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## Can the evolution of male contraception lead to a revolution? Review of the current state of knowledge

[Author's unedited version]

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**Introduction** Great advances in medical research concerning methods of contraception have been achieved in recent years, however still more than 25% of couples worldwide rely on condoms – a method with poor efficacy. Despite the fact that there is a spectrum of 11 different contraceptive methods for women, there are only 4 commonly used by men (condoms, periodic abstinence, withdrawal and vasectomy). In this review, advances and present state-of-the-art both hormonal and non-hormonal male contraceptive methods will be presented and evaluated. Potential novel targets that warrant greater research will be highlighted.

**Material and methods** A comprehensive literature search without a time limit was performed using the Medline database on May 2017. The terms 'male contraception' in conjunction with 'RISUG', 'hormonal', 'non-hormonal', 'vasectomy' or 'testosterone' were used. The articles were limited to these published in English, Polish or French language.

**Results** There are various contraceptives currently available to regulate male fertility. Vasectomy is still the most effective permanent form of male contraceptive with failure rate lower than 1%. Reversible non hormonal methods of male contraception like reversible inhibition of sperm under guidance are very promising and close to be introduced into the market. In regard to hormonal contraception research, the use of testosterone injections has been widely studied yet they often harbor undesirable side effects and still need further development.

**Conclusions** Despite continuous efforts worldwide, it seems that another several years of further research is needed to provide safe, effective and affordable male contraceptives which will allow both men and women to participate fully in family planning.

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## INTRODUCTION

### Methods of contraception

Inadequate use or access to methods of contraception is one of the main reasons for the high number of unplanned pregnancies. Despite the fact that there is a spectrum of 11 different contraceptive methods for women, there are only 4 commonly used by men (condoms, periodic abstinence, withdrawal and vasectomy). Moreover, three of them have been in use for hundreds of years and its effectiveness is far from ideal, mainly because of high first-year failure rates (periodic abstinence- 20%, withdrawal- 19%, condoms – 3 – 14%). According to Glasier et al. (2000) men are willing to participate equally in family planning with their partner [1].

In order to be successfully introduced into the market, desirable men contraceptive has to fulfill major conditions: cheapness, reversibility and effectiveness. The male contraceptives can be achieved by reacting to several different mechanisms that can be divided into categories:

- 1) methods that suppress spermatogenesis;
- 2) blocking the maturation or fertilizing ability of spermatozoa
- 3) preventing sperm from reaching the in vivo site of fertilization
- 4) interfering with the sperm capacitation in the female genital tract
- 5) interfering with sperm functions necessary for normal fertilization

### Existing contraceptives

#### Condoms

The oldest method of contraception used by 5.7% of couples worldwide with much higher percentage of users in developed countries. In United Kingdom the condom is the second most common method of birth control (22%) while in the United States it is the third most common (15%) [2, 3]. Technically it is a sheath-shaped barrier device used during sexual intercourse to reduce the probability of pregnancy. About six to nine billion are sold every year [4]. The typical use pregnancy rate among condom users varies depending on the population being studied, ranging from 10 to 18% per year which undoubtedly make condoms unreliable as a contraceptive [5]. However, their important feature is the protection from sexually transmitted infections (STIs) [6]. According to a 2000 report by the National Institutes of Health (NIH), consistent use of latex condoms reduces the risk of HIV/AIDS transmission by approximately 85% relative to risk when unprotected (according to the World Health Organization the risk reductions reach 80–95%) [7].

#### Vasectomy

Procedure which technically involves dissection of the vas deferens often followed by electrocoagulation of the two ends to prevent recannulation. After this minimally invasive procedure, the testes remain in the scrotum where Leydig cells continue to produce testosterone and other male hormones. These continue to be secreted into the blood-stream which minimizes the risk of adverse side effects. The volume of ejaculate remains unchanged.

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It is the most effective permanent form of contraception available to men with failure rate lower than 1% [8]. High effectiveness and low complication rates made vasectomy the foremost utilized non-diagnostic operation performed by urologists in the United States [9]. According to European Association of Urology (EAU) Guidelines, vasectomy meets best the criteria for male contribution to permanent contraception.

The main disadvantage of this method is its poor reversibility. Despite the fact that the restoration rates using the modern microsurgical techniques reach around 90% [10], the pregnancy rates are in fact much lower, because of the post-operational re-occlusion of the vas deferens (50%) and latency of anti-sperm antibodies (70%) [11]. The longer the interval from vasectomy to reversal, the lower the pregnancy rate is (pregnancy rates 76% for an interval up to three years after vasectomy vs. 30% for > fifteen years) [12].

An attempt to eliminate this problem is an implantable ligation device- the VasClip. It achieves male sterilization without cutting the vas deferent thus is considered reversible. Successful sterilization, defined by azoospermia at 10 to 14 months, was observed in 116 of 119 subjects. In 3 subjects with persistent presence of sperm, histological examination after traditional vasectomy indicated that misalignment of the device led to partial vas incision with recanalization [13]. The effectiveness seemed to be equivalent to that of vasectomy. However because of the lack of research on a large group of patients, further research is needed.

Potential systemic effects of vasectomy, including atherosclerosis, have not been proven, and there is no evidence of a significant increase in any systemic disease after vasectomy. Thus, clinicians do not need to routinely discuss coronary heart disease, stroke, hypertension, dementia or testicular cancer in pre-vasectomy counseling of patients. There have been also concerns about association of increased prostate cancer risk after vasectomy, however both EAU and AUA (American Urological Association) guidelines clearly state that vasectomy is not a risk factor for prostate cancer [14]. According to a recent systematic review and meta-analysis including 53 studies, there was a weak, clinically insignificant association between vasectomy and risk of high-grade, advanced, or fatal prostate cancer. This association is unlikely to be causal and should not preclude the use of vasectomy [15]. Acute local complications associated with vasectomy include haematoma, wound infection, and epididymitis in up to 5% of cases. 1–2% of patients may experience chronic testicular pain for greater than three months after vasectomy procedure. Post-vasectomy pain syndrome (PVPS) is diagnosis of exclusion, and may be caused by direct damage to spermatic cord structures, compression of nerves in the spermatic cord via inflammation, back pressure from epididymal congestion, and perineural fibrosis [16, 17]. According to some authors, the procedure may also be followed by psychological complications, such as depression, irritability, and medically unexplained somatic symptoms. Such symptoms occur only in a minority of patients; in most men, vasectomy is not associated with an excess of psychological morbidity compared with other contraceptive methods [18].

## **Advances in male contraception methods**

### **Hormonal contraception**

All of the methods used by male nowadays prevent sperm from reaching the oocyte. A potential game changer that could revitalize the entire male contraception concept has been the hormonal male contraception based on exogenous testosterone. Male hormonal contraceptives all involve the administration of some form of testosterone, which functions as a contraceptive by suppressing secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary. The suppression of LH and FSH deprives the testes of the

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stimulatory signals required for spermatogenesis, leading to markedly decreased sperm counts and infertility. A sperm concentration below 1 million sperm per milliliter of ejaculate is associated with a risk of pregnancy of approximately 1% per year [19]. Induction of such severe oligospermia is considered a reasonable goal of male contraceptive development. Contrary to expectations, multicenter international clinical trials sponsored by World Health Organization (WHO) revealed already in the 1980s and 1990s, that the administration of testosterone alone fails to completely suppress the sperm production in 15–25% of men [20].

## 1. Testosterone monotherapy

Major clinical trials of androgen monotherapy investigated Testosterone enanthate (TE), Testosterone undecanoate (TU) and Testosterone buciclate (TB). What is more, androgen-related adverse effects such as weight gain and suppression of high-density lipoprotein cholesterol levels dampened the enthusiasm of the researchers. Other common side effects included: acne, oiliness of skin, decreased libido and mood disorders.

## 2. Testosterone with progesterone agents

The method nearest to being generally available clinically is hormonal male contraception based on suppression of gonadotropins and testosterone substitution to reduce side effects. Researchers evaluated various combinations of testosterone with progesterone agents such as cyproterone acetate [21], levonorgestrel [22], etonogestrel [23], desogestrel [24], norethisterone enanthate [25] and medroxyprogesterone acetate [26]. The exact mechanism of progesterone's role in male contraception is not fully described, however these agents affect both levels of the pituitary and testes to maximally suppress gonadotropins and, possibly, to directly decrease spermatogenesis [27]. Promising results were presented concerning a transdermal gel containing Testosterone and Nestorone with efficacy of suppression of spermatogenesis to <1 million/ml in 88.5% of patients without serious adverse effects [28].

## 3. Transdermal testosterone

Testosterone gels have been marketed for the treatment of hypogonadism. These gels achieve higher serum testosterone concentrations and are less irritating to the skin than the patches which are also unable to effectively suppress gonadotropin secretion from the pituitary because of lower peak serum levels of testosterone [29]. Testosterone gels also overcome the problem of skin reactions to the patch [30]. The combination of Testosterone gel combined with a depot formulation of the progestin, depomedroxyprogesterone acetate (DMPA) turned out to be a promising new regimen in male contraception, however further studies are required as still only 90% of the subjects became severely oligospermic [31].

In the future, testosterone gel could be combined with a progestin gel or cream as a transdermal approach to male contraception.

## 4. Androgens with Gonadotropin-releasing hormone (GnRH) -analogues

There have been also trials with a direct suppression of gonadotropin-releasing hormone (GnRH) release from the hypothalamus and prevention of testosterone metabolism by 5 $\alpha$ -

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reductase, but unfortunately they demonstrated a less efficacy of suppression of spermatogenesis [32].

## Non-hormonal contraception

The non-hormonal methods of male contraception (NHC) play an important role as potential novel targets that warrant greater research emphasis. According to the name, NHC is a contraceptive that does not involve the administration of hormones or hormone blockers. These methods can be categorized into those that inhibit spermatogenesis and those that disrupt the movement and maturation of sperm in the epididymis. The aim of developing non-hormonal methods of contraception is to target specific biological processes, hence reduce the adverse effects of methods that were described in this review. At the moment of this publication almost all of the NHC are still in experimental stages. The only method that has already been used clinically, principally in China, is a herbal extract- gossypol. However, there was a systematic review of studies with gossypol and triptolite (Chinese herb *Trypterigium* that inhibit spermatogenesis) that concluded that these substances were unsafe and ineffective. WHO recommended the discontinuation of further investigations on gossypol, hence this method will not be described in more detail in this review. On the other hand, there are two promising approaches to male non-hormonal contraception- gamendazole and adjudin, two derivatives of the potent anti-spermatogenic compound lonidamine and a second one, based on the conception of inhibition of retinoic acid at the testicular level- blockers of retinoic acid function and synthesis.

## Non-mechanical methods

### 1. Adjudin

Adjudin is a derivative of 1H-indazole-3-carboxylic acid that demonstrated potent anti-spermatogenic activity in rats, rabbits, and dogs. As recent studies showed, adjudin exerts its effect in the seminiferous epithelium, causing exfoliation of germ cells in the testis [33]. It is an analog of lonidamine which was initially explored as an anti-cancer drug but unlike most other anti-cancer drugs- without anti-mitotic activity [34]. The mechanism is based on interfering at the connections of germ cells with the Sertoli cells resulting in infertility because of the loss of functional mature sperm in semen. Despite its reversibility and high efficacy, the problem appeared during the research on animals - unexpected adverse effects such as hepatic malaise and muscle atrophy.

### 2. Retinoic acid inhibition

The fact that vitamin-A (retinol) is crucial for normal spermatogenesis has been already proved almost 100 years ago (1925) [35]. The researchers said that retinoic acid binds one of several retinoic acid receptors (RARs), which regulate gene expression. Male RAR knockout animals are sterile due to various problems in spermatogenesis. Hence, blockade of retinoic acid function or synthesis has the potential to inhibit spermatogenesis. WIN 18,446 (Bisdichloroacetyldiamine) has been one of the first attempts at pharmaceutical contraception in US men in the 1960s with promising results causing fully reversible oligozoospermia (<1

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million/ml). Unfortunately, subjects taking WIN 18,446 experienced a 'disulfiram reaction' consisting of nausea, vomiting, palpitations and sweating, when they drank alcohol [36]. Although, the retinoid acid inhibition still remains the topic of ongoing researches which concern the deployment of specific inhibitors of the RAR alpha selectively in the testis.

## Mechanical methods

### 1. RISUG (Reversible Inhibition of Sperm Under Guidance)

The main mechanism of these methods is the prevention of an easy passage of sperm to the ejaculate. As such it could be treated as a reversible version of present 'gold standard'-vasectomy. In early 80s Misro et al. first introduced a revolutionary occlusive polymer which was claimed to sterilize subjects by single injection of styrene maleic anhydride (SMA) dissolved in dimethyl sulfoxide (DMSO), in both vas deferens. It was presented under a name RISUG (Reversible Inhibition of Sperm Under Guidance) [37]. At the moment, there have already been introduced a phase I and II study in the Indian male population, in which RISUG provided effective and reversible contraception for up to 10 years after a single application [38,39]. During RISUG, a solution of 60 mg of styrene maleic anhydride (SMA), a crystal clear polymer dissolved in 120 µl of dimethyl sulfoxide (DMSO) (1:2), is injected into the vas deferens and induces infertility within 10 days. SMA (Xiran<sup>®</sup>) partially occludes the vas deferens and at the same time develops morphological aberrations of the sperm that manage to pass through. Adverse effects include slight testicular swelling without associated pain, which is self-limited within 15 days. As of 2016 phase III clinical trials were underway in India, though the process has been slowed down by the lack of volunteers [40]. The technology was licensed to an American non-profit which is developing it under the brand name Vasalgel. At the moment of this publication it remains under development.

### 2. Intra-vas plugs

Intravasal injection of formed-in-place silicone rubber for vas occlusion has been tried on a small number of human volunteers [41]. Occlusion of a 1-cm length of the vas was achieved. Azoospermia was obtained after 5 months in 3 men and by 9 months in all 14 men. Despite these promising results it has not been unequivocally proven that silicone rubber does not interfere significantly in vas physiology. Thus further study involving safety of this procedure is required.

## CONCLUSIONS

Despite great advances in medical research in recent years, still more than 25% of couples worldwide rely on condoms- a male method of contraception which presents poor efficacy. This fact undoubtedly shows the need for development of new effective, reversible, male-focused contraceptive method. A lot of research has already been done to investigate this topic, however, there is a lack of properly designed and sponsored multicenter studies. Steroid based male contraceptive regimens, despite being clinically effective, still face a problem of adverse effects. There is a need for greater understanding of their action within the testis, yet their effects on the reproductive tract and other body systems have to be investigated in a detailed way. At the moment vasectomy still plays a key role in MHC. However, it is a

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procedure difficult to inverse. Nowadays at times of higher divorce rates and labile family planning variability that becomes an increasing obstacle [42]. Thus development and acceptance of novel, reversible, male contraceptive methods such as non-hormonal MHC or RISUG could revolutionize the way that contraceptive delivery occurs around the world giving men and their partners mindful control without significant burdens. Intravasal injection of formed-in-place silicone rubber for vas occlusion may play an important role in new male contraceptives but still needs further study involving safety of this procedure.

## Conflicts of interest

The authors declare no conflicts of interest.

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