Prevention of syphilis: another positive benefit of male circumcision

See Articles page e664

Although rates of syphilis in the USA and Europe have increased slightly in the past decade, the greatest burden of syphilis lies in sub-Saharan Africa and Asia, where nearly 10 million cases occur every year, and more than 36 million people globally harbour the disease.[1] Recent studies have estimated that more than 5% of pregnant women in sub-Saharan Africa are infected with the spirochaete bacterium, *Treponema pallidum*, which causes syphilis.[2] *T pallidum* is mainly spread by sexual contact and disease begins with a painless genital ulcer. However, if untreated, it can cause influenza-like symptoms, a diffuse maculopapular rash, meningoencephalitis, tabes dorsalis, cardiovascular syphilis, and gummatous disease. In pregnancy, untreated early syphilis results in a stillbirth rate of 25% and is responsible for 14% of neonatal deaths, with an overall perinatal mortality of 40%.[2]

More than 40 observational studies and three randomised trials have shown that male circumcision reduces HIV acquisition in men by 50–60%, and long-term follow-up studies show even higher efficacy of male circumcision.[3,4] The randomised trials also showed that male circumcision decreases the risk of men acquiring genital ulcer disease, herpes simplex virus type 2, and oncogenic high-risk human papillomavirus.[3-5] Additionally, male circumcision has direct benefits for female partners with reduced transmission rates of high-risk human papillomavirus, bacterial vaginosis, and trichomoniasis.[3,4]

Although the data showing male circumcision reduces viral sexually transmitted infections (STIs) in men are clear, observational studies and randomised trials have had conflicting results about bacterial STIs. Some observational studies have shown that male circumcision reduces syphilis, but others have found no association.[3] A meta-analysis of 13 observational studies estimated that male circumcision significantly decreased syphilis by 33%.[6] However, the two randomised trials that assessed *T pallidum* incidence in Rakai, Uganda (adjusted hazard ratio 1·10, 95% CI 0·75–1·65)[5] and Kisumu, Kenya (risk ratio 1·23, 95% CI 0·41–3·65)[7] showed that male circumcision had no effect on acquisition of syphilis.

In *The Lancet Global Health*, Jillian Pintye and colleagues[8] from the Partners PrEP study team present one of the largest and most comprehensive analyses of syphilis incidence in men and women and the effect of male circumcision. The investigators followed 4716 HIV-1 serodiscordant couples, of whom roughly 50% of the men were circumcised. During follow-up (median time of 2·75 years), they noted that male circumcision significantly decreased incident syphilis by 42% in men compared with uncircumcised men, and male circumcision was most protective for men with HIV with a reduction of 62%. They also showed that male circumcision reduced female partner syphilis incidence by 59%, with a 75% reduction in the women without HIV and a 48% reduction in women with HIV. Thus, in this large prospective cohort, male circumcision was strongly associated with reductions in syphilis acquisition in both men and their female partners.

There could be several reasons for the discordance between the randomised trial data and the cohort study by Pintye and colleagues. The incidence of syphilis in the two trials was low, which restricted the power to detect a difference. The two trials assessed *T pallidum* incidence in men, but did not know their exposure status. A strength of Pintye and colleagues' study was that the investigators were able to measure syphilis acquisition in men with known exposures. Additionally, the study assessed syphilis in HIV-1 discordant couples, whereas the randomised trials only assessed HIV-1 negative men with few men being in discordant relationships.

The pathophysiology of male circumcision to reduce viral and bacterial STIs is probably due both to anatomical and cellular factors.[3] Male circumcision removes a warm, moist subpreputial cavity that is formed by the foreskin, likely reducing the survival of viruses and bacteria. Male circumcision also removes a thinly keratinised, vascular foreskin tissue that is stretched and exposed to vaginal fluids when the penis is erect. The foreskin tissue is also prone to microabrasions that might allow STIs to penetrate. In addition to anatomical factors, the foreskin mucosa contains a high density of CD4+ T cells, CD8+ T cells, and CD1a+ dendritic cells.[9] These cellular and anatomical factors for the protective role of male

circumcision are supported by the finding that risk of HIV is highest in men with the largest foreskin surface area.[10]

After the randomised trials showed that male circumcision reduces acquisition of HIV in men, in 2007 WHO–UNAIDS recommended that male circumcision should be promoted and scaled up to curb heterosexual transmission of HIV.[4] After these initial findings were released, the medical benefits of male circumcision have only become stronger with additional protection shown against herpes simplex virus type 2, high-risk human papillomavirus, and now syphilis.[4] These new data should squelch concerns that there are no medical benefits of male circumcision, and should continue to support programmes that encourage neonatal male circumcision and adult male circumcision globally, especially in the 14 priority countries in eastern and southern sub-Saharan Africa with large HIV epidemics. These programmes will not only have a substantial effect by improving the health of men and their female partners, but also by reducing health-care costs associated with the long-term treatment of STIs.[11]

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