Chapter 49
The potential reproductive effects of male circumcision

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Foreskin and male circumcision

The foreskin, also known as the prepuce, is the double layer of skin covering the male phallus protecting the glans penis and urethral meatus. The foreskin length is variable and flexible, therefore, its coverage in both the flaccid and erect state varies. While it is attached to the glans at birth, it is generally retractable by adolescence and adulthood. The outer preputial skin is contiguous with the penile shaft, but the inner layer is more similar to a mucous membrane. As a result, the inner surface of the foreskin contains a higher density of Langerhans' cells, which may be implicated in predisposition to certain genitourinary conditions.

Male circumcision (MC), or removal of the foreskin, is among the oldest and most widely performed male procedures surgically, culturally and religiously. An estimated one-third of males are circumcised worldwide with evidence dating back to 2300 BC with Egyptian wall paintings depicting men without foreskin. MC was performed for religious or cultural practice in many cases, but its use and indications have expanded over time. Currently, voluntary medical male circumcision (VMMC) is performed for various reasons, such as individual preference and cosmesis, and critical medical indications such as recurrent infections, phimosis, discomfort, and HIV prevention.

To date, a significant body of research, including large randomized controlled trials, have focused on MC's role in HIV prevention. In 2007, The World Health Organization (WHO) and the Joint United National Program on HIV/AIDS (UNAIDS) endorsed VMMC in countries with low rates of MC and high rates of HIV as a critical strategy for HIV prevention (up to 60%). Such programs continue to expand, including broadening indications for VMMC to adults and adolescents, and its role in infants is currently being investigated. Furthermore, VMMC is also supported by the U.S.

Centers for Disease Control and Prevention, given its numerous benefits for HIV prevention and other health outcomes.

Effects on reproductive health

The primary evidence of the impact of MC and its reproductive effects arises from its potential ability to reduce genitourinary infections. For some infections, the evidence is compelling about the reproductive impacts, and in other cases, the data remains deficient. A summary is presented in Table 1.

Human Immunodeficiency Virus (HIV)

HIV is a member of the *Lentivirus* family of retroviruses and consists of two sub-types, HIV-1 and HIV-2. The virus has claimed over 30 million lives worldwide and is transmitted through various bodily fluids, with sexual transmission remaining the most common transmission source. Infection is believed to occur secondary to smaller lesions or ulcerations of the genital and rectal mucosa with a virus targeting host antigen-presenting cells (APCs) via binding of CD4 and chemokine receptors, resulting in depletion of the immune system. According to data from three clinical trials in Africa, MC can reduce a man's risk of acquiring HIV infection by over 50% to 60% during sex with HIV-infected female partners. Mechanistically, this impact is hypothesized to occur through surface area reduction, including limiting Langerhans' cells, alteration of microflora, increased viral susceptibility and permeability of the inner foreskin (Fig. 1), and variable tissue structure permitting viral entry. The role of HIV in male fertility includes a reduction in semen quality such as motility, morphology, and increased risks of aneuploidy. HIV in the testis is also linked to chronic orchitis, which may potentially lead to testicular failure, impaired semen quality and hypogonadism. Finally, treatment for HIV in anti-retroviral therapy has also been suggested to impair semen quality.

Human Papilloma Virus (HPV)

HPV is a DNA virus from the *Papillomaviridae* family with over 150 subtypes, of which multiple are cancer-causing, commonly HPV 6, 11, 16, and 18 in humans. Typically, these present as anogenital warts, with the majority being asymptomatic and resolving without intervention. While the evidence is variable, MC has a suggested protective effect in HPV infection and transmission in many reports. Potential etiologic mechanisms include limiting viral access as the inner prepuce is non-keratinized, and therefore, more susceptible to

injury and viral infection during intercourse, reduction in surface area for viral entry, exposure to areas that may be otherwise missed for HPV detection, and finally, reduction of the moist environment which may assist in HPV infection and transmission. HPV infections have been described to impact fertility, including impacts on semen parameters such as sperm concentration, motility and morphology, production of anti-sperm antibodies, and the virus may be transmitted at the time of fertilization, potentially resulting in failed implantation. MC has also been shown to reduce the risk of HPV-related cancers such as penile cancer in men and cervical cancer in female sexual partners.

Herpes Simplex Virus (HSV)

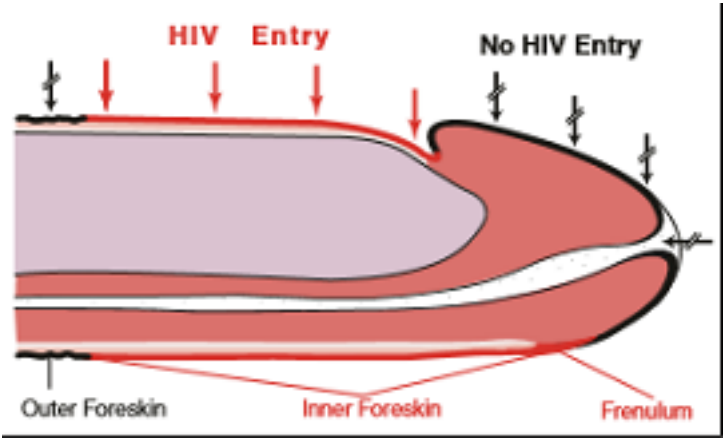

Figure 1. Illustration of how the inner foreskin permits HIV viral entry (https://circumcisionandsex.wordpress.com/2017/01/04/biological-and-evolutionary-plausibility-of-the-benefits-of-circumcision)

HSV arises from the *Herpesviridae* family and includes both HSV-1 and HSV-2. The former has generally been associated with non-genital lesions, and the latter is the more common culprit for genital herpetic lesions. In most cases, infection is limited to beefy red ulcers with possible lymphadenopathy but may result in more severe systemic symptoms and central nervous system involvement. The data for transmission reduction of MC in HSV is variably reported in the literature. The mechanistic etiology includes the removal of epithelial, dendritic, and Langerhans' cells, which permit viral entry.

The role of HSV in male fertility is similarly controversial. Animal studies have suggested impacts on sperm morphology and germ cell apoptosis. In humans, the infection has resulted in some instances of impaired semen quality, such as reduced sperm count and morphologic changes. These changes are thought to occur secondary to a viral gametotoxic effect on spermatogenesis, viral sperm DNA damage, and cross-reactivity, thereby disrupting spermatogenesis and/or an inflammatory response resulting in prostatic dysfunction and changes to seminal fluid.

Syphilis, Chancroid, Gonorrhea and Chlamydia

Syphilis is caused by *Treponema pallidum*, a spirochete bacteria, and has approximately 12 million cases each year globally. It may produce primary localized painless genital lesions, secondary systemic symptoms and may result in latent syphilis with cardiovascular and neurologic impacts. The evidence supporting the role of MC in infection reduction is controversial but is mechanistically similar to other conditions and are thought to occur due to reduction of surface area and susceptibility of micro-tears which may act as sites of bacterial infection. Limited data have been reported on the impacts of syphilis on semen quality. However, syphilis may result in epididymal obstruction or impaired testicular function from tertiary syphilis and is well known to have a role in spontaneous abortion and stillbirth.

Chancroid arises from *Haemophilus ducreyi*, a gram-negative bacterium, and usually results in painful genital sores as well as inguinal lymphadenitis. The evidence for MC in chancroid reduction is limited and controversial, and the evidence about its impacts on fertility is scant.

Gonorrhea is caused by the gram-negative diplococcus, *Neisseria gonorrohae,* and Chlamydia the gram-negative bacteria, *Chlamydia trachomatis*. Generally, these infections are uncomplicated but may result in severe sequalae with more systemic symptoms and genitourinary tract complications of urethritis and epididymoorchitis. Again limited and conflicting data exists for infection prevention by MC, with more data favoring a reduction in gonorrohea infection.

MC does reduce the risk that a female partner will acquire a new syphilis infection by up to 60%. Furthermore, it is hypothesized that the impacts on fertility may result from the genitourinary complications of urethritis and epididymoorchitis.

Table 1. Summary of the impact of male circumcision on male genitourinary infections and fertility

Infection	MC and infection		MC and infertility	
	Role in infection prevention	Mechanism	Role in infertility	Mechanism
HPV	Favorable association	Limits injury of the non-keratinized inner prepuce epithelium Reduces surface area for infection Eliminates environment for HIV transmission	May help decrease the effect of HPV	HPV virions may harm semen parameters Reduce possible anti-sperm antibody production Reduce transmission during oocyte fertilization
HIV	Decreased risk of heterosexual HIV transmission in areas with high viral incidence	Reduces injury to non-keratinized inner prepuce epithelium Reduction of Langerhans cells which act as a site of viral entry	May help mitigate the negative effects of HIV	Direct viral impact on sperm quality Possible testicular failure from chronic orchitis Anti-retroviral therapy impacts to semen parameters
HSV	Some impact reported	Removal of epithelial, dendritic, and Langerhans cells, which facilitate viral replication	Controversial evidence of the link between HSV and fertility. Possible benefits derived from MC	Direct viral toxic effects impairing semen parameters and causing sperm DNA damage Inflammatory response altering seminal fluid Cross-reactivity to self disrupting spermatogenesis
Syphillis	Suggestions of protective effects	Removal of surface for pathogen replication Reduces micro-trauma and subsequent bacterial infection	May be protective through reduction of long-term genitourinary tract complications	Severe disease may lead to epididymal obstruction or testicular lesions impacting testicular function
Chancroid	Possibly protective	Reduces surface area for infection	Limited data to draw conclusions	N/A
Gonorrohea & chlamydia	Limited data for protective role	Impairs moist environment for bacterial replication Reduces micro-trauma and subsequent bacterial infection	May be protective through reduction of long-term genitourinary tract complications	Urethral strictures Epididymo-orchitis which may result in impaired testicular function and spermatogenesis

MC: male circumcision, HPV: human papilloma virus, HIV: human immunodeficiency virus, HSV: herples simplex virus, N/A: not availablena:

Conclusion

In conclusion, the role of MC and reproduction continues to be elucidated. Its protective role is anchored in genitourinary infection reduction. In addition, there is reasonable and compelling evidence to support that MC reduces some infections, such as HIV and HPV. However, with limited variable and controversial data, further prospective studies are needed to explore these relationships and the overall reproductive impact.

Suggested reading

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