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Genitourinary Infections Related to Circumcision and the Potential Impact on Male Infertility

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Male circumcision (MC) is one of the oldest surgical procedures still completed today. Medical indications for MC include phimosis, recurrent balanitis, cosmesis, and infection prevention. In this review, we mainly focus on the role of MC in the prevention of human immunodeficiency virus, human papillomavirus, herpes simplex virus, gonorrhea, chlamydia, chancroid, and syphilis, and the subsequent impact of these genitourinary infections on male fertility. Overall, many compelling data support that MC may play an essential role in both genitourinary infection prevention and male fertility.

Keywords: Infections; Infertility; Male circumcision

INTRODUCTION

Male circumcision (MC) represents one of the oldest and most widely performed surgical procedures, with an estimated one-third of males worldwide being circumcised [1]. Some of the earliest robust evidence of MC arises from ancient Egyptian wall paintings around 2300 BC depicting men without foreskin [1]. Historically, MC has been described as both a religious or cultural practice and a procedure with perceived medical benefits [2]. Today, MC is performed for reasons including personal preference and cosmetic considerations, in addition to various medical indications such as recurrent infections (balanitis), phimosis, pain or discomfort, and for human immunodeficiency virus (HIV) prevention [3].

There is a wide range of evidence on the impact of MC in reducing the risk of genitourinary infections [4-6]. In addition, MC has also been shown to have a protective role against penile and cervical cancers [7-10]. Many infections such as herpes simplex virus (HSV), human papilloma virus (HPV), and HIV have been shown to impact semen quality and therefore place men at risk of fertility concerns [11-13].

This review will mainly discuss and focus on the impact of circumcision on HPV, HIV, HSV, syphilis, chancroid, gonorrhea, and chlamydia and review the subsequent impact of these infections on male fertility, suggesting a role for MC in fertility preservation.

GENITOURINARY INFECTIONS

1. Human papilloma virus

HPV is a DNA virus from the Papillomaviridae family and is the most common sexually transmitted infection (STI) among men and women [14]. Although over 150 HPV subtypes have been described, at least 14 are cancer-causing (*i.e.,* cervical, anal, and penile), and the most common causing infection in humans are 6, 11, 16, and 18. While HPV 6 and 11 cause more than 90% of genital warts in males, HPV 16 and 18 are also associated with anal and penile cancers [15]. The majority of HPV infections are either asymptomatic or resolve spontaneously without intervention. The most common clinical presentation includes anogenital warts and premalignant or cancerous lesions in the genital region [14].

1) Male circumcision and human papilloma virus

MC reduces the penile prevalence of high-risk HPV on both the coronal sulcus and shaft, and it has been speculated to prevent HPV infection and transmission. Several mechanisms that explain the protective role of circumcision against HPV infection have been described [16]. First, MC limits viral access to basal keratinocytes in the more cornified epithelium of the circumcised penis. The mucosal epithelium of the inner prepuce is non-keratinized and, thus, is more susceptible to both injury and subsequent risk of viral infection following intercourse [17]. Second, the foreskin provides a larger surface for viral entrance and, therefore, its removal can be beneficial. Third, HPV detection can vary by anatomical location, thus biasing the potential protective role of MC [18]. For example, HPV is more frequently detected on the coronal sulcus or the urethra than the penile shaft of uncircumcised men. Finally, the moist environment under the prepuce can facilitate HPV infection and transmission [19]. However, despite multiple described pathophysiological mechanisms of the protective relationship between MC and HPV infection, a definitive relation remains unclear.

Multiple studies have demonstrated no association between MC status and HPV infection. Albero et al [20] performed a longitudinal analysis of the incidence and clearance of HPV in the United States and Brazil by following more than four thousand men every six months for a total of 18 months. The authors found that HPV's overall incidence and clearance did not differ by MC status (hazard ratio [HR], 1.08; 95% confidence interval [CI] 0.91–1.20). However, they showed significant differences in the clearance of certain HPV subtypes according to MC status. For example, HPV subtypes 33 (p=0.02) and 64 (p=0.04) had shorter median clearance times among circumcised relative to uncircumcised men, while HPV subtypes 6 (p<0.001), 16 (p<0.001), and 51 (p=0.02) had longer median clearance times. Van Howe [21] performed a systematic review and meta-analysis in 2007 that included 16 studies and showed no significant association between MC status and HPV infection (odds ratio [OR] 1.20; 95% CI, 0.80–1.79). However, the authors emphasized that to avoid under sampling and perform a correct assessment of the HPV infection risk in circumcised males, the penile shaft needs to be sampled.

Conversely, the association between MC and a reduction in HPV prevalence among men has also been described. Larke et al [22] performed a systematic review and meta-analysis in 2010 and demonstrated that circumcised men were less likely to have prevalent genital HPV infection than uncircumcised men (OR, 0.57; 95% CI, 0.45–0.71). Interestingly, the authors showed that the effect of MC was stronger at the glans and corona (OR, 0.47; 95% CI, 0.37–0.60) and urethra (OR, 0.35; 95% CI, 0.12–1.05) compared to the proximal penile shaft. Furthermore, MC was associated with decreased HPV incidence (OR, 0.75; 95% CI, 0.57–0.99). More recently, Zhu et al [19] performed a more comprehensive meta-analysis that included more than 12,000 circumcised and uncircumcised men. In this study, circumcised men had significantly reduced odds of genital HPV prevalence (adjusted OR, 0.68; 95% CI, 0.56–0.82) [19]. However, there was no significant association between MC and acquisition of new genital HPV infections (OR, 0.99; 95% CI, 0.62–1.60), genital HPV clearance (OR, 1.38; 95% CI, 0.96–1.97), and prevalence of genital warts (OR, 1.17; 95% CI, 0.63–2.17) [19].

The reported studies on MC and HPV infection have several limitations, making it difficult to draw definitive conclusions about their relationship. First, most studies include men from different geographic areas that have variable HPV prevalence. Second, sampling and specimen collection methodologies often vary among different sites within studies and/or between studies. Finally, most studies do not report information on the HPV status of female partners and the timing

or success of MC for circumcised men.

2) Human papilloma virus and male infertility

Chronic viral infections of the genitourinary tract and region, such as HPV, may negatively impact male fertility secondary to urethral inflammation and harmfully impact semen quality. Subclinical HPV infections in men have been linked to unexplained infertility. Some studies have reported that HPV can be found in semen where the virus binds to the head of sperm, which can negatively impact sperm motility and morphology, and thus, can lead to male infertility [23]. Furthermore, Xiong et al recently performed a metanalysis that included 1,955 men and demonstrated that HPV infection of semen is a significant risk factor for infertility in men [24].

Multiple mechanisms underlie the deleterious effect of HPV infection on male fertility [25]. First, several studies have shown that HPV virions can harm sperm parameters, such as concentration and morphology. Lai et al [26] demonstrated that HPV-infected sperm have reduced curvilinear velocity, straight-line velocity, and mean amplitude of lateral head displacement. Second, HPV infection has been associated with the production of anti-sperm antibodies. Anti-sperm antibodies are known to reduce male fertility by affecting sperm motility and sperm-oocyte interaction [25,27]. Finally, it has been shown that sperm can carry HPV into the oocyte during fertilization. Therefore, the infectious viral genome can be subsequently transferred to the newly formed blastocysts and lead to infertility *via* failed implantation [28,29].

Multiple studies have demonstrated that HPV-DNA levels in semen from infertile males are 3 to 4 times higher relative to fertile controls [30,31]. Recently, Garolla et al [32] demonstrated that HPV vaccination in infected males is associated with higher rates of pregnancy and delivery of healthy newborns as well as a lower rate of miscarriages. In this study, vaccinated patients had improved sperm motility and reduced levels of anti-sperm antibodies compared to non-vaccinated subjects. Furthermore, in the same study, the most predictive parameter of successful pregnancy and delivery was the absence of HPV in sperm. None of the male patients from couples that conceived had HPV-DNA in their sperm. On the other hand, all miscarriages were associated with the presence of HPV-DNA in sperm

cells [32].

2. Human immunodeficiency virus

HIV is a member of the Lentivirus subfamily of retroviruses that was first detected in the 1980s [33,34]. Two subtypes have been identified: HIV-1, more predominant and most studied, and HIV-2, mainly confined to West Africa and overall less pathogenic [35]. To date, it is estimated to have claimed the lives of 32.7 million individuals worldwide [36]. Although vectors include different types of bodily fluids (semen, blood, or breast milk), sexual contact remains the major mode of transmission. Mechanistically, the viral infection is thought to occur via micro-traumatic lesions or small ulcerations of the genital and rectal mucosa. The retrovirus then targets the host's antigen presenting cells (APCs) through dual binding of the CD4 and a select chemokine (CCR5 or CXCR4) receptors [37-39]. Preferential infection of APCs, when untreated, eventually leads to severe depletion of the immune system and results in an immunocompromised state known as the Acquired Immunodeficiency Syndrome (AIDS) once CD4+ cell counts are lower than 200 cell/mm^3. At this stage, patients exhibit characteristic constellations of opportunistic infections (including *Pneumocystis carinii* pneumonia and tuberculosis) and neoplasms (such as Kaposi's sarcoma) resulting in high mortality [33,40]. The licensing of the first effective antiretroviral therapy azidothymidine in 1987 was the first step toward developing the "cocktail" of Highly Active Antiretrovirals Therapy (HAART) currently responsible for the significant decrease in the disease's lethality [33].

1) Male circumcision and human immunodeficiency virus

MC was suggested in the 1980's to confer protective benefits against HIV infection after the observation of lower rates of HIV heterosexual American couples, where a high proportion of neonates were circumcised (up to 80%–90%) [41]. Mechanistically, MC is proposed to decrease exposed preputial skin areas that are non-keratinized and susceptible to trauma [42]. The foreskin was also found to harbor a higher density of Langerhans cells, which may be the initial site for viral entry [42-44]. Lastly, MC may diminish the risk of HIV transmission indirectly by reducing incidence of other STIs that cause inflammatory and ulcerative lesions which can, in turn, serve as HIV entry sites

[37,42,45].

Several studies have supported that the presence of foreskin was associated with increased risks of HIV transmission [37]. A prospective study of 415 serodiscordant heterosexual couples (an HIV positive male or female and their HIV negative partner) in Rakai, Uganda followed over 30 months revealed that the rate of female-to-male HIV transmission was significantly higher among the couples where the male partner was uncircumcised (16.7 per 100 person-year compared with 0 per 100 person-years in couples with circumcised males, p<0.001) [46]. Similarly, a systematic review and meta-analysis of 28 studies conducted in Sub-Saharan Africa found that MC is associated with a significantly reduced risk of HIV infection among circumcised men, with an adjusted risk ratio (RR) of 0.42 (95% CI, 0.34–0.54) [42].

In addition to observational data, prospective and randomized data have supported these findings. Three different large prospective randomized controlled trials of similar study design aimed to assess MC's impact on HIV incidence in Sub-Saharan Africa [47-49]. Over 10,000 males were randomized to immediate *vs.* delayed circumcisions and followed over varying time periods. A meta-analysis of the various study results favored circumcision with a RR of 0.44 (95% CI, 0.33–0.60; p≤0.0001), which corresponds to a relative risk reduction of 56% (95% CI, 40%–67%) and a number-needed-to-treat of 72 (95% CI, 50–143) [50].

Overall, MC has demonstrated benefits in risk reduction of HIV transmission countries with a high rate of heterosexual infections and low rates of MC. This has led the World Health Organization (WHO) to recommend scale-up of voluntary medical MC as a tool for HIV reduction in Sub-Saharan Africa [51]. One such strategy includes the ShangRing (Wuhu Snnda Medical Treatment Appliance Technology Co. Ltd, Wuhu, China) which is the only pre-qualified WHO device for voluntary medical MC in sub-Saharan Africa. It has demonstrated safety and efficacy in adults and adolescents and is currently being studied for early infant MC (<60 days of age) [52-54].

2) Human immunodeficiency virus and male infertility

Approximately 85% of people affected by HIV are of reproductive age (15–44 years old), with nearly a third expressing a desire to have children [55]. Grossly abnormal sperm quality has been seen in HIV infected men with more pronounced changes in AIDS cases, including reduced ejaculate volume, reduced motility, abnormal sperm morphology, and increased risk of sperm aneuploidy. These changes have possible impacts on the fertility potential of males with HIV, as demonstrated by a study from Iyer et al [56] In this report, a total of 334 serodiscordant or seroconcordant HIV positive African couples experiencing "sub-fertility", defined as the inability to conceive naturally within 6 months, were analyzed with male HIV positive status correlating with increased risk of sub-fertility or infertility on multivariable regression (RR, 1.31; 95% CI, 1.02–1.68).

Since HIV-1 has been detected in semen shortly after infection and at all subsequent stages of the disease, the presence of the virus and secondary chronic inflammation have been advanced as possible mechanisms for decreased semen quality [57]. Increased semen-to-blood ratio of innate and adaptive inflammatory markers have since been identified in the seminal environment of HIV positive men compared to healthy controls [58,59]. Progressive hypogonadism from chronic orchitis has also been seen with HIV-1 infections, suggesting the possibility of a testicular failure component to the observed impaired semen parameters [60].

In addition to a direct cause from the virus, ART used to control disease in HIV positive men has also been associated with impaired fertility and semen parameters. Frapsauce et al. reported a 30% significant difference in sperm velocity in males receiving efavirenz (a non-nucleoside reverse transcriptase inhibitor frequently used as part of HAART) (p<0.0001) in a case-control study of 378 HIV-1 in serodiscordant couples [61].

Overall, HIV status has been linked to changes in seminal parameters in the context of chronic inflammation, lower CD4 count, and as a possible side effect of antiretrovirals.

3. Herpes simplex virus

The Herpesviridae family includes HSV both type 1 and 2, cytomegalovirus, Epstein–Barr virus, and human herpes virus types 6, 7, and 8. Prevalence of HSV varies but has been reported in as many as 50% in some populations [62]. HSV-2 is generally sexually transmitted and related to genital herpetic lesions, whereas HSV-1 has generally been associated with non-genital lesions. However, there have been rising

rates of primary HSV-1 infection in genital lesions [63]. While cases are generally mild, severe HSV cases with systemic manifestations such as central nervous system involvement have been reported [64]. Herpetic genital lesions generally present as painful beefy red ulcers and may be associated with lymphadenopathy [63]. Treatment is generally completed with a course of antiretrovirals [64].

1) Male circumcision and herpes simplex virus

Numerous studies have examined the impact of MC and HSV infection, of which a subset has examined both serotypes HSV-1 and HSV-2.

Retrospective data from the United States of over 6,000 men using publicly available data revealed no association between HSV-2 infection and circumcision [65]. Similarly, a randomized controlled trial of 2,778 men in Kenya demonstrated that men who underwent MC *versus* controls had no difference in HSV-2 incidence [66]. However, another large study of over 5,000 men found a reduced risk of HSV-2 seroconversion of circumcised compared to uncircumcised men after two years of follow-up (7.8% circumcised *vs.* 10.3% control; HR, 0.72; p=0.008) [6]. A trial of 1,000 men in Papua New Guinea examined men with various forms of foreskin manipulation, instead of just circumcision itself. In this report, participants received either a dorsal longitudinal slit or complete removal of the foreskin. They found that overall HSV-2 rates were lower in men with manipulated foreskin *versus* those uncircumcised. Therefore, MC with manipulated foreskin suggests that exposure of the glans and inner foreskin may confer protection for HSV-2 [67].

A large meta-analysis of over 25 studies by Van Howe [68] demonstrated that uncircumcised men were at higher risk of HSV infection, but when adjusted for lead-time bias, this relationship became non-significant. In another systematic review examining the relationship between HSV-2 and circumcision in ten studies, only one study was protective against seropositivity in their adjusted analysis. However, when meta-analyzed, they reported a RR of 0.88 (95% CI, 0.77–1.01) which became significant when excluding studies without adjusted analyses (RR, 0.85; 95% CI, 0.74–0.98) [69].

Overall, the limited protective effect of MC on HSV infection can be explained by two possible opposing mechanisms. First, it is hypothesized that MC removes epithelial, dendritic, and Langerhans cells, which provide a substrate for viral replication. Conversely, it is suggested that the removal of these cells leads to diminished immune protection [69].

2) Herpes simplex virus and male infertility

Numerous reports have investigated the impact of HSV infection and male fertility, but the data is controversial. The virus has certainly been detected in the semen of infertile men [62,68].

In vitro testing with HSV virus in the ejaculate demonstrated poor adherence of HSV-2 to sperm secondary to the presence of seminal fluid [70]. Animal studies in transgenic mice testis suggest that HSV is associated with structural sperm defects, including acrosomal aberrations, neck and flagella abnormalities, and developmental arrest [71]. Studies in transgenic rats with spermatic-specific expression of HSV-1 thymidine kinase have shown spermatogenic cell degeneration, failure of Sertoli-germ cell interaction and apoptosis of germ cells [70].

In humans, the data continues to be controversial. Previous studies have shown that HSV DNA may be found in infertile men who are seropositive, suggesting a possible role in fertility [71]. Despite HSV-1 and HSV-2 viral detection rates in 2% to 50% of semen samples, modest and limited differences have been demonstrated between fertile and infertile men [70]. A study of 172 men compared rates of multiple viruses from the Herpesviridae family between men with and without abnormal semen parameters and also showed no significant differences [62].

Alternatively, other studies have demonstrated some relationship. A study of 808 men showed that HSV detection directly correlated with reduced sperm motility and smaller portions of normal germ cells (p<0.001) [72]. A study completed in Greece examined the impact of HSV-1 in semen and found that in 113 men presenting to an infertility clinic, almost half (49.5%) had HSV DNA detected and were subsequently found to have lower sperm counts (HSV+ 19.8 million/mL *vs.* HSV- 54.5 million/mL; p<0.001) and reduced motility (HSV+ 39.1% *vs.* HSV- 48.6%, p=0.005) [71]. Another study examined 153 semen samples from an infertility clinic that observed HSV DNA in approximately 25%. In their studies the authors concluded a significant association between HSV and infertility (p=0.02) [73]. In another study of 70 semen samples, 16 (22.9%) had HSV-

1 infection and 10 (14.3%) had HSV-2 infection, and all of the HSV positive patients had abnormal semen parameters. Only HSV-1 infection had a statistically significant relationship with reduced sperm count, and no motility or morphology changes were associated with either subtype [74]. This was similar to another study of 100 men which showed that HSV positive men had higher rates of oligospermia but no difference in other parameters [75]. With respect to sperm morphology, structural changes have been noted, including the presence of sperm microheads and improper cytoplasmic drop migration [75]. Finally, a study from Brazil examined 279 semen samples, of which HSV-2 was seen in 3.2% and HSV-1 in 10.7%. HSV-2 in this series was associated with hematospermia and lower seminal volume and HSV-1 a lower sperm count [76].

Some theories to explain the impact of HSV on sperm and fertility include a direct viral gametotoxic effect on spermatogenesis, which causes an increase in the number of apoptotic cells and lowers sperm concentration [76]. Alternatively, this may be due to an inflammatory response, which may induce prostate dysfunction and changes to seminal fluid. Others suggest a theory of cross-reactivity to self, subsequently disrupting spermatogenesis. Finally, these observed changes may also be due to direct viral effects causing sperm DNA damage [76].

4. Syphilis

Syphilis is a relatively common STI caused by *Treponema pallidum*, with up to 12 million cases each year globally [77]. Syphilis infection may present in numerous stages: primary syphilis with localized genital lesions, secondary syphilis, which includes systemic symptoms (*i.e.*, rash), and latent syphilis, which may have cardiovascular and neurologic impacts [77]. In general, syphilis lesions are painless, and treatment consists of penicillin-based antimicrobial therapy [78].

1) Male circumcision and syphilis
Evidence exists regarding the impact of MC on syphilis. The most extensive primary data includes a large randomized controlled trial of 2,778 men in Kenya randomized to undergo MC *versus* observation. However, no difference in syphilis rates were noted between groups [66].

A systematic review identified fourteen studies from across the globe (the United States, sub-Saharan Af-

rica, Australia, South America, and Asia) that explored the relationship between MC and syphilis seropositivity [69]. While heterogeneity existed concerning syphilis infection reporting (either lifelong or recent infection), they concluded an overall relative risk reduction of 33% favoring circumcision (RR, 0.67; 95% CI, 0.54–0.83) [69]. Conversely, another large meta-analysis demonstrated no significant impact of MC on the incidence of syphilis infection but did demonstrate an association with syphilis prevalence (OR, 1.31; 95% CI, 1.11–1.53) [68].

The potential protective effect of MC has been hypothesized to result from either prevention of pathogen replication secondary to foreskin removal or from loss of increased foreskin susceptibility to micro-tears with sexual activity in uncircumcised men that would otherwise increase the risk of infection [69].

2) Syphilis and infertility
Almost no literature has reported a direct impact of syphilis on spermatogenesis or semen parameters, however, long term complications of syphilis may impact fertility [79]. It is hypothesized that syphilis infection of the epididymis may lead to epididymal obstruction, and tertiary syphilis may cause small fibrotic testis and testicular lesions which may impact testicular function [79].

Furthermore, while the role of syphilis in male infertility is less well defined, it is well implicated in spontaneous abortion and stillbirth. While women are screened during pregnancy, a male partner's reduction in transmission has been suggested to have a protective role for a successful pregnancy [80].

5. Chancroid

Chancroid is an ulcerative STI caused by the gram-negative bacteria *Haemophilus ducreyi,* which is usually also associated with inguinal lymphadenitis [81]. Treatment usually consists of antimicrobial therapy and individuals often present because of pain [81].

1) Male circumcision and chancroid
Few studies have examined the association between chancroid and MC. A systematic review of seven studies revealed six studies showing a reduced risk of chancroid among circumcised men [69]. However, given the large study heterogeneity the authors were not able to report a summary statistic. The findings of this meta-analysis have been contested, and these critics

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 effect of HPV	HPV virions may harm semen parameters Reduce possible anti-sperm antibody production Reduce transmission during o ocyte 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 negative effect 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 and 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: herpes simplex virus, N/A: not available.

have importantly highlighted three series which have shown reduced chancroid prevalence in circumcised men [82].

2) Chancroid and infertility

To date, there is no evidence for the impact of chancroid on infertility [83].

6. Gonorrhea and chlamydia

Gonorrhea is a bacterial infection caused by *Neisseria gonorrhoae*, a gram-negative diplococcus [84]. Chlamydia is similarly a gram-negative bacterial infection caused by *Chlamydia trachomatis* [85]. Gonorrhea affects approximately 60 million people annually worldwide, and Chlamydia over 131 million cases annually worldwide [84,85]. These infections are generally uncomplicated and can be effectively treated with antibiotic therapy. A subset of individuals develop more severe infection sequelae, with women at particular risk for salpingitis, pelvic inflammatory disease, ectopic pregnancy, infertility, and disseminated infection in the blood [86]. In men, long term sequalae include infectious complications of the genitourinary tract such as urethritis and epididymoorchitis [87].

1) Circumcision and gonorrhea and chlamydia

Limited data exists for the role of MC in gonorrhea and chlamydia (GC) prevention. The largest series arises from a large randomized controlled trial from Kisumu, Kenya consisting of 2,655 men randomized to MC *versus* no MC. The trial showed no difference in STI risk by circumcision status in this cohort [88]. Additionally, a large meta-analysis illustrated no significant impact of MC on gonorrhea prevalence based on pooled effect estimates [68].

Alternatively, data from an extensive study of 2,000 men seen at STI clinics in the United States demonstrated that uncircumcised men had an increased incidence of gonorrhea infection with a reported OR of 1.6 (95% CI, 1.0–2.6). However, no statistically significant difference was seen for Chlamydia (OR, 0.9; 95% CI, 0.5–1.5) [89,90].

2) Gonorrhea and chlamydia and infertility

Minimal data exist for the impact of GC on fertility. One series reports that while gonorrhea may not impair sperm directly or impact any direct semen parameters, its role in infertility arises from the potential to create urethral strictures, resulting in infertility [83]. Other studies have shown that these bacterial infections may induce epididymo-orchitis, which may impact testicular function or sperm maturation through the epididymis in some severe cases. A study in Sweden indicated that eradication of gonococcal infections demonstrated a reduction in secondary male subfertility [83].

CONCLUSIONS

While the data remains heterogeneous in some series, MC may prevent genitourinary infections and sequentially maintain male fertility (Table 1). The strongest relationships appear to be for HPV and HIV with more limited evidence for other genitourinary infections. Furthermore it is difficult to discern in some of these studies if concomitant and overlapping STIs may be responsible for the observed outcomes. Given this limited and varied data, further prospective studies exploring this relationship are needed.

Conflict of Interest

The authors have nothing to disclose.

Author Contribution

Conceptualization: NP, SPB, QGN, PSL. Supervision: PSL. Writing – original draft: NP, SPB, QGN. Writing – review & editing: NP, SPB, QGN, RKL, MG, JPA, PSL.

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