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ANDROLOGY

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CLINICAL PRACTICE GUIDELINES

Practice and development of male contraception: European Academy of Andrology and American Society of Andrology guidelines

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Abstract

Backgrounds: Despite a wide spectrum of contraceptive methods for women, the unintended pregnancy rate remains high (45% in the US), with 50% resulting in abortion. Currently, 20% of global contraceptive use is male-directed, with a wide variation among countries due to limited availability and lack of efficacy. Worldwide studies indicate that >50% of men would opt to use a reversible method, and 90% of women would rely on their partner to use a contraceptive. Additional reasons for novel male

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contraceptive methods to be available include the increased life expectancy, sharing the reproductive risks among partners, social issues, the lack of pharma industry involvement and the lack of opinion makers advocating for male contraception.

Aim: The present guidelines aim to review the status regarding male contraception, the current state of the art to support the clinical practice, recommend minimal requirements for new male contraceptive development and provide and grade updated, evidence-based recommendations from the European Society of Andrology (EAA) and the American Society of Andrology (ASA).

Methods: An expert panel of academicians appointed by the EAA and the ASA generated a consensus guideline according to the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) system.

Results: Sixty evidence-based and graded recommendations were produced on couple-centered communication, behaviors, barrier methods, semen analysis and contraceptive efficacy, physical agents, surgical methods, actions before initiating male contraception, hormonal methods, non-hormonal methods, vaccines, and social and ethical considerations.

Conclusion: As gender roles transform and gender equity is established in relationships, the male contribution to family planning must be facilitated. Efficient and safe male-directed methods must be evaluated and introduced into clinical practice, preferably reversible, either hormonal or non-hormonal. From a future perspective, identifying new hormonal combinations, suitable testicular targets, and emerging vas occlusion methods will produce novel molecules and products for male contraception.

KEYWORDS

barrier methods, behaviors, contraceptive efficacy, couple-centerd communication, guidelines, hormonal methods, male contraception, non-hormonal methods, physical agents, semen analysis, social and ethical considerations, surgical methods, vaccines

1 | INTRODUCTION AND AIM

Despite a wide spectrum of contraceptive methods for women, the unintended pregnancy rate remains high (45% in the USA), with 50% resulting in abortion.[1] The recent (June 2022: https://d3i6fh83elv35t.cloudfront.net/static/2022/06/19-1392_6j37-2.pdf) Supreme Court decision (overturning the Roe versus Wade decision in 1973) in the USA and the resulting loss of access to safe abortion in some states of the USA made the prevention of unplanned pregnancies essential.

The female methods (combined hormonal contraceptives [oral pills, rings, patches], other hormonal preparations [injections, implants, intrauterine systems], and the copper intrauterine device [IUD]) are effective and safe.[2] Nevertheless, some women experience adverse effects or have comorbidities restricting their use.

Currently, 20% of global contraceptive use is male directed (condoms, vasectomy, withdrawal),[3,4] with a wide variation among countries due to limited availability and lack of efficacy (failure rates of 13% for condoms and 20% for withdrawal). Worldwide studies indicate that >50% of men would opt to use a reversible method,[5] and 90% of women would rely on their partner to use a contraceptive.[6] Additional reasons for novel male contraceptive methods to be available include the increased life expectancy (worldwide mean: 70.4 years for men), sharing the reproductive risks among partners, social issues (programs for family planning are directed mainly towards women), the lack of pharma industry involvement (which make crucial the role of the public sector), and lack of "protagonists" (opinion makers advocating for male contraception).[7]

As gender roles transform and gender equity is established in relationships, the male contribution to family planning must be facilitated. Efficient and safe male-directed methods, preferably reversible, either hormonal or non-hormonal, must be evaluated and introduced into clinical practice. From a future perspective, identifying new hormonal combinations, suitable testicular targets, and emerging vas occlusion methods will produce novel molecules and products for male contraception.[8]

The present guidelines aim to review the status regarding male contraception, the present state of the art to support the clinical practice, recommend minimal requirements for new male contraceptive development, and provide and grade updated, evidence-based recommendations from the European Society of Andrology (EAA) and the American Society of Andrology (ASA).

2 | METHODOLOGY

2.1 | Panel

An expert panel of academicians appointed by the EAA and the ASA generated a consensus guideline according to the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) system.

2.2 | Data identification

The PubMed electronic database was searched for relevant papers in English. In each section, search strings were constructed by combining appropriate terms. To enhance the value of the provided recommendations, the GRADE system was applied to grade the quality of the evidence and the strength of the recommendations.[9]

The present task does not follow the principles of a systematic review, but it is evidence-based and reflects the interpretation of the data by the expert panel members.

2.3 | Format

Each section of the guidelines includes the following:

- *Recommendations:* A limited number of recommendations, in the form of a bulleted list, are constructed according to the GRADE system.[9]
- *Evidence:* A paragraph summarizing the key papers that support the recommendations. Selected references are presented rather than a comprehensive literature review.
- *Values:* A paragraph emphasizing the high-grade evidence and recommendations proposed in the guidelines.
- *Remarks:* A paragraph emphasizing areas of uncertainty or technical or specific issues.

2.4 | Levels of evidence and grades of recommendation

The GRADE system develops evidence-based guidelines involving key recommendations and uses consistent language and graphic descriptions to standardize the strength of recommendations and the quality of the evidence. According to GRADE, the expert group used the following coding system: (1) "we recommend," indicating a strong recommendation and (2) "we suggest," indicating a weak recommendation. As far as the evidence grading is concerned, ⊕◯◯◯ denotes "very low-quality evidence," ⊕⊕◯◯ "low quality," ⊕⊕⊕◯ "moderate quality," and ⊕⊕⊕⊕ "high quality."

Largely, a "⊕⊕⊕⊕" score is awarded to evidence based on randomized controlled trials (RCTs) and meta-analyses of RCTs, and a "⊕⊕◯◯" score to evidence based on observational studies. Specific methodological characteristics (quality, consistency, directness, effect size) increase or decrease this score.

3 | COUPLE-CENTERED COMMUNICATION

3.1 | Couple-centered care and shared decision-making

Recommendations

1.	We suggest the shared decision-making approach through couple-centered contraceptive counseling.	GPS
2.	We suggest incorporating the reproductive justice framework into contraceptive counseling.	GPS

Shared decision-making on birth control is a type of couple-centered care that involves both partners in the decision-making process with the guidance of their healthcare providers. Couple-centered contraceptive counseling allows healthcare providers to help couples choose contraceptive methods that best suit their values, needs, and priorities. This means that both partners should be involved in the discussion and come to a mutual agreement about what type of birth control is best for them. This approach allows couples to weigh the risks and benefits of different types of birth control and select one that best suits their needs. In addition, it allows couples to openly discuss adverse effects, effectiveness, cost, and other factors that can influence the decision. Having both partners actively involved in the decision-making process helps to ensure that the selected birth control works best for the couple and helps build a stronger and more trusting relationship (Table 1).

TABLE 1 Approach of the couple desiring contraception.

1.	Encourage couples to openly discuss their options regarding male and female contraceptives and their individual and collective preferences.
2.	Provide information about the different types of male and female contraceptives, how they work, and their advantages and disadvantages.
3.	Assess each partner's needs and preferences, such as their access to healthcare and personal comfort with medications and side effects.
4.	Work with the couple to create a shared decision-making process that works best for them.
5.	Help the couple identify any potential barriers to using or continuing to use male or female contraceptives, such as cost and access to care.
6.	Encourage regular follow-up appointments to monitor the effectiveness of the chosen contraceptive and assess any side effects.
7.	Provide emotional and social support to the couple throughout their contraceptive journey.
8.	If needed, refer the couple to other resources, such as financial assistance programs and support groups.

In addition, recognizing the couple's family values, medical, and other factors that influence their decision, healthcare providers should also incorporate the reproductive justice framework into contraceptive counseling by the American College of Obstetricians and Gynecologists[10,11]:

- Acknowledging historical and ongoing reproductive mistreatment of people of color and other marginalized individuals whose reproductive desires have been devalued;
- Recognizing that counselor bias, unconscious or otherwise, can affect care and working to minimize the effect of bias on counseling and care provision;
- Prioritizing men's values, preferences, and life experiences in selecting or discontinuing a contraceptive method.

False expectations about contraception are associated with lower adherence and compliance and a higher discontinuation rate. Women with greater knowledge of how the contraceptive works, its benefits, and adverse effects are more likely to continue taking their contraceptive than less informed women.[12] Therefore, counseling on male contraceptives should also include comprehensive information about different aspects (see Section 9.1), including the time to become effective of different contraceptives, the time needed for spermatogenesis to recover or irreversibility, adverse effects, and proven benefits.

3.2 | Female contraception

- Available reversible and irreversible female contraceptive methods and their effectiveness should be integral to contraceptive counseling for couples.
- Reversible female contraceptives include combined estrogen–progestin contraceptives—the oral pill, the skin patch, the vaginal ring- or progestin-only contraceptives—the oral, the injectable (medroxyprogesterone acetate depot), implants, and the levonorgestrel-IUD (https://www.acog.org/womens-health/faqs/birth-control).[13,14]
- The high effectiveness of long-acting reversible contraceptives, LNG-IUD, implants and injections, which is the same in perfect use and typical use and the lesser effectiveness of short-acting reversible contraceptives method in typical use, should also be discussed with the couples.
- Non-hormonal IUDs, barrier methods, and emergency contraception should also be illustrated to the couple.[15]

4 | BEHAVIORS

4.1 | Withdrawal (coitus interruptus)

Recommendations

3. We suggest that withdrawal and fertility awareness methods are **not** recommended for family planning.	2 ⊕◯◯◯

Evidence

The effectiveness of withdrawal and fertility awareness-based methods (FABM) depends on the couple's education, the female's cycle regularity, the female partner's commitment to daily evaluation of first-morning temperature and cervical mucous consistency, and the couple's ability to avoid intercourse and ejaculation during the time determined to be of peak fertility. Data on pregnancy rates are frequently of poor quality and highly dependent on study design.[16] The failure rates are estimated at 20% for typical use and 4% for perfect use.

Withdrawal or coitus interruptus is frequently used as a contraceptive method, but it is not frequently discussed with the couple during contraceptive counseling, nor is it well studied.[17] Efficacy rates for perfect use are generally based on some evidence that there are few motile spermatozoa in pre-ejaculatory fluid. Typical use failure rates are estimated using National Survey of Family Growth (NSFG) data and are notably high.[18] Clinical trial data are not available to calculate the failure rates for consistent and correct use of coitus interruptus, but the estimated failure rate would be approximately 4% with perfect use. Typical-use first-year failure rates have been measured to be 18%.[19] The benefits of this method are obvious: it requires no drugs or devices; it does not interfere with foreplay or pre-coital spontaneity; and it is readily portable and available[20] (Table 2).

4.2 | Fertility awareness-based methods

Evidence

Ovulation and Two-Day methods are based on the evaluation of cervical mucus. The "standard days" method avoids intercourse on cycle days 8–19. The symptom-thermal method is a double-check method based on evaluating cervical mucus to determine the first fertile day and the evaluation of cervical mucus and basal body temperature to determine the last fertile day. These methods are utilized by teaching couples how to predict high and low fertility days.[21] Data suggest that 22% of men in the USA have used FABM at least once, and 2–3% of contraceptive users are doing so currently, based on the US NSFG.[10] This is based on abstinence or barrier methods during the "most fertile period." It appears that only 50% of couples will time high fertility days appropriately, suggesting less-than-perfect use in most situations.

There are over 100 smartphone applications ("apps") to help track menstrual cycles (clearblue fertility monitor, natural cycles, dynamic optimal timing, my fertility MD). Perfect use of these apps suggests an annual failure rate of about 1%. Multiple kits are available to measure a combination of urinary hormone concentrations, cervical mucus, and basal body temperature observations.

There are multiple protocols for detecting or predicting a woman's fertile days and avoiding intercourse on those days. Studies of these methods have involved intensive training of participants regarding the protocol and close follow-up to ensure participants understood how to use the method correctly. The Two-Day method relies only on the detection of changes in cervical mucus. Perfect use demonstrates

TABLE 2 Contraceptive efficacy and effectiveness by method.

Method	Women experiencing an unintended pregnancy within the first year of use (%)		Women continuing use at 1 year (%)
	Typical use	*Perfect use*	
No method	85	85	
Spermicides	28	18	42
Fertility awareness methods	24		47
Standard days		5	
Two-Day		4	
Ovulation		3	
Symptothermal		0.4	
Withdrawal	22	4	46
Sponge			36
Parous women	24	20	
Nulliparous women	12	9	
Male condom	18	2	43
Diaphragm	12	6	57
Combination pill and progestin-only pill	9	0.3	67
Combination patch	9	0.3	67
Combination ring	9	0.3	67
Depot medroxyprogesterone acetate	6	0.2	56
Intrauterine device			
Copper	0.8	0.6	78
Levonorgestrel	0.2	0.2	80
Contraceptive implant	0.05	0.05	84
Female sterilization	0.5	0.5	100
Male sterilization	0.15	0.10	100

Source: Refs. 2 and 3.

a pregnancy rate of 35% after 13 cycles of use.[22,23] The symptom-thermal method combines cervical mucus changes and basal body temperature to determine fertile windows. This method performs best in clinical research, where failure rates are reported as low as 1.78% in women utilizing this method over 13 cycles.[24]

Standard calendar methods for determining fertile days are also based on menstrual cycle length. These methods were associated with a 3–5% pregnancy rate at 1 year.[22,25] Unfortunately, typical use (engaging in intercourse on one of the days identified as fertile) is as high as 29%. Therefore, periodic abstinence can be very effective when used perfectly, but very ineffective when used in the general population where motivation may be less or opportunity to educate about the method is limited.

A meta-analysis of higher quality prospective studies of women at risk for undesired pregnancy reported failure rates of 22 pregnancies per 100 women–years for fertility awareness methods.[18] In addition, the probability of pregnancy with typical use across the board (self-reported) is about 15%/year from an unpublished estimate from the 2006–2010 NSFG (which is adjusted for underreporting of abortion.[2] The NSFG has been utilized to assess typical failure rates. Clinical trials are also utilized, but these couples are highly selected and have frequent contact with investigators and study staff; thus, they may not be completely relevant to the general population.

Studies from the National Health Service in the United Kingdom showed that the time required to teach or learn varies with different methods (less than 20 min for the standard days method and 4–6 h for cervical mucous and basal body temperature measurements.[26]

4.3 | Abstinence

Abstinence can be defined in several ways, including no sexual activity or penetrative penile–vaginal intercourse.[27]

In theory, complete abstinence should result in no pregnancy. However, adherence to this method is flawed and the contraceptive failure rate was 13.9, 25.8, and 32.4% at 12, 24, and 36 months, respectively, for periodic abstinence.[28] A systemic review showed that periodic abstinence is more prevalent in young men, single status, those with low socioeconomic status, lower educational level, conservative religious practices, and lack of knowledge of sexually transmitted infections (STIs).[29]

5 | BARRIER METHODS

Recommendations

4.	We recommend the correct and consistent use of condoms, alone or with other contraceptive methods, when there is a risk of sexually transmitted infections, such as persons with sexually transmitted infections and high-risk sexual behaviors (multiple sex partners and casual sex).	1 ⊕⊕⊕⊕
5.	We recommend the correct and consistent use of condoms if there are contraindications to other contraceptive methods.	GPS
6.	We recommend using non-latex condoms in people with known allergies to latex, informing them that non-latex condoms are associated with higher rates of clinical breakage.	1 ⊕◯◯◯
7.	We recommend using condoms as backup contraception in cases of errors with other contraceptive methods (such as missed female oral contraceptives).	GPS
8.	We recommend more condom promotion programs, information campaigns, education programs, and counseling on the correct use of male condoms, especially in adolescents and young adults.	GPS

Evidence

The male condom is a reversible barrier method of male contraception, consisting of a thin sheath placed over the glans and shaft of the penis to provide a physical barrier against the deposition of semen into the vagina during intercourse. Most commercially produced condoms are made of latex. Non-latex condoms are available, generally made of polyurethane film or synthetic elastomers.

The condom is the most widely used male contraceptive method (10–20%),[4,30] although substantial differences exist worldwide. Importantly, only 1/4–1/5 of couples use condoms consistently (100% of the time).[4] Men with high educational attainment, those of Hispanic or Black origin,[2,8] and those with more opposite-sex partners are likelier to use a condom every time they have sexual intercourse.[31]

Condoms have an estimated method-specific failure rate of 2–3%, but the typical-use failure rate is estimated to be 13–14%. This difference can be attributed to improper and inconsistent use at every intercourse.[2,32]

Of all the contraceptive methods available, the male condom provides the best protection against STIs, including human immunodeficiency virus, trichomoniasis, chlamydia, and gonorrhea, as well as human papilloma virus and associated cervical diseases. Protection against human papilloma virus is partial because the virus can also be transmitted by skin contact and is found in male genital areas not covered by a condom.[33]

Sexual behaviors that increase the risk of STIs include casual sex and multiple concurrent or overlapping sex partners. Furthermore, STIs are particularly problematic for adolescents and young adults (15–24 years old), as they account for nearly half of all incidences of STIs.[34] Indeed, a recent study reported that only 50% of sexually active undergraduate students in the USA use condoms "most of the time" or "always" for vaginal sex within the last 30 days (American College Health Association: National College Health Assessment II: Undergraduate Student Reference Group Data Report, Fall 2018. Retrieved from: https://www.acha.org/documents/ncha/NCHA-II_Fall_2018_Undergraduate_Reference_Group_Executive_Summary.pdf).

Values

Condom use is the only available reversible method of male contraception that has no adverse effects and, when used consistently and correctly, can protect against both pregnancy and STIs, resulting in healthcare cost savings. Therefore, they are the method of choice, alone or in combination with other contraceptive methods, in people with STIs and/or at higher risk of STIs (multiple sex partners, casual sex). Condoms are relatively inexpensive, easy to use and can be added to other birth control methods to give additional contraceptive protection. Furthermore, condoms are useful as a backup in errors with other contraceptive methods (such as missed female oral contraceptives). Condoms do not have side effects of hormones, can be used without seeing a healthcare provider, do not require a prescription, and no examinations or tests are needed before initiating their use. Therefore, they are particularly useful for birth control and STI prevention in adolescents and young adults. Condoms are produced in different materials, sizes, and shapes to increase safety and reliability and flavors to increase pleasure. They are also available with a wide selection of lubricants on the condom to help enhance sensitivity and pleasure for both partners. Condoms may help premature ejaculation because they reduce sensitivity.

Remarks

Condoms have a high failure rate in typical use because they must be used correctly, and effectiveness depends on the skill and experience of the user and the partner. Counseling before condoms use is therefore strongly recommended, as correct and consistent use is fundamental to reducing the risk of pregnancy. Discontinuation rates for condoms are high, and use is often sporadic; many men and women do not like them because they reduce sexual spontaneity and sensitivity. Other problems include breakage, slippage, and leakage during intercourse.

Adverse effects of condoms include potential interference with the maintenance of an erection in cases of psychogenic erectile dysfunction and extremely rare allergic reactions to latex. In men allergic and sensitive to latex, non-latex condoms might be used; however, they are associated with higher rates of clinical breakage.[35]

The European standard EN ISO 4074:2015 specifies requirements and test methods for male condoms made from natural rubber latex.

Condoms may be relatively expensive in some countries. Condom promotion programs are warranted.[36]

6 | SEMEN ANALYSIS AND CONTRACEPTIVE EFFICACY

This section applies to all male contraceptive methods.

6.1 | Semen analysis

Recommendations

9.	We recommend that if semen analysis is necessary to assess the effectiveness of a male contraceptive, the laboratory should follow the WHO Laboratory Manual for the Examination and Processing of Human Semen (6th Edition). The laboratory should also participate in external quality control programs.	1 ⊕⊕⊕⊕

Evidence

The WHO laboratory manual for examining and processing human semen is regarded globally as the standard for laboratories performing semen analyses. The section for basic laboratory methods for measuring the volume of the semen, sperm concentration, motility, morphology, and vitality can be performed and standardized in any laboratory. In the 6th Edition of the *Semen Manual*, how a semen sample is handled depends on what data are required; non-centrifuged samples are used to detect motile spermatozoa, whereas centrifuged samples are generally used to detect presence of spermatozoa irrespective of motility.[37] The semen analysis following the methods recommended by the manual should yield similar results among many laboratories. The results of semen analyses for each laboratory should be

comparable across laboratories and improved and validated by internal and external quality control programs.[37–39]

6.2 | Contraceptive efficacy for non-surgical male contraception

Recommendations

10.	We recommend that contraceptive efficacy be assessed by the Kaplan–Meier Method—Time-to-event (pregnancy) outcomes analyzed by cumulative survival probabilities (95% confidence interval) using the Kaplan–Meier method.	1 ⊕⊕⊕⊕

Evidence

Contraceptive efficacy is the probability of method failure (pregnancy in the female partner).[40] Using the Kaplan–Meier method based on months of exposure will avoid using female menstrual cycles as a factor in the calculation. The Pearl Index is commonly used to calculate failure rates in all female methods.[41]

In addition, contraceptive efficacy may be calculated by the Pearl Index Method. The Pearl Index is defined as the number of contraceptive failures per 100 women years of exposure. It uses as the denominator the total evaluable cycles (where intercourse occurs, and no other or backup contraception is used) of exposure from the initiation of the product to the end of the study or the discontinuation of the product. It is calculated as follows (assuming 28-day cycles):

Pearl Index = number of pregnancies × 13 cycles × 100/number of evaluable 28-day cycles.

7 | PHYSICAL AGENTS

Recommendations

11.	We recommend **against** heat or other physical agents to decrease sperm output for male contraception because of the lack of large-scale clinical trials to demonstrate efficacy and long-term safety.	1 ⊕⊕⊕⊕

Evidence

The testis is a temperature-sensitive organ that needs to be maintained 2–3°C below core body temperature to ensure normal spermatogenesis. The scrotum serves as a location in the male body where the temperature is lower than that of the core body temperature, thus protecting the fertility capacity. Elevation of scrotal testes temperature by immersion of scrotal testes in warm water, as in a Jacuzzi, hot tub, or exposing the scrotum and testes to increased ambient temperature (e.g., saunas) by 4–6°C even for short periods (i.e., 30 min daily for 6 days), has been shown to reduce sperm counts transiently in studies.[42] Studies have been done in rodents, monkeys, and men showing that testicular immersion in carefully warmed water will increase the testicular temperature of the testes in the scrotum and markedly lower sperm counts without creating non-reversible tissue damage.[43–45] Leydig cells are quite resistant to the modest temperature increase. Because stem cells and spermatogonia are less sensitive to the heat effect, the reduction in sperm count is reversible. It has also been shown that heat-induced germ cell apoptosis will enhance the sperm count suppression produced by androgens.[45] Studies reported that pushing and keeping the testes in the inguinal canal using adapted athletic support[46] or tight-fitting underwear[47] to raise scrotal/testicular temperature caused transient but significant suppression of sperm output and prevented pregnancies in the female partner. A recent small study showed that maintaining the testes at a supra-scrotal position for 3 months increased sperm aneuploidy which was reversible.[48] It is unclear if chronic use of increased scrotal testes temperature to lower sperm counts will continue to be reversible or if such methods will create an increased risk of sperm DNA damage or aneuploidy. While heat is an interesting non-hormonal approach or could be additive to lower doses of androgen/progestins, the practical means of applying this knowledge have not been developed to a level of clinical application.

Values

Other physical devices have been considered experimental and not applicable to future clinical practice. It is well known that radiation causes significant and frequently irreversible damage to spermatogenesis and results in male infertility, but it should not be used for male contraception because of testicular and genotoxicity and causes genomic instability.[49] The safety and effects of other physical agents, such as microwave and electromagnetic, on spermatogenesis have not been carefully evaluated.

Remarks

We reserve the recommendation of heat or another physical agent approach until larger-scale studies provide better efficacy, reversibility data, and long-term safety to tissue damage and neoplasia.[2]

8 | SURGICAL METHODS

8.1 | Vasectomy

8.1.1 | Existing topics

Recommendations

12.	We recommend utilizing the existing guidelines for vasectomy from the American Urological Association (AUA); the Canadian Urological Association; the Association of Biomedical Andrologists, the British Andrology Society and the British Association of Urologic Surgeons; the European Association of Urology (EAU); and the Committee of Andrology and Sexual Medicine of the Association Française d' Urologie (AFU).	1 ⊕⊕⊕⊕

Evidence

The American Urological Association (AUA) Guideline for Vasectomy[50]; the Canadian Urological Association Vasectomy

Guideline[51]; the Association of Biomedical Andrologists, the British Andrology Society and the British Association of Urologic Surgeons[52]; the European Association of Urology (EAU)[53]; and the Committee of Andrology and Sexual Medicine of the Association Française d' Urologie (AFU)[54] have published guidelines focused on **the success of vasectomy** (see Appendix A2). When post-vasectomy semen analyses showed azoospermia or rare non-motile spermatozoa (<100,000 sperm/mL), the contraceptive effectiveness is very high comparable to female permanent contraception.[50]

8.1.2 | New topics

The following are "new topics" for consideration since the review of the AUA Guidelines and other guidelines.

Is post-vasectomy azoospermia or rare non-motile sperm required for efficacious male contraception?

Recommendations

13.	We suggest that the threshold for efficacious male contraception may be reconsidered due to the low contraceptive failure rate with sperm counts that are slightly higher (<250,000 sperm/mL) than the current recommendation of azoospermia or <100,000 non-motile sperm/mL.	2 ⊕⊕⊕◯

Evidence

Studies on the risk of pregnancy after vasectomy using thresholds >100,000 motile sperm/mL are not available. A recent report on measuring sperm concentration in over 9000 post-vasectomy semen analyses indicated that using the World Health Organization Laboratory Manual for the Examination and Processing of Human Semen[37] was sufficiently robust to confirm the success of vasectomy and efforts to detect occasional motile spermatozoa were futile.[55] Another study questioned the requirement of assessing sperm motility in post-vasectomy semen analyses in over 6000 first post-vasectomy semen samples ordered by a urologist, given the low likelihood of finding motile spermatozoa at very low sperm concentrations (when sperm concentration was <1 million or <250,000 or <100,000 sperm/mL, only 0.5% and 0.3% for both <250,000 and <100,000 sperm/mL of samples had motile spermatozoa).[56] Estimating sperm concentration to ≤100,000 sperm/mL without motility assessment is likely to be sufficient to classify the success/failure of vasectomy. More data are necessary to clarify this concept.

Is home/mail testing a viable option for post-vasectomy semen analysis?

Recommendations

14.	We suggest a sample collected at home may be mailed to a laboratory (preferably by courier service) to confirm vasectomy success. Success can **only** be granted if absolutely no spermatozoa are seen in the semen sample evaluated. This sample should be examined within 7 days of collection.	2 ⊕⊕◯◯

Although no data exist, the AUA Guidelines[50] suggest the following as "expert opinion": "Some clinicians recommend, for convenience and compliance reasons, that post-vasectomy semen analyses specimens can be sent by mail (following regulations regarding shipping biohazards). This approach is adequate to assess only the presence or absence of sperm. Motility cannot be evaluated reliably in a semen sample produced more than two hours before microscopic examination."

15.	We recommend that at-home tests, which measure sperm concentration only, must be confirmed with a semen analysis by a laboratory to assess sperm motility until more data become available.	1 ⊕⊕◯◯

Evidence

Any mail-in test result that shows any spermatozoa should NOT be used for clearance of vasectomy success but should be repeated in a laboratory and checked within 2 h of production.[57]

Currently, no at-home test has evidence-based data showing azoospermia or ≤100,000 non-motile spermatozoa.[52] Only one home test can evaluate for motility. There are home tests that evaluate ≤250,000 sperm/mL but do not measure motility.[58] Using the at-home test may be adequate for male hormonal contraception (MHC) where spermatogenesis is severely suppressed, and low motility is associated with low sperm concentration. However, it may not be adequate for post-vasectomy as spermatogenesis is normal in vasectomized men.[58] Home testing that reports ≤250,000 sperm/mL[58] should be followed by a formal uncentrifuged fresh specimen evaluation. Therefore, clearance cannot be offered with the home sperm testing kits currently available in some countries, but many new methods of at-home sperm testing are being developed.

What is the best option for man compliance for post-vasectomy semen analysis?

Recommendations

16.	We recommend a scheduled date (in-person or video visit) to bring in or review semen analysis results since compliance appears to be higher.	1 ⊕⊕◯◯
17.	We suggest that compliance may be slightly better with home or mail-in testing. However, see published guidelines for recommendations on the efficacy of these tests before utilizing them for post-vasectomy semen analysis.	2 ⊕◯◯◯

Evidence

Recent studies by Trussler et al.[58] suggest no statistically significant difference in compliance with an office-based test versus a home-based test. Bradshaw et al.[59] reported that the compliance rate with the performance of post-vasectomy semen analyses in 533 men was 53%. The primary barriers to semen analysis completion were distance (38%), time constraints (34%), and forgetfulness (23%).[59] However, 92% reported an increased likelihood of completion with home-based semen testing. In 58,900 post-vasectomy semen analyses in the UK from 2008 to 2019, the compliance rates were significantly higher with postal-sent specimens (80%) versus non-postal specimens (59%).[57] Despite written and verbal reminders, 946 consecutive men

underwent a vasectomy. The compliance rate with one semen analysis was only 48%.[60]

There are mixed data regarding compliance based on a scheduled post-op visit versus man self-follow-up. Belker et al.[61] evaluated 1029 consecutive men and noted that only 64% returned for post-vasectomy semen analyses. There was a statistically significant improvement in compliance when the office made a follow-up appointment (81%) versus the men just following-up (61%).[61] Jacobsen et al.[62] evaluated post-vasectomy semen analyses' impact on compliance with scheduled follow-up versus a "drop-in" option and showed no statistically significant difference in compliance, whereas Dhar et al.[63] demonstrated a statistically significant higher rate of compliance with the scheduled group (84%) versus the no appointment group (65%).

Telehealth role in vasectomy counseling

Recommendations

18.	We suggest that it is reasonable to perform an initial visit for vasectomy via telehealth, but a physical exam on both sides should be done on the day of vasectomy before initiating the procedure.	2 ⊕⊕◯◯

Evidence

A clinical study showed no difference between telehealth versus an in-office pre-vasectomy consultation on the completion rate of in-office vasectomy, suggesting that telehealth can improve access to male contraception procedures.[64] Men also preferred a telephone over an in-person consultation if given a choice.[65] Following urological guidelines, a physical examination is recommended to examine the presence of vas on both sides on the day of vasectomy if the man did not have a pre-vasectomy in-office visit with an examination.

Childless person counseling and regret

Recommendations

19.	We suggest that vasectomy is a reasonable option for men who are childless and those with children where there is no desire for children in the future and are counseled on the risks of regret.	2 ⊕⊕◯◯

Evidence

The incidence of regret for childless men undergoing vasectomy, while higher than that with men with children, is still quite low (7%).[66,67] Counseling alleviates regret after vasectomy.[68]

Post-vasectomy pain management

Recommendations

20.	We suggest that post-vasectomy pain control should be managed with non-opioid medication unless complications arise. Clinicians should weigh the need for pain control versus the potential abuse of opioids in their decision-making process for post-operative pain control.	2 ⊕⊕◯◯

Evidence

Men who are not prescribed opioids after vasectomy do not generate additional phone calls, clinic, or emergency department visits compared with those that were routinely prescribed opioids.[69] Baker et al.[70] that in 76 men who were given non-steroidal anti-inflammatories (NSAIDs) and narcotics, 88% had good pain control. Nam et al.[71] evaluated 4900 men via an insurance database, and men were incentivized to lower costs if they did not use narcotic medications. In this study, 32% of men required opioids, and 12.6% did not.[71]

Data suggest that men undergoing minor urologic surgery are associated with an increased risk of new persistent opioid use. Welk et al.[72] reviewed a database of 91,000 men (78% of these were vasectomy men) and found that there was an increased risk (odds ratio 1.4) for persistent opioid use if an opioid prescription was filled and an odds ratio of 3.0 for risk of opioid overdose. Barham et al.[73] evaluated 229 men and noted a persistent opioid use of 7.8 versus 1.5% in men who utilized opioids versus non-opioids for vasectomy. No difference in scrotal pain was noted.

8.2 | Vas occlusion

Recommendations

21.	We recommend **against**, at present, any non-FDA/EMA-approved new intravasal vas occlusion method. Novel vas occlusion reversible methods are **not** yet approved and will be regulated as an Investigational Device Exemption (IDE) at the US FDA. An investigational device exemption will allow the investigational device to be used in a first clinical study.	1 ⊕⊕⊕⊕

Evidence

Initial studies in rats, rabbits, and monkeys showed that injection of styrene maleic anhydride (SMA) in dimethyl sulfoxide (DMSO) into the lumen of vas forming non-adherent polymer was safe and blocked sperm transport through the vas. This procedure was named Reversible Inhibition of Sperm Under Guidance.[74] As the polymer was

not adherent, it could be removed from the vas or flushed with DMSO or sodium bicarbonate.[75] A phase I study in men showed that injection of ≥70 mg of SMA resulted in azoospermia 34–80 days after the procedure.[67] A small phase II study in 12 men showed azoospermia after intravasal injection of SMA. Azoospermia persisted for 12 months and prevented pregnancy in their partners.[66] A subsequent limited phase III study of 139 men showed that the Reversible Inhibition of Sperm Under Guidance procedure produced persistent azoospermia in 82.7% of men. Adverse events of the procedure included scrotal swelling and pain, and failure rate occurred in about 4% of men.[68]

Similar studies were also performed using percutaneous injections of polyurethane elastomer or silicone plugs and demonstrated an azoospermia rate similar to vasectomy.[76–78] This cured-in-place plug may be removed by minimally invasive surgery to reverse the occlusion.[78] While others showed that compared with minimally invasive vasectomy, vas occlusion was markedly less efficient in inducing azoospermia though there were less pain and swelling.[79] Other studies implanted an intravasal device and compared results with no-scalpel vasectomy and showed no differences in contraceptive efficacy, and the complication rates were low.[80,81]

Remarks

At the current time, the development of intravasal hydrogel products to produce long-acting, non-hormonal contraceptive hydrogel for men has been supported by the Parsemus Foundation (https://www.parsemus.org/humanhealth/male-contraceptive-research/vasalgel-male-contraceptive/) and Male Contraceptive Initiative (https://www.malecontraceptive.org). Vasalgel™ is developed based on studies using styrene-alt-maleic acid dissolved in DMSO. It is a polymer that forms a hydrogel when implanted into the vas deferens, preventing the passage of spermatozoa. In rabbits, after Vasalgel™ injection in the vas, there was a decrease in sperm motility and loss of acrosome reaction. The effects were reversed with an intravasal injection of sodium bicarbonate,[82] The clinical studies are being planned, but clinical trial data in humans are lacking. ADAM™, developed by Contraline, is another hydrogel that can be injected into the vas, forming a barrier to block spermatozoa from traveling through the vas. The hydrogel will liquefy at the end of its life, and the vas will become patent again. Phase I short-term studies of ADAM™ are being performed in Australia, with early favorable data reported in a few men (https://www.medpagetoday.com/meetingcoverage/aua/104327?xid=nl_mpt_confroundup_2023-05-05&eun=g20985350d41r).
Recently a hydrogel (composed of sodium alginate with thioketal, titanium dioxide, and calcium chloride) when injected into the vas deferens solidified into a hydrogel inhibiting transit of spermatozoa through the vas. When fertility is desired, a non-invasive ultrasound induced titanium oxide to generate reactive oxygen species that can break down the hydrogel.[83]

Values

These new vas occlusion methods must demonstrate safety, tolerability, success of occlusion by measuring spermatozoa in the ejaculate, and reversibility in randomized-controlled, multicenter clinical trials in men.

Regulatory aspects for vas occlusive methods for male contraception

Vasectomy is a surgical procedure not regulated by government agencies, but the provider must follow the recommendations from published guidelines on vasectomy.

Recommendations

22.	Guidelines (USA, Canada, UK, Europe) for vasectomy are published. Vasectomy is intended to be a permanent form of contraception. There are no absolute contraindications for vasectomy except under the legal age of consent.	1 ⊕⊕⊕⊕
23.	For experimental new post-vas occlusion methods, we recommend, in a first study, documenting a decrease in sperm count for at least 1 year with regular sperm count monitoring to maintain persistent azoospermia or ≤100,000 motile sperm/mL to demonstrate success of vas occlusion and at least 200 couples to complete 1-year study to document efficacy on pregnancy rate.	1 ⊕⊕⊕⊕
24.	For experimental new vas occlusion methods, we recommend, for safety assessment, recording adverse events information for at least 300 men for a 1-year device and 100 men followed for 3 years. Procedure and device adverse events are to be recorded during vas insertion of the hydrogel (or other reversible options) and reversal procedure. Recovery time, post-procedural swelling, and discomfort should be recorded for man information.	1 ⊕⊕⊕⊕
25.	We suggest assessing the efficacy of a vas occlusive method as the percentage of subjects achieving absolute azoospermia and the percentage of subjects achieving virtual azoospermia, defined as a sperm count of ≤100,000 non-motile sperm per mL. The azoospermia should be maintained for 1–3 years according to the duration anticipated for approval.	2 ⊕⊕○○

Evidence

There are no specific regulations for surgical procedures. However, regulation of surgical procedures seems morally acceptable and able to provide reliable scientific evidence, but also desirable and justified from an ethical-political standpoint.[84] Guidance documents from the urological societies are to be followed by surgeons and training providers who will perform vas occlusion procedures.[50,51,53] The novel methods of vas occlusion aim to allow easier access to this form of permanent contraception for men but also allow a possible reversal on demand. If fulfilled, this objective would permit trained health providers, not necessarily surgeons, to perform the procedures. The success of the vas occlusion should follow the vasectomy success criteria of ≤100,000 motile sperm/mL. To claim the method for pregnancy prevention, the efficacy of the new vas occlusion method by injecting new material into the vas should follow current female contraceptive product guidelines and document efficacy in 200 couples completing 1-year study for a short-acting method and longer for a method designed to be efficacious for a few years

(https://www.fda.gov/regulatory-information/search-fda-guidance-documents/establishing-effectiveness-and-safety-hormonal-drug-products-intended-prevent-pregnancy-guidance).

As far as safety requirements are concerned, the International Council on Harmonization established guidance is to record safety information for 1500 men exposure in total, including at least 300 men for 6 months of exposure and at least 100 men for 1-year exposure for any new chemical entity or new product (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e1a-extent-population-exposure-assess-clinical-safety-drugs-intended-long-term-treatment-non-life). From a regulatory perspective, the clinical evaluation of devices that have not been cleared for marketing requires an investigational plan approved by an institutional review board. If the study involves a significant risk device, the IDE must also be approved by the United States Food and Drug Administration (US FDA); informed consent from all men; labeling stating that the device is for investigational use only; monitoring of the study; and required records and reports (https://www.fda.gov/medical-devices/premarket-submissions-selecting-and-preparing-correct-submission/investigational-device-exemption-ide; https://www.clinicaltrials.gov/ct2/show/NCT05134428).

Remarks

The components and degradation products of the new hydrogels tested for vas occlusion should only use Good Manufacture Practice material and (https://www.fda.gov/media/85865/download) should be tested for toxicity before requesting a clinical trial authorization (and IDE). The novel vas occlusive techniques of injecting a polymer percutaneously target a faster recovery time with less post-procedural swelling and discomfort than traditional vasectomy (https://www.pharmtech.com/view/the-next-generation-of-male-contraceptives). This claim should be assessed post-procedure, and general safety over the following years should be documented.

9 | ACTIONS BEFORE INITIATING MALE CONTRACEPTIVE METHODS

These guidelines primarily address clinical practice in various provider settings when new male contraception products are approved for general clinical application. Since there is currently no approved reversible male contraceptive product, our views are based only on the experience and conditions of clinical trials using hormonal contraceptives regimes, including testosterone alone or a combination of testosterone or equivalent androgenic compound with a progestin administered as injectable, transdermal, oral, or implantable formulations.

9.1 | Counseling and information

Counseling and information can be offered via face-to-face interviews or telemedicine. Men should be given accurate information about all methods of contraception for which they (and their partners) are medically eligible and helped to decide which might best suit their needs. They should be informed that clinical experience with new reversible male contraception is limited to clinical trials only, but this will continue to expand as more results accrue from current and future studies. Health professionals who advise about contraception should be competent to give information about the efficacy, risks and side effects, advantages and disadvantages, and non-contraceptive benefits of all available methods.

9.2 | Indications

Recommendations

26.	We recommend against using **non-reversible** male contraception methods in men who desire fertility in the future.	GPS
27.	We recommend **against** using new male contraception methods in men <18 and >50 years of age.	1 ⊕⊕⊕◯
28.	We recommend **against** male hormonal contraception methods in men with prostate cancer (locally advanced or metastatic), breast cancer (untreated and treated) and other active cancer (metastatic, on therapy, or within 6 months after clinical remission), excluding non-melanoma skin cancer.	1 ⊕⊕⊕◯
29.	We suggest that male hormonal contraception methods should be used with **caution** in men with severe heart failure, recent major acute cardiovascular events (including stroke), severe and uncontrolled hypertension, polycythemia, renal failure, uncontrolled diabetes, or serious liver disease.	2 ⊕◯◯◯

Evidence

Clinical experience with male contraception methods is currently limited to six phase II clinical efficacy trials (where the failure rate is defined by pregnancy in the female partner) in healthy male volunteers (n = 2356) 18–50 years of age with the longest individual exposure up to 30 months.[8,85,86] Therefore, these guidelines can only apply to healthy men 18–50 years of age receiving MHC methods in the short term. As the administration of exogenous testosterone or equivalent androgenic compounds forms an obligatory part of MHC (Section 10; *Hormonal Methods*), it is appropriate, in general, to follow the latest guidelines on testosterone replacement therapy for male hypogonadism.[87–91] Some regulatory warnings highlighted the potential risks of heart attack and stroke, and venous blood clots associated with the clinical use of testosterone products (https://www.fda.gov/media/91048/download, http://www.safetyalertregistry.com/alerts/2558). However, recent data from the TRAVERSE trial showed no increase in the incidence of major adverse cardiac events in 45–80-year-old hypogonadal men with pre-existing or a high risk of cardiovascular disease treated by testosterone gel for 21.7 ± 14.1 months and followed-up for 33.0 ± 12.1 months.[92] We recognize no substantive safety data on using progestins in men outside these

clinical trials. It is inappropriate to extrapolate safety or eligibility considerations from female hormonal contraception since estrogens are not being administered, and estradiol concentrations are not elevated in MHC or other non-hormonal methods. As more clinical trial data from future Phase III studies and new licensed male contraception products become available for general use, these guidelines will likely be modified incrementally.

Remarks

In general, prescribing MHC methods should follow the clinical guidelines for testosterone replacement therapy to treat hypogonadism.[87–91]

9.3 | History

Recommendations

30.	We suggest performing a complete personal and family history to identify specific conditions that may increase the risks for adverse effects associated with testosterone supplementation as part of male hormonal contraception.	GPS

Remarks

Some anamnestic elements are useful as a baseline for the possible appearance of adverse effects and their evolution during the use of male contraception methods. It is rare that medical history (and physical examination, see below) will lead to diagnostic investigations before initiating male contraception (Table 3).

TABLE 3 History items.

Personal health history • Chronic diseases • Oncological diseases • Thrombophilic diseases[a] • Medications[b]
Andrological history • Low sperm counts/infertility • Undescended testes • Chemotherapy or radiotherapy • Testicular/pelvic/inguinal surgery
Family health history • Prostate cancer (first-degree relatives) • Thrombophilic diseases[a] (first-degree relative age <45 years) • Hyperlipidemia
Lifestyle • Smoking (cigarettes/other) • Medications[b] alcohol and substance abuse • Sexual dysfunction • Behavioral disorders (mood dysphoria, depression, major psychiatric disorders) • Gender identity

[a]Classic thrombophilia mutations associated with—antithrombin deficiency, protein C deficiency, protein S deficiency, resistance to activated protein C due to Factor V Leiden (rs6025), prothrombin mutations (prothrombin G20210A, rs1799963), and systemic lupus erythematosus (SLE) with positive antiphospholipid antibodies.[93.]

[b]Medications that reduce the effectiveness of male hormonal contraceptives (androgenic and progestogenic steroids)—barbiturates, carbamazepine, oxcarbazepine, phenytoin, primidone, topiramate, rifampicin, or rifabutin. HIV antiviral ritonavir-boosted protease inhibitors and St John's Wort. Male hormonal contraceptives can decrease the effectiveness of lamotrigine.

9.4 | Physical examination

Recommendations

31.	We suggest that a general physical examination and an andrological examination are **not** required in healthy men (age <50 years) unless indicated by history before initiating male contraception methods.	2 ⊕◯◯◯
32.	We recommend that baseline weight and body mass index (BMI: weight [kg]/height [m]^2) should be recorded, and blood pressure measurement should be performed before prescribing male hormonal contraception methods.	1 ⊕⊕⊕◯

Evidence

Current recommendations for female contraception agree that a pelvic examination is unnecessary before initiating or prescribing contraception, except for an IUD.[15,94] Analogously, we believe that general physical and andrological examinations are not routinely required in healthy men <50 years of age who are candidates for male contraception methods.

Obesity (BMI < 35 kg/m^2, WHO grade 1) is not a contraindication to commencing male contraception methods. However, body weight has been reported to increase with MHC.[95] Therefore, having a baseline weight measurement might help monitor any changes in case weight management advice is appropriate in men concerned about weight change perceived to be associated with their contraceptive method. More severe obesity (BMI > 35 kg/m^2, WHO grade 2 and 3) is associated with increased risks of thromboembolic disease, hypertension, and cardiovascular diseases,[96] which may be exacerbated by some androgen–progestin regimens.

Men with more severe hypertension who use hormonal methods of contraception may potentially have an increased risk for cardiovascular events. A small increase in blood pressure of uncertain clinical significance has been reported in healthy men participating in trials of hormonal male contraceptive trials[40,95] and some new oral[97,98] and injectable[99] testosterone preparations.

Values

These recommendations reflect our wish to avoid the potential harms of unwarranted examinations/tests associated with anxiety, false-positive findings, overdiagnosis, and unnecessary/costly treatment.[100] Andrological examinations should be performed only when indicated by medical history or symptoms. Our recommendation also reflects the imperative to avoid escalating potential barriers to accessing male contraception compared with female

methods. This could be considered a bias against choosing a male contraceptive.

9.5 | Investigations

Recommendations

33.	We suggest that semen analyses are **not** routinely required before initiating male hormonal contraception based upon the demonstration of reversibility in 99% of all men in clinical efficacy trials.	GPS
34.	We recommend that hemoglobin and hematocrit testing are required if androgens are used since exogenous androgens may stimulate erythropoiesis; testosterone may be used **with caution** if hematocrit is higher than the upper reference value of the laboratory, depending on local altitude and associated comorbidities and cardiovascular risks.	1 ⊕⊕⊕⊕
35.	We recommend that prostate-specific antigen is **not** required for prospective users of male hormonal contraceptives <50 years of age (<40 years in individuals at high risk for prostate cancer, such as African Americans or men with first-degree relatives who have prostate cancer).	1 ⊕⊕⊕○
36.	We suggest that men with known pre-existing medical problems or other special conditions might need additional examinations or tests before being determined to be appropriate candidates for male contraception methods.	GPS

Evidence

Male contraception should be available to all interested men regardless of their semen parameters. A retrospective analysis of individual participant data integrating all then-available studies demonstrated that it is realistic to expect full recovery of spermatogenesis to levels consistent with normal male fertility (20 M/mL) for all men (with normal baseline semen analysis), ceasing hormonal male contraceptive regimens after exposure for up to a maximum of 30 months.[101] The median recovery time was 3.4 (95% CI 3.2–3.5) months with a highly predictable trajectory of recovery of spermatogenesis (to concentrations of 20 M/mL): 67, 90, and 100% of all men expected to recover by 6, 12, and 24 months, respectively—the rate of recovery being dependent upon treatment duration.[102] We accept that a small number of men requesting contraception may have abnormal semen parameters. However, there is evidence to suggest that recovery to the baseline (oligozoospermic) range, similar to the normospermic men, can be expected after (34 weeks) of exposure to male hormonal contraceptives.[103]

Hemoglobin (Hgb) or hematocrit (Hct) is required if androgens are part of the male contraceptive method since exogenous androgens may stimulate erythropoiesis.[104] Moreover, clinical trials of male hormonal contraceptives have excluded men with abnormal baseline Hgb/Hct. When male hormonal contraceptives contain physiologic doses of androgen combined with progestin, clinically significant increases in erythropoiesis, including erythrocytosis (Hct higher than the upper reference value of the laboratory), have not been observed.[40,105,106] Exogenous testosterone administered in physiologic doses to healthy men does not increase Hgb/Hct[97] but may do so in men with concurrent diseases such as obstructive sleep apnea, hypoxic lung diseases or obesity/diabetes.[104]

The pros and cons of PSA measurement before and during androgen treatment are discussed comprehensively in many guidelines.[87–91] Clinical trials of male hormonal contraceptives have excluded men ≥50 years of age and those with abnormal baseline PSA. However, PSA measurement and digital rectal examination should be considered in men ≥40 years of age who are at increased risk for high-grade cancers, such as African Americans and men with a first-degree male relative with diagnosed prostate cancer.

Values

Semen analysis before initiating male contraception methods may add an unacceptable burden to users and providers with no clear benefits. Given the natural fluctuation in sperm counts, we risk needing more than one analysis to confirm normality. It could potentially be a deterrent to the acceptability of male contraception methods. We put a value on simplifying the general application of male contraception methods by dispensing with a detailed fertility workup of the potential contraceptive user, as would be required if those with subnormal semen parameters were to be excluded. It is also unclear what degree of subnormality should exclude the use of male contraception methods. Even if male contraception methods may be prescribed to a few azoospermic men, there is no justification to do it routinely.

10 | HORMONAL METHODS

Male hormonal contraception clinical trial phases

- "Suppression phase" is the period where men are using the hormonal product to reduce sperm concentration to a level that would allow entry into the efficacy phase of a clinical trial. During this phase, the couple must use another form of contraception to prevent pregnancy.
- "Efficacy phase" is the period when the couples are using the new treatment as the only method of contraception.
- "Recovery phase" is the period when men have stopped using the new treatment and the couples have resumed another method of contraception (unless pregnancy is desired). In this phase, men are monitored for recovery of sperm concentrations as a surrogate marker of fertility (and pregnancy events are counted).

Mechanism of action

MHC is based on the use of exogenously administered androgen (alone or together with another gonadotropin inhibiting agent, usually a progestin or a gonadotropin-releasing hormone (GnRH)-antagonist), to suppress secretion or action of GnRH and the pituitary production of both gonadotropins, luteinizing hormone (LH) and follicle-stimulating

hormone (FSH). The suppression of LH reduces the intratesticular production of testosterone. Testosterone is required for maintaining the blood–testis barrier, completion of meiosis, Sertoli cell-spermatid adhesion, and spermiation.[107] Concurrent suppression of FSH collaborates with deprivation of intratesticular testosterone to induce marked suppression of spermatogenesis and sperm production without affecting the spermatogonial stem cells.[108] The expected efficacy of hormonal contraception is demonstrated by the suppression of sperm concentration to very low levels (currently defined as ≤1 million/mL of ejaculate) by the recommendations at the 10th Summit meeting on MHC.[109] It should be noted that this recommendation differed from the recommendation for the success of vasectomy (azoospermia or <100,000 motile sperm/mL). In hormonal-based male contraception, severe suppression of spermatogenesis occurs and is generally associated with marked suppression of sperm motility and decreased normal sperm morphology.[110,111] Thus, motility assessment is not necessary for MHC, unlike vasectomy, where there is no suppression of spermatogenesis.

Because of the marked suppression of endogenous testosterone levels produced by the testis resulting from MHC, these methods require the concomitant use of an androgen administered exogenously to support the testosterone-dependent reproductive and nonreproductive function in the male, including sexual function and male sexual characteristics. The administered androgen maintains serum testosterone in the adult male range without interfering with the suppressed low intratesticular testosterone. Withdrawal of the exogenously administered hormones leads to a rapid return of LH, FSH, and testosterone and spermatogenesis is reinitiated. MHC is a reversible method of male contraception.[101]

Recommendations

Phase I studies assessing pharmacokinetics, phase II dose-finding, and phase III studies of 1-year duration will be required to confirm safety and efficacy. Specific pre-clinical requirements for each formulation would relate to the type of delivery and duration foreseen for the method.

37.	We recommend that male hormonal contraception (when approved by regulatory agencies) should be considered for couples desiring reversible family planning.	1 ⊕⊕⊕◯
38.	We recommend that sperm concentration and total sperm count in the ejaculate be used as surrogate markers of spermatogenesis suppression in the context of male hormonal contraception.	1 ⊕⊕⊕⊕
39.	We recommend that when sperm concentration is suppressed to ≤1 million/mL consistently, the couple can use male hormonal contraception to prevent pregnancy.	1 ⊕⊕⊕⊕
40.	We suggest that androgens (injections and implants, when approved for contraception) may be used as a single-agent hormonal contraceptive in men highly responsive to androgens alone.	2 ⊕⊕⊕◯
41.	We suggest that androgen and progestin combinations (when approved by relevant regulatory agencies) could be used for contraception.	2 ⊕⊕⊕◯
42.	We recommend **against** a combination of androgens with GnRH antagonists for hormonal male contraception.	1 ⊕⊕⊕◯
43.	We recommend that initial clinical trials of a new product's efficacy be based on surrogate markers: Suppression of LH and FSH in a 4-week study and suppression of spermatogenesis (sperm concentration ≤1 million/mL) in a 6-month study.	1 ⊕⊕⊕⊕
44.	We recommend for comprehensive safety assessment to follow ICH (International Council of Harmonization) guidance: To record safety information (adverse events, blood pressure, laboratory findings) for 1500 men exposed in total, including at least 300 men for 6 months exposure and at least 100 men for 1-year exposure.	1 ⊕⊕⊕⊕
45.	We recommend that contraceptive efficacy trials should require that suppression of sperm concentration to ≤1 million/mL be reached before allowing the method to be tested for contraception efficacy.	1 ⊕⊕⊕⊕
46.	We recommend demonstrating contraceptive efficacy based on the failure rate (pregnancies in the female partner) observed over 1 year, using the Kaplan–Meier statistical approach to estimate the 1-year cumulative pregnancy probability and 95% confidence interval.	1 ⊕⊕⊕⊕
47.	We recommend the assessment of the return of sperm concentration to the adult reference range in all men in phase IIb and III studies over 6 months. The time to recovery depends on the duration of action and/or product formulation.	1 ⊕⊕⊕⊕

(Continues)

10.1 | Use of androgens alone

Evidence

Based on studies in the 1970s showing that weekly testosterone enanthate intramuscular injections effectively suppressed sperm concentrations to a very low level,[112] in the 1990s, the World Health Organization (WHO) conducted two pivotal clinical trials where a dose of testosterone enanthate 200 mg weekly was administered to healthy men for 18 months (Table 4). The first trial demonstrated that when sperm concentration was suppressed to azoospermia in 70% of 225 men, the Pearl Index was 0.8 per 100 person-years (95% CI 0.02—4.5) (referred to as the "WHO Azoospermia trial").[113] In the second study, when men were suppressed to azoospermia or severe oligozoospermia (arbitrarily defined as ≤3 million/mL) in 98% of 357 men, the overall contraceptive failure rate (Pearl Index) was 1.4 per 100 person-years (95% CI 0.4—3.7), but the Pearl Index was 0.0 (95% CI 0.0—1.6) for the azoospermic group and 8.1 (95% CI 2.2—20.7) for the oligozoospermic group respectively (referred to as the "WHO Oligozoospermia

TABLE 4 Male hormonal contraception: androgens only.

Androgens	
Oral	Testosterone undecanoate
Transdermal gel, patch, and cream	Testosterone
Injections	Testosterone enanthate[a]
Implants	Testosterone undecanoate[a]
	Testosterone[a]
	7α-methyl-19-nortestosterone acetate (MENT)
Androgens with progestin activity	
Oral and Injections	7α, 11β-Dimethyl-19-nor testosterone (dimethandrolone, DMA) and DMA undecanoate (DMAU)
	11β-Methyl-19-nor-testosterone (11β-MNT) and 11β-MNT dodecylcarbonate (11β-MNTDC)

[a]Agents tested in contraceptive efficacy clinical trials.

Trial").[113] These studies involving >700 couples conclusively showed that when sperm output is markedly reduced to very low concentrations, the contraceptive efficacy of weekly testosterone enanthate injections was comparable to female hormonal methods. Subsequently, a phase II clinical trial,[114] as well as a phase III clinical trial, confirmed that utilization of monthly testosterone undecanoate (TU) injections for 30 months in over 1000 Chinese couples provided very high contraceptive efficacy (Pearl Index of 1.1).[115] In another study, testosterone implants in a clinical trial of 36 couples showed no pregnancy in female partners [10]. In these trials, rebound of sperm concentrations after spermatogenesis suppression during testosterone administration alone was uncommon, occurring from 0.2 to 2.3% of men.[115,116]

The testosterone injection dosage in most of these clinical trials was higher than that used for hormone replacement in men with testosterone deficiency. In the WHO Oligozoospermia Study, adverse events included injection site pain (7.5%) and the known effects of testosterone, including acne (25%) and weight gain (4.4%), with 4.4% of men reporting changes in sexual function or mood. Five percent of men discontinued because of adverse events.[117] After stopping the male hormonal contraceptive agents, the typical probability of recovery of sperm concentration to 20 million/mL was 67, 90, and 90% within 6, 12, and 16 months.[101] It is anticipated that all men will recover when followed for more than 12 months.

Orally administered contraceptives are desired by many men.[118,119] Derivatives of 19-nor-testosterone are in development as potential male oral hormonal contraceptives. Two such agents, 7α, 11β-dimethyl-19-nortestosterone undecanoate (DMAU)[120] and 11β-methyl-19-nortestosterone dodecylcarbonate (11β-MNTDC),[121] have been shown to suppress gonadotropin and testosterone production in healthy male volunteers when administered once daily with food. These steroids bind both the androgen and progesterone receptors, suppressing gonadotropin and testosterone production.[122,123] Concurrently, because they are potent androgens, study participants did not experience symptoms of hypogonadism during short-term clinical trials. Moreover, in contrast to early studies of oral methyltestosterone, there was no evidence of liver dysfunction with these oral-modified androgens.[120,121] Longer studies are required to demonstrate suppression of spermatogenesis with these oral "progestogenic androgens."

Values

When administered alone, other testosterone formulations, including oral TU, transdermal testosterone gel, patch, or cream, have not been shown to suppress spermatogenesis to very low levels in most men. This is likely related to the lower testosterone concentration achieved with these oral or topical preparations compared with intramuscular administration.[110] The modified androgen MENT (7α-methyl-19-nortestosterone) developed as an implant showed initial promise, but technology improvement is needed to reduce the number of implants required to deliver the effective dose.[124]

In studying male hormonal contraceptive methods, sperm concentration has been used as the biomarker for pregnancy prevention in the female partner. In the WHO Oligozoospermia Study, pregnancy rates were related to sperm concentration, with no pregnancy when men were azoospermic and four when sperm concentration was between 0.1 and 3 million/mL.[116] These data led to recommendations that the couple should use MHC as the sole method of contraception when sperm concentration reached ≤1 million/mL.[109] All clinical trials on or after 2007 utilized this threshold as entry criteria for the efficacy phase.

In the WHO azoospermia study, 91% of men in Chinese centers attained azoospermia, compared with 60% in other centers. In the WHO oligozoospermia study, 85.7% of men in Asian centers achieved azoospermia compared with 67.8% of men in other centers. The proportion of men with suppression of sperm concentration <3 and 1 million/mL (oligozoospermia) in these two studies was 97 and 91%, respectively, and not different between the centers. This observation led to studies that added another gonadotropin-suppressing agent to testosterone alone to more fully suppress spermatogenesis.[116]

Remarks

Acceptability was assessed in some of these clinical trials using structured questionnaires, focus group discussions, and in-depth interviews that included men and their partners enrolled in the trials, potential users, the investigator and the team, and policymakers. In the TU monthly injections phase III clinical trial in China completed over 15 years ago, men found the method acceptable and reported no change or improvement in their well-being. Their female partner supported the male using a contraceptive method. The frequency of the injections and monthly semen analyses were reported as inconveniences of the trial.[125]

10.2 | Use of androgens in combination with progestins

Evidence

The rationale for combining androgens with progestins to suppress fertility in men is based on the known additive and/or synergistic

TABLE 5 Male hormonal contraception: Androgens plus progestins. Combinations tested in clinical trials.

Androgens	Progestins
Testosterone patch	Levonorgestrel oral Levonorgestrel implants
	Desogestrel oral
Testosterone implants	Depot medroxyprogesterone acetate[a]
	Desogestrel oral
Testosterone gel	Medroxyprogesteorne acetate[a]
	Nestorone® gel (segesterone acetate)[a]
Testosterone enanthate injection	Depot medroxyprogesterone acetate[a]
	Levonorgestrel oral
	Levonorgestrel implants
	Cyproterone acetate oral
Testosterone decanoate injection	Desogestrel oral
Testosterone undecanoate injection	Desogestrel oral
	Cyproterone acetate oral[126]
	Norethisterone acetate oral[111]
	Etonogestrel implants
	Norethisterone enanthate injections[a]
MENT implants	Levonorgestrel implants

[a]Agents tested in contraceptive efficacy clinical trials.
MENT, 7α-methyl-19-nortestosterone.

effects of progestins on the suppression of gonadotropins and, thus, spermatogenesis.[127–129] Progestins are gonadotropin suppressors and, when added to androgens, improve the rate and extent of spermatogenesis suppression, at the same time allowing for the use of lower, more physiological, and potentially safer doses of androgen. Progestins may also have a direct inhibitory effect on the testis.[130]

Different progestins have been tested in combination with short-acting, long-acting oral pills, transdermal patches, and gel formulations of testosterone (Table 5). These studies have confirmed an enhancing effect of adding progestin to androgens resulting in a more rapid and profound spermatogenesis suppression.[101] While the use of oral testosterone formulations in combination with different progestins resulted in inadequate sperm suppression, the use of injectable testosterone esters and implants with oral, injectable, or implantable progestins led to azoospermia or severe oligozoospermia (≤1 million/mL) in over 90% of the men.

A few of these testosterone–progestin combinations have been further tested in efficacy trials. In one clinical trial, subcutaneous testosterone implants in combination with depot medroxyprogesterone acetate (DMPA) injections suppressed spermatogenesis in 53 out of 54 azoospermia and in the remaining man to <1 million sperm/mL and no pregnancies occurred in the female partners after an exposure of 35.5 person-years.[131] In another study, oral medroxyprogesterone acetate was given in combination with percutaneous testosterone gel. In this study, 27 out of 29 men achieved azoospermia or severe oligozoospermia, and one pregnancy occurred (which is thought to have resulted from poor adherence to treatment) in 8 person-months of exposure.[132]

Combinations of TU and norethisterone enanthate (NETE) injections were shown to be highly effective in the suppression of sperm output to <1 million/mL in over 90% of men treated with the regimen for up to 48 weeks.[133,134] These favorable results prompted WHO and the Contraceptive Research and Development Program to set up a multicenter phase IIb efficacy trial in which 8-weekly injections of TU 1000 and 200 mg NETE were administered to 320 men for at least once and up to 24 weeks for suppression of sperm concentration. By 24 weeks, 274 men had sperm count suppressed to ≤1 million/mL (95.9 per 100 continuing users), and 266 couples decided to enter the efficacy period of the clinical trial (where the couple used the combined TU/NETE injections as the only method of contraception). Four pregnancies occurred with a pregnancy rate of 1.57 per 100 continuing users and a Pearl index of 2.18 pregnancies per 100 person-years.[40]

Since the early 2000s, NICHD, partnered with the Population Council, has sponsored the development of a daily transdermal male contraceptive gel containing the progestin Nestorone® (segesterone acetate, US FDA-approved in a first female contraceptive and further referenced as "NES") in combination with testosterone (NES/T gel). When applied as directed, the NES/T gel (provided as NES 8 mg/T100 mg dose) suppressed gonadotropins within 24 h[135,136] with negligible transfer to the partner.[137] Suppression of both LH and FSH was used as a surrogate marker of suppression of spermatogenesis when sex steroids were administered to men. A Phase II study using NES and T in two different transdermal gels demonstrated the combined product's safety and effective sperm suppression in 89% of participants who were adherent with the protocol,[106] with acne reported by 21%, weight gain in 7%, insomnia in 6%, and changes in libido in 4% of men. Based upon these results, a formulation containing both steroids in a volume of 5 mL/dose was developed with a lower dose of T. This gel is being tested in an international Phase IIb efficacy study currently underway at 17 study sites that have enrolled 462 couples to establish the effectiveness of daily NES/T gel in preventing pregnancy.[138] Results are anticipated in 2024. This is the first self-administered male hormonal contraceptive to undergo efficacy evaluation.

Values

Though the use of an androgen plus progestin combination for male contraception is based on the progestin acting to suppress the hypothalamic–pituitary–testis axis, and exogenous administration of testosterone replaces the suppressed testicular testosterone production to maintain male characteristics, this depends on the potency of the progestins. When implants or oral levonorgestrel were combined with transdermal testosterone patches, the suppression of spermatogenesis was inadequate. Only when injectable testosterone was administered with oral or levonorgestrel implants was spermatogenesis markedly suppressed, suggesting the additive/synergistic role of testosterone to the progestins.[110,139]

Adverse events were few when physiologic replacement dosages of testosterone were used and were generally related to the characteristics of the progestins used. Androgenic-derived progestins, in combination with testosterone, induced weight gain, acne, a decrease

in HDL-cholesterol and some mood swings.[40] On the other hand, antiandrogenic progestin like cyproterone acetate caused a decrease in Hct and libido when used at doses that suppress spermatogenesis.[140] Non-androgenic progestins such as segesterone acetate (Nestorone®) do not affect lipids and are expected to be well tolerated.[106]

Remarks

Despite demonstrating the effectiveness of suppression of spermatogenesis, the TU/NETE efficacy trial was stopped for "safety reasons" by the WHO review committee.[40] The safety reasons cited were mood changes and depression. It should be noted that 99% of these events were classified as "mild" or "moderate" in severity and were not uniformly reported in all centers. Despite these adverse events, a "high satisfaction rate" was reported.

In the TU/NETE efficacy trial, the incidence of depression in the volunteers at baseline was not recorded. Thus, prospective tracking of mood changes using standardized questionnaires was instituted in all subsequent NICHD-supported clinical trials. Notably, in a separate placebo-controlled clinical trial, many male participants (81%) reported adverse events in the placebo group.[141] In general, users and their partners' perspectives and acceptability of androgen–progestin regimens have been evaluated in most clinical trials. In all these studies, acceptability was high among male partners, and female partners supported using the method.[40,142]

10.3 | Use of androgens with GnRH-antagonists

Evidence

GnRH-antagonists are highly effective suppressors of LH and FSH secretion. In contrast to GnRH-agonists, GnRH-antagonists do not lead to an initial stimulation of LH and FSH, as they do not act via downregulation but via a competitive blockade of the pituitary GnRH receptors. This GnRH receptor blockade leads to a rapid drop in LH and FSH concentrations, thus suppressing spermatogenesis.

The hormonal combination approach using androgens with GnRH-antagonists is supported by several small clinical studies in which different GnRH-antagonists were tested in combination with different androgen preparations to suppress spermatogenesis. Azoospermia was achieved in 47 of 55 men participating in these clinical trials.[143]

In a subsequent study, the GnRH-antagonist Nal-Glu was used in combination with testosterone enanthate injections for 12 weeks to induce azoospermia or severe oligozoospermia. The suppression of spermatogenesis was maintained on weekly injections of testosterone enanthate alone for an additional 20 weeks.[144] Although this study demonstrated suppression of spermatogenesis, studies of the GnRH-antagonist Cetrorelix for 12 weeks combined with injections of 19-nortestosterone followed by injections of 19-nortestosterone alone every 3 weeks up to study week 26 did not demonstrate effectiveness.[145]

In another study, the addition of the GnRH-antagonist acyline during the first 12 weeks of treatment did not significantly accelerate spermatogenic suppression or improve the rate of severe oligozoospermia achieved by administering testosterone gel in combination with DMPA injections for 24 weeks.[146]

Values

To date, only small clinical trials with androgens and GnRH-antagonists have examined sperm concentration as a surrogate marker for male contraception. No studies have been conducted on pregnancy prevention.

Remarks

Currently, orally active GnRH-antagonists are being successfully tested for reproductive endocrinology indications, so the practicality of this approach to hormonal contraception could improve significantly. However, the costs of manufacturing GnRH-antagonists are high, but with advances in the pharmaceutical industry, these costs may be reduced in the future. Developing an orally active GnRH-antagonist combined with an orally active androgen for male contraception could be a potential candidate for a "male pill."

10.4 | Proposed regulatory recommendations for MHC, including androgens alone, and androgens in combination with progestins or GnRH-antagonists

Evidence

1. The initial clinical trials of a new male hormonal contraceptive product's efficacy should be based on surrogate markers. It has been shown that suppression of serum LH correlates with suppression of spermatogenesis.[106,136] It has also been demonstrated that suppression of spermatogenesis correlates with pregnancy prevention.[116] For men with sperm concentrations in the range of 0–3 million/mL, the pregnancy rate was 1.4 (95% CI 0.4–3.7) per 100 person-years with 82% exposure time to azoospermia.[116] The primary outcome analysis to assess efficacy in suppressing LH and FSH should use the calculation of the percentage and 95% confidence interval of men with both FSH and LH suppressed to ≤1.0 IU/L after 4 weeks (day 28) of treatment.[135] Based on the 10th Summit recommendations[135] and the WHO study showing a correlation of sperm concentration with pregnancy occurrence,[116] it is recognized that azoospermia or sperm concentration of ≤1 million/mL is proposed as a threshold for efficacy to allow testing to prevent pregnancy in the female partner.
2. The International Council on Harmonization has established safety requirements. Recording of adverse events, measures of blood pressure, and laboratory evaluations are needed as recommended by regulatory agencies (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e1a-extent-population-exposure-assess-clinical-safety-drugs-intended-long-term-treatment-non-life).
3. Previous studies have demonstrated that a suppression phase of about 12 weeks allows most men to reach azoospermia or severe oligozoospermia with a sperm count of ≤1 million/mL.[40,116] Reaching this suppression threshold would allow entry into the efficacy

phase (reliance on the new contraception method) of a clinical trial. We recommend that in the efficacy phase, the couple has at least one episode of intercourse per cycle. Follow-up of sperm suppression is recommended monthly during phase II (dose-finding). The rationale for testing at intervals defined during phase III remains to be documented.

4. There is no specific regulatory guidance for male contraception. In regulatory guidance for female hormonal contraceptives, the efficacy assessment is made on the Pearl index based on the number of pregnancies according to 10,000 or 20,000 exposure cycles to the test agent. For male methods (which are not based on menstrual cycles), we propose that the most appropriate method to assess contraceptive efficacy (pregnancy rate) would be to use Kaplan–Meier estimate over 365 days of product use to estimate the 1-year cumulative pregnancy probability and that 5000 men-months of exposure would be sufficient to demonstrate efficacy.
5. Hormonal methods are designed to be reversible. We recommend assessing the return of sperm concentration to the adult male range in phase IIb and III studies over 6 months, expecting time to recovery would be about 12 weeks and full recovery at 6 months.[37,147] The acceptable goal of recovery after hormonal male contraception should be over 95%.

Values

Hormonal methods must maintain serum concentrations of androgen and progestin relatively constant either from a continuous release from an implant or injection or daily administration is required to prevent rebound of sperm output and maintain expected efficacy. Efficacy studies likely require a first phase of suppression with an enrollment of couples before men reach azoospermia or severe oligozoospermia (sperm concentration ≤1 million/mL).

Remarks

Male contraception studies present a unique situation where the treatment is taken by the male, but the efficacy is measured in his partner. Proper counseling for the couple is needed about the possible risk of failure and information on options available in case of pregnancy according to the country's regulations.

Surrogate markers of efficacy in the male subject are indicators of efficacy but are insufficient to document the actual contraceptive efficacy. A threshold of sperm concentration of ≤1 million/mL is proposed for a product to be studied as a male hormonal contraceptive.

11 | NON-HORMONAL METHODS (AGENTS AFFECTING SPERMATOGENESIS, SPERM MOTILITY OR FUNCTION)

Recommendations

48.	We suggest including in the pre-clinical investigation of non-hormonal contraceptives the determination of the mechanism of action, pharmacodynamics, reversibility, and toxicology studies.	2 ⊕⊕⊕◯
49.	We suggest confirming the reversibility of all non-hormonal male contraceptive agents in pre-clinical studies and initial human studies (first in man); the male participant should be counseled that the method may be irreversible and alternate methods are available.	2 ⊕⊕◯◯
50.	We suggest documenting the time to suppressing spermatogenesis or sperm function in a 6-month study. There are insufficient data to define a specific threshold for contraceptive efficacy. Each product will need to develop the threshold of using the method for contraception.Examples include: • For products designed to suppress spermatogenesis, marked decreased sperm concentration and total sperm number/ejaculate. • For products designed to suppress motility, very low sperm motility. • For products that affect sperm morphology, almost all spermatozoa have abnormal morphology. • For products designed to affect sperm function, a loss of sperm function in most sperm. However, such testing needs further research.	GPS
51.	We recommend following the ICH (International Council for Harmonization) guidance for the safety assessment of any new chemical entity (NCE): to record adverse event information for 1500 men exposure, including at least 300 men for 6-month exposure and at least 100 for 1-year exposure.	1 ⊕⊕⊕⊕
52.	We suggest demonstrating contraceptive efficacy based on the failure rate observed in the female partner monthly over 1-year treatment with time to event (pregnancy) using cumulative survival probabilities (95% confidence interval) analyzed by the Kaplan–Meier statistical approach. In any clinical efficacy study of a male contraceptive, the couple should enter an efficacy phase of the study where there is no other form of contraception used, and the couple engages in at least one episode of vaginal intercourse in each of the woman's menstrual cycle.	2 ⊕⊕⊕◯

(Continues)

11.1 | Agents not currently in development

Evidence

Gossypol (derived from the cotton seed) and triptolide (from the root of *Tripterygium wilfordii*) were evaluated in clinical trials in China in the 1970s and 1980s. Gossypol was extensively studied in clinical trials in two large phase III studies in China, enrolling more than 8000 men. In these studies, gossypol was demonstrated to reduce sperm production, motility and morphology, with most men

achieving azoospermia resulting in 90% efficacy in preventing pregnancy. Importantly, related to dosage and duration of exposure to gossypol, spermatogenesis was not fully restored in 20% of men suggesting that gossypol was not fully reversible in a significant number of men. In addition, gossypol caused hypokalemic periodic paralysis in susceptible men and for both reasons, development was halted.[148] Triptolide was tested in pre-clinical and clinical studies but was not developed further because of possible immuno-suppressive effects.[149] These studies demonstrate that full toxicology and reversibility studies should be demonstrated in animal studies before human studies. The toxicology plan is well defined by regulatory guidelines before testing a new molecule in humans. If the intention is for an agent to be reversible, men participating in first-in-human studies must be counseled that the new method may be irreversible and clinical trials may consider enrolling men who do not desire future fertility of non-hormonal male contraceptives until reversibility of spermatogenesis in humans has been demonstrated.[150] Another plant product from *Justica gendarussa*, when taken by mouth, was reported to have contraceptive activity in Indonesia, but no prospective clinical trial has been conducted.[151]

Miglustat (N-butyldeoxynojirimycin) is used in the treatment of Gaucher disease. When tested in certain strains of mice, impaired spermatogenesis and reversible fertility were observed. Miglustat had no effect on other strains of mice, rabbits, and men.[152] Indazole carboxylic derivatives Gamendazole, H_2-Gamendazole, and Adjudin target Sertoli cell-germ cell interactions and induced infertility in rodents, but higher doses were irreversible with significant off-target effects.[153] Attempts to specifically target meiotic and post-meiotic cells were difficult because of the requirement for these drugs to penetrate the blood–testis barrier, and these agents were not further developed. In retrospect, a more comprehensive evaluation of the mechanism of action may have allowed for more streamlined development and pre-clinical studies to establish a no-adverse event level (NOAEL) and an effective dose with a good margin for safety.

Values

We have gained considerable knowledge from non-hormonal male contraceptive agents that are no longer in clinical development. These include gossypol, triptolide, gendarussa, Misglustat, and indenopyridines, adjudin, and H_2-Gamendazole. These investigations support the concept that a male contraceptive may be effective through targeted interruption of different steps of male germ cell development required for effective conception, including spermatogenesis, spermiation, and sperm motility. Agents that impact more than one of these aspects may also be effective. Historically, some agents investigated as non-hormonal male contraceptives have not had full interrogation of their mechanism of action prior to evaluation in human studies.[86,150] We have also learned from these that contraceptive effectiveness and reversibility in rodents may not uniformly translate into similar effects in humans and the importance of considering non-human primate (NHP) models for pre-clinical testing for some agents. However, research in NHPs represents a serious ethical dilemma, which gives rise to a high level of concern from European Union (EU) citizens. Therefore, human interest in potential benefits for mankind must be balanced against avoiding harm to NHPs and adopting ethical limits or boundaries on NHP use. NHPs should only be used when there are no alternatives, and it is scientifically demonstrated that none of the other non-rodent species commonly used in safety testing is appropriate for the study. In addition, NHP use can be avoided when in vitro preliminary studies demonstrate that NHP are not a suitable animal model. (Final Opinion on The need for NHPs in biomedical research, production and testing of products and devices—update 2017) (https://ec.europa.eu/environment/chemicals/lab_animals/pdf/Scheer_may2017.pdf).

Remarks

Historically, some agents investigated as non-hormonal male contraceptives have not had full interrogation of their mechanism of action prior to evaluation in human studies.

11.2 | Potential non-hormonal methods in development

Evidence

There are recent reviews on the development of male non-hormonal contraception.[86,150] Table 6 summarizes the validated targets, their mechanisms of action, and potential surrogate markers of suppressive effects on spermatogenesis, sperm motility, morphology, or function. Some other targets, not included in this table, are currently under early development.

11.2.1 | Eppin

Eppin is a protein located on the sperm surface that helps liquefy the ejaculate. Contraceptive research in this area has focused on developing small molecules that inhibit Eppin binding to semenogelin, a necessary step in sperm liquefaction. Intravenous administration of the small molecule EP055 reduced sperm motility by 80% in male macaques.[154] Research is now focused on developing oral compounds as an "on-demand" male contraceptive.

11.2.2 | Retinoic acid receptor antagonists or synthesis inhibitors

Mice with deletion of one of several of the Retinoic acid receptors are sterile. A specific retinoic acid-alpha antagonist for male contraception, YCT-529, has been reported in the literature and is effective and reversible in mice; more recent versions may hold some promise for non-hormonal male contraception.[155] Almost 60 years ago, WIN 18,446 was shown to suppress sperm production in men dramatically. WIN 18,446 functions via inhibition of testicular retinoic acid biosynthesis. Work in this area is now focused on producing novel products that inhibit retinoic acid biosynthesis without the other side effects of WIN 18,446.[156]

TABLE 6 Non-hormonal agents in development.

Agent	Mechanism of action	Surrogate marker
Retinoic acid receptor antagonists or synthesis inhibitors	Inhibition of retinoic acid signaling leads to a block in spermatogonial differentiation, spermiogenesis, and spermiation	Absence of, or very few sperm on semen analysis
Testis-specific bromodomain inhibitors	Blockade of chromatin remodeling leading to a cessation of spermatogenesis	Absence of, or very few sperm on semen analysis
EPPIN (epididymal peptidase inhibitor)	Blockade of Eppin-semenogelin interaction in semen	Inhibition of sperm liquefaction and motility on semen analysis
Sperm-specific ion channel targets (CatSper, SLO3)		
CatSper (Specific calcium channel)	Inhibition of calcium influx—Block of sperm hyperactivation	The defects in these channels are not seen in semen analysis—they might be causes of normozoospermic infertility—Methods for clinical detection are under investigation
SLO3 (Sperm-specific K^+ channel)	Inhibition of K^+ efflux—Block of sperm acrosome reaction and hyperactivation	The defects in these channels are not seen in semen analysis—they might be causes of normozoospermic infertility—Methods for clinical detection are under investigation
Soluble adenylate cyclase	Inhibition of cAMP production in spermatozoa	Reduction in sperm motility and capacitation markers on semen analysis
Testis-specific serine/threonine kinases	Inhibition of post-meiotic spermiogenesis	Absence of spermatozoa with normal morphology on semen analysis
SPEM1	Inhibition of SPEM1 interactions (Triptonide)	Absence of spermatozoa with normal morphology on semen analysis
LDH-C	Inhibition of spermatozoa-specific lactate dehydrogenase function	Absence of sperm motility and inability to undergo capacitation

11.2.3 | Testis-specific bromodomain inhibitors

Testis-specific bromodomain (BRDT) is expressed in the spermatocyte and spermatids. Knockout of the BRDT gene led to male sterility in mice and administration of a BRDT inhibitor led to reversible suppression of spermatogenesis in mice, but this compound also inhibited non-testicular bromodomains. Novel, orally bioavailable, specific inhibitors of BRDT are currently being identified.[157,158]

11.2.4 | CatSper

Deletion of CatSper in mice causes a decrease in calcium entry during sperm capacitation, failure of sperm hyperactivation, and infertility.[159,160] Infertile men with CatSper mutations have been identified.[161]

11.2.5 | SLO3

SLO3 is a sperm-specific K^+-channel[162] that controls sperm membrane potential.[163] SLO3 knockout (KO) mice are infertile due to impaired acrosome reaction and hyperactivated motility.[164] Recently, a SLO3-specific inhibitor has been reported, opening the door for developing these drugs as novel non-hormonal contraceptive options.[165] Two men lacking functional SLO3 were identified who were infertile.[166]

11.2.6 | Soluble adenylate cyclase

Soluble adenylate cyclase (sAC) is a unique adenylase cyclase required for sperm motility. Recently, a novel sAC inhibitor was shown to induce rapid, reversible motility defects in sperm that prevented fertility in mice. Inhibition of sAC may have promise as an "on-demand" contraceptive for men.[167]

11.2.7 | Testis-specific serine/threonine kinases

Testis-specific serine and threonine kinases are exclusively expressed in post-meiotic sperm and play an essential role in germ cell differentiation and male fertility, as the knockout of specific isoforms of these genes leads to sterility or subfertility.[168] Developing specific inhibitors of these kinases may allow for a reversible male contraceptive.[168]

11.2.8 | Triptonide

Triptonide is a natural compound chemically related to triptolide and purified from the root of *Tripterygium wilfordii*. Oral administration of triptonide to rodents and cynomolgus monkeys led to reversible induction of abnormal sperm morphology that precluded fertility in both species.[169] It is thought that triptonide acts by blocking

interactions between the target junction plakoglobulin protein with SPEM1 during spermiogenesis, leading to the observed morphological abnormalities.[169]

11.2.9 | Lactase dehydrogenase-isoform C

Lactase dehydrogenase-isoform C (LDH-C) is a sperm-specific enzyme expressed during the first meiotic division of spermatogenesis and localized to the principal piece of the sperm tail, where it is thought to be involved in glycolysis and sperm motility.[170] Mice lacking LDH-C are infertile due to absent sperm motility and an inability to undergo capacitation.[171] Preliminary work on inhibitor development has been undertaken, but potent and specific inhibitors have not yet been identified for this target.

Values

Multiple avenues toward a non-hormonal male contraceptive are under active investigation, with some promising developments. Significantly more effort, however, will be required prior to clinical testing of these compounds as male contraceptives.

Remarks

Significant resources must be invested in developing non-hormonal contraceptives to allow the most promising candidates to be tested in men.

11.3 | Regulatory aspects for non-hormonal contraception

Evidence

1. New molecules designed to inhibit specific targets in the male reproductive system would need to be studied based on the anticipated mechanism of action. Proof of concept testing based on mechanism of action could include assessment of changes in sperm number, sperm motility, morphology, maturation, and/or function, and other yet-to-be-determined surrogate markers of inhibition of sperm function or fertilizing capacity. Although there is rapid progress in this area, this is a challenging research area, and decision limits for any assay(s) will need rigorous validation.
2. A platform based on imaging and flow cytometry that measures two fundamental aspects of sperm behavior, motility and acrosome reaction, has been developed for male contraceptive target screening. The method allows for the rapid screening of compounds but is not designed to validate surrogate markers of efficacy in clinical trials.[172] The parameters such as motility, capacitation, hyperactivation, and acrosome reaction could be assessed in vitro; however, they only mimic the condition of the female reproductive tract and do not ideally replace it.
3. The possible surrogate markers using semen analysis for the effectiveness of male non-hormonal contraception are listed in Table 6. However, the threshold for entering contraceptive efficacy, except for sperm concentration suppression after hormonal methods, has not been established. The only surrogate data we have are based on semen analyses from over 3590 fertile men (in couples starting a pregnancy within 1 year of unprotected sexual intercourse to a natural conception) (Table 7),[147] if the 0.5 centiles are used (one in 500 fertile men), the threshold sperm concentration is 4.8 million/mL, total sperm count is 13 million/mL, total sperm motility 25%, progressive motility 10 and 1% of spermatozoa with normal morphology, these thresholds may be too high for couples to stop using other methods of contraception. The data do not have sufficient fertile men to provide a distribution limit lower than 0.5 centiles.
4. Each new method will need to provide a threshold when the couple may use the new method and stop all other methods of contraception. When each product is developed, the threshold to enter contraceptive efficacy should be determined as appropriate based on studies where the surrogate marker is the endpoint in a 6-month clinical trial or duration appropriate for the mechanism of action and potential use.
5. Regarding safety requirements, the International Council on Harmonization established requirements for any new chemical entity or new product. (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e1a-extent-population-exposure-assess-clinical-safety-drugs-intended-long-term-treatment-non-life). Adverse event information should be available for 1500 men exposure in total, including at least 300 men for 6-month exposure and at least 100 for 1-year exposure.
6. In male contraception development, the male is using the product for 12 months, and the female partner not using any contraception will experience spontaneous cycles of various lengths. We suggest demonstrating contraceptive efficacy based on the failure rate observed monthly over a 1-year treatment of the man. The time to event (pregnancy) observed in the female partner, using cumulative survival probabilities (95% confidence interval) analyzed by the Kaplan–Meier statistical approach.

TABLE 7 Distribution of semen examination results from fertile men (in couples starting a pregnancy within 1 year of unprotected sexual intercourse to a natural conception).

Centile	0.1	0.5	1.0	5
Sperm concentration (millions/mL)	1.5	4.8	7	16
Total spermatozoa/ejaculate (millions)	4	13	17	39
Sperm motility (%)	4.5	25	29	42
Sperm progressive motility (%)	0	10	15	30
Normal sperm morphology (%)	1	1	2	4

Source: Ref. 147.

Values

A non-hormonal male contraceptive could work in different ways. For example, it could completely halt spermatogenesis, block an essential function of the spermatozoa (such as motility), disrupt sperm

morphology, or perturb a cellular process that fails capacitation or interaction with the oocyte (such as prematurely triggering the acrosome reaction, and/or by blocking exocytosis or inhibiting zona binding). Developing such new approaches is challenging as there are no specific surrogate markers of efficacy that can conclusively determine whether a product inhibits a specific function of the sperm besides motility that is easily measured in a semen analysis.

Remarks

Male contraception studies present a unique situation where the treatment is taken by the male, but the efficacy is measured in his female partner. Proper counseling is needed for the couple to consider the possible risk of failure and options available in case of pregnancy according to the local/country regulations. Surrogate markers of efficacy in the male subject are useful indicators but insufficient to confirm contraceptive efficacy. With different approaches to specific targets in the male reproductive system, practical methods must be developed to estimate markers of functional ability to reach and fertilize an egg.

12 | VACCINES

Recommendations

53.	We recommend **against** using any vaccine for male contraception outside of clinical trials, as these approaches remain experimental.	1 ⊕◯◯◯

Evidence

Vaccines targeting spermatozoa for disrupting fertility have been reported as early as 1937.[173,174] The rationale of this approach is that spermatozoa express antigens within the adluminal compartment of the seminiferous tubules. The latter is immunologically protected long after establishing immune self-tolerance, explaining the potential auto-immunogenicity of the antigens. Spermatozoa autoimmunity contributes to subfertility after vasectomy reversal.

One targeted antigen is Eppin, a testes-epididymal-specific protease inhibitor found in spermatozoa (see Section 11 on non-hormonal methods). Eppin is involved in sperm–semenogelin interaction in the coagulum of human ejaculation.[175] In animal studies (monkeys), Eppin vaccination resulted in a reversible reduction of sperm counts[176]; nevertheless, its effect and reversibility are inconsistent. Additionally, the vaccine requires booster doses.

In another animal model, a multivalent chimeric protein sperm vaccine targeting surface-expressed antigens has been applied.[177] The method is characterized by variability of individual immune responses, restricted access of antibodies into the seminiferous tubules and epididymis and risks of autoimmune orchitis.

Values

Vaccines for male contraception are restricted to animal studies; these approaches remain purely experimental.

Remarks

Besides Eppin, GnRH and FSH are potential targets for vaccination.[178]

13 | SOCIAL AND ETHICAL CONSIDERATIONS

13.1 | Diversity, equity, and inclusion

Recommendations

54.	We recommend that both partners should share equal opportunities for family planning. Male contraception provides a necessary alternative to female contraception and relieves women from the burden of contraception, since the introduction of hormonal contraception, by default, weighs heavily on them.	1 ⊕⊕⊕⊕
55.	We recommend that the couples' needs and wishes be respected, and contraceptive providers should be able to set aside personal judgments and opinions.	1 ⊕⊕⊕⊕
56.	We recommend that all male contraceptive needs be met without discrimination based on sex, sexual orientation, gender identity, age, race, language, economic, or social status.	1 ⊕⊕⊕⊕

Evidence

Progress in developing novel practical contraceptive methods for men has lagged significantly behind developments for women, with the result that the health-related burden and financial burdens of contraception have fallen mainly on women. Many surveys across various cultural and ethnic groups have shown that interest in male contraceptives is high among men worldwide and suggest that they are willing to share this burden, as well as the benefits of family planning, by increasing their share of responsibility.[5,40,142,179–181]

One survey also showed that women in stable monogamous relationships would trust their partner to use a male hormonal contraceptive.[182] In efficacy trials for MHC, 78% of the female partners of the couple enrolled said to be satisfied or very satisfied with the tested regimen, and 76% of them would use the methods in the future.[40]

Recently an ethical call for a "shared risk" model for contraception among partners has been advocated.[7,183]

As reported by WHO, people have a right to determine "whether and when to have children, how many and with whom." In this respect, women and men should be able to freely choose whether and when to use contraceptives and the choice of contraception. Counseling should be non-directive, non-coercive, and respect the man's choice.[184]

Diversity and equity should be addressed so that all men and women of different sexual orientations, gender identity, age, race, language, and economic or social statuses needing contraception can be counseled without stigma or discrimination in full respect of their needs and

preferences. This includes that all transgender and non-binary individuals should be able to access contraception "while having their gender identity respected."[184–186]

Value

We recognize the importance that men become more involved in family planning to alleviate the burden of family planning from women and avoid parenthood and its obligations.

Female and male contraceptive options will allow each partner to control their family size and decision to be a parent. The contribution of men to family planning will greatly enhance gender equality by increasing the choice of contraceptive methods and equity, fulfilling more needs and preferences.

More than 200 million women currently have an unmet need for family planning, meaning they do not want to get pregnant but are not using modern contraceptive methods.[30] Increased availability of contraceptives correlates with higher contraceptive usage and reduced family size.[187] We value that the possibility of sharing the contraceptive burden will improve the contribution of men and women in limiting population growth and all its consequences.[188]

We value the importance that family planning providers "recognize and address diversity so that all individual clients and couples seeking family planning can access them without stigma or discrimination, and in ways that encourage them to make decisions that are safe, appropriate and best meet their needs and their preferences."[184]

We highlight the principle of respect for the individual. While this principle is about respect for the user, and their autonomy to make decisions about their health and preferences, it is also the commitment to listen, understand and learn from men who want contraception but are currently unsatisfied with condoms or permanent solutions.[189]

13.2 | Access to contraception

Recommendations

57.	We recommend that male contraceptives should be available, affordable, and accessible to all couples that seek them worldwide to promote gender equity and enable men to take responsibility for their sexual and reproductive behavior.	1 ⊕◯◯◯
58.	We recommend that male contraceptives available on the market should be equally accessible and affordable as female contraceptives so that couples can choose according to their preferences without any coercion.	1 ⊕◯◯◯
59.	We recommend that men should be free to choose whether and when to use contraceptives and which kind of male contraceptive to use if they decide so. Access to contraception should **not** be restricted, nor should the choice be directed towards any male or female contraceptive by any means, economic, religious, social, or cultural.	1 ⊕◯◯◯
60.	We recommend that both male and female contraceptive options be offered to the couples during the counseling. Men and women have the right to make an informed decision about contraception, including the right to receive appropriate, accurate, scientifically accurate and comprehensive information, counseling, and support.	1 ⊕◯◯◯

(Continues)

Male contraception studies present a unique situation where the treatment is taken by a subject, but the contraceptive efficacy is measured in his partner. Proper counseling is needed for the couple about the possible risk of failure and options available in case of pregnancy according to the country's regulations.

Evidence

Worldwide, most family planning programs continue to be focused on women. Including men would help them to receive adequate information on the effectiveness of the method in perfect and typical use, how it works, common side effects, health risks and benefits, reversibility, and protection from STIs. Healthcare systems and contraceptive delivery services should be organized to provide couples advice that includes the ability to provide information and delivery of both female and male contraceptives.

Value

Free access to contraceptives, including all available female and male contraceptives, reduces unintended pregnancies, maternal mortality, preterm birth, and abortions and improves the health of women and families.[190]

14 | CONCLUSIONS

This set of guidelines is the first where the EAA and the ASA collaborate to produce comprehensive guidance. We anticipate many will come as the ASA has not initiated many guidelines. These guidelines were also different except for abstinence, withdrawal, condoms, and vasectomy, all the other male contraceptive technology and methods are in development, some in late phase II studies, and many are in the pre-clinical phase. The authors have been asked to provide information for those in current clinical practice and those in development, including new vas occlusion methods and hormonal and non-hormonal methods for male contraception. For the new methods, a regulatory consideration section is included as a proposal for the minimal clinical studies that must be completed before approval as a new contraceptive method.

Of note, surgical methods such as vasectomy are not regulated by government agencies but by professional societies. Because professional societies have written several editions of the guidelines for vasectomy, we have decided to use the widely accepted AUA's vasectomy guideline template and build on recommendations from other urological societies. New issues these organizations have not systematically reviewed are presented for future discussion and possible inclusion in the respective guidelines.

Because sections on new male contraceptive technology may not be familiar to our readers, the authors decided to include key references for further reading. Though some methods are not currently in development, they have been included with a brief explanation of why the development was discontinued.

The authors of the guidelines were selected by the ASA and EAA not only because of their expertise but also based on their experience with prior guideline development. They represent different disciplines with different expertise and geographical areas of the two societies. We understand that these guidelines will be updated when there is a new method, guidance from regulatory agencies, or scientific society recommendations. We welcome comments on the initial version of the EAE–ASA Guidelines on Male Contraception.

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ENDORSEMENTS

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APPENDIX A1

GLOSSARY

The health authorities require an Investigational New Drug in the USA or Investigational Medicinal Product Dossier in Europe before a first clinical trial to review the pre-clinical safety and the chemical characteristics of the formulation to be used. It includes the pharmacology and toxicology studies, the product manufacturing description, the first protocol, and the investigators' qualifications.

CLINICAL TRIALS

- Phase I: Researchers test a drug or treatment in a small group of people (20–80) for the first time. The purpose is to learn about safety and identify side effects by studying the dose and administration of the new drug or treatment. It includes pharmacokinetic parameters to determine absorption.
- Phase II: Phase IIa is a dose-finding study to determine in small groups the lowest effective dose on a specific marker. In Phase IIb, the new drug or treatment is given to a larger group of people (100–300) to determine its effectiveness and further study its safety.
- Phase III: The new drug or treatment is given to large groups of people (1000–3000) to confirm its effectiveness, monitor adverse effects, compare it with standard or similar treatments, and collect information that will allow the new drug or treatment to be used safely.
- Phase IV: After a drug is approved by the drug regulatory agencies and made available to the public to check for safety in the general population, seek more information about a drug or treatment's benefits and optimal use.

APPENDIX A2

AUA GUIDELINES[50]

1.	A pre-operative interactive consultation should be conducted, preferably in person. If an in-person consultation is not possible, then pre-operative consultation by telephone or electronic communication is an acceptable alternative.	*Expert Opinion*
2.	The minimum and necessary concepts that should be discussed in a pre-operative vasectomy consultation include the following:	
	Vasectomy is intended to be a permanent form of contraception. Vasectomy does not produce immediate sterility. Following vasectomy, another form of contraception is required until vas occlusion is confirmed by post-vasectomy semen analysis (PVSA). Even after vas occlusion is confirmed, vasectomy is not 100% reliable in preventing pregnancy. The risk of pregnancy after vasectomy is approximately one in 2000 for men who have post-vasectomy azoospermia or PVSA showing rare non-motile sperm (RNMS). Repeat vasectomy is necessary for ≤1% of vasectomies, provided that a technique for vas occlusion known to have a low occlusive failure rate has been used. Men should refrain from ejaculation for approximately 1 week after vasectomy. Options for fertility after vasectomy include vasectomy reversal and sperm retrieval with in vitro fertilization. These options are not always successful, and they may be expensive. The rates of surgical complications such as symptomatic hematoma and infection are 1–2%. These rates vary with the surgeon's experience and the criteria for diagnosing these conditions. Chronic scrotal pain associated with a negative impact on quality of life occurs after vasectomy in about 1–2% of men. Few of these men require additional surgery. Other permanent and non-permanent alternatives to vasectomy are available.	*Expert Opinion*
3.	Clinicians do **not** need to routinely discuss prostate cancer, coronary heart disease, stroke, hypertension, dementia, or testicular cancer in pre-vasectomy counseling of men because vasectomy is not a risk factor for these conditions.	*Standard (Evidence Strength Grade B)*
4.	Prophylactic antimicrobials are **not** indicated for routine vasectomy unless the man presents a high risk of infection.	*Recommendation (Evidence Strength Grade C)*
5.	Vasectomy should be performed with local anesthesia with or without oral sedation. If the man declines local anesthesia or the surgeon believes that local anesthesia with or without oral sedation will not be adequate for a particular man, then vasectomy may be performed with intravenous sedation or general anesthesia.	*Expert Opinion*
6.	Isolation of the vas should be performed using a minimally invasive vasectomy (MIV) technique such as the no-scalpel vasectomy (NSV) or other MIV techniques.	*Standard (Evidence Strength Grade B)*
7.	The ends of the vas should be occluded by one of three divisional methods: Mucosal cautery (MC) with fascial interposition (FI) and without ligatures or clips applied on the vas; MC without FI and ligatures or clips applied on the vas; Open-ended vasectomy leaving the testicular end of the vas unoccluded, using MC on the abdominal end and FI; OR by the non-divisional method of extended electrocautery.	*Recommendation (Evidence Strength Grade C)*
8.	The divided vas may be occluded by ligatures or clips applied to the ends of the vas, with or without FI and with or without excision of a short segment of the vas, by surgeons whose personal training and/or experience enable them to obtain satisfactory results with such methods consistently.	*Option (Evidence Strength Grade C)*
9.	Routine histologic examination of the excised vas segments is **not** required.	*Expert Opinion*
10.	Men or their partners should use other contraceptive methods until vasectomy success is confirmed by PVSA.	*Clinical Principle*
11.	To evaluate sperm motility, a fresh, uncentrifuged semen sample should be examined within 2 h after ejaculation.	*Expert Opinion*
12.	Men may **stop** using other contraception methods when examining one well-mixed, uncentrifuged, fresh post-vasectomy semen specimen that shows azoospermia or only rare non-motile sperm (RNMS or ≤100,000 non-motile sperm/mL).	*Recommendation (Evidence Strength Grade C)*

(Continues)

13.	Eight to sixteen weeks after vasectomy is the appropriate time range for the first PVSA. The time to do the first PVSA should be left to the surgeon's judgment.	*Option (Evidence Strength Grade C)*
14.	Vasectomy should be considered a failure if any motile spermatozoa are seen on PVSA 6 months after, in which case repeat vasectomy should be considered.	*Expert Opinion*
15.	If >100,000 non-motile sperm/mL persist beyond 6 months after vasectomy, then trends of serial PVSAs and clinical judgment should be used to decide whether the vasectomy is a failure and whether repeat vasectomy should be considered.	*Expert Opinion*

ADDITIONAL GUIDELINES

By the Canadian Urological Association Vasectomy Guideline[51]; the Association of Biomedical Andrologists, the British Andrology Society and the British Association of Urologic Surgeons[52]; the European Association of Urology (EAU)[53]; and the Committee of Andrology and Sexual Medicine of the Association Française d' Urologie (AFU).[54]

1.	No-scalpel vasectomy is associated with a lower risk of post-operative complications than conventional vasectomy.
2.	Leaving the proximal end of the vas deferens open seems to reduce the risk of post-vasectomy pain syndrome without increasing the risk of failure or complications.
3.	An information pamphlet should be provided to all men. There is a summary sheet in the American Urology Association Guidelines.
4.	Vasectomy is permanent but has a high probability of reversibility. Pre-operative sperm banking should be discussed if men are concerned about the permanent nature of the procedure, particularly in men who may have a high level of regret (i.e., single, divorced or separated men and men under 30 years).
5.	There is **no need** for a "cool down period" for couples to determine whether the man will undergo vasectomy after consultation before vasectomy.
6.	Extra care should be given to men with a prior varicocoele repair, as the blood supply to the testis may be compromised. Extra care in preserving the vasal artery is recommended.
7.	No-scalpel vasectomy is recommended because this procedure is associated with a significantly lower risk of post-operative complications (hematoma, pain, infection) than conventional vasectomy.
8.	Postal/courier specimens should only be used to detect the absence of spermatozoa. However, if outside the recommended 4-h window, there is insufficient data to validate the accuracy of any results obtained, particularly concerning "uncontrolled" transport situations. Semen analysis should be performed according to the WHO Laboratory Manual for the Examination and Processing Human Semen (6th Edition).
9.	Laboratories should participate in quality control with an accredited andrology protocol for semen analysis.
10.	Men should receive written information regarding vasectomy and communication about post-vasectomy semen analysis results. Results must be communicated by phone or in writing to the man (or in person).