The landscape of male contraception: A narrative review

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ABSTRACT

Reproductive medicine has made significant advancements over the last 70 years, much of it in the way of female contraception. Reliable male contraception continues to be restricted to condoms and vasectomy. The purpose of this narrative review is to provide an overview of the contemporary usage of male contraceptive methods, including ethical and political standpoints, as well as, to summarize the current and future studies being done on male hormonal and non-hormonal contraceptive options.

KEY MESSAGES

- Reproductive medicine has changed significantly due to novel technologies and contraceptive strategies.
- Reliable and approved male contraception remains limited to condoms and vasectomies.
- The political landscape and ethics surrounding family planning strongly impacts contraceptive choice in men and the funding necessary to grow the options available.
- Much work has been done demonstrating the efficacy of hormonal contraceptive options in men, though not yet FDA approved, and further work is underway to provide safe, reversible, and reliable male contraceptives.

INTRODUCTION

The ethical, medical, and legal considerations surrounding fertility and contraception within clinical practice have been a long-standing and sensitive debate. The landscape of human reproduction has undergone significant transformation due to advances in contraceptive methods and assisted reproductive technology.[1] The approved forms of male contraception, apart from condom usage, are limited to vasectomies as endorsed by the Canadian and American Urological Associations.[2] However, ongoing research into novel contraception holds promise for expanding the options available to men. This review explores the ethical principles, historical context, as well as the current and future works on male contraception.

THE CURRENT LANDSCAPE OF CONTRACEPTION

Reliable family planning has been and continues to be a large part of modern North American culture. Over the past century, significant progress has been made to elucidate effective contraception methods further.[3] Most of this research has focused on developing and improving female contraceptives via physical devices such as diaphragms, vaginal rings, implants, and intrauterine devices (IUDs), and oral birth control pills or injections. Recently, more attention has been focused on male contraception. This would allow males to have more options for reliable contraception and, in theory, allow for a more active role in family planning. In fact, of the 21 commonly listed forms of contraception, only three have active male participation: the male condom, withdrawal, and vasectomy.[4] Historically, family planning has been under the purview of females, likely correlated to the relatively more efficacious female contraception options. However, this responsibility can be viewed as both an empowerment and a burden.[5] In the current societal paradigm, the perception that women bear the role of contraception has also led them to bear the financial and health consequences associated with this.[6]. Though male hormonal contraception is not yet offered, its acceptability has been polled by general public surveys worldwide, demonstrating that at least a quarter of men would consider hormonal contraception.[7]

ROE V. WADE

The medicalization of reproduction poses ethical dilemmas pertaining to women's health. Issues such as female sterilization, assisted reproduction, and interventions following contraception failure have always sparked complex discussions and debates, especially in recent years. These matters predominantly impact women, potentially resulting in marginalization. In pursuit of fairness, a shared responsibility of contraception may provide a more equitable solution.

On June 24, 2022, the US Supreme Court reversed the landmark decision of Roe v. Wade, a 1973 ruling that affirmed the constitutional right to abortion. This ruling marked the end of constitutionally protected abortion rights, granting individual states the exclusive authority to regulate abortion. The Supreme Court draft leaked on May 2, 2022, began with the sentence, "Abortion presents a profound moral issue on which Americans hold sharply opposing views," setting a clear direction for the case by asserting, "Roe was egregiously wrong from the start"

and "We hold that Roe and Casey must be overruled." Against this legal backdrop, there has been a trend towards increased numbers of men seeking contraceptive methods, most notably vasectomy.[8]

Ghomeshi et al. (2022), analyzed Google Trends data for the search volume of the keyword's "vasectomy" and "tubal ligation" across the United States, comparing data from two distinct time periods: April 25th to May 1st, 2022, and May 2nd to May 8th, 2022. The term "vasectomy" saw a 121% increase with a relative surge in the North and Southwestern states (most notably, Idaho), while tubal ligation saw a 70% increase.[9] Datta et al. (2022) further analyzed Google Trends search data between April 6 to July 5, 2022, for the following key terms: "tubal ligation, birth control pill, condom, IUD, vasectomy, birth control pill, morning after pill, and birth control shot."[10] Among these search terms, the keyword "vasectomy" showed the most significant surge in search interest, with a spike ratio of 7.14 times higher than the preceding baseline. Additionally, when quantified on the standardized scale of the Google Trends algorithm, with the highest indicator set at 100 and the lowest at 0, "vasectomy" exhibited a peak search interest value of 100 following the verdict.[10] Tubal ligation also had a spike ratio of 5.89 with a search interest value of 53, while the terms "IUD," "Birth control pill," and "Condom" collectively had an average spike ratio of 1.7 (1.8, 1.75, and 1.57 respectively). Although limited, these search results give insight into what American residents may have been thinking after the controversial decision. This demonstrated a clear and growing interest in long-term or permanent contraception. It is possible that this reaction arises from a sudden sense of loss of control over reproductive autonomy. Moving towards more definitive sterilization, whether for men or women, enables individuals to decisively regain that sense of empowerment.[11,12]

Months later, Zhang et al. (2023) further quantified this by comparing vasectomy rates before and after June 24th, 2022, via a retrospective database study capturing over 87 million men aged 18-60 years across the US.[13] They demonstrated a 20% increase in vasectomy volume when comparing the seven months prior and seven months following the court decision (Roe vs Wade). More recent vasectomy prevalence rates for men aged between 15-49 range between 7.4-11.3% in Canada and the United States [14], however these rates may increase in the coming years. Nevertheless, although an active role for men would allow for a shared framework, the share wouldn't be equal, as the ultimate result of contraceptive failure will always affect the female partner the most given the nature of pregnancy. Hence, novel restrictive legislation around female contraception and abortion services has reverberations outside women's health. Such aftereffects may propagate pressure in the realm of male reproductive research to develop alternatives to vasectomy.[15]

MALE CONTRACEPTION RESEARCH

The above limitations of male contraception methods could serve as the catalyst that both the medical and political spheres require to address the shortcomings in this space. Specifically, the idea of developing a dependable and widely accessible form of male hormonal contraception

akin to "the pill" for women holds the potential to bridge this gap.[16] Page et al. (2022) discussed the main challenge of male hormonal contraception being the development of an accessible and efficacious market product that would be "the elusive male pill".[17] This underscores the challenges associated with the current state of male hormonal contraception development and utilization.[18]

This challenge is compounded not only by the stigma associated with testosterone as a pharmaceutical drug and the historical perspective through which its utilization has been and still is perceived but also by the mode of administration. Testosterone is primarily administered via injections, further complicating its acceptance and accessibility. Oral administration is unfavourable due to first-pass metabolism and the associated liver toxicity. Such adverse effects have made the development of an oral pill challenging, and thus, nasal, buccal, subdermal, and transdermal routes have also been explored.[19] Theoretically, if all options were available, the decision would come down to treatment burden and patient preference. Nevertheless, even with frequent injections of testosterone at regular intervals, infertility is not guaranteed. Interference with spermatogenesis using exogenous androgens allows for the suppression of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). However, steroidal inhibition has not been proven as some studies have shown incomplete suppression of the hypothalamic-pituitary-adrenal (HPA) axis.[20] A failure rate averaged from eight studies of male contraceptive efficacy demonstrates an effectivity of 97.7% and thus a Pearl Index value of 2.3, signifying the number of pregnancies that may happen for a method per 100 women over a year. To compare with female oral contraceptives at a Pearl Index rating of 6.9% and male condoms at 13%.[17,21] It is crucial to mention that vasectomies also suffer from early failure rates ranging from 0.3-9% within 3-6 months post-vasectomy, and late failure rates between 0.04-0.08%.[22]

Past studies have demonstrated the efficacy of hormonal contraception using injectable regimes and non-injectable regimes. Three WHO studies demonstrated that weekly intramuscular injections of T were able to provide highly effective, sustained, and reversible contraception within 120 days of treatment.[23–25] To date, only 8 hormonal male contraceptive efficacy studies have been conducted, showing a collective failure rate of 2.3%, defined as a sperm threshold of < 1 million/ml with full reversibility.[26,27] To compare with other contraceptive methods, the female oral contraceptive pill and male condoms have failure rates of 6.9% and 13%, respectively.[17,21] It is crucial to mention that vasectomies also suffer from early failure rates ranging from 0.3-9% within 3-6 months post-vasectomy, and late failure rates between 0.04-0.08%.[22]The threshold however for fertility doesn't have a specific threshold above which you are considered fertile, but rather seems to have a correlated spectrum of pregnancy success/expectancy. A normal sperm count is defined as >20 million/ml and as per a study of 430 couples within 6 months 65% of those men with concentrations above 40 million/ml were successful, while 51.2% of men above 20 million/ml were successful.[27]Additionally, if below 20 million/ml there was only a 36.4% chance of success. That said, most men will have recovery of the HGPA after testosterone use with a varied timeline.[28] A

2006 study by Liu and Swerdloff stated that nearly all men will eventually demonstrate full reversibility from hormonal ale contraceptive regimens following a predictable time course within 24 months. Their dataset of 1549 previously eugonadal men aged 18-51 years showed that 67% of patients returned to a level of 20 million/ml within 6 months, and 90% by 93 months. The speed of this recovery seemed to be directly related to patients of older age, Asian origin, shorter treatment duration, shorter-acting testosterone preparations, higher baseline sperm concentrations, faster onset of initial spermatogenic suppression, and lower baseline blood concentrations of luteinising hormone.[29] Although most patients recover within half a year; some men may take multiple years to regain adequate sperm quality for reproduction depending on their specific interaction with testosterone replacement or supplementation.

Beyond efficacy, there seems to be more interest in a new method of male contraception. Multiple studies across the world have used surveys to validate interest in male hormonal contraception, finding that the majority of respondents would be willing to use such a method.[30–33] Overall, at least 25% of men in any setting, among many countries, expressed their willingness to use "the pill" if it were available as an option.[7] However, an additional question arose regarding whether, in such a scenario, women would trust men to reliably and effectively use this contraceptive pill.[34] Consequently, studies have also sought to determine the credibility of this cultural phenomenon, largely debunking its significance as Glasier et al. (2000) found that only 2% of 1894 women attending family planning clinics across Scotland, China, and South Africa would not trust their partner to use the male equivalent of an oral pill.[32]

FUTURE DIRECTIONS

Further studies are underway exploring transdermal, oral, and injectable hormonal contraception as well as non-hormonal vaso-occlusive, motility-based inhibition, and spermatogenesis inhibitive mechanisms.[35,36]

Hormonal contraception is based on the inhibition of spermatogenesis via exogenous stimulation of the HGPA – the negative feedback from which shuts down the HGPA. There are three contenders in the current male hormonal contraceptive space that are most promising for commercial use: Segesterone acetate + testosterone (nestorone/T), Dimethandrolone undecanoate (DMAU), and finally 11β-methyl- 19-nortestosterone dodecylcarbonate (11β-MNTDC).[37,38]

Nestorone, (segesterone acetate) is a synthetic progesterone that suppresses the hypothalamic-pituitary-gonadal axis (HPGA) when used as an exogenous agonist. Nestorone/T is a gel formulation. Combined with testosterone, it allows the maintenance of serum testosterone via transdermal absorption in this capacity while shutting down intratesticular testosterone. There is currently an ongoing multicenter phase IIb RCT with 420 couples enrolled and designated to conclude in 2024-07.[17]

DMAU (Dimethandrolone undecanoate) acts as a prodrug to DMA an agonist to both progesterone and androgen receptors.[52] With a relative affinity of 18% to progesterone at the progesterone receptor and 400% that of T at the androgen receptor, it effectively shuts down the HGPA while maintaining androgenic stimulation – thereby avoiding low T symptoms. It is an

injectable/oral compound. The intervention of oral testosterone compounds bypassing first metabolism represents a novelty in itself. There is currently an ongoing phase I multicenter, double-blind RCT with an estimated 84 participants designated to conclude in 2024-12 comparing intramuscular to subcutaneous injection pharmacodynamics.[39,40] Additionally, there is another study looking at the use of oral DMAU with and without levonorgestrel at three different doses currently recruiting a goal of 80 participants between two centers.

Thirdly, 11β-MNTDC is an oral formulation that has already completed a phase IIb RCT between two centers in 2020, showing well-tolerated efficacy.[41,42] One limitation of this study was the small sample size, including only 42 men and therefore, requiring further high-powered concretizing work.[43] 11β-MNTDC also works as a prodrug like DMAU converting to 11β-MNT, however with a significantly lower conversion rate ($1/10^{th}$ of DMAU to DMA).[44] 11β-MNT is a modified testosterone which exhibits both progestin and androgen stimulation with oral daily dosing dependent upon administration with food.

Numerous non-hormonal methods have shown reversible efficacy while being minimally invasive. These include mechanisms that limit spermatogenesis and sperm motility, as well as vas deferens occlusion to limit the passage of otherwise viable sperm. Spermatogenesis itself is, a hormone-dependent process via Sertoli and Leydig cells downstream of LH and FSH stimulation, however this process also necessitates further building blocks such as bromodomains, which work to facilitate protein-protein interactions needed for sperm morphology and motility, as well as testis-specific serine/threonine kinases (TSSK) needed for spermatogenesis.[45] Targeting bromodomain testis-specific protein/s (BRDT) and TSSK/s, reversible infertility has been shown in mice models, but has yet to demonstrated seen in human trials.[46] One study evaluated this is pathway in humans subjects but used a non-testis-specific antagonist resulting in systemic toxicity from disulfiram-like reaction.[47]

Selectively inhibition of proteins that promote motility and capacitation are another target for male contraception.[48,49] Eppin, soluble adenylyl cyclase, and specific spermatic ion channels, are all proteins shown to be critical for this function. Many compounds have been studied and shown to inhibit these proteins in proof-of-concept animal studies; however, human trials have not yet been done. Lastly, physical obstruction of the vas – effectively causing a synthetic reversible obstructive azoospermia has been an active area of research. This technique relies on the bilateral injection of a polymer into the vas that may be dissolved or cleared at a later date.[50–52] The leading contenders in this space include the three following compounds – reversible inhibition of sperm under guidance (RISUG), Valsalgel, otherwise known as "Plan A,". All of these are injectable dissolvable hydrogel-like polymers allow fluid to pass selectively but block sperm passage. They have been popularized in India, the United States and Australia. Each of these has undergone confirmatory animal trials demonstrating efficacy.[53] A human study as early as 1992 demonstrated the recovery of fertility in a group of 130 males post polyurethane gel removal. Zhao et al. investigated a Chinese population where 260 polyurethane elastomer plugs were able to be surgically removed, resulting in all 130 participants partners conceiving by four

years post-removel.[53] Similarly, a study done in 2022 demonstrated efficacy of RISUG of vas occlusion and its reversibility in a group of 28 males.[54]

A DOUBLE STANDARD?

To date, numerous studies have demonstrated nearly complete reversible suppression of spermatogenesis using intramuscular injection-based testosterone esters. A study by Behre et al. (2016) precisely showed this with an intramuscular injection of 200mg norethisterone enanthate combined with 1000mg testosterone undecanoate administered every eight weeks; however, it was terminated early as per the recommendation of an external safety review committee established by the World Health Organization (WHO) based on adverse events documented in the study, which included reports of depression and mood changes, injection site pain, acne, and increased libido. [55] It is well known that testosterone supplementation causes increases in baseline hematocrit and may increase thromboembolic events. Additionally, it is contraindicated in the use of patients with metastatic prostate cancer, breast cancer, obstructive sleep apnea and uncontrolled heart failure. Thus, testosterone is by no means a benign drug and requires consistent monitoring to avoid supratherapeutic toxicity.[56] Interestingly, of all TRT formulations injectables tend to carry the most significant risk of increased hemoglobin and hematocrit.[57] However, if the goal is management of hypogonadal symptoms, TRT may achieve this at the cost or gain of infertility during treatment, but so too may human chorionic gonadotropin (hCG) and clomiphene citrate (CC). The difference being that hCG allows for the preservation of fertility while raising T levels by stimulating the HGPA.[55]

Interestingly, when compared to the initial Enovid study - the first oral pill developed in 1960 that received FDA approval, patients experienced significantly higher rates of objectively more severe adverse health effects.[58] Through a retrospective lens, it may be easy to judge the ethics surrounding its FDA approval but it's important to note that the research milieu of the 1960s is considerably different then today. That said, Suzanne W. Junod, FDA historian, released a statement in 1998 justifying these actions in the context of the political and medical climate of that time. The response seemingly seeks to address the "disillusionment... [and] varying interpretations of the wisdom of the Pill's original approval" she states.[59] Contemporary research and healthcare landscape differs significantly from 60 years ago, making it challenging to claim a clear double standard in male and female contraception. Additionally, the paucity of data regarding the imbalance in research funding between male and female fertility makes this question ever harder to answer. However, one can argue that male contraception could and should have been developed simultaneously. This raises questions about why it was not revealing a complex historical narrative that goes beyond simple gender biases. The first study to examine the difference between male and female reproductive health funding by Eva Gumerova et al. described the value difference in both UK and US systems over a three-year period. Between January of 2016 and December of 2019 UK agencies award £11,767,190 to 18 projects for male-based research and £29,850,945 to 40 projects for female-based research.[60] While US agencies

funded 76 projects totalling $59,257,746 for male-based research and 99 projects totalling $83,272,898 for female-based research.

Nevertheless, proof of concept that testosterone-based injections have the ability to suppress spermatogenesis while being reversible was shown in 1939. There has been little further research in this regard, as opposed to an abundance of female contraceptive research may suggest a sex-based imbalance in priority and funding globally.

A MEDICAL ETHICS PERSPECTIVE

Medical ethics traditionally stands upon the four following pillars: respect for justice, beneficence, nonmaleficence, and autonomy, with a concern for scope of application.[61]

As it pertains to beneficence and nonmaleficence, physicians work for the benefit of their patients in balance with minimal harm. This ultimately leads one to analyze a benefit and risk ratio. Campelia et al. (2020) recently discussed a novel shared risk analysis framework to address this ethical.[62] They argue a need for an equitable distribution of risks and benefits in contraception in the context of interdependent relationships. The benefit being an objectively greater reproductive autonomy and participation in family planning. In so doing, the male may avoid an unplanned parenthood and its obligations. This autonomy is especially exemplified in both Planned Parenthood v Danforth and Planned Parenthood v Casey. The Supreme Court determined that laws requiring a spouse's consent for an abortion and equally that spousal notification of abortion were unconstitutional, respectively.[63] Considering these limits, an increase in vasectomy rates and interest in male contraception is understandable.

Ultimately, these methods give rise to reproductive autonomy and procreative liberty, allowing to better share the load of family planning. Historically, the autonomy gained by female contraceptive methods in women's rights movements was a stride of empowerment.[64] It was not until much later that the biopsychosocial and financial burdens of this power were recognized.[65] This perspective means that reproductive autonomy or procreative liberty comes at a cost. That said, if the first step is choice, the second would be accessibility.[66] Once or if available, male hormone contraception would then have to surmount barriers of access such as family planning provider education, public education and awareness, distance to care, inadequate insurance and refilling regimens, amongst others.[67] The limits of access are critical to consider because although autonomy is basically a right to choose, it questions the virtue of such autonomy when choices are limited. This restricted access to various contraceptive methods may create an illusion of reproductive choice.[68]

Overall, as compared to the mid-1900s during the birth of female hormonal contraception, the landscape surrounding contraception has drastically changed. Such a change primarily results from an evolved ethical approach via a shared risk framework. Currently, vasectomy and condoms currently provide methods for male contraception, however these have pitfalls. The first has a relatively high fail rate and inconsistent use, the latter being a surgical procedure in which reversibility can be challenging.[69,70] The architecture of choice amongst

men's current contraception methods is thus limited. Therein lies the ethical responsibility to provide or at least pursue alternative options.

CONCLUSIONS

The above narrative reflects a review of past, present, and potential future male contraceptive methods with commentary on the politics that may surround these.[71] With an almost 60-year gap in research, further study would help to help meet an unmet need and allow more options for family planning.[62] Reproductive medicine is an evolving field, heavily influenced by basic science advancements, social stressors, and changes in political climate.

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