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RISUG as a Male Contraceptive: Breakthrough or Risk? A Critical Review

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ABSTRACT

Background: Male contraceptive development has lagged behind female methods, creating a gap in available options. RISUG (Reversible Inhibition of Sperm Under Guidance) has emerged as a potential non-hormonal alternative. ***Reviews:*** This review examines both the upside and downside of RISUG through its mechanism, safety profile, effectiveness, and reversibility. RISUG uses styrene maleic anhydride (SMA) polymer, which is then injected into the vas deferens, resulting in sperm disruption through pH and electrostatic interactions. Animal studies in rats, rabbits, and primates consistently demonstrate reliable contraceptive effects and successful reversal using DMSO or sodium bicarbonate. Phase I–III human trials show consistent reports of high rates of azoospermia with only mild, transient side effects such as temporary scrotal swelling. However, human evidence for reversibility remains incomplete, and isolated inconsistent outcomes occur. The review also discusses sociocultural and psychological barriers including masculinity norms, stigma, and limited awareness that may hinder uptake despite growing interest among men. ***Conclusion:*** RISUG has promising potential to be a long-term, effective, yet flexible male contraceptive. However, broader human trials and clearer reversibility data are necessary before widespread adoption.

Keywords: RISUG; reversible inhibition of sperm under guidance; male contraception; non-hormonal contraceptive methods; reproductive health technology; fertility regulation

INTRODUCTION

Millions of couples worldwide rely on female contraception, with a global prevalence reaching 77%. [1,2] However, despite this long history, a significant gender imbalance exists effective male contraceptive options remain limited. [3] In Indonesia, for instance, the prevalence of modern female contraceptives sits at 57.0% [4], with injectable methods being the most popular (57.0%, 21,897,319/38,408,597). [5, 6]

Limitation of male hormones' effectiveness stems from the inherent complexity of spermatogenesis. Researchers have explored reversible hormonal methods, yet they have not achieved the same level of efficacy and tolerability observed in female hormonal contraceptives. [7] Male hormonal contraceptive trials report effectiveness ranging only from 80 to 90%, with safety concerns hindering their approval. [9] However, no severe side effects were reported; only mild side effects might manifest, ranging from mood swings and decreased libido to injection site reactions. [10] Moreover, female combined oral contraceptives (COCs) and long-acting reversible contraceptives (LARCs) boast typical use failure rates as low as 0.6% and 1%, respectively. [8]

Another factor, such as psychology, poses a significant barrier to their use. Religious doctrines, household dynamics, and societal pressures play a huge influence in making decisions, with some cultures associating male contraceptive use with a loss of masculinity. [11] Other factors such as socioeconomic status can be seen in men with higher education, wealthier households, or living in urban areas, who displayed more positive attitudes towards contraception. Sociodemographic seem to influence these attitudes as well, with fathers and middle-aged men being more accepting than younger or older demographics. [12]

A different perspective by Kerry L.D. et al. (2015) shows variation in disagreement with the idea that "women using contraception become promiscuous," ranging from 34% to 84% across surveyed countries. However, a more consistent trend emerged regarding male involvement: over 50% of men in all countries surveyed disagreed with the statement that "contraception is a woman's business." [12]

Contraception holds a pivotal role in a male's fertility dynamics. Fertility in males is characterized by the ability of a man's sperm to fertilize an egg. [1,13]

This transformation can be achieved through various methods that obstruct specific stages in sperm production. These methods include hormonal inhibitors, suppression of spermatogenesis, motility inhibitors, and vas occlusion. Each method plays a unique role in inducing male infertility, thereby contributing to the effectiveness of contraception. [3,10] Despite numerous studies exploring male contraceptive methods, a significant gap exists in the evaluation of specific options, particularly RISUG (reversible infertility with sperm underglaciation). Our research aims to address this gap by investigating the potential benefits and drawbacks of RISUG, ultimately contributing to a more comprehensive understanding of male contraception.

RISUG Overview

RISUG (Reversible Inhibition of Sperm Under Guidance) is a novel approach to non-hormonal male contraception methods, made of a co-polymer of styrene maleic anhydride (SMA) dissolved in dimethyl sulphoxide (DMSO) at a 1:2 ratio. [14] The contraception is administered into the vas deferens' lumen using a no-scalpel technique. [15] The idea behind this contraception is to prevent sperm from passing through by lowering the pH and creating electrical disturbances in the sperm membrane, leading to their denaturation. [16]

The fundamental process of this contraception is based on the hydrolysis process of SMA to SMAc. This process causes a pH decrease in the seminal fluid and generates free hydrides within the vas deferens, creating a cationic charge that attracts anionic molecules to it. The fact that sperm membranes are anionic in nature means that an attraction to cationic charges causes an imbalance in charge across the membrane, which eventually destroys the sperm membrane. [17] A study by Ansari et al. (2021) shows that the ovicidal ability of RISUG also indicates its potential as a female fertility-regulating agent. [18]

RISUG's ability to be removed from the walls of the vas deferens presents an advantage over other male contraceptive methods. By injecting an alkaline copolymer dissolving agent, such as DMSO or sodium bicarbonate ($NaHCO_3$), which acts as a partial solvent, its components become unstable at higher pH levels, resulting in the inability to serve as a contraception. [16, 19]

Pro RISUG

RISUG (Reversible Inhibition of Sperm Under Guidance) presents significant advantages, primarily due to its successful completion of the third phase of clinical trials, its reversibility, and its proven effectiveness. A study in 2014 revealed that the first phase of clinical trials provided valuable information regarding sperm count and the behavioral study of RISUG. The most effective results were observed at a 70 mg SMA dose, which resulted in azoospermia within the initial three weeks, with subjects remaining azoospermic for 292 days. The second phase of clinical trials determined the optimal dose for a long-lasting and immediate contraceptive effect, concluding that dosages ranging from 40 to 70 mg of SMA were effective in providing more than 2 years of fertility control, regardless of their azoospermic or non-azoospermic stage. The third phase of clinical trials, also conducted by Lohiya NK et al., primarily showed immotile and abnormal spermatozoa in all subjects post-RISUG injection. [20]

Another multicentric-limited phase-III clinical trial in 2019 tested the efficacy and safety of RISUG in humans. The six-month follow-up results showed that the healthy male volunteers and their wives appeared normal with no notable side effects, except for temporary scrotal enlargement and mild pain in the scrotal and inguinal region in most individuals. However, the pain resolved within a month without any impairment to routine activities. The study found that 82.7% of individuals continued to be azoospermic from the month following the first semen examination, while the remaining 17.3% manifested azoospermia within 3 to 6 months. [21] These findings suggest that RISUG shows promising results by inducing azoospermic sperm outcomes in subjects.

Prior to the clinical trials phases, RISUG (Reversible Inhibition of Sperm Under Guidance) underwent extensive testing on various animal models to evaluate its safety and contraceptive effects in 1981. The copolymer of styrene maleic anhydride (SMA) was dissolved in DMSO and injected into the vas deferens of rats. Histological observations revealed that the polymer was retained in the vas deferens, with morphological changes confined to the mucosa. Remarkably, upon removal of the polymer by flushing DMSO, the mucosal structure normalized within two weeks, indicating successful reversibility by RISUG. [22] Further support for RISUG's reversibility was provided by a study where SMA was evaluated as a contraceptive in male rabbits by Sethi et al. The results demonstrated no teratogenic potential at the doses of 1.25 mg, 2.5 mg, and 5.0 mg used in the experiment. [23] Additionally, RISUG was tested in rhesus monkeys and langur monkeys, with both tests yielding positive results. In conclusion, these studies collectively affirm that RISUG is safe for use. [24]

The reversibility of RISUG (Reversible Inhibition of Sperm Under Guidance) is facilitated by the use of DMSO (Dimethyl Sulfoxide) and sodium bicarbonate ($NaHCO_3$), as elucidated in the studies in 1998. These components are used to dissolve the styrene maleic anhydride (SMA), which is produced by the lumen of the vas deferens upon injection with DMSO. [25] Consequently, DMSO and $NaHCO_3$ have been employed to flush RISUG out from the vas deferens through the urethra, thereby demonstrating the reversibility of RISUG. However, subsequent studies have reported that larger amounts of DMSO can have adverse effects on the surrounding tissue or skin. Therefore, $NaHCO_3$ has been proposed as a superior alternative to mitigate the binding of RISUG to the epithelial cells of the vas deferens and facilitate its removal. [26]

Contra RISUG

Despite having good potential as a male contraceptives, RISUG faces several challenges. The majority of existing research primarily focuses on the effectiveness rate from phase I-III clinical trials. However, RISUG remains an underdeveloped drug due to limited trial data and inconsistent results, with a few subjects yielding erroneous outcomes.

Most of the studies on the reversibility effects of RISUG have predominantly been conducted on animals. In rats and rabbits, the SMA polymer can be removed by injecting DMSO or $NaHCO_3$ without causing any changes in the mucosal structure of the vas deferens. Both animal models concluded that the reversing effects of RISUG were successful and not associated with any toxicity, as evidenced by genotoxicity tests. [19] Similar evidence was found in langur monkeys, where the reversal of an injected drug can already be achieved non-invasively through squeezing and giving electric stimulation via the skin of the vas deferens, pushing the intravasal SMA to the urethra. However, due to structural differences in the human vas deferens, this technique is unfortunately not feasible in humans. Additionally, histological examinations in monkeys revealed transient epithelial exfoliation and degeneration of the seminiferous epithelium after polymer exposure, although normal morphology was restored within approximately five months following reversal. [19, 27] These findings suggest a good reversal potential for RISUG, yet there is no human evidence to validate it, which resulted in skepticism.

In a separate clinical study, a single-dose administration of RISUG led to individuals noticing mild scrotal enlargement and scrotal tissue edema within the first week. Although both the enlargement and edema disappeared within a month, a scrotal nodule at the injection site remained visible for six months. [28, 29] Social-economic challenges piqued some interest from pharmaceutical companies since studies show up to 82.3% of men are willing to take novel male contraceptives. A proportion of men want to share the responsibility of pregnancy by using male contraceptives. However, the remaining proportion still had internal conflicts between social stigma and traditional and modern gender roles, leading to their concern that using contraceptives will make them look “feminine” and reduce their “masculinity.” This fact is also exacerbated by the fact that there are currently no countries that have specific regulations and laws governing men to use male contraceptives. There are only regulations that advise families to use contraceptives with a varied choice in the market. Therefore, current contraceptives are commonly used by women, and there is little awareness of the availability of contraceptives for men, especially in developing countries.

SUMMARY

Male contraceptive options are still limited nowadays. The RISUG novel approach offers promising long-term flexibility with both high safety profile and effectiveness. However, its progress is slowed down by insufficient trial data and inconsistent results, with some subjects experiencing unexpected outcomes. This can amplify the challenges in conducting studies involving human subjects, who often had difficulties from discussing their experiences post-injection unless complications arise, necessitating prolonged follow-up periods. Nevertheless, further research with a larger and longer-term sample size is warranted to ensure the future development of this breakthrough technology.

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