Circumcision and Lifetime Risk of Urinary Tract Infection: A Systematic Review and Meta-Analysis

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Abbreviations and Acronyms

UTI = urinary tract infection

VUR = vesicoureteral reflux

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The complete list of references including numbers 31 through 77 is available at http://jurology.com/.

Nothing to disclose.

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Purpose: Urinary tract infection is common in infant males who are uncircumcised and can lead to renal parenchymal disease of the still growing pediatric kidney. Although the rate of urinary tract infection is highest in the first year of life, the cumulative incidence during the rest of the lifetime is under-recognized, but is expected to be nontrivial. Thus, any intervention that might prevent urinary tract infection would be expected to reduce suffering and medical costs.

Materials and Methods: We conducted a meta-analysis of 22 studies examining the single risk factor of lack of circumcision, then determined the prevalence and relative risk of urinary tract infection in different age groups (0 to 1, 1 to 16 and older than 16 years). From these data we estimated the lifetime prevalence.

Results: For age 0 to 1 year the relative risk was 9.91 (95% CI 7.49–13.1), for age 1 to 16 years RR was 6.56 (95% CI 3.26–13.2) and for older than 16 years it was 3.41-fold (95% CI 0.916–12.7) higher in uncircumcised males. We then calculated that 32.1% (95% CI 15.6–49.8) of uncircumcised males experience a urinary tract infection in their lifetime compared with 8.8% (95% CI 4.15–13.2) of circumcised males (RR 3.65, 95% CI 1.15–11.8). The number needed to treat was 4.29 (95% CI 2.20–27.2).

Conclusions: The single risk factor of lack of circumcision confers a 23.3% chance of urinary tract infection during the lifetime. This greatly exceeds the prevalence of circumcision complications (1.5%), which are mostly minor. The potential seriousness of urinary tract infection supports circumcision as a desirable preventive health intervention in infant males.

Key Words: circumcision, male; foreskin; urinary tract infections; meta-analysis; male

Urinary tract infections are common in infancy[1] and can lead to significant morbidity.[2] The younger the infant, the more likely and severe will be the UTI, and the greater the risk of sepsis and death.[3] By the age of 7 years 2% (definitely) and another 5% (probably) of boys have had at least 1 UTI.[4] Apart from severe pain and fever, the infant kidney is still growing, thus increasing susceptibility to renal injury and scarring from UTI.[5,6] This exposes half to serious, life threatening conditions later in life.[7]

Rushton and Majd found that 50% to 86% of children with febrile UTI and presumed pyelonephritis had renal parenchymal defects which persisted.[8] Others reported pyelonephritis in 34% to 70% of febrile UTI cases in the first year of life[9] and another estimate was 90%.[10] Nuclear scans in febrile infants after treatment for UTI noted scarring in 10% to 30%.[11] Acute pyelonephritis is a major cause of renal scarring[12] and the likelihood of renal scarring after acute pyelone-

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phritis is 36% to 52%.[10,13–15] The majority with renal scarring do not have VUR.[16] Moreover, recurrent UTI can occur in the absence of VUR with an incidence of 36%.[17] It is the parenchymal infection with inflammation rather than the VUR that is the prerequisite for renal scarring.[14–16] Roberts estimated that infant circumcision prevents 20,000 cases of acute pyelonephritis annually.[18] A 27-year followup study of pyelonephritis in childhood noted a 10% to 20% risk of hypertension associated with hyperreninemia and hypernatremia, consistent with renal involvement.[19] Post-infection scarring may occasionally progress to renal insufficiency and end stage renal disease. As a result, measures that can be put in place to prevent UTI would seem worthy of consideration.

The first evidence that infant male circumcision might protect against UTI emerged in the early 1980s,[20] although the association had been suspected since 1972.[21] The studies that followed, involving a variety of designs including a small randomized controlled trial,[22] attested to the protection afforded by circumcision against UTI in infancy. The Pediatric Research in Office Settings Febrile Infant Study of 219 United States practices found that being uncircumcised was the strongest multivariate predictor of UTI (OR 11.6, 95% CI 5.9–22.6).[23] Among boys with UTI one study demonstrated that 19% experienced recurrent UTIs if not circumcised compared with zero for the circumcised.[24] In another study recurrent UTI was seen in 34% of those with nonretractile foreskins compared with 18% of those whose foreskin could be retracted.[17] Acute pyelonephritis increased the likelihood of recurrent UTI by 4.6,[17] nonretractile foreskin and acute pyelonephritis being the greatest risk factors for recurrent UTI. In premature uncircumcised boys whose risk of UTI was increased elevenfold, Cason et al found that circumcision eliminated the risk of recurrence.[25]

Previously published meta-analyses have noted a consistent protective effect of circumcision against UTIs of approximately tenfold.[26–28] Most studies have been of infants, with only a few examining the prevalence of UTIs in children. Studies in men are scarce.[29] To our knowledge an estimate of the prevalence of UTI by circumcision status during the entire lifetime has never been done. This deficit poses particular difficulties for evidence-based decision making. Authors attempting to weigh risks vs benefits have tended to use the cumulative incidence in infancy as an approximation of the lifetime risk. Typical estimates of the risk of UTI among uncircumcised males have been 1% to 2%,[27] 1.4% to 1.6%[30] and 2.5%.[31] Although the risk of UTI in males is greatest during the first month of life,[32] the risk after infancy is not zero and, therefore, such analyses would inevitably have underestimated the absolute risk reduction attributable to circumcision. Moreover, not only is the prevalence of UTI highest in infancy, but it is a much more severe and generalized disease at this age, with fever the predominant sign due to pyelonephritis.

Therefore, we generated estimates of the protective effect of circumcision against UTI during the lifetime of a male. We devised a strategy to 1) generate best estimates of the relative risk among uncircumcised males through a meta-analysis of published data, and 2) use these figures, in addition to estimates of lifetime risk and circumcision rates for populations in which these were known, to generate projected risk of UTI by circumcision status.

MATERIALS AND METHODS

The inclusion criteria for our meta-analysis were publication in a peer reviewed journal, publication before September 9, 2011, the presence of an adjusted RR or odds ratio or sufficient data to allow the calculation of crude or adjusted RR or OR for UTI by circumcision status. Articles were identified by searching the PubMed® database and by hand searching the bibliographies of published reports, including those of previously published meta-analyses. We searched for articles matching 1 or more of the keywords circumcision, circumcised or uncircumcised plus 1 or more of the keywords UTI, urinary tract infection or bacteriuria. The abstracts of papers were used to judge whether they met our inclusion criteria (for convenience, the "Limits" facility was used to exclude articles without abstracts).[33] We retrieved the full text of every article except when this was not possible or it was in a language other than English. Previously published meta-analyses and systematic reviews of circumcision and UTIs were examined in full. No attempt was made to contact authors to identify additional studies they might have performed or of which they might have been aware.

We performed random effects inverse variance meta-analyses using the natural logarithm of the OR as the effect size. Adjusted measures were considered more reliable than crude effect estimates since they partially controlled for confounding factors and, therefore, were used in our analysis where available. Otherwise we calculated the appropriate crude measure and CI from published frequencies. When frequencies of zero were shown we added 0.5 to the relevant cell. For one study we estimated RR using the quotient of published means and standard error of the mean for UTI incidence.[34] When data in 1 report represented a subset of data reported in another, we used the most complete report.

To assess the impact of age we created 3 binary valued variables representing participant age, namely 0 to 1 year, 1 to 16 years and 16+ years. These particular boundaries were chosen largely for convenient analysis rather than for any biological reason. When studies presented data for current UTI and history of UTI, we preferred the former as this facilitated classification of participant age. The age ranges for some studies included 2 of these categories, meaning that age groups were poorly isolated.