

# Male Contraception History and Development

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## 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.<sup>1</sup> Surveys have demonstrated that nearly 80% of men believe contraception is a shared responsibility<sup>2,3</sup> and globally more than 50% of men endorsed interest in an alternative male contraceptive.<sup>3</sup> 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.<sup>4</sup> 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,<sup>5</sup> with actual use, the failure rate is 17% per year.<sup>6</sup> 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

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procedure first performed on dogs.<sup>7</sup> 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<sup>8,9</sup> until it was realized that it offered no benefit in this regard. It was then used in the treatment of postprostatectomy epididymo-orchitis and it was not until the 1970s that routine vasectomies stopped being performed with prostatectomies. Oschner<sup>10</sup> 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.<sup>11</sup> In the United States, nearly 3 times as many couples elect to have tubal sterilization compared with vasectomy.<sup>12,13</sup> 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.<sup>14,15</sup> It is a highly effective procedure with failure rates typically less than 1%.<sup>16</sup> In the United States, most vasectomies are performed by urologists as an outpatient procedure under local anesthesia.<sup>15</sup> 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.<sup>17</sup> 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.<sup>18</sup>

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.<sup>16</sup> 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<sup>19</sup> 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

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