive purposes.

Time to sperm clearance after vasectomy is dependent on a variety of factors, including frequency of ejaculation and age. **Eight to 16 weeks after vasectomy is the appropriate time range for the first PVSA and is at the discretion of the surgeon, balancing the desire to minimize the number of PVSAs needed to establish sterility but still allow men to abandon other forms of contraception as soon as possible after vasectomy.**

Success and Failure: Although some men fail to achieve azoospermia after vasectomy, they do not go on to father a pregnancy, and studies show that the risk of pregnancy associated with rare non-motile sperm is very low and similar to the risk when sperm are absent.[17] **Therefore, a post-vasectomy semen analysis with azoospermia (absence of sperm) as well as rare non-motile sperm (≤100,000 non-motile sperm/ml) during microscopic examination of at least 50 high-powered fields in a single well-mixed, uncentrifuged semen specimen is considered successful.** However, recanalization can occur after vas occlusion. Early recanalization occurs within the first 4–6 weeks and happens in approximately 1:500 procedures. Late recanalization (return of motile sperm after confirmatory PVSA) happens in approximately 1:2000 procedures.[18] For persistent motile sperm, additional PVSAs should be performed at intervals of 4 to 6 weeks, for up to 6 months after vasectomy. **Vasectomy is considered a failure if any motile sperm are seen on PVSA at 6 months after vasectomy, and a repeat vasectomy should be considered.**

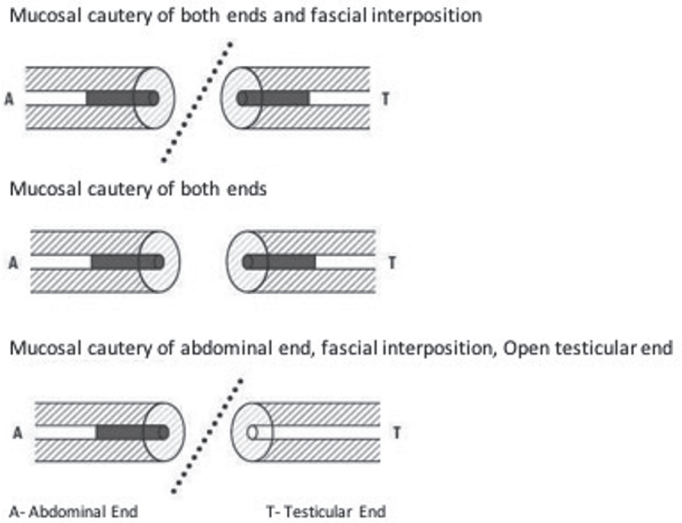

Figure 1. Recommended vas separation and occlusion techniques.

Reversibility. Options for conception after vasectomy include microsurgical vasectomy reversal or sperm aspiration combined with in vitro fertilization.[19] Several factors should be considered by the couple when choosing between these 2 options, such as time to pregnancy, number of desired children, time commitment, cost and maternal age or other female fertility factors.

Studies of vasectomy reversals show that patency can be achieved, irrespective of the obstructive interval, but vasectomy reversal does become more technically challenging as the obstructive interval increases, due to the higher likelihood of needing a vasoepididymostomy.[20] A meta-analysis demonstrated vasectomy reversal patency rate of 89% (range 69%–98%) and a pregnancy rate of 73% (range 37%–93%).[21] Another consideration is time to return of sperm and recovery of physiological fertility. For vasectomy reversal, motile sperm were observed at a mean of 2.1 months (SE±0.2) following vasovasostomy and 5.8 months (SE±0.8) following vasoepididymostomy.[22]

Another option for fertility after vasectomy is to use testicular or epididymal sperm, but the quantity/maturity of the sperm is only adequate for in vitro fertilization, not for intrauterine insemination. Sperm retrieval methods include percutaneous epididymal sperm aspiration ("PESA"), microsurgical epididymal sperm aspiration ("MESA"), testicular sperm aspiration ("TESA") and testicular sperm extraction ("TESE"), and these specimens can be used either as fresh or frozen sperm for intracytoplasmic sperm injection and in vitro fertilization.

NOVEL MALE CONTRACEPTIVE METHODS

The ideal contraceptive should be safe, affordable, 100% effective and reversible, with no short or long-term side effects. This contraceptive does not exist at the present time. Oral contraception in females, or "the Pill," gives a lowest expected failure rate of 0.1%, and with "typical" use has a 7.6% failure rate with 1 year of use.[23] This is the minimum bar that a male contraceptive needs to reach or approach. Suppression of sperm concentration to <1 million/cc decreases the chance of conception to <1%/year.[24] Novel male contraceptive techniques are aimed at either disrupting the ability of sperm to reach the egg, inhibiting spermatogenesis or disrupting sperm's ability to function.

Hormonal. The foundation of male hormonal contraception is understanding the male hypothalamic-pituitary-gonadal axis and the basic science of spermatogenesis (fig. 2). **Spermatogenesis is regulated by the pulsatile release of gonadotropin-releasing**

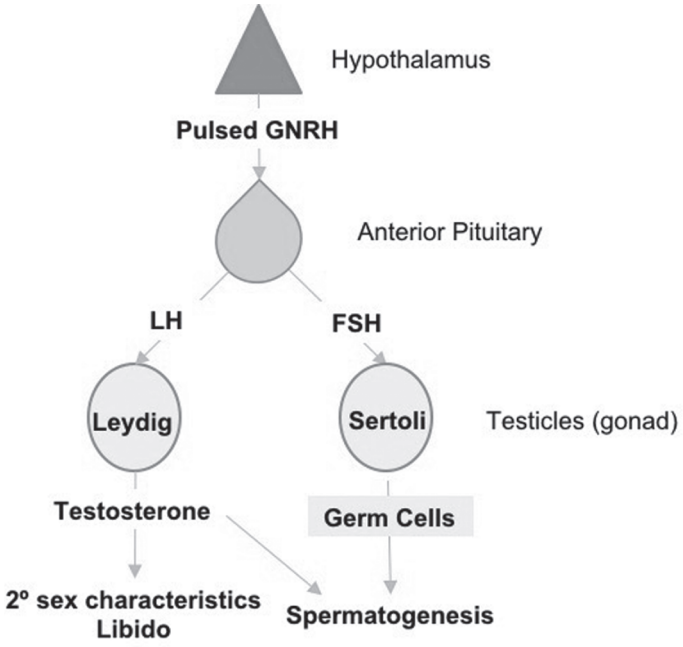

Figure 2. Hypothalamic-pituitary-gonadal axis.

hormone, which stimulates the anterior pituitary to episodically release follicle-stimulating hormone and luteinizing hormone. LH stimulates the Leydig cells to produce testosterone, inducing an effect on the interstitium and seminiferous tubules, resulting in sperm production and maturation. FSH acts directly on the Sertoli cells of the testicle to promote spermatogenesis. Suppression of LH and FSH results in inhibition of spermatogenesis and testosterone production. Various manipulations of this axis can be utilized for hormonal contraception (table 2).

Testosterone: It was discovered that testosterone alone was able to reversibly suppress sperm concentrations to very low levels, with return of spermatogenesis after discontinuation of therapy.[25] Further studies confirmed testosterone's effectiveness at inducing azoospermia or severe oligospermia, defined as less than 1 million sperm. In the initial study, 70% of men were azoospermic after 6 months and there was 1 pregnancy in the efficacy phase. The time to sperm recovery was 3–7 months. Another study showed sperm suppression to less than 3 million/cc in 98% of men.[26] The overall failure rate was calculated to be 3.4%. No serious adverse reactions occurred in the "proof of concept" trials but weekly testosterone injections were not well tolerated. Pain at the injection site, high doses of testosterone required to reach azoospermia/oligospermia and the mean time to achieve low sperm count limited subject participation. A longer-acting testosterone undecanoate was evaluated in 2 studies from China that showed 95% of men had sperm concentrations below 1 million/cc.[27,28] This 6- to 12-week depot injection resulted in about a 95% efficacy rate with a 7% increase in hematocrit and 23% decrease in HDL cholesterol. The majority of the studies of testosterone for contraception were of 1-year follow-up. Therefore, expectations of return of sperm to the ejaculate with longer periods of exogenous testosterone may not be able to be extrapolated from these data.

Progestin/Testosterone Combinations: The combination of progesterone and testosterone has been utilized with the goal of higher rates of azoospermia. Both suppress the hypothalamic-pituitary-gonadal axis. Trials combining testosterone with progestin demonstrated a decreased time to azoospermia/severe oligospermia, reduction in testosterone dosing and longer lasting effects.[29] Behre et al studied 320 men injected with 200 mg norethisterone enanthate combined with 1000 mg testosterone undecanoate.[30] The rate of suppression of sperm concentration less than 1 million/ml by the end of 24 weeks was 95.9 per 100 continuing users. Pregnancies occurred at a rate of 1.57 per 100 continuing users, while 94.8 per 100 continuing users recovered sperm concentration of more than 15 million sperm/ml by 52 weeks of the recovery phase. Side effects were mostly mild and related to androgen effects. However, moderate to severe mood disturbances, including 1 suicide, led to a safety review and early termination of the study.

Nestorone® (segesterone acetate; Population Council, New York, New York) is a 19-norprogesterone-derived progestin without androgenic, estrogenic or glucocorticoid effects, making the regimen well-tolerated without serious side effects. Recent studies have combined Nestorone gel in combination with testosterone gel to suppress spermatogenesis.[31] When using both gels daily, nearly 89% of subjects exhibited sperm suppression below 1 million/ml, which is statistically significant compared to testosterone gel alone ($p < 0.001$). A novel combination gel containing Nestorone and testosterone into a small volume, daily application suppressed FSH and LH concentrations (< 1.0 IU/l) in nearly 85% of participants with no serious adverse reactions.[32]

Oral Formulations: The "male Pill," dimethandrolone undecanoate, is a derivative of 19-nortestosterone with both androgenic and pregestational activity and is a "single agent" that binds both androgen and progesterone receptors. Initial animal studies showed suppression of gonadotropins, suppression of sperm production with complete reversibility and no pregnancies.[33] A total of 82 subjects were enrolled in a 28-day study that showed tolerability and efficacy, and 18 out of 19 subjects who received 400 mg dimethandrolone undecanoate achieved marked suppression of LH, FSH and gonadotropins consistent with levels effective for contraception.[34] Longer term studies are ongoing to evaluate effectiveness against spermatogenesis.

Another compound, 11-beta-methyl-19-nortestosterone 17-beta-dodecylcarbonate (11-BMNTDC), a derivative of 19-nortestosterone, was evaluated in 12 healthy males.[35] The medication was well-tolerated without severe adverse events, and doses of 200 mg or greater suppressed serum testosterone concentrations ($p < 0.05$). Further, larger scale studies would need to be completed to evaluate its potential for male contraception, particularly looking at sperm concentrations.

GnRH Antagonists: GnRH antagonists act by competitively binding to receptors and reducing both LH and FSH to undetectable levels, suppressing spermatogenesis. Short-term studies show a promising role for GnRH antagonists plus testosterone in suppression of spermatogenesis.[36] The limitation to these studies was frequent injections. The development of long-acting (1-year) GnRH antagonist formulations, such as degarelix, will allow for future studies to explore GnRH as an option for male contraception. These could be combined with long-acting testosterone supplementation.

Non-hormonal. Non-hormonal contraception therapies may be appealing to men as they would avoid the impacts on testosterone and impacts on sexual function, muscle/bone mass and sex drive (table 3).

Gossypol: Gossypol is a complex phenolic molecule derived from the seeds of the cotton plant. Although the mechanism of action is unknown, it reduced both sperm production and sperm motility, resulting in a 90% efficacy rate in preventing pregnancy. However, it had severe side effects, including hypokalemia and irreversibility. Triptolide, derived from the Chinese herb Tripterygium wilfordii, showed impaired sperm motility and decreased sperm counts but also showed irreversibility. The mechanism of action is unknown.[28]

Lonidamine Derivatives: Several other compounds have been studied, including 2 lonidamine derivatives in animals only. Adjudin disrupts the bridges between spermatids and Sertoli cells, thus inhibiting sperm maturation, and H2-gamendazole impairs the function of the apical ectoplasmic specialization. Both aim to interfere with adhesion of spermatids to Sertoli cells, which appears to cause the premature release of spermatids. Unfortunately, both studies had severe adverse events that led to discontinuation.[28]

Sperm Transport Blockers: An alpha-1A-specific antagonist, silodosin, which is approved by the U.S. Food and Drug Administration for benign prostatic hyperplasia, has been tested as a male contraceptive. The mechanism of action is via an effect on receptors that lower ejaculate volume. One study showed there were no pregnancies in men taking 8 mg on demand 3 hours prior to intercourse.[37] Future studies will be necessary here.

An occlusive procedure called RISUG (reversible inhibition of sperm under guidance; Vasalgel, Parsemus Foundation, San Francisco, California) was developed in India. Ultrasound guidance is used to inject an occlusive solution of styrene maleic anhydrate into both vasa deferentia. The goal is to occlude the vas and prevent sperm passage. Phase I and II trials confirmed its safety, efficacy and reversibility in animals only. Animal phase III trials are underway, with data demonstrating no significant adverse events. Studies have shown that 82.7% of individuals were azoospermic within 2 months and the remaining 17.3% were azoospermic in 3–6 months after injection. Future trials will need a larger sample, longer duration of follow-up and reversibility studies.[38]

Silicone plugs ("Shugs") have been investigated in animal models and a small clinical trial. The Shug is composed of 2 silicone plugs with nylon tails to anchor the plugs to the vas. They are inserted into the vas without a scalpel and can be removed with a minor procedure. Of treated men, 97% had a reduction in sperm motility.[39] However, reversibility remained a major issue, and further studies were not performed.

CONCLUSIONS

With nearly half of pregnancies around the world being unplanned, there is great opportunity for male contraceptive techniques.[40] Condoms are widely used but with significant limitations. Vasectomy remains a commonly performed procedure as a form of permanent contraception, is well studied and has widely accepted guidelines. Several studies are ongoing for novel methods of male contraception. However, no novel method at this time has been implemented into routine clinical practice. Issues with safety, efficacy, affordability and reversibility have been major factors affecting widespread acceptance. Patient and partner acceptance is a major factor as well. Future large-scale studies will be required to make advances in the field concerning efficacy, safety and reliability.

DID YOU KNOW?

- Vasectomy consultation should include intention for permanent contraception, post-vasectomy semen analysis is required to confirm success, and complication rates include 1%–2% for hematoma and infection, and 1%–2% for clinically significant chronic scrotal pain.
- Recommended techniques for vas occlusion are 1) mucosal cautery with fascial interposition, 2) mucosal cautery and 3) open-ended vasectomy leaving the testicular end of the vas unconcluded, using mucosal cautery on the abdominal end and fascial interposition.
- Patients can stop using contraception when post-vasectomy semen specimen shows azoospermia or only rare non-motile sperm (≤100,000 non-motile sperm/ml).
- Spermatogenesis is regulated by the pulsatile release of GnRH, which stimulates the anterior pituitary to release FSH and LH. LH stimulates the Leydig cells to produce testosterone, resulting in sperm production and maturation. FSH acts directly on the Sertoli cells of the testicle to promote spermatogenesis.
- There are both hormonal and non-hormonal novel male contraceptive options being studied at the present time.

Table 1. Success of vas separation and occlusion techniques

Technique	No. Study Arms	No. Pts	Range of Occlusive Failure Rates
Recommended techniques			
Mucosal cautery of both ends and fascial interposition	13	18,456	0.0%–0.55%
Mucosal cautery of both ends	6	13,851	0.0%–1.0%
Mucosal cautery of abdominal end, fascial interposition, open testicular end	4	4,600	0.0%–0.5%
Optional techniques*			
Ligation of both ends	31	24,797	0.0%–13.79%
Ligation of both ends and fascial interposition	9	2,782	0.0%–5.85%
Clips on both ends	7	4,337	0.0%–8.67%

*For surgeons with training and/or experience that may produce acceptable failure rates.

Table 2. Hormonal contraceptives

Product	Delivery	Efficacy	Side Effects	Limitations
Testosterone only	Injectable	95%–98% Azoospermic after 2–6 mos	Pain at injection site, altered libido, acne, changes in mood, increased hematocrit, decrease in HDL cholesterol	3-mo recovery period for reversibility
Progestin/ testosterone	Injectable	95%–96% Azoospermic by 6 mos	Mood disturbance, depression, rare though significant mood disturbance leading to termination of study	
GnRH antagonists	Injectable	75% Azoospermic by 6–12 wks	Weight gain, increase in hematocrit	Frequent injections, cost
Testosterone +Nestorone	Transdermal	85%–89% Azoospermic	Acne	No studies demonstrating long-term efficacy
"Male pill" (dimethandrolone undecanoate)	Oral	95% Azoospermic	Androgenic side effects	Small study samples

Table 3. Non-hormonal contraceptives

Drug or Treatment	Mechanism of Action	Efficacy	Side Effects	Limitations
Gossypol	Unknown, reduces sperm production and motility	90% Efficacy	Hypokalemia	Irreversible
Triptolide	Unknown, reduces sperm motility and decreases sperm counts	Rat studies show complete infertility		Irreversible, narrow therapeutic window
Adjudin	Disrupts bridges between spermatids and Sertoli cells, perturbing sperm maturation	100% Infertility in rat studies		
Gamendazole	Impairs function of apical ectoplasmic specialization–early release of spermatids	100% Infertility in rat studies	Toxicity, death	Irreversible in 50%
Silodosin	Effect on receptors to lower ejaculate volume	No pregnancies reported	Diminished ejaculate volume	Small study
RISUG	Occlusive solution injected into vas deferens	82.7% Azoospermic in 2 mos, remaining 17.3% in 3–6 mos	Scrotal swelling	Reversibility unclear, phase III human trials in progress

REFERENCES

1. Sailani MR and Moeini H: Effect of Ruta graveolens and Cannabis sativa alcoholic extract on spermatogenesis in the adult Wistar male rats. Ind J Urol 2007; **23:** 257.
2. Heinemann K., Saad F., Wiesemes M et al: Attitudes toward male fertility control: results of a multinational survey on four continents. Hum Reprod 2005; **20:** 549.
3. Martinez GM, Chandra A, Amba JC et al: Fertility, contraception, and fatherhood: data on men and women from cycle 6 (2002) of the 2002 National Survey of Family Growth. Vital Health Stat 2006; **23:** 1.
4. Jones J, Mosher W and Daniels K: Current contraceptive use in the United States, 2006–2010, and changes in patterns of use since 1995. National Health Statistics Reports, No. 60. Hyattsville, Maryland: National Center for Health Statistics 2012. Available at http://www.cdc.gov/nchs/data/nhsr/nhsr060.pdf.
5. Beksinska M, Wong R and Smit J: Male and female condoms: their key role in pregnancy and STI/HIV prevention. Best Pract Res Clin Obstet Gynaecol 2020; **66:** 55.
6. Ostrowski KA, Holt SK, Haynes B et al: Evaluation of vasectomy trends in the United States. Urology 2018; **118:** 76.
7. Trussell J, Lalla AM, Doan QV et al: Cost effectiveness of contraceptives in the United States. Contraception 2009; **79:** 5.
8. Anderson JE, Warner L, Jamieson DJ et al: Contraceptive sterilization use among married men in the United States: results from the male sample of the National Survey of Family Growth. Contraception 2010; **82:** 230.
9. Poddar AK and Roy S: Disappearance of spermatozoa from semen after vasectomy. J Popul Res 1976; **3:** 61.
10. De Los Rios Osorio J and Castro Alvarez EA: Analysis of 5000 vasectomies in a family planning centre in Medellin-Colombia. Arch Esp Urol 2003; **56:** 53.
11. Leslie TA, Illing RO, Cranston DW et al: The incidence of chronic scrotal pain after vasectomy: a prospective audit. BJU Int 2007; **100:** 1330.
12. Wolf JS Jr, Bennett CJ, Dmochowski RR et al; Urologic Surgery Antimicrobial Prophylaxis Best Practice Policy Panel. Best practice policy statement on urologic surgery antimicrobial prophylaxis. J Urol 2008; **179:** 1379.
13. Cooper TP: Use of EMLA cream with vasectomy. Urology 2002; **60:** 135.
14. Weiss RS and Li PS: No-needle jet anesthetic technique for no-scalpel vasectomy. J Urol 2005; **173:** 1677.
15. Cook LA, Pun A, van Vliet H et al: Scalpel versus no-scalpel incision for vasectomy. Cochrane Database Syst Rev 2007; **2:** CD004112.
16. Shapiro EI and Silber SJ: Open-ended vasectomy, sperm granuloma, and postvasectomy orchialgia. Fertil Steril 1979; **32:** 546.
17. Freund MJ and Couture M: The presence of spermatozoa in the semen of vasectomized men. J Androl 1982; **3:** 313.
18. Alderman PM: The lurking sperm. JAMA 1988; **259:** 3142.
19. Schwarzer JU and Steinfatt H: Current status of vasectomy reversal. Nat Rev Urol 2013; **10:** 195.
20. Belker AM, Thomas AJ Jr, Fuchs EF et al: Results of 1,469 microsurgical vasectomy reversals by the Vasovasostomy Study Group. J Urol 1991; **145:** 505.
21. Herrel LA, Goodman M, Goldstein M et al: Outcomes of microsurgical vasovasostomy for vasectomy reversal: a meta-analysis and systematic review. Urology 2015; **85:** 819.
22. Matthews GJ, Schlegel PN and Goldstein M: Patency following microsurgical vasoepididymostomy and vasovasostomy: temporal considerations. J Urol 1995; **154:** 2070.
23. Sundaram A, Vaughan B, Kost K et al: Contraceptive failure in the United States: estimates from the 2006–2010 National Survey of Family Growth. Perspect Sex Reprod Health 2017; **49:** 7.
24. World Health Organization Task Force on Methods for the Regulation of Male Fertility: Contraceptive efficacy of testosterone-induced azoospermia and oligozoospermia in normal men. Fertil Steril 1996; **65:** 821.
25. Steinberger E and Smith KD: Testosterone enanthate a possible reversible male contraceptive. Contraception 1977; **16:** 261.
26. World Health Organization Task Force on Methods for the Regulation of Male Fertility. Contraceptive efficacy of testosterone-induced azoospermia in normal men. Lancet Lond Engl 1990; **336:** 955.
27. Gava G and Meriggiola MC: Update on male hormonal contraception. Ther Adv Endocrinol Metab 2019; **10:** 2042018819834846.
28. Amory JK: Development of novel male contraceptives. Clin Transl Sci 2020; **13:** 228.
29. Page ST, Amory JK and Bremner WJ: Advances in male contraception. Endocr Rev 2008; **29:** 465.
30. Behre HM, Zitzmann M, Anderson RA et al: Efficacy and safety of an injectable combination hormonal contraceptive for men. J Clin Endocrinol Metab 2016; **101:** 4779.
31. Roth MY, Ilani N, Wang C et al: Characteristics associated with suppression of spermatogenesis in a male hormonal contraceptive trial using testosterone and Nestorone® gels. Andrology 2013; **1:** 899.
32. Anawalt BD, Roth MY, Ceponis J et al: Combined Nestorone-testosterone gel suppresses serum gonadotropins to concentrations associated with effective hormonal contraception in men. Andrology 2019; **7:** 878.
33. Hild SA, Attardi BJ, Koduri S et al: Development of dimethandrolone 17B-undecanoate (DMAU) as an oral male hormonal contraceptive: induction of infertility and recovery of fertility in adult male rabbits. Biol Reprod 2008; **78:** 174.
34. Thirumalai A, Ceponis J, Amory JK et al: Effects of 28 days of oral dimethandrolone undecanoate in healthy men: a prototype male pill. J Clin Endocrinol Metab 2019; **104:** 423.
35. Wu S, Yuen F, Swerdloff RS et al: Safety and pharmacokinetics of single-dose novel oral androgen 11β-methyl-19-nortestosterone-17β-dodecylcarbonate in men. J Clin Endocrinol Metab 2019; **104:** 629.
36. Tornoe CW, Agerso H, Nielsen HA et al: Population pharmacokinetic modeling of a subcutaneous depot for GnRH antagonist Degarelix. Pharm Res 2004; **21:** 574.
37. Zaneveld LJD, De Castro MP, Faria G et al: The soft, hollow plug ("Shug"): a potentially reversible vas deferens occlusive device. In: Male Contraception: Present and Future. Edited by M Rajalakshmi and PD Griffin. New Delhi, India: New Age Int Ltd 1999; pp. 293–307.

38. Sharma RS, Mathur AK, Singh R et al: Safety and efficacy of an intravasal, one-time injectable and non-hormonal male contraceptive (RISUG): a clinical experience. Indian J Med Res 2019; **150:** 81.
39. Bhat GS and Shastry A: A prospective double-blind, randomized placebo- controlled study to evaluate the efficacy of silodosin 8 mg as an on-demand, reversible, nonhormonal oral contraceptive for males: a pilot study. World J Urol 2020; **38:** 747.
40. Plana O: Male contraception: research, new methods, and implications for marginalized populations. Am J Men's Health 2017; **11:** 1182.

Study Questions Volume 40 Lesson 27

1. A vasectomy consultation should ideally include a review of medical history, including bleeding disorders or anticoagulation, a physical examination and
   a. sexually transmitted infections
   b. exercise
   c. smoking status
   d. reproductive history

2. The vas separation and occlusion technique with the lowest failure rate post-vasectomy is
   a. mucosal cautery and ligation of both ends
   b. open testicular end; ligation of abdominal end
   c. open testicular end; mucosal cautery of abdominal end
   d. mucosal cautery of both ends with fascial interposition

3. After vasectomy, patients may stop using other methods of contraception when examination of one well-mixed, uncentrifuged, fresh post-vasectomy semen specimen shows azoospermia or rare non-motile sperm, defined as
   a. ≤10,000 non-motile sperm/ml
   b. ≤100,000 non-motile sperm/ml
   c. ≤200,000 non-motile sperm/ml
   d. ≤500,000 non-motile sperm/ml

4. The mechanism of action of testosterone hormonal contraception is
   a. lack of semen ejaculation
   b. direct inhibition of spermatid release
   c. via direct effects inhibiting sperm motility
   d. inhibition of production of intratesticular testosterone

5. The ideal contraceptive should be safe, effective, affordable, with no short or long-term side effects and
   a. reversible
   b. increase testosterone
   c. reduce the risk of testicular cancer
   d. have a narrow therapeutic window