Biological Times

Volume No. 3| Issue No. 5|Pages 7-8

Clinical Trials and Efficacy of Male Contraceptives

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ABSTRACT

Clinical trials on male contraceptives have shown significant progress, with innovative hormonal formulations demonstrating high efficacy in suppressing spermatogenesis. Studies since the 1970s have explored various methods and biological agents, including testosterone enanthate, cypionate, and undecanoate, often combined with progestins, achieving azoospermia in up to 95% of men. Recent trials with new hormonal entities like dimethandrolone undecanoate and segesterone acetate are promising, with phase II trials ongoing. Despite these advancements, acceptance and access remain challenges. Side effects such as acne, weight gain, and mood changes have been reported, but they are generally reversible. Ensuring the development of effective, reversible, and safe male contraceptives is crucial for comprehensive family planning. The current research aims to address these issues, with results from large-scale studies expected by late 2024. This article highlights the significant advancements and ongoing efforts in clinical trials to enhance the efficacy and acceptance of male contraceptives.

Introduction

Approximately 40-50% of pregnancies are unintentional, and the use of contraceptives significantly reduces this risk. About 70% of females and 30% of males use contraceptives in a couple, which highlights the low reliability of contraceptives in males due to conventional methods [1]. Primitive methods for male contraception (condoms and vasectomy) have their shortcomings, including high rates of unplanned births with condoms, invasiveness, and the irreversible process of vasectomy [2]. To address these limitations and ensure their effectiveness, innovative oral male contraceptives are emerging. However, a significant challenge remains in accessing these contraceptive agents. Ensuring access to efficient contraception is imperative for the reproductive health of both males and females [3]. Although there are several contraceptives available for women in the market, to avoid unplanned pregnancies and to prevent the side effects of contraceptives by long-term use in females requires the need to develop male contraceptives. Recent surveys give the impression that both men and their partners are eager for male contraceptive options to help in family planning [4].

The major hurdle is the acceptance of contraceptives by males, which is influenced by many factors, including age, educational level, culture, religion, and economic and also by relationship status. Several other factors contribute, the major one being the high rate of sperm production. Millions of sperm are produced per day, about 1,000 per second, and to prevent them from reaching eggs, there is a need for a highly effective product [5]. These oral male contraceptives work similarly to female hormonal contraceptives by using external steroids, which interact with the body's natural reproductive processes (physiologic hypothalamic-pituitary-gonadal pathways) to prevent conception effectively. Gonadotrophins, LH, and FSH secretion will be suppressed by these steroids, resulting in impaired testosterone production and maturation of sperm in the testes [6].

Early studies have shown that the administration of testosterone arrests sperm production and, when combined with progestogens or GnRH antagonists, further suppresses the pituitary gonadotrophins and enhances its contraceptive efficacy. The hormonal approach offers exciting potential for providing reversible and effective contraception, but still, there is no product available on the market [7]. Many hormonal male contraceptives have underdone clinical trials, including 11β-methyl-nor-testosterone dodecyl carbonate, dimethyl-nandrolone undecanoate, and 7α-methyl-19-nortestosterone. Pre-clinical stages of efficacious non-hormonal methods are underway. Several non-hormonal male contraceptive targets that affect sperm function, sperm production, or transport have been identified [8].

Clinical Trials

Studies have shown that men are in favour of the development of male contraceptives, leading to increased research and progress in this crucial field. In the last decades, many studies have been performed to find out the suppression of spermatogenesis by different male hormonal contraceptive formulations. These studies differ in duration, size, and the molecules used, but they all show that testosterone has enough capacity to suppress sperm concentration.In the 1970s, it was found that Leydig cells played a significant role in spermatogenesis, leading to the development of male contraceptive strategies that interact with the HPG(Hypothalamic-pituitary-gonadal axis) axis [9]. In the late 1970s, the National Institute of Health(NIH) demonstrated the efficacy of 200mg weekly IM injection of testosterone enanthate(TE) on 271 healthy fertile males. This intramuscular injection causes hormonally induced azoospermia with side effects.

In 1996 the WHO studied testosterone enanthate in 15 centres in nine countries. Weekly injections of 200mg of TE also show severe oligozoospermia or azoospermia. The data obtained from this study shows notable pregnancies despite patients being oligoozospermic [10]. Injections of testosterone cypionate and testosterone undecanoate were also tested afterwards, revealing the potential for ethnic differences in spermatogenesis suppression with hormonal therapy.[11][12]. Further studies combining androgens and progestins have also been conducted, which show a 95% success rate in achieving azoospermia when the treatment is combined, compared to a 65% success rate with individual treatment [13]. In another study of combined androgen-progestin therapy, Buchter et al. studied the efficacy of a combined regimen of oral levonorgestrel (LNG) and transdermal T. The result shows inadequate efficacy in suppressing spermatogenesis [14].

Turner et al. studied the efficacy of testosterone implants with depot medroxyprogesterone acetate (DMPA) at regular intervals. The results show suppression of spermatogenesis in 94% of men [15]. Hay et al. administered a combination of intramuscular testosterone decanoate and oral etonogestrel (ENG) and studied its effect [16]. Roth et al. conducted a study on the impact of transdermal testosterone and Nestorone (NES) on 99 subjects. The study found a % success rate of 89% in suppressing spermatogenesis in men [17]. Behr et al. recently studied the efficacy of intramuscular injection of norethisterone enanthate (NET-EN) combined with testosterone undecanoate (TU). The study shows that out of 320 men, 274 show high rates of suppression of sperm production [18].

Efficacy of Oral Male Contraceptives

Oral contraceptives are in demand because of an accessible mode of delivery. Injections and transdermal gels are not ideal because they can cause unwanted side effects and disrupt your daily routine [19]. However, recent studies show that work is undergoing on injections

To cite this article: Rahman MU & H Akram. 2024. Clinical trials and efficacy of male contraceptives. Biological Times, 3(5): 7-8.

and other dosage forms to increase bioavailability and long-term beneficial effects. The main goal is to form a new entity for male hormonal contraceptives similar to female hormonal contraceptives, which include oral formulations, contraceptive patches for males, birth control pills and several other hormonal methods. Several non-hormonal methods are also under investigation [20].

After years of clinical trials, the positive news is that efficacy to prevent unwanted pregnancy is <1% per year when azoospermia is achieved [21] . In recent trials, severe oligozoospermia, i.e., sperm concentration <1 million per ml of ejaculate, have been achieved in almost 95% of men. This result shows that the male hormonal contraceptive efficacy rate is similar to that of female oral contraceptives [22]. Earlier reversibility of fertility was demonstrated in individuals who received a shorter duration of treatment with short-acting testosterone formulations, faster suppression of spermatogenesis, and had low blood concentration of LH at baseline. After discontinuation of therapy, clinical trial data of most studies indicates it takes 5 to 6 months to restore spermatogenesis to 20 million/ml [23].

Safety and Side Effects

The most common side effects reported in male contraceptive use trials are acne and weight gain [24]. Experiencing slight fluctuations in sex drive without affecting sexual performance has also been reported [25]. Androgen-related side effects were also observed in some studies, including decreased HDL-cholesterol. Analysis of serious adverse effects include headaches, night sweats, and mood changes. These side effects are reversible after stopping MHC, but more clinical trials are necessary to determine the complete adverse profile [26].

Future Perspective

Oral administration of testosterone is challenging because of hepatotoxicity associated with long-term use. New entities are underdeveloped, emphasising minimizing side effects while maximizing effectiveness. Dimethandrolone undecanoate (DMAU) is a derivative of 19-nortestosterone, having both progestational and androgenic activities in pre-clinical studies[27]. Another new entity, including segesterone acetate [28] and 11-beta-methyl-19-nortestosterone 17-beta-dodecyl carbonate(11-βMNTDC), is also under research [29].

Recent researches focus on developing formulations based on ethnic differences, body mass index, and initial sperm count. The complete understanding of all these co-factors is still a work in progress. In June 2023, two hormonal contraceptive methods underwent phase II clinical trials for efficacy and safety. A large-scale study involving more than 460 couples using testosterone gel and transdermal segesterone acetate (Nestorone) is undergoing and is estimated to be complete in late 2024. Similarly, the second study using Dimethandrolone undecanoate is under process and is estimated to be completed in December 2024 [30].

Conclusion

Male contraceptive development has advanced significantly, with clinical trials showing high efficacy in suppressing spermatogenesis using innovative hormonal formulations. Compounds like dimethandrolone undecanoate have shown promising results, but challenges in acceptance, access, and side effects persist. Reported side effects are generally reversible, but more research is needed to address them fully. Ensuring effective, reversible, and safe male contraceptives is essential for equitable family planning. Large-scale studies aim to increase the use of these contraceptives, with results of studies expected by late 2024. Continued research is necessary to improve the clinical efficacy and acceptance of male contraceptives.

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