Male Contraception
History and Development

Paul Kogan, MD, Moshe Wald, MD*

KEYWORDS

• Male contraception • History • Vasectomy • Condoms • Testosterone

KEY POINTS

- Hormonal contraception has offered the most promising results with the greatest amount of clinical research. It will likely include a combination of androgen and a progesterone analogue with extended-interval depot injections and/or implants, although a tremendous amount of research is ongoing to develop alternative oral or transdermal formulations.
- Inhibition of the testicular retinoic acid pathway through existing agents such as WIN-18,466 or BMS-18943 seems to offer a viable, safe, and reversible mechanism for male contraception although more clinical work needs to be done.
- Interruption of the postepididymal extracellular eppin-semenogelin complex, either through proven immunologic methods or theoretic pharmacologic antagonists, has a promising safety and reversibility profile.

INTRODUCTION

Compared with female contraceptive methods, male alternatives are few and relatively underused. Currently, the only readily available methods of contraception for men include vasectomy, condoms, and withdrawal. The first 2 methods account for only 8.9% of global contraceptive use.[1] Surveys have demonstrated that nearly 80% of men believe contraception is a shared responsibility[2,3] and globally more than 50% of men endorsed interest in an alternative male contraceptive.[3] These studies demonstrate an unmet need for alternative male contraception. This review discusses currently available, soon to be available, and potential targets for male contraception.

CURRENTLY AVAILABLE METHODS

Condoms

Reports of barrier methods date back to Imperial Rome; however, the first recorded descriptions of a condom were in the 16th century.[4] For more than 400 years, sheathlike barrier methods of contraception have been used to prevent infection and pregnancy. They have evolved from animal intestines to latex and polyurethane-based products. Compared with other contraceptive methods, condoms offer low cost, ease of use, near absence of side effects, and reduction in transmission of sexually transmitted infections. Although the perfect-use failure rate of condoms is 2% in 1 year of use,[5] with actual use, the failure rate is 17% per year.[6] The relatively high failure rate, coital-dependent slippage, and perceived reduction in pleasure are common reasons for lack of use. Because of their safety and ability to protect against sexually transmitted infections, condoms are likely to remain the recommended method for young men who have not fathered children and are not in a stable monogamous relationship.

Vasectomy

Vasectomy was first described in the early nineteenth century in the United Kingdom as a

Funding Sources: None.
Conflict of Interest: None.
Department of Urology, University of Iowa, 200 Hawkins Drive, 3 RCP, Iowa City, IA 52242-1089, USA
* Corresponding author.
E-mail address: moshe-wald@uiowa.edu

Urol Clin N Am 41 (2014) 145–161
http://dx.doi.org/10.1016/j.ucl.2013.08.012
0094-0143/14/$ – see front matter

procedure first performed on dogs.[7] It first came into clinical practice in the late nineteenth century as a treatment of prostatic enlargement as an alternative to castration, and enjoyed moderate popularity as such[8,9] until it was realized that it offered no benefit in this regard. It was then used in the treatment of postprostatectomy epididymoorchitis and it was not until the 1970s that routine vasectomies stopped being performed with prostatectomies. Oschner[10] first suggested vasectomy as a contraceptive method, not, however, for elective purposes but rather as a eugenic procedure and an alternative to castration for "criminals, degenerates and perverts." For the first half of the twentieth century, vasectomy was a popular means of eugenic sterilization in the United States and in Europe. In the second half of the twentieth century, as eugenic vasectomy fell out of favor, elective vasectomy became increasingly more popular in the United States and globally.

Compared with elective female sterilization (laparoscopic tubal ligation or transcervical hysteroscopic methods), vasectomy is underused. Globally, 5 times as many female sterilizations are performed as vasectomies despite being associated with increased morbidity and mortality, higher cost, and increased use of general anesthesia.[11] In the United States, nearly 3 times as many couples elect to have tubal sterilization compared with vasectomy.[12,13] In addition, there are distinct ethnic and socioeconomic differences among those who elect to have male or female sterilization. Vasectomy is most common in non-Hispanic whites (17.4%) with a college education (16.7% compared with 3.0% among those without a high school diploma), whereas tubal sterilization is most common in non-Hispanic blacks (32.7%) and those without a high school education (36.4% compared with 13.0% of college-educated women).

It is estimated that between 175,000 and 550,000 vasectomies are performed annually.[14,15] It is a highly effective procedure with failure rates typically less than 1%.[16] In the United States, most vasectomies are performed by urologists as an outpatient procedure under local anesthesia.[15] Although vasectomy reversal procedures exist and are practiced regularly by specialists, vasectomy is intended to be a permanent form of contraception. Vasectomy requires a postoperative period of alternative contraception until azoospermia is documented. The most common side effects include a 1% to 2% incidence of symptomatic hematoma, a 3.4% incidence of infections, and a 15% to 52% incidence of chronic scrotal pain.[17] However, a recent prospective study of 625 men followed at 7 months found that 15% had some degree of scrotal pain and only 0.04% had pain severe enough to affect quality of life.[18]

Although the procedure is by no means novel, there are multiple variations in technical approaches, such as no-scalpel vasectomy and other minimally invasive approaches versus scalpel vasectomy. Incisions may be singular and midline or bilateral. Perivasal fascia may be interposed between the 2 cut segments or not. Cautery may be mucosal, intraluminal, extended nondivisional, or not used at all. The testicular end may be left open in an attempt to minimize chronic pain or closed to reduce recanalization or failure. Ligation of the ends may be preformed with clips or suture. The 2012 American Urological Association guidelines on vasectomies found that the evidence studying the effectiveness of these technical variations is limited and only grade C evidence exists.[16] However, the expert opinion was that as long as the procedure is performed through a minimally invasive approach, such as no-scalpel vasectomy or with a small (<10 mm) incision using specialized instruments for vasal isolation, uses mucosal cautery and fascial interposition when the open testicular end is opted for, virtually all of the technical variations have documented approximately less than 1% failure rate and are acceptable as long as the surgeon has a similarly acceptable failure rate.

HORMONAL

By far the most widely studied form of male contraception that currently remains unavailable is hormonal contraception. Known since the 1930s[19] and actively pursued since the 1970s, male hormonal contraception is analogous to female hormonal contraception, working primarily through inhibition of the hypothalamic-pituitary-gonadal axis. Sometimes called pretesticular contraception, hormonal contraception inhibits spermatogenesis by inhibiting release of pituitary luteinizing hormone (LH) and follicle-stimulating hormone (FSH), thereby decreasing intratesticular testosterone levels. Because viable sperm can exist for up to 8 weeks after production, there is a delay of several months before sufficient oligospermia or azoospermia is achieved, during which alternative contraception must be used. This suppressive effect of testosterone on spermatogenesis can be augmented by the addition of progesterone analogues and GnRH antagonists. Numerous formulations of testosterone in various injectable, implantable, transdermal, or oral forms, along with their modulators in different iterations of

doses and frequencies have been studied and published. In developing an alternative male contraceptive, an ideal agent should have the following parameters fulfilled, as outlined by Nieschlag and colleagues[20] (Fig. 1):

- Applied independent of the sexual act
- Acceptable for both partners
- Not interference with libido, potency, and sexual activity
- Have no short-term or long-term toxic side effects
- Have no impact on the eventual offspring
- Rapidly effective and fully reversible
- More effective than condoms

Pure Androgen

High-dose testosterone depot injections alone, for the purpose of achieving azoospermia, have

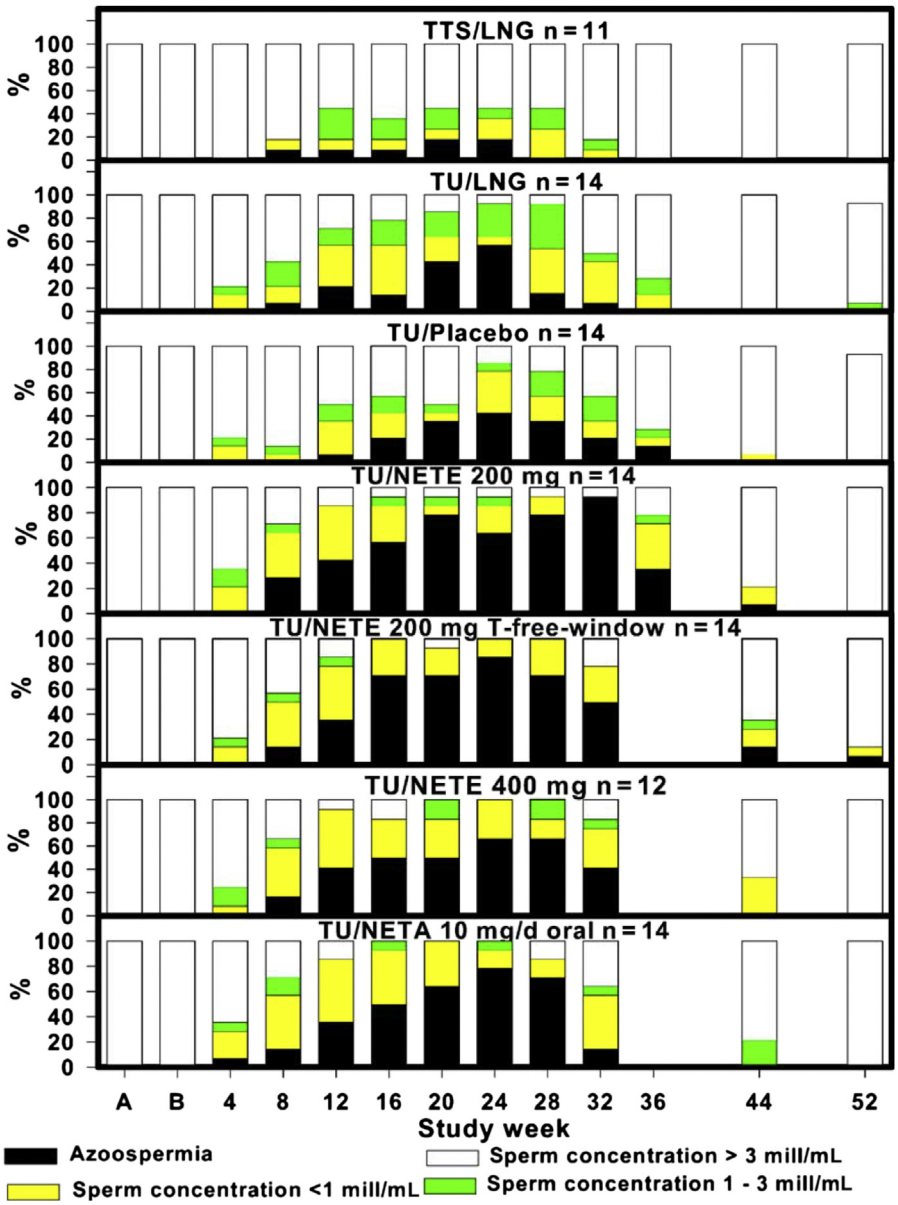

Fig. 1. Effectiveness of various testosterone (T) and progestin combinations in terms of suppression of spermatogenesis. LNG, levonorgestrel; NETA, noresthisterone acetate; NETE, noresthisterone enanthate intramuscular; TTS, transdermal T; TU, T undecanoate intramuscular. (*From* Nieschlag E, Zitzmann M, Kamischke A. Use of progestins in male contraception. Steroids 2003;68:968; with permission.)

been studied extensively since the 1970s. Unfortunately, most oral testosterone formulations have either poor bioavailability or hepatic toxicity and exogenous administration currently requires depot injections, implants, or transdermal gels to achieve consistent levels without frequent dosing several times a day.[21–23]

Two large, multinational, multicenter studies sponsored by the World Health Organization published in the 1990s showed that 200 mg intramuscular injections of testosterone enanthate (TE) every week produced azoospermia in 65% of men after 4 months with 0–0.8 pregnancies per 100 person-years and oligospermia (defined as <3 million sperm/mL) in all but 2.2% with associated pregnancy rates of 8.1 per 100 person-years.[24,25] The combined failure rate of the regimen was 1.4 pregnancies per 100 person-years, comparable with the female contraceptive pill, and improved with increasing severity of azoospermia. Although less than 3 million sperm/mL was seen as sufficiently adequate compared with currently available methods, oligospermia of less than 1 million sperm was seen as ideal.

This regimen was largely well tolerated with minimal reversible side effects seen in a quarter of the subjects (weight gain, acne, increased aggressiveness and libido, hypertension, depression, tiredness, decrease in testicular volume, increase in hemoglobin, and decrease in high-density lipoprotein [HDL]). Largely, the failure in 2% of patients to achieve sufficient oligospermia and the inconvenience of weekly injections along with side effects leading to high attrition rates in the studies were seen as the major disadvantages of this regimen. Some of the side effects seen in these studies were believed to be caused by the unstable pharmacokinetics of early preparations of testosterone leading to the use of testosterone undecanoate (TU) in later studies, which can be administered every 1 to 2 months.

Ethnic Differences

One of the important findings of these studies was an increased effectiveness in East-Asian populations with lower sterilization rates seen in whites after exogenous testosterone administration. This led to the oft-quoted figure of one-third of whites not responding to testosterone alone. The reasons for this are uncertain and may be related to differences observed between these groups in terms of cultural acceptance, general adiposity, testicular parenchymal weight, testosterone production rates, sex-hormone binding globulin affinity, 5α-reductase activity levels, prevalence of certain polymorphisms of the uridine diphosphoglucuronosyl transferase (UDGT) gene responsible for hepatic glucuronidation of testosterone, the number of CAG or GGC repeats at the N-terminus of the androgen receptor affecting affinity for testosterone, or suppressibility of LH.[26]

Certain practical features of this ethnic difference have been noted, such as the observations that addition of progestins closes the gap[27] and that Asian men recover faster after withdrawal of exogenous testosterone.[28] In addition, it has undermined certain uncontrolled studies in East Asia that found high efficacy rates in combined progestin and androgen regimens in that the added benefit of the progestin and applicability to white populations was uncertain given the known difference in response.[29]

Studies of monthly injectable TU in Chinese men have been promising. A recent study of 1045 men found effective suppression to the level of less than 1 million sperm/mL in 94% of men with a pregnancy rate of 1.1 per 100 men after 2 years of study and 1554.1 person-years of exposure.[30] The most common side effects were acne, severe cough after injection, mood or behavior changes, and incomplete recovery of testicular volume in 28% of men at the end of the 12-month recovery phase. Theoretically, this dosing interval could be further extended to 10 to 14 weeks if castor oil were used as a solvent rather than tea seed oil,[31] further adding to patient satisfaction. Although these results are promising, this regimen is unlikely to be as effective in white groups based on the findings from the large multinational World Health Organization (WHO) studies.

Testosterone + Progestin

The addition of progesterone derivatives (called progestins or progestagens) to testosterone increases the rates of spermatogenesis inhibition by further inhibiting pituitary production of gonadotropins and possibly acting directly on germ cells.[32] Progestins alone may be sufficient for inhibiting spermatogenesis; however, without exogenous testosterone, a hypogonadal state would be induced with its resultant undesirable side effects. Together, progestins and testosterone have synergistic effects, affording a lower dose of testosterone to achieve sufficient suppression of spermatogenesis and achieve it in a shorter time than testosterone alone.[33] The lower doses of testosterone required with concomitant progesterone more closely approximates a eugonadal state. This is important because the high doses required for spermatogenesis inhibition in the testosterone-only regimens may actually support spermatogenesis in nonresponders by maintaining intratesticular testosterone levels.[34]

Various progestins have been combined with testosterone including cyproterone acetate, levonorgestrel, desogestrel, etonogestrel, norethisterone enanthate, medroxyprogesterone acetate, and depot medroxyprogesterone acetate (DMPA).[22,23,27,33–37] As progestins may be formulated in effective oral, injectable, implantable or transdermal forms, testosterone remains the limiting agent with regard to bioavailable formulation when the 2 are combined. Progestins can have proandrogenic (norethisterone) or antiandrogenic (cyproterone) activity, resulting in increased weight gain, lower HDL levels, lower sex-hormone binding globulin levels. They may also promote proinflammatory cytokines that are linked to adverse cardiovascular events,[38] leading to a preferred practice of giving only the minimal necessary dose.

Bebb and colleagues[33] randomized 36 patients to 100 mg of weekly intramuscular TE alone or TE with daily oral levonorgestrel and found that 96% of the combined group achieved oligospermia (defined as <3 million sperm/mL) on average in 9 weeks and 5 weeks faster than with TE alone. This regimen was well tolerated with comparable rates of weight gain, acne, and decrease in HDL between the 2 groups.

In another promising study by Kamischke and colleagues,[39] the dosing interval was spread out to every 6 weeks of intramuscular 1000 mg TU with concomitant depot injections of norethisterone enanthate. With this regimen, 13/14 patients achieved azoospermia with only 1 having insufficient oligospermia of 10 million/mL. Azoospermia was achieved on average by 8 weeks. This regimen was also well tolerated with several volunteers experiencing mild acne, mild nocturnal sweating, and a maximum reversible weight gain of 3.7 kg.

The TU/NET-EN study was the most recent multinational WHO study on combined depot injections of TU and norethisterone enanthate every 2 months. The study was stopped prematurely and results are soon to be published.[40] Patients were enrolled from 2008 to 2010 and the study was discontinued by the review panel in 2011 for concerns of depression, other mood changes, increase in sexual desire, and pain at the injection site at higher rates than expected. In addition, 2 serious adverse events were judged to be either possibly or probably related to the study regimen but the specifics are unavailable for scrutiny at this time. By April 2011, 321 men were enrolled, 110 of whom completed the 12-month efficacy phase and 103 of whom were completing the recovery phase. The regimen was reportedly efficacious with few pregnancies reported; however, because of the previously mentioned concerns and early termination, it is unlikely that this regimen will be further developed clinically.

Oral Testosterone

Oral TU with progesterone has been studied for the purposes of male contraception and was reported as early as 1980.[41,42] These early studies demonstrated suppression of spermatogenesis, but not to levels sufficient for infertility. Current regimens still require dosing 2 to 3 times a day, making it inconvenient for contraceptive purposes.[43] In 1 small cohort of 8 men taking oral TU with oral cyproterone acetate, oligospermia of less than 3 million sperm/mL and azoospermia was achieved in 75% of men; however, a reversible 1 g/dL decrease in hemoglobin level was seen as well.[44] This induced mild anemia was believed to be caused by the antiandrogenic property of cyproterone acetate, making it fall out of favor relative to the other progestins. Perhaps with future developments and improved pharmacokinetics, male oral contraception may show more promise.

Implants

Crystalline testosterone pellet formulations have been around for more than 70 years and were largely outside clinical focus.[45] With the goal of achieving steady levels of testosterone with zero-order release kinetics, these testosterone implants were rediscovered and investigated for contraceptive purposes.[46,47] The pellets are made of fused crystalline testosterone and injected subdermally under local anesthesia into the abdominal wall and dissolve without need for removal. They provide the benefit of administration at intervals of up to 6 months apart. Occasionally, they can extrude from the injection site although this occurs relatively infrequently and improves with operator experience.[48]

Handelsman and colleagues[46] demonstrated severe oligospermia of less than 1 million sperm/mL or azoospermia in 9/9 patients after 2 months after 1200 mg of testosterone-only pellet. This small study was done after the first large WHO-sponsored study but before the second in which severe oligospermia of less than 3 million sperm/mL was found to have acceptable pregnancy rates. As a result, Handelsman's goal was azoospermia, making their rate of 56% seem inadequate. In a follow-up study, they achieved similar results at a lower dose of 800 mg testosterone only, but when DMPA was added, azoospermia was produced in 9 of 10 men, with severe oligospermia in the remaining man.[47] Recovery was

seen at 7 months after implant and 2 extrusion episodes occurred in 30 administrations. In yet another study with repeated dosing of this regimen every 4 months in 55 men for 12 months, no pregnancies were seen over the 35.5 person-years studied.[22] Only 2 of 55 men did not achieve azoospermia and did not enter the efficacy phase. They experienced a fairly high attrition rate of 49% but did not attribute this to medical reasons or intolerance of the formulation but rather an absence of a financial incentive strong enough to offset the inconvenience of study participation. In another installment in this series of studies, the addition of implantable estradiol at 10 mg or 20 mg was found to add insignificant rates of azoospermia and had unacceptable side effects of androgen deficiency and estrogen excess.[49]

A separate series of studies by Martin and colleagues[50] of 31 men given 300 mg of testosterone implants with varying doses of oral desogestrel over 8 weeks found no significant adverse metabolic or behavioral effects. Although their objective was primarily to study the hormonal and metabolic effects of this regimen, they were able to demonstrate azoospermia and oligospermia with 300 μg of desogestrel in 10 of 10 patients at 8 weeks.

Given the historical difference in spermatogenesis suppression between white and Asian men, Kinniburgh and colleagues[27] compared daily oral desonogestrel at 150 or 300 μg with 400 mg testosterone pellet implants every 12 weeks between 2 cohorts in Edinburgh, Scotland (n = 30) and Shanghai, China (n = 36). There were slight differences between the 2 in the rate at which severe oligospermia was achieved but overall, each cohort achieved azoospermia with 300 μg desonogestrel by 24 weeks with 90% achieving it by 16 weeks. Paradoxically, the white cohort achieved azoospermia faster and at the lower dose of desonogestrel. The regimen was well tolerated with single individuals experiencing labile mood, worsening acne, hypertension, pellet discomfort, and weight gain, and 2 men experienced pellet expulsion.

Kinniburgh and colleagues[51] also demonstrated no added benefit of the 5α-reductase inhibitor finasteride to spermatogenesis inhibition with a regimen of 150 μg desonogestrel (a known submaximal dose) with 400 mg implantable testosterone. The rationale behind that study was that some of the nonresponders may have increased intratesticular testosterone levels being converted to the more powerful androgen dihydrotestosterone (DHT) by 5α-reductase and supporting spermatogenesis. However, finasteride and other 5α-reductase inhibitors have no action on testosterone directly and thus any intratesticular testosterone present may still support spermatogenesis. In addition, intratesticular testosterone levels may increase as a result of finasteride, counteracting any reduction in DHT. In yet another follow-up study, efficacy of implantable testosterone was also demonstrated with etonogestrel implants.[52] Single etonogestrel implants may be effective for up to 3 years in women, however, 3 pellets at a time were required to achieve sufficient azoospermia. One of 9 men did not sustain azoospermia after 40 weeks, raising the question of relative durability of the etonogestrel implants, which need to be removed surgically.

Transdermal

With the intention of facilitating patient autonomy and allowing self-administration (or user-independent administration), several groups have studied transdermal formulations of testosterone for contraceptive purposes. Historically, these studies have not been promising, even with the addition of a progestin because of low serum levels insufficient for LH and FSH suppression.[53,54] Guerin and Rollet[37] achieved azoospermia with testosterone gel and oral norethisterone acetate in 12 of 12 volunteers but this was not a durable response and by 3 months the average count was more than 3 million sperm/mL.

Several recent proof-of-concept studies of testosterone gels combined with either progesterone monthly depot injections or gels have been able to achieve severe oligospermia of less than 1 million sperm/mL in approximately 90% in moderate-sized cohorts.[55,56] Ilani and colleagues[55] achieved this with a nonandrogenic progestin nestoron gel with testosterone gel in 99 patients at around 22 weeks and azoospermia in 78% of patients. This regimen was fairly well tolerated with no severe adverse events and only side effects of mild-to-moderate acne in 21% and headaches in 17%, with the remaining side effects occurring infrequently.

Page and colleagues[56] achieved this using testosterone gel with DMPA every 3 months in 38 men. Although they did not report any azoospermia, they found the addition of the injectable GnRH antagonist acyline to progesterone and testosterone had no improvement. This regimen was also fairly well tolerated but had a high incidence of mild acne (26 of 38 men) as had been seen in previous studies. The primary consideration of testosterone gel is the avoidance of contact with the applied area to female partners and other persons shortly after application because of concern for androgenization.

Addition of GnRH Antagonists

Gonadotropin-releasing hormone (GnRH) antagonists compete with endogenous GnRH but do not activate pituitary receptors and thereby inhibit production and release of FSH and LH. In addition, GnRH agonists have similar effects when given in a nonpulsatile continuous fashion but have proved to be ineffective in demonstrating durable suppression of spermatogenesis and blunt the suppressive effects of androgens.[57–59]

Similar to progestins, GnRH antagonists have synergy when combined with testosterone in inhibiting spermatogenesis. Several antagonists have been studied in combination with androgens such as Nal-Glu, acyline, cetrorelix, and abarelix.

Bagatell and colleagues[60] found no increased efficacy of daily subcutaneous injections of Nal-Glu to weekly 200 mg intramuscular injections of TE in a study of 22 men. This is not a surprising finding considering that the same dose of TE alone had already been found to be relatively efficacious in previous studies.[24,25] In a follow-up study of 15 men, the same group found that Nal-Glu combined with TE was an effective induction agent for contraception with weekly low (100 mg) intramuscular TE injections as maintenance for 20 weeks with a failure rate of 6.7%.[61]

Another small study of 6 men induced with cetrorelix and maintained on intramuscular injections of the selective androgen 19-nortestosterone hexyloxyphenylpropionate (19-NT-HPP) every 3 weeks did not show durable spermatogenesis suppression.[62] This was believed to be partly due to the nonaromatizable property of 19-NT, which eliminated the suppressive effects that estradiol has on LH and FSH release seen with testosterone-based regimens.

Although further developments of GnRH/androgen combinations are expected, the disadvantages of GnRH antagonists include their relatively frequent local skin reactions, and cost. These may improve with future developments and do not constitute a reason for abandoning further efforts.

7α-Methyl-19-Nortestosterone

7α-Methyl-19-nortestosterone (MENT) is a potent synthetic androgen resistant to 5α-reductase but sensitive to aromatase. MENT is classified as a selective androgen receptor modulator (SARM), a class of drugs currently under early development. SARMs are of particular interest, not only because of a potentially favorable side effect profile but also because a particular subclass of SARMs called nonsteroidal SARMs exist in oral formulations that may make male hormonal contraception more appealing to a broader group of men.[63] MENT's properties make it an appealing agent for its minimal effects on prostatic hypertrophy as well increased potency for spermatogenesis inhibition. MENT has already demonstrated efficacy in small studies as a solitary agent in an implantable form for up to 1 year.[64] However, further development is needed as a recent study demonstrated inferiority when combined with implantable etonogestrel compared with an implantable testosterone and etonogestrel combination with regard to rate of azoospermia and durability of severe oligospermia.[65] This was believed to be caused by inadequate release of MENT from the currently manufactured implants and follow-up studies are expected in the near future on improved implants.[66]

Overview of Hormonal Contraceptives

A meta-analysis of 1549 men who underwent 1283.5 man-years of treatment and 705-man-years of recovery showed a median time to recovery of 20 million sperm/mL of 3.4 months and 100% recovered within 24 months.[28] As can be expected, longer-acting preparations, such as TU or implants, were associated with longer recovery and the opposite for shorter-acting agents such as transdermal, TE, or oral formulations. A follow-up meta-analysis confirmed that addition of progesterone increases the rate and extent of spermatogenesis suppression, recommending its addition to any hormonal regimen.[67]

Although most men do not experience loss of testicular volume, a reversible loss of 4 to 5 mL is not uncommon.[68] Alterations in mood such as irritability, depression, lability, or libido changes have been reported in less than 1%[30] to 73% of men.[69] Clearly, the preliminary news of the TU/NET-EN study being prematurely terminated at least partially due to a greater than expected incidence of effects on mood and libido is concerning. However, until final reports are published, it is difficult to draw any conclusions, especially when previous reports have been generally favorable.

Effects on lipids have been variable with generally decreased lipids either isolated to HDL or total lipids or increased total lipids or low-density lipoprotein, alternating between being proatherosclerotic or antiatherosclerotic.[68] This is also balanced by an increased percentage of lean body mass with lower body fat. Overall, the effects of testosterone on cardiovascular health are not known, with conflicting literature suggesting that the effects are likely negligible.[70]

Relatively common complaints pertaining to acne or night sweats may be bothersome to some individuals and should not be a deterrent to use. In a large-scale study of 1045 men, 7% reported acne but none withdrew because of it.[30] Other dermatologic complaints such as skin irritation or injection site tenderness may be more concerning and are limited to the route of administration.

Exogenous testosterone does not increase the risk of prostate hyperplasia and carcinoma, particularly when attempting to achieve a eugonadal state.[70] However, in a patient with known prostate hypertrophy or carcinoma, it would be reasonable to avoid these agents until further data are gathered.

Studies attempting to predict responders from nonresponders by measuring changes in FSH and LH have not been able to differentiate the two. This point has also been rendered moot with the high efficacy rates under regimens using supplemental progestin analogues.

NONHORMONAL CONTRACEPTION

Nonhormonal male contraception has been in development for as long as hormonal contraception but with less clinical success. Conceptually, it is appealing for the theoretic lack of systemic side effects seen with hormonal contraception. Unfortunately, less development has taken place than with hormonal contraception and most agents have been plagued by side effects, reversibility, and efficacy issues, leading to few phase 2 or 3 studies.

Pharmacologic

Gossypol

Gossypol is a phenolic compound derived from the cotton plant. It may be second to hormonal contraception in the volume of published literature including phase 3 trials of more than 8000 subjects.[71,72] It has been studied for its male-specific antifertility effects since the 1970s[73] and is believed to work by inhibiting spermatogenesis and sperm motility. Although highly efficacious in 90%,[72] it has exhibited a narrow therapeutic range with a frequent association with hypokalemia, a 1% incidence of periodic paralysis, and a 5% to 50% incidence of irreversible sterility. Despite numerous attempts at chemical modification and purification of gossypol, it has been all but disqualified from further clinical development for contraceptive purposes.[74]

Triptolide

Triptolide is derived from the Chinese herb *Tripterigium wilfordii* and belongs to the class of chemicals called diterpene epoxides. Having been used for medicinal and insecticide purposes for centuries, it gained attention for its infertility effects in the 1980s.[75] As an orally administered agent, triptolide impairs sperm motility and has been shown to decrease epididymal sperm counts at the posttesticular level.[76,77] It was incidentally found in studies of patients with rheumatoid arthritis where it was studied for its immunosuppressive effects.[78] Unfortunately, prolonged exposure was associated with irreversible inhibition of spermatogenesis and further studies as a contraceptive have been all but abandoned.[63,77]

Indenopyridines

Indenopyridines have been shown to inhibit spermatogenesis in several animal studies since the 1970s.[79] They are believed to affect Sertoli cells and recent primate studies of *l*-CDB-4022 especially have been promising.[80] Concerns about indenopyridines have centered on Sertoli cell toxicity and irreversibility, which was seen in rat models. *l*-CDB-4022, as a newer formulation, may have a more favorable profile but further studies are needed to evaluate its safety and efficacy.

Lonidamine derivates

Lonidamine, initially studied for its anticancer properties, was found to be antispermatogenic in the 1970s.[81] Side effects of muscular pain, testicular pain, vomiting, and liver damage halted further development; however, its less toxic derivatives adjudin and gamendazole were also investigated and developed for contraceptive purposes.

Adjudin, formerly called AF-2364, was discovered in the early 2000s.[82] It works primarily through disruption of the adhesion between spermatids and Sertoli cells causing premature spermiation. Because of the localized effect and absence of toxicity to Sertoli cells, this agent has drawn significant attention. By disrupting the sperm-Sertoli cell junction, the developing sperm are depleted but without toxicity or affecting FSH or LH levels, thereby maintaining future fertility. This site of action is also called the apical ectoplasmic specialization (apical ES). Although initial studies were promising with no detectable toxicity and 100% efficacy, in extended studies, 3 of 10 male rats treated with daily adjudin for 29 days developed minimal liver inflammation and skeletal muscle atrophy.[83] No female rats displayed any adverse effects. This prompted a series of studies pairing adjudin with FSH to lower the effective dose as FSH receptors in men are only found in the Sertoli cells. This lowered the minimum dose necessary but proved to be too costly and active

efforts are underway to continue to lower the effective dose required.[81]

Gamendazole was another product of the search for a less toxic lonidamine derivative. Although effective at well below toxic doses, gamendazole was irreversible in 43% of rats treated with the dose required to produce 100% infertility.[84]

CDB-4022 is an indenopyridine that also has shown effectiveness in nonhuman primate models in disrupting the Sertoli cell-germ cell junctions.[80] Unlike gamendazole, reversibility was readily achieved at effective doses and it was well tolerated overall with no observable adverse effects.

The lonidamine derivatives are an exciting new class of drugs for male contraception because of their selective activity at the Sertoli cell-germ cell junction, near complete absence of systemic effects, oral dosing with potential for extended dosing intervals, and reversibility.

Testicular retinoic acid inhibition

Vitamin A (retinol or retinoic acid) was first found to be essential to spermatogenesis when Wolbach and Howe[85] demonstrated the devastating effects its absence had on the testes in 1925 when they deprived rats of dietary vitamin A. Through studies of genetically manipulated mice and rats, the significance of retinoic acid and its receptor in spermatogenesis was elucidated and several promising male contraceptive agents working in this pathway have been studied.

WIN 18,446 is a potent bisdichloroacetyl diamine (BDAD) known to have selective and reversible inhibition of spermatogenesis since the 1960s.[86,87] In a study of 9 men, orally administered WIN 18,446 twice daily for 23 weeks, sperm counts were decreased to 0 to 4 million/mL within 8 to 11 weeks.[87] To our knowledge, this is the only reported clinical study of WIN 18,446 in humans; it was subsequently abandoned because of reports of disulfiram effects. Heller and colleagues[87] made no mention of a disulfiram reaction and the only reported complaint was related to gas and bloating. Regardless, interest in this agent has been renewed and modern studies have found that WIN 18,446 inhibits testicular retinoic acid synthesis from retinol through inhibition of the testis-specific acetaldehyde dehydrogenase ALDH1a2.[88] Blockade of this pathway results in a hormone-independent suppression of spermatogenesis while preserving normal testosterone levels and a eugonadal state. It is thought that WIN 18,446 also inhibits ALDH2 causing the disulfiram effect and that a more refined agent with selectivity for testicular ALDH1a2 would not cause the reported undesirable effects of WIN 18,446. In any event, repeat modern clinical studies of WIN 18,446 are warranted given its favorable safety profile.

Inhibition of testicular retinoic acid production results in decreased expression of the cytoplasmic factor Stra8 (stimulated by retinoic acid gene 8), which inhibits the entry of the spermatogonia into meiosis and thereby inhibits spermatogenesis.[89,90] This effect can be reversed simply by administering retinoic acid.[91] In addition, Stra8 may become a future pharmacologic target for male contraception.

Besides inhibition of testicular retinoic acid production, advancements have been made in selective inhibition of nuclear retinoic acid receptors (RAR). BMS (Bristol-Meyers-Squibb)-189453 is an arotinoid oral RAR antagonist. Unlike WIN 18,446, which works by depleting testicular retinoic acid and takes up to 16 weeks to produce azoospermia, BMS-189453 has a faster onset of 1 month with durable effects for 4 months after dosing.[92,93] Although low doses are effective at inhibiting spermatogenesis, high doses in rats are associated with toxicity and death with effects mimicking vitamin A toxicity or excessive retinoid agonists.[92] A repeat efficacy study in rats demonstrated 100% efficacy with no discernible side effects at low doses with almost total reversibility based on histologic appearance.[93]

Calcium channel blockers

Calcium has long been known to be important to sperm motility. However, before the discovery of CatSper (cation channels of sperm) in 2001, little was actually known about sperm calcium regulation.[94] Before this discovery, the effects of nifedipine, verapamil, and other calcium channel blockers on sperm motility were debated and reported on primarily through anecdotal or observational studies.[95,96] Although numerous CatSper knock-out mice studies exist,[97,98] little work has been done on developing CatSper blockers or antagonists. Carlson and colleagues[99] reported on a candidate CatSper blocker, HC-056456, with promising in vitro results. Li and colleagues[100] were able to decrease mouse pregnancy rates to 12.5% by immunizing male mice with extracellular epitopes of CatSper. Although CatSper understanding is in its infancy, its blockers offer a promising mechanism for future contraceptive agents.

Sperm Na^+/H^+ exchanger

Similar to CatSper, a novel class of sperm-specific Na^+/H^+ exchangers (sNHE) has been identified and found to be crucial to regulation of the intracellular pH of spermatozoa.[101,102] Mice with inactivated sNHEs produced morphologically normal sperm with impaired motility resulting in infertility.

Further work needs to done on sNHE blockers, but current data allows for optimism about the possibility of these agents.

Inhibitors of glycosphingolipid synthesis

Miglustat, or *N*-butyldeoxynojirimycin (NB-DNJ), is an alkylated imino sugar that inhibits ceramide-specific glucosyltransferase. It is approved for the treatment of type I Gaucher disease, which results in excess glycosphingolipids. Oral administration of NB-DNJ in mice has demonstrated significant, reversible infertility in a dose-responsive pattern producing morphologically abnormal sperm with impaired motility[103] and ultimately oligospermia.[104] Unfortunately, in a small pilot study of 7 men over 6 weeks, miglustat had no discernible effect on sperm concentration, motility, or morphology despite attaining comparable serum levels.[105] Possibilities for the discordant findings are that there is a species-specific response, 6 weeks was insufficient to detect a significant difference in spermatogenesis, or the dose was insufficient. Although it may seem tempting to use an agent already approved by the US Food and Drug Administration, further work needs to be done to demonstrate efficacy in humans before miglustat is seen as a potential male contraceptive.

Bromodomain BRDT inhibitor (JQ1)

The latest class of agents to find usefulness as male contraceptives are the inhibitors of the testis-specific protein BRDT. BRDT functions to reorganize hyperacetylated histones through recognition modules called bromodomains. Male mice with selective mutation of BRDT were found to have isolated infertility.[106] In a study of healthy men with idiopathic oligospermia or azoospermia, single nucleotide polymorphisms associated with the BRDT gene were found to be a significantly associated factor.[107] BRDT is activated at the onset of meiosis of spermatocytes,[108] making it a desirable target of reversible infertility.

JQ1 is an orally bioavailable triazolothienodiazepine, related to benzodiazepines, and is the first BRDT inhibitor. In mice, its administration results in impaired spermatogenesis, reduced sperm motility, and decreased testicular volume, mimicking the features of BRDT mutated mice.[109] These effects are reversible and have no discernible hormonal or other systemic effects.

Thermal

Although spermatogenesis is negatively affected by temperature increases, heating the scrotum 0.8 to 1.0°C with thermal supports or underwear alone is not a reliable mechanism for contraception.[110] However, in a recent study, the addition of scrotal submersion in a 43°C water bath for 30 minutes per day for 6 days was found to accelerate oligospermia when combined with TU injections every 6 weeks but not to the extent of TU combined with oral levonorgestrel and never to contraceptive levels of less than 1 million sperm/mL.[111] Perhaps future studies will find other contraceptive regimens, hormonal or otherwise, that are enhanced or activated by the addition of heat.

Ultrasound

Ultrasound application for male contraceptive purposes has many appealing conceptual features. First, ultrasound machines are relatively inexpensive and widely available. Second, ultrasound works locally with no systemic effects and, third, it would be appealing to those who are averse to taking medications regularly. In the 1970s, a series of experiments by Fahim demonstrated reversible inhibition of spermatogenesis with ultrasound.[112–114] However, subsequent efforts to reproduce or study ultrasound-mediated male contraception were not promising.[115,116] Recently, Tsuruta and colleagues[117] revisited this concept attempting to reproduce Fahim's results while characterizing and optimizing the ultrasound application. They demonstrated a depletion of rat epididymal sperm reserves within 2 weeks of treatment. VandeVoort[118] studied 4 monkeys using slightly higher settings and demonstrated decreased sperm count and motility and reversibility.

The mechanism of action is uncertain and may be a combined effect of localized tissue heating combined with an additional ultrasound-mediated local phenomenon. Treatments are administered by placing the scrotum in a water bath within the beam filed of an ultrasound transducer. Tsuruta and colleagues[117] used a treatment time of 15 minutes and interval of 2 days between treatments, whereas Vandevoort[118] used a treatment time of 30 minutes and a similar interval of every 2 days for 3 treatments.

Vasal Occlusion/Interruption

Intravas device

Vasectomy alternatives with higher rates of reversal have been sought out since the 1960s.[119] To this end, a class of implants named intravas devices (IVD) was developed. A group in China has developed a urethane device filled with nylon thread that blocks sperm but allows the passage of fluid and is inserted through a small scrotal incision identical to that used for vasectomy. In a randomized control study of 288 patients comparing no-scalpel vasectomy to this device, both groups

tolerated the procedure well.[120] However, statistically insignificant inferiority was seen with the device with a contraceptive success rate of 94.3% at 12 months compared with 98.6% for the vasectomy group. Reversal was not studied.

Another group in China developed a nano-SiO_2-copper polymer composite IVD and studied the effect in 8 dogs over 12 months.[121] After 3 months, no motile sperm were seen and no obvious damage was seen to the testes, epididymis, or vas, histologically suggesting that fertility was preserved and the potential for reversibility was high. In a follow-up study, the same group evaluated the same device in dogs and rabbits randomly assigned to vasectomy, sham procedure, IVD, or reversal for 12 months.[122] Reversal success was measured with birth rates in rabbits, which were 60% for the device reversal but only 80% for the sham reversal, suggesting perhaps an inadequate recovery period, which was not stated.

Reversible inhibition of sperm under guidance

Reversible inhibition of sperm under guidance (RISUG) is the trademark name of an injectable contraceptive technique developed in the 1970s.[123] RISUG involves injection of styrene maleic anhydride (SMA) dissolved in dimethyl sulfoxide (DMSO) into the vas under direct visualization through a small incision. A nonsclerosing porous polymer then forms and disrupts the sperm cell membranes as they traverse the vas, producing damaged, nonviable sperm. Primarily developed in India, several phase 2 studies have demonstrated efficacy of RISUG.[124,125] In these studies, men attained azoospermia within 1 to 4 months and over 6 months no pregnancies were reported.

In achieving reversal of RISUG, clearly noninvasive methods are preferable to a repeat surgery. In a study of 9 monkeys treated with RISUG for 3 months, 100% reversibility was achieved using a progressive percutaneous method of squeezing the vas toward the inguinal canal, application of electrical stimulation, and digital rectal massage over the ampullary segment of the vas.[126]

In a study of monkeys 1.5 years after RISUG injection, testicular biopsies demonstrated focal changes consistent with vasal occlusion with damage to the seminiferous epithelium; however, most of the testicle showed active and viable spermatogenesis and this was believed to be due to oxidative stress and not from occlusive pressure.[127] Sperm viability and reversibility were evaluated in a later study that showed equivalent reversal to shorter trials.[128]

In a rat study, Lohiya and colleagues[129] demonstrated 100% fertility 3 months after reversal of RISUG with DMSO directly injected into the vas under visualization. In a follow-up study, the same group showed no evidence of DNA damage in a group of similarly treated rats.[130]

RISUG is currently being evaluated in preclinical trials under the trademark name Vasalgel in the United States.[131,132] Although the proof of principle has been established with intravasal injection of SMA polymer and the results have been promising, significant evaluation still remains to be done with larger multicenter clinical trials. Concerns regarding intravasal SMA center primarily on the teratogenic effects they may have on sperm and reversibility. This method may ultimately be advertised primarily as a vasectomy alternative with higher rates of reversibility but not as high as an ideal reversible contraceptive.

Immunologic

The development of vaccines against sperm or their components has been studied since the 1930s.[133] Female animal studies in the 1950s, 1960s, and 1970s showed effective induced infertility when inoculated with varied sperm preparations.[134–137] These crude formulations also caused early termination of pregnancy leading to concern about birth abnormalities. Similar to other nonhormonal contraceptive methods, immunologic induction of infertility offers the promise of localized action and absence of systemic effects. Up to 60% of men develop antisperm antibodies after vasectomy without any clinical effects except a lower probability of success after vasectomy reversal.[138]

Primakoff and colleagues[139] demonstrated effective and reversible infertility in both male and female guinea pigs immunized with sperm plasma and inner acrosomal membrane protein PH-20. However, PH-20 immunization is associated with orchitis and little development has taken place since the initial proof-of-principle study.[140]

Eppin (epididymal protease inhibitor) is a protein expressed in the testis and epididymis only. It forms a complex on ejaculated spermatozoa with the major seminal vesicle protein semenogelin and is believed to protect the sperm from microbes and proteolysis and to facilitate sperm motility.[141] In addition, eppin facilitates the cleavage of semenogelin by prostate-specific antigen (PSA) resulting in liquefaction of the coagulum and facilitating spermatozoal motility.[142] In 1 primate study, injections of eppin into male monkeys every 3 weeks produced infertility in 78% with measurably high antieppin antibody titers.[143] Seventy-one percent of those monkeys recovered fertility after cessation of immunizations. Recovery and nonresponsiveness were associated with low titers, suggesting

a direct reversible immunologic contraceptive mechanism. It is thought that the antieppin antibody-eppin complex that forms on spermatozoa is equivalent to the eppin-semenogelin complex with regard to intracellular signaling; however, it is not cleaved by PSA like the native complex and, as a result, motility is impaired.[144] Through mechanisms that remain unknown, this complex keeps the intracellular calcium levels low in sperm and prevents capacitation.[145] Clearly, substitution of unpredictable biological inhibition achieved with immunization of the eppin-semenogelin complex for a pharmacologic compound would be more favorable as it would provide more precise regulation with less variability. Efforts are already underway to generate a recombinant semenogelin that would perform the same task as the antieppin antibodies without requiring immune activation.[146,147]

SUMMARY

Despite not a single new male contraceptive being brought to the market since the advent of vasectomy, a tremendous amount of research has been done in the field. Occasionally, these agents have brought devastatingly disappointing findings, side effects, incomplete efficacy, or irreversibility, and nearly all require further development. But pharmaceutical financial investment in developing agents has all but been abandoned since 2006.[148] Current efforts rely on nonprofit organizations and charities such as the WHO, Population Council, and Parsemus Foundation despite evidence that a strong market exists for alternative male contraception.[2,3,149,150] However, even these endowments are dwindling. In a recent communication with Tsuruta, the Gates Foundation had recently withdrawn further support on ultrasound-based male contraception in an effort to focus efforts on female contraceptive measures. The attention and narrative of male contraception needs to change from witty headlines about the possibility of a male pill to an acceptance of these as viable alternatives.

Hormonal contraceptives in the form of a parenterally administered androgen and progesterone with extended dosing intervals are at the forefront of upcoming options. Many more promising agents such as adjudin, CBD-4022, WIN 18,446, eppin antagonists, BMS-189453, JQ1, CatSper blockers, sNHE blockers, and RISUG offer promising alternatives to the few options currently available to men. The prolonged period of relative male contraceptive unavailability may have been a blessing in disguise in that it has spurred the development of many promising alternatives. Had an alternative agent been brought to market long ago, it may have dominated like the female hormonal contraceptive and suppressed investigation of improved and refined alternative agents. With time, it is to be hoped that these agents will come to market, decreasing the contraceptive burden on women and help avoid unplanned pregnancies.

FUTURE PERSPECTIVES

We believe that in 20 years, men will share a greater portion of contraceptive responsibilities. The decades spent on research and development will potentially offer a greater variety of options ranging from surgical, mechanical, or pharmacologic than those currently available. With the progressive miniaturization of electronics, it seems conceivable that a small electronic cuff could be surgically implanted around the vasa that constricts or releases via external wireless signaling. This could offer easy reversibility in the event it is either poorly tolerated or fertility is desired. Ultimately, more than most if not all aspects of medicine, contraceptive use is driven by the patient consumer.

REFERENCES

1. World contraceptive use 2009. United Nations, Department of Economic and Social Affairs, Population Division (2009). Available at: http://www.un.org/esa/population/publications/WCU2009/WCP_2009/Data.html. Accessed March 17, 2013.
2. Grady WR, Tanfer K, Billy JO, et al. Men's perceptions of their roles and responsibilities regarding sex, contraception and childrearing. Fam Plann Perspect 1996;28:221–6.
3. Heinemann K, Saad F, Wiesemes M, et al. Attitudes toward male fertility control: results of a multinational survey on four continents. Hum Reprod 2005;20:549–56.
4. Youssef H. The history of the condom. J R Soc Med 1993;86:226–8.
5. Trussell J. Contraceptive failure in the United States. Contraception 2011;83:397–404.
6. Kost K, Singh S, Vaughan B, et al. Estimates of contraceptive failure from the 2002 National Survey of Family Growth. Contraception 2008;77:10–21.
7. Sheynkin YR. History of vasectomy. Urol Clin North Am 2009;36:285–94.
8. Some of the indications for vasectomy. J Am Med Assoc 1900;35:1412.
9. Castration and vasectomy in hypertrophy of the prostate. Lancet 1897;149:1286.
10. Ochsner AJ. Surgical treatment of habitual criminals. J Am Med Assoc 1899;32:867–8.

11. Pile JM, Barone MA. Demographics of vasectomy–USA and international. Urol Clin North Am 2009;36:295–305.
12. Chandra A, Martinez GM, Mosher WD, et al. Fertility, family planning, and reproductive health of U.S. women: data from the 2002 National Survey of Family Growth. Vital Health Stat 23 2005;(25):1–160.
13. Anderson JE, Jamieson DJ, Warner L, et al. Contraceptive sterilization among married adults: national data on who chooses vasectomy and tubal sterilization. Contraception 2012;85:552–7.
14. Eisenberg ML, Lipshultz LI. Estimating the number of vasectomies performed annually in the United States: data from the National Survey of Family Growth. J Urol 2010;184:2068–72.
15. Barone MA, Hutchinson PL, Johnson CH, et al. Vasectomy in the United States, 2002. J Urol 2006;176:232–6.
16. Sharlip ID, Belker AM, Honig S, et al. Vasectomy: AUA guideline. J Urol 2012;188(Suppl 6):2482–91.
17. Awsare NS, Krishnan J, Boustead GB, et al. Complications of vasectomy. Ann R Coll Surg Engl 2005;87:406–10.
18. Leslie TA, Illing RO, Cranston DW, et al. The incidence of chronic scrotal pain after vasectomy: a prospective audit. BJU Int 2007;100:1330–3.
19. Heckel NJ. Production of oligospermia in a man by the use of testosterone propionate. Proc Soc Exp Biol Med 1939;40:658–9.
20. Nieschlag E, Zitzmann M, Kamischke A. Use of progestins in male contraception. Steroids 2003;68:965–72.
21. Wu FC. Hormonal approaches to male contraception: approaching reality. Mol Cell Endocrinol 2006;250:2–7.
22. Turner L, Conway AJ, Jiminez M, et al. Contraceptive efficacy of a depot progestin and androgen combination in men. J Clin Endocrinol Metab 2003;88:4659–67.
23. Amory JK, Page ST, Anawalt BD, et al. Acceptability of a combination testosterone gel and depomedroxyprogesterone acetate male contraceptive regimen. Contraception 2007;75:218–23.
24. Contraceptive efficacy of testosterone-induced azoospermia and oligozoospermia in normal men. Fertil Steril 1996;65:821–9.
25. Contraceptive efficacy of testosterone-induced azoospermia in normal men. World Health Organization Task Force on methods for the regulation of male fertility. Lancet 1990;336:955–9.
26. Ilani N, Liu PY, Swerdloff RS, et al. Does ethnicity matter in male hormonal contraceptive efficacy? Asian J Androl 2011;13:579–84.
27. Kinniburgh D, Zhu H, Cheng L, et al. Oral desogestrel with testosterone pellets induces consistent suppression of spermatogenesis to azoospermia in both Caucasian and Chinese men. Hum Reprod 2002;17:1490–501.
28. Liu PY, Swerdloff RS, Christenson PD, et al. Rate, extent, and modifiers of spermatogenic recovery after hormonal male contraception: an integrated analysis. Lancet 2006;367:1412–20.
29. Comparison of two androgens plus depot-medroxyprogesterone acetate for suppression to azoospermia in Indonesian men. World Health Organization. Task Force on Methods for the Regulation of Male Fertility. Fertil Steril 1993;60:1062–8.
30. Gu Y, Liang X, Wu W, et al. Multicenter contraceptive efficacy trial of injectable testosterone undecanoate in Chinese men. J Clin Endocrinol Metab 2009;94:1910–5.
31. Nieschlag E. Testosterone treatment comes of age: new options for hypogonadal men. Clin Endocrinol (Oxf) 2006;65:275–81.
32. Lue Y, Wang C, Cui Y, et al. Levonorgestrel enhances spermatogenesis suppression by testosterone with greater alteration in testicular gene expression in men. Biol Reprod 2009;80:484–92.
33. Bebb RA, Anawalt BD, Christensen RB, et al. Combined administration of levonorgestrel and testosterone induces more rapid and effective suppression of spermatogenesis than testosterone alone: a promising male contraceptive approach. J Clin Endocrinol Metab 1996;81:757–62.
34. Wu FC, Balasubramanian R, Mulders TM, et al. Oral progestogen combined with testosterone as a potential male contraceptive: additive effects between desogestrel and testosterone enanthate in suppression of spermatogenesis, pituitary-testicular axis, and lipid metabolism. J Clin Endocrinol Metab 1999;84:112–22.
35. Meriggiola MC, Bremner WJ, Costantino A, et al. Low dose of cyproterone acetate and testosterone enanthate for contraception in men. Hum Reprod 1998;13:1225–9.
36. Soufir JC, Meduri G, Ziyyat A. Spermatogenetic inhibition in men taking a combination of oral medroxyprogesterone acetate and percutaneous testosterone as a male contraceptive method. Hum Reprod 2011;26:1708–14.
37. Guerin JF, Rollet J. Inhibition of spermatogenesis in men using various combinations of oral progestagens and percutaneous or oral androgens. Int J Androl 1988;11:187–99.
38. Zitzmann M, Erren M, Kamischke A, et al. Endogenous progesterone and the exogenous progestin norethisterone enanthate are associated with a proinflammatory profile in healthy men. J Clin Endocrinol Metab 2005;90:6603–8.
39. Kamischke A, Venherm S, Plöger D, et al. Intramuscular testosterone undecanoate and norethisterone enanthate in a clinical trial for male contraception. J Clin Endocrinol Metab 2001;86:303–9.

40. Larkin A. Male hormonal contraceptive trial ending early 2011. Available at: http://www.conrad.org/news-pressreleases-63.html. Accessed May 17, 2013.
41. Foegh M, Damgaard-Pedersen F, Gormsen J, et al. Oral levo-norgestrel - testosterone effects on spermatogenesis, hormone levels, coagulation factors and lipoproteins in normal men. Contraception 1980;21:381–91.
42. Bain J, Rachlis V, Robert E, et al. The combined use of oral medroxyprogesterone acetate and methyltestosterone in a male contraceptive trial programme. Contraception 1980;21:365–79.
43. Amory JK, Bush MA, Zhi H, et al. Oral testosterone with and without concomitant inhibition of 5alpha-reductase by dutasteride in hypogonadal men for 28 days. J Urol 2011;185:626–32.
44. Meriggiola MC, Bremner WJ, Costantino A, et al. An oral regimen of cyproterone acetate and testosterone undecanoate for spermatogenic suppression in men. Fertil Steril 1997;68:844–50.
45. Vest SA, Howard JE. Clinical experiments with androgens: IV. A method of implantation of crystalline testosterone. J Am Med Assoc 1939;113:1869–72.
46. Handelsman DJ, Conway AJ, Boylan LM. Suppression of human spermatogenesis by testosterone implants. J Clin Endocrinol Metab 1992; 75:1326–32.
47. Handelsman DJ, Conway AJ, Howe CJ, et al. Establishing the minimum effective dose and additive effects of depot progestin in suppression of human spermatogenesis by a testosterone depot. J Clin Endocrinol Metab 1996;81:4113–21.
48. Handelsman DJ, Conway AJ, Boylan LM. Pharmacokinetics and pharmacodynamics of testosterone pellets in man. J Clin Endocrinol Metab 1990;71: 216–22.
49. Handelsman DJ, Wishart S, Conway AJ. Oestradiol enhances testosterone-induced suppression of human spermatogenesis. Hum Reprod 2000; 15:672–9.
50. Martin CW, Riley SC, Everington D, et al. Dose-finding study of oral desogestrel with testosterone pellets for suppression of the pituitary-testicular axis in normal men. Hum Reprod 2000;15:1515–24.
51. Kinniburgh D, Anderson RA, Baird DT. Suppression of spermatogenesis with desogestrel and testosterone pellets is not enhanced by addition of finasteride. J Androl 2001;22:88–95.
52. Brady BM, Walton M, Hollow N, et al. Depot testosterone with etonogestrel implants result in induction of azoospermia in all men for long-term contraception. Hum Reprod 2004;19:2658–67.
53. Pollanen P, Nikkanen V, Huhtaniemi I. Combination of subcutaneous levonorgestrel implants and transdermal dihydrotestosterone gel for male hormonal contraception. Int J Androl 2001;24:369–80.
54. Büchter D, von Eckardstein S, von Eckardstein A, et al. Clinical trial of transdermal testosterone and oral levonorgestrel for male contraception. J Clin Endocrinol Metab 1999;84:1244–9.
55. Ilani N, Roth MY, Amory JK, et al. A new combination of testosterone and nestorone transdermal gels for male hormonal contraception. J Clin Endocrinol Metab 2012;97:3476–86.
56. Page ST, Amory JK, Anawalt BD, et al. Testosterone gel combined with depomedroxyprogesterone acetate is an effective male hormonal contraceptive regimen and is not enhanced by the addition of a GnRH antagonist. J Clin Endocrinol Metab 2006; 91:4374–80.
57. Rabin D, Evans RM, Alexander AN, et al. Heterogeneity of sperm density profiles following 20-week therapy with high-dose LHRH analog plus testosterone. J Androl 1984;5:176–80.
58. Behre HM, Nashan D, Hubert W, et al. Depot gonadotropin-releasing hormone agonist blunts the androgen-induced suppression of spermatogenesis in a clinical trial of male contraception. J Clin Endocrinol Metab 1992;74:84–90.
59. Linde R, Doelle GC, Alexander N, et al. Reversible inhibition of testicular steroidogenesis and spermatogenesis by a potent gonadotropin-releasing hormone agonist in normal men: an approach toward the development of a male contraceptive. N Engl J Med 1981;305:663–7.
60. Bagatell CJ, Matsumoto AM, Christensen RB, et al. Comparison of a gonadotropin releasing-hormone antagonist plus testosterone (T) versus T alone as potential male contraceptive regimens. J Clin Endocrinol Metab 1993;77:427–32.
61. Swerdloff RS, Bagatell CJ, Wang C, et al. Suppression of spermatogenesis in man induced by Nal-Glu gonadotropin releasing hormone antagonist and testosterone enanthate (TE) is maintained by TE alone. J Clin Endocrinol Metab 1998;83:3527–33.
62. Behre HM, Kliesch S, Lemcke B, et al. Suppression of spermatogenesis to azoospermia by combined administration of GnRH antagonist and 19-nortestosterone cannot be maintained by this non-aromatizable androgen alone. Hum Reprod 2001; 16:2570–7.
63. Page ST, Amory JK, Bremner WJ. Advances in male contraception. Endocr Rev 2008;29:465–93.
64. von Eckardstein S, Noe G, Brache V, et al. A clinical trial of 7 alpha-methyl-19-nortestosterone implants for possible use as a long-acting contraceptive for men. J Clin Endocrinol Metab 2003;88:5232–9.
65. Walton MJ, Kumar N, Baird DT, et al. 7alpha-methyl-19-nortestosterone (MENT) vs testosterone in combination with etonogestrel implants for spermatogenic suppression in healthy men. J Androl 2007;28:679–88.

66. Nieschlag E, Kumar N, Sitruk-Ware R. 7alpha-Methyl-19-nortestosterone (MENTR): the Population Council's contribution to research on male contraception and treatment of hypogonadism. Contraception 2013;87:288–95.
67. Liu PY, Swerdloff RS, Anawalt BD, et al. Determinants of the rate and extent of spermatogenic suppression during hormonal male contraception: an integrated analysis. J Clin Endocrinol Metab 2008;93:1774–83.
68. Ilani N, Swerdloff RS, Wang C. Male hormonal contraception: potential risks and benefits. Rev Endocr Metab Disord 2011;12:107–17.
69. Mommers E, Kersemaekers WM, Elliesen J, et al. Male hormonal contraception: a double-blind, placebo-controlled study. J Clin Endocrinol Metab 2008;93:2572–80.
70. Fernández-Balsells MM, Murad MH, Lane M, et al. Adverse effects of testosterone therapy in adult men: a systematic review and meta-analysis. J Clin Endocrinol Metab 2010;95:2560–75.
71. Liu GZ, Lyle KC. Clinical trial of gossypol as a male contraceptive drug. Part II. Hypokalemia study. Fertil Steril 1987;48:462–5.
72. Liu GZ, Lyle KC, Cao J. Clinical trial of gossypol as a male contraceptive drug. Part I. Efficacy study. Fertil Steril 1987;48:459–61.
73. Gossypol–a new antifertility agent for males. Gynecol Obstet Invest 1979;10:163–76.
74. Waites GM, Wang C, Griffin PD. Gossypol: reasons for its failure to be accepted as a safe, reversible male antifertility drug. Int J Androl 1998;21:8–12.
75. Zhen QS, Ye X, Wei ZJ. Recent progress in research on tripterygium – a male antifertility plant. Contraception 1995;51:121–9.
76. Lue YH, Hikim AP, Wang C, et al. Triptolide: a potential male contraceptive. J Androl 1998;19:479–86.
77. Huynh PN, Hikim AP, Wang C, et al. Long-term effects of triptolide on spermatogenesis, epididymal sperm function, and fertility in male rats. J Androl 2000;21:689–99.
78. Qian SZ. *Tripterygium wilfordii*, a Chinese herb effective in male fertility regulation. Contraception 1987;36:335–45.
79. Vickery BH. Non-steroidal interference with male fertility. Adv Contracept 1986;2:1–30.
80. Hild SA, Marshall GR, Attardi BJ, et al. Development of I-CDB-4022 as a nonsteroidal male oral contraceptive: induction and recovery from severe oligospermia in the adult male cynomolgus monkey (*Macaca fascicularis*). Endocrinology 2007;148:1784–96.
81. Mok KW, Mruk DD, Lie PP, et al. Adjudin, a potential male contraceptive, exerts its effects locally in the seminiferous epithelium of mammalian testes. Reproduction 2011;141:571–80.
82. Cheng CY, Silvestrini B, Grima J, et al. Two new male contraceptives exert their effects by depleting germ cells prematurely from the testis. Biol Reprod 2001;65:449–61.
83. Mruk DD, Wong CH, Silvestrini B, et al. A male contraceptive targeting germ cell adhesion. Nat Med 2006;12:1323–8.
84. Tash JS, Attardi B, Hild SA, et al. A novel potent indazole carboxylic acid derivative blocks spermatogenesis and is contraceptive in rats after a single oral dose. Biol Reprod 2008;78:1127–38.
85. Wolbach SB, Howe PR. Tissue changes following deprivation of fat-soluble A vitamin. J Exp Med 1925;42:753–77.
86. Coulston F, Beyler AL, Drobeck HP. The biologic actions of a new series of Bis(dichloroacetyel) diamines. Toxicol Appl Pharmacol 1960;2:715–31.
87. Heller CG, Moore DJ, Paulsen CA. Suppression of spermatogenesis and chronic toxicity in men by a new series of Bis(dichloroacetyel) diamines. Toxicol Appl Pharmacol 1961;3:1–7.
88. Amory JK, Muller CH, Shimshoni JA, et al. Suppression of spermatogenesis by bisdichloroacetyldiamines is mediated by inhibition of testicular retinoic acid biosynthesis. J Androl 2011;32:111–9.
89. Hogarth CA, Evanoff R, Snyder E, et al. Suppression of Stra8 expression in the mouse gonad by WIN 18,446. Biol Reprod 2011;84:957–65.
90. Anderson EL, Baltus AE, Roepers-Gajadien HL, et al. Stra8 and its inducer, retinoic acid, regulate meiotic initiation in both spermatogenesis and oogenesis in mice. Proc Natl Acad Sci U S A 2008;105:14976–80.
91. Hogarth CA, Evanoff R, Mitchell D, et al. Turning a spermatogenic wave into a tsunami: synchronizing murine spermatogenesis using WIN 18,446. Biol Reprod 2013;88:40.
92. Schulze GE, Clay RJ, Mezza LE, et al. BMS-189453, a novel retinoid receptor antagonist, is a potent testicular toxin. Toxicol Sci 2001;59:297–308.
93. Chung SS, Wang X, Roberts SS, et al. Oral administration of a retinoic acid receptor antagonist reversibly inhibits spermatogenesis in mice. Endocrinology 2011;52:2492–502.
94. Lishko PV, Kirichok Y, Ren D, et al. The control of male fertility by spermatozoan ion channels. Annu Rev Physiol 2012;74:453–75.
95. Hershlag A, Cooper GW, Benoff S. Pregnancy following discontinuation of a calcium channel blocker in the male partner. Hum Reprod 1995;10:599–606.
96. Katsoff D, Check JH. A challenge to the concept that the use of calcium channel blockers causes reversible male infertility. Hum Reprod 1997;12:1480–2.

97. Qi H, MOran MM, Navarro B, et al. All four CatSper ion channel proteins are required for male fertility and sperm cell hyperactivated motility. Proc Natl Acad Sci U S A 2007;104:1219–23.
98. Ren DJ, Navarro B, Perez G, et al. A sperm ion channel required for sperm motility and male fertility. Nature 2001;413:603–9.
99. Carlson AE, Burnett LA, del Camino D, et al. Pharmacological targeting of native CatSper channels reveals a required role in maintenance of sperm hyperactivation. PLoS One 2009;4:e6844.
100. Li H, Ding X, Guo C, et al. Immunization of male mice with B-cell epitopes in transmembrane domains of CatSper1 inhibits fertility. Fertil Steril 2012;97:445–52.
101. Wang D, King SM, Quill TA, et al. A new sperm-specific Na+/H+ exchanger required for sperm motility and fertility. Nat Cell Biol 2003;5:1117–22.
102. Wang D, Hu J, Bobulescu IA, et al. A sperm-specific Na+/H+ exchanger (sNHE) is critical for expression and in vivo bicarbonate regulation of the soluble adenylyl cyclase (sAC). Proc Natl Acad Sci U S A 2007;104:9325–30.
103. van der Spoel AC, Jeyakumar M, Butters TD, et al. Reversible infertility in male mice after oral administration of alkylated imino sugars: a nonhormonal approach to male contraception. Proc Natl Acad Sci U S A 2002;99:17173–8.
104. Walden CM, Butters TD, Dwek RA, et al. Long-term non-hormonal male contraception in mice using N-butyldeoxynojirimycin. Hum Reprod 2006;21:1309–15.
105. Amory JK, Muller CH, Page ST, et al. Miglustat has no apparent effect on spermatogenesis in normal men. Hum Reprod 2007;22:702–7.
106. Shang E, Nickerson HD, Wen D, et al. The first bromodomain of Brdt, a testis-specific member of the BET sub-family of double-bromodomain-containing proteins, is essential for male germ cell differentiation. Development 2007;134:3507–15.
107. Aston KI, Krausz C, Laface I, et al. Evaluation of 172 candidate polymorphisms for association with oligozoospermia or azoospermia in a large cohort of men of European descent. Hum Reprod 2010; 25:1383–97.
108. Gaucher J, Boussouar F, Montellier E, et al. Bromodomain-dependent stage-specific male genome programming by Brdt. EMBO J 2012;31:3809–20.
109. Matzuk MM, McKeown MR, Filippalopolous P, et al. Small-molecule inhibition of BRDT for male contraception. Cell 2012;150:673–84.
110. Wang C, McDonald V, Leung A, et al. Effect of increased scrotal temperature on sperm production in normal men. Fertil Steril 1997;68:334–9.
111. Wang C, Cui YG, Wang XH, et al. Transient scrotal hyperthermia and levonorgestrel enhance testosterone-induced spermatogenesis suppression in men through increased germ cell apoptosis. J Clin Endocrinol Metab 2007; 92:3292–304.
112. Fahim MS, Fahim Z, Harman J, et al. Ultrasound as a new method of male contraception. Fertil Steril 1977;28:823–31.
113. Fahim MS, Fahim Z, Der R, et al. Heat in male contraception (hot water 60 degrees C, infrared, microwave, and ultrasound). Contraception 1975; 11:549–62.
114. Dumontier A, Burdick A, Ewigman B, et al. Effects of sonication on mature rat testes. Fertil Steril 1977;28:195–204.
115. Bailey KI, Obrien WD, Dunn F. Ultrasonically induced, in vivo morphological damage in mouse testicular tissue. Arch Androl 1981;6:301–6.
116. Urry RL, Dougherty KA, Child SA, et al. Ultrasound and spermatogenesis in the rat. Ultrasound Med Biol 1988;14:213–7.
117. Tsuruta JK, Dayton PA, Gallippi CM, et al. Therapeutic ultrasound as a potential male contraceptive: power, frequency and temperature required to deplete rat testes of meiotic cells and epididymides of sperm determined using a commercially available system. Reprod Biol Endocrinol 2012;10:7.
118. VandeVoort CA, Tollner TL. The efficacy of ultrasound treatment as a reversible male contraceptive in the rhesus monkey. Reprod Biol Endocrinol 2012;10:81.
119. Lee HY. Experimental studies on reversible vas occlusion by intravasal thread. Fertil Steril 1969;20: 735–7.
120. Song L, Gu Y, Liang X, et al. A phase II randomized controlled trial of a novel male contraception, an intra-vas device. Int J Androl 2006; 29:489–95.
121. Huang XB, Suo JP, Chen CY, et al. Initial studies on a novel filtering-type intra-vas device in male dogs. Contraception 2010;81:350–4.
122. Chen ZL, Huang XB, Suo JP, et al. The contraceptive effect of a novel filtering-type nano-copper complex/polymer composites intra-vas device on male animals. Int J Androl 2010;33:810–7.
123. Misro M, Guha SK, Singh H, et al. Injectable non-occlusive chemical contraception in the male-I. Contraception 1979;20:467–73.
124. Guha SK, Singh G, Ansari S, et al. Phase II clinical trial of a vas deferens injectable contraceptive for the male. Contraception 1997;56:245–50.
125. Chaki SP, Das HC, Misro MM. A short-term evaluation of semen and accessory sex gland function in phase III trial subjects receiving intravasal contraceptive RISUG. Contraception 2003;67:73–8.
126. Lohiya NK, Manivannan B, Mishra PK, et al. Intravasal contraception with styrene maleic anhydride and its noninvasive reversal in langur monkeys

(*Presbytis entellus entellus*). Contraception 1998; 58:119–28.
127. Mishra PK, Manivannan B, Pathak N, et al. Status of spermatogenesis and sperm parameters in langur monkeys following long-term maleic anhydride vas occlusion with styrene. J Androl 2003;24:501–9.
128. Lohiya NK, Manivannan B, Mishra PK, et al. Preclinical evaluation for noninvasive reversal following long-term vas occlusion with styrene maleic anhydride in langur monkeys. Contraception 2005;71: 214–26.
129. Lohiya NK, Suthar R, Khandelwal A, et al. Sperm characteristics and teratology in rats following vas deferens occlusion with RISUG and its reversal. Int J Androl 2010;33:e198–206.
130. Ansari AS, Alam I, Hussain M, et al. Evaluation of genotoxicity in leukocytes and testis following intra-vasal contraception with RISUG and its reversal by DMSO and NaHCO3 in Wistar albino rats. Reprod Toxicol 2013;36:53–9.
131. Beck M. Honey, it's your turn. Wall Street Journal 2011. Available at: http://online.wsj.com/article/SB10001424052702303848104576383730320049892.html.
132. Gifford B. The revolutionary new birth control method for men. 2011. Available at: http://www.wired.com/magazine/2011/04/ff_vasectomy/all/. Accessed May 22, 2013.
133. Henle W, Henle G, Chambers LA. Studies on the antigenic structure of some mammalian spermatozoa. J Exp Med 1938;68:335–52.
134. Kummerfeld HL, Foote RH. Infertility and embryonic mortality in female rabbits immunized with different sperm preparations. Biol Reprod 1976; 14:300–5.
135. Munoz MG, Metz CB. Infertility in female rabbits isoimmunized with subcellular sperm fractions. Biol Reprod 1978;18:669–78.
136. Isojima S, Graham RM, Graham JB. Sterility in female guinea pigs induced by injection with testis. Science 1959;129:44.
137. Menge AC, Peegel H, Riolo ML. Sperm fractions responsible for immunological induction of prefertilization and post-fertilization in rabbits. Biol Reprod 1979;20:931–7.
138. Fuchs EF, Alexander NJ. Immunologic considerations before and after vasovasostomy. Fertil Steril 1983;40:497–9.
139. Primakoff P, Lathrop W, Woolman L, et al. Fully effective contraception in male and female guinea pigs immunized with the sperm protein PH-20. Nature 1988;335:543–6.
140. Tung KS, Primakoff P, Woolman-Gamer L, et al. Mechanism of infertility in male guinea pigs immunized with sperm PH-20. Biol Reprod 1997;56: 1133–41.
141. Wang ZJ, Widgren EE, Sivashanmugam P, et al. Association of Eppin with semenogelin on human spermatozoa. Biol Reprod 2005;72:1064–70.
142. De Lamirande E, Yoshida K, Yoshiike TM, et al. Semenogelin, the main protein of semen coagulum, inhibits human sperm capacitation by interfering with the superoxide anion generated during this process. J Androl 2001;22:672–9.
143. O'Rand MG, Widgren EE, Sivashanmugam P, et al. Reversible immunocontraception in male monkeys immunized with Eppin. Science 2004;306:1189–90.
144. O'Rand MG, Widgren EE, Beyler S, et al. Inhibition of human sperm motility by contraceptive anti-eppin antibodies from infertile male monkeys: effect on cyclic adenosine monophosphate. Biol Reprod 2009;80:279–85.
145. O'Rand MG, Widgren EE. Loss of calcium in human spermatozoa via EPPIN, the semenogelin receptor. Biol Reprod 2012;86:55.
146. Silva EJ, Hamil KG, Richardson RT, et al. Characterization of EPPIN's semenogelin I binding site: a contraceptive drug target. Biol Reprod 2012;87:56.
147. Mitra A, Richardson RT, O'Rand MG. Analysis of recombinant human semenogelin as an inhibitor of human sperm motility. Biol Reprod 2010;82:489–96.
148. Goodman A. The long wait for male birth control. Time 2008. Available at: http://content.time.com/time/health/article/0,8599,1829107,00.html.
149. Piccinino LJ, Mosher WD. Trends in contraceptive use in the United States: 1982-1995. Fam Plann Perspect 1998;30:4–10.
150. Glasier AF, Anakwe R, Everington D, et al. Would women trust their partners to use a male pill? Hum Reprod 2000;15:646–9.