Circumcision for the prevention of urinary tract infection in boys: a systematic review of randomised trials and observational studies

D Singh-Grewal, J Macdessi, J Craig

Objective: To undertake a meta-analysis of published data on the effect of circumcision on the risk of urinary tract infection (UTI) in boys.

Data sources: Randomised controlled trials and observational studies comparing the frequency of UTI in circumcised and uncircumcised boys were identified from the Cochrane controlled trials register, MEDLINE, EMBASE, reference lists of retrieved articles, and contact with known investigators.

Methods: Two of the authors independently assessed study quality using the guidelines provided by the MOOSE statement for quality of observational studies. A random effects model was used to estimate a summary odds ratio (OR) with 95% confidence intervals (CI).

Results: Data on 402,908 children were identified from 12 studies (one randomised controlled trial, four cohort studies, and seven case-control studies). Circumcision was associated with a significantly reduced risk of UTI (OR = 0.13; 95% CI, 0.08 to 0.20; p < 0.001) with the same odds ratio (0.13) for all three types of study design.

Conclusions: Circumcision reduces the risk of UTI. Given a risk in normal boys of about 1%, the number-needed-to-treat to prevent one UTI is 111. In boys with recurrent UTI or high grade vesicoureteric reflux, the risk of UTI recurrence is 10% and 30% and the numbers-needed-to-treat are 11 and 4, respectively. Haemorrhage and infection are the commonest complications of circumcision, occurring at rate of about 2%. Assuming equal utility of benefits and harms, net clinical benefit is likely only in boys at high risk of UTI.

Methods

All steps of the review, including literature search, data extraction, and data analysis, were carried out independently by two of us (JM and DSG) without blinding to authorship. Resolution of discrepancies was by consensus and the involvement of the third author (JC) when necessary.

Data sources

The Cochrane controlled trials register (issue 4, November 2002), MEDLINE (1966 to November 2002), and EMBASE (1980 to November 2002) databases were searched.

MEDLINE and EMBASE were searched using “circumcision” as both a text word and medical subject heading (MeSH) term. The search was not limited by language, and bibliographies of identified publications were examined for any relevant material that may have been overlooked. Details of any additional published or unpublished data were sought from authors identified in the literature search.

Following the computerised database search, all titles were screened and abstracts of relevant or possibly relevant articles were reviewed in full. Studies in languages other than English were translated before assessment. When more than one report of the same data was found, data were extracted only from the paper containing the most complete data.

Study selection

All studies examining the effect of male circumcision on UTI were included. The population of interest was male without any age restriction, and the intervention evaluated was circumcision. Diagnosis with UTI was the only outcome investigated. Studies were included only if they provided sufficient information for a 2x2 contingency table to be constructed, so that the odds of UTI in the circumcised group could be compared with those in the uncircumcised group.

Abbreviations: CONSORT, consolidated standards for reporting trials; MOOSE, meta-analysis of observational studies in epidemiology; UTI, urinary tract infection
Data extraction
Randomised studies were assessed using the guidelines provided by the CONSORT statement. Aspects of study design including allocation concealment, blinding, follow up, outcome measurement, and analysis by intention to treat were assessed.

Quality assessment for observational studies was carried out using the guidelines provided by the MOOSE statement. The quality of studies identified was assessed according to the study setting, completeness and duration of follow up, validity and completeness of exposure and outcome ascertainment, comparability of the control group, and adjustment for known confounding variables.

Data synthesis
Statistical analysis was done with Review Manager (version 4.2). An odds ratio (OR) with 95% confidence interval (CI) was calculated for each individual study and a summary OR using a random effects model was first calculated for subgroups based on study type (that is, randomised controlled trial, cohort study, or case–control study) and then an overall OR was calculated across all study types if no heterogeneity was present.

Consistency of the intervention effects across studies was evaluated using the Cochrane Q statistic for heterogeneity with $n-1$ degrees of freedom and an $\alpha$ of 0.05. This method calculates a $\chi^2$ statistic, with $p<0.05$ suggesting that the observed variation in the OR is unlikely to be a result of chance alone. The $I^2$ statistic was calculated as an estimate of the percentage of the variability in the OR due to heterogeneity rather than chance, with an $I^2$ of greater than 50% indicating significant heterogeneity. Heterogeneity between and within subgroups, and between individual studies when combined, was assessed. Possible sources of heterogeneity included study type, setting, study population, and follow up.

There were insufficient studies to construct a funnel plot to assess for publication bias.

RESULTS
Literature search
The study selection process is outlined in fig 1. From 2166 titles and abstracts retrieved, 12 fulfilled the inclusion criteria (one randomised trial, four cohort studies, and seven case–control studies).

Characteristics of the studies included
The characteristics of the studies included are outlined in table 1. All were published between 1987 and 2001. Most originated from North America and relied on hospital inpatient and outpatient data. These 12 studies provided data on 402 908 children and 1953 separate episodes of UTI. Most of the studies included examined UTI in infants. One included adults and four others included boys beyond the first year of life. Studies generally reported episodes of UTI rather than patients with UTI, and only one reported recurrent episodes of UTI in individual patients.

The single randomised controlled trial by Nayir was a study of recurrent UTI. Seventy uncircumcised patients with proven UTI were recruited and then randomised into circumcision and non-circumcision groups. UTI was defined as a positive urine culture with $>10^6$/l pure growth from a bag or clean catch specimen in the presence of urinary symptoms. The presence of urinary tract abnormality was the only exclusion criterion. Although this trial ran for 12 months, only the six months of parallel follow up was included in the systematic review as the boys randomised to the no circumcision group were circumcised at six months.

Quality of the included studies
For the single randomised trial, follow up was complete and analysis was by intention to treat but no details were provided about the method of randomisation, concealment of allocation, or blinding. No demographic details other than age were available for comparison between the two groups.

The quality of these studies the case–control and cohort studies was variable, with variable UTI definitions used and different methods employed to ascertain circumcision status and UTI outcome. Exclusion criteria and adjustment for confounding also varied among the studies. Only one of the cohort studies followed patients beyond one year, and in the case–control studies all controls were obtained from hospital based populations (tables 2 and 3).

The confounding variables that were adjusted for included age, socioeconomic status, and ethnicity. Both socioeconomic status and ethnicity were associated with circumcision status in several studies but there was no evidence of an association between these factors and UTI outcome between the circumcised and uncircumcised groups.

Association between circumcision and UTI
Figure 2 summarises the results of our meta-analysis.

Randomised controlled trial
The randomised study from Nayir had an OR of 0.13 (95% CI, 0.01 to 2.63).

Cohort studies
All four cohort studies showed benefit with a summary OR of 0.13 (95% CI, 0.07 to 0.23). There was significant
heterogeneity between the cohort studies ($\chi^2 = 82.48$, df = 3, $p<0.001$), with the study by To et al being the outlier. When the study by To was excluded, the heterogeneity between cohort studies was non-significant ($\chi^2 = 0.88$, df = 2, $p = 0.64$).

The reasons for the observed heterogeneity are uncertain but may reflect varying methods of circumcision and UTI ascertainment, and the differing follow up periods of the studies.

In relation to circumcision status, To et al were able to access information regarding circumcision beyond the neonatal period and excluded subjects circumcised after the age of one month. The three other cohort studies were unable to account for circumcisions undertaken after the neonatal inpatient stay. If there were significant numbers of circumcisions carried out beyond the neonatal inpatient period, these studies would underestimate UTI occurrence in the circumcised group and thus result in misclassification.

### Follow up duration

The study by To extended follow up to as long as three years compared with a maximum of one year for the other cohort studies. To showed a progressive reduction in the protective effect of circumcision on UTI with increasing age. Thus the inclusion of older subjects may have contributed to the difference in results. The Craig study, however, which stratified for age, found no such difference, but was small and may have been subject to type II error.

<table>
<thead>
<tr>
<th>Study design</th>
<th>Reference</th>
<th>Year</th>
<th>Country</th>
<th>Setting</th>
<th>n</th>
<th>No of UTI episodes</th>
<th>Age (months, years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT</td>
<td>Nayfeh21</td>
<td>2001</td>
<td>Turkey</td>
<td>Hospital outpatients</td>
<td>70</td>
<td>3</td>
<td>3 months to 10 years</td>
</tr>
<tr>
<td>Cohort studies</td>
<td>Schoen et al22</td>
<td>2000</td>
<td>USA</td>
<td>Hospital in/outpatient</td>
<td>14,893</td>
<td>154</td>
<td>&lt;1 year</td>
</tr>
<tr>
<td></td>
<td>To et al*</td>
<td>1998</td>
<td>Canada</td>
<td>Hospital in/outpatient*</td>
<td>58,434</td>
<td>330</td>
<td>&lt;3 years</td>
</tr>
<tr>
<td></td>
<td>Wiswell and Hachey6</td>
<td>1993</td>
<td>USA</td>
<td>Hospital inpatient</td>
<td>107,598</td>
<td>496</td>
<td>&lt;1 year</td>
</tr>
<tr>
<td></td>
<td>Wiswell et al26</td>
<td>1987</td>
<td>USA</td>
<td>Hospital inpatient</td>
<td>219,775</td>
<td>610</td>
<td>&lt;1 year</td>
</tr>
<tr>
<td>Case-control studies</td>
<td>Craig et al23</td>
<td>1996</td>
<td>Australia</td>
<td>Hospital in/outpatient</td>
<td>886</td>
<td>144</td>
<td>&lt;5 years</td>
</tr>
<tr>
<td></td>
<td>Newman et al24</td>
<td>2002</td>
<td>USA</td>
<td>Hospital inpatient</td>
<td>769</td>
<td>56</td>
<td>&lt;3 months</td>
</tr>
<tr>
<td></td>
<td>Rushton and Majd28</td>
<td>1992</td>
<td>USA</td>
<td>Hospital inpatient</td>
<td>86</td>
<td>23</td>
<td>&lt;6 months</td>
</tr>
<tr>
<td></td>
<td>Spach et al26</td>
<td>1992</td>
<td>USA</td>
<td>Community sexually transmitted diseases clinic</td>
<td>78</td>
<td>26</td>
<td>Adult</td>
</tr>
<tr>
<td></td>
<td>Crain and Gershel27</td>
<td>1990</td>
<td>USA</td>
<td>Hospital outpatient</td>
<td>81</td>
<td>22</td>
<td>&lt;2 months</td>
</tr>
<tr>
<td></td>
<td>Kashani and Faraday29</td>
<td>1989</td>
<td>USA</td>
<td>Hospital inpatient</td>
<td>126</td>
<td>17</td>
<td>1 month to 2 years</td>
</tr>
<tr>
<td></td>
<td>Hazeg29</td>
<td>1989</td>
<td>USA</td>
<td>Hospital outpatient</td>
<td>112</td>
<td>36</td>
<td>&lt;1 year</td>
</tr>
</tbody>
</table>

*Outpatient data not included in analysis as they did not accurately define UTI events.

RCT, randomised controlled trial; UTI, urinary tract infection.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Quality of cohort studies examining the effect of circumcision on urinary tract infection in male subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference</td>
<td>Determination of circumcision status</td>
</tr>
<tr>
<td>Schoen et al22</td>
<td>&gt; 10^6/ml pure growth in 90% from any means of collection</td>
</tr>
<tr>
<td>To et al*</td>
<td>Inpatients: ICD-9 coding (kidney infection, cystitis, urethritis or urinary tract infection)</td>
</tr>
<tr>
<td>Wiswell and Hachey6</td>
<td>Outpatients: OHIP data</td>
</tr>
<tr>
<td>Wiswell et al26</td>
<td>US Army patient administration systems and biostatistics activity database</td>
</tr>
</tbody>
</table>

ICD-9, International Classification of Diseases, 9th revision; KPNC, Kaiser Permanente Medical Care Program, Northern California, USA; OHIP, Ontario Health Insurance Plan; SES, socioeconomic status.
UTI diagnostic criteria
The Wiswell studies did not specify diagnostic criteria for defining UTI, while the study by To et al. used International Classification of Diseases, 9th revision and Ontario Health Insurance Plan data coding, and the Schoen study used laboratory data. These differing definitions of UTI are an unlikely source of variability in the results.

The study by To was also the only one to account for repeat episodes of UTI in individual patients and showed that the contributory effect of these repeat episodes was minimal. The other studies recorded the overall number of UTI episodes rather than the number of patients with UTI.

Case–control studies
All seven case–control studies included showed benefit, with a combined OR of 0.13 (95% CI, 0.07 to 0.23). There was no significant heterogeneity between the studies within this group ($\chi^2 = 8.15$, df = 6, $p = 0.2$).

DISCUSSION
The odds of UTI in circumcised boys are about 0.1 when compared with uncircumcised boys. This represents a reduction in odds of nearly 90%.

What is striking from these results is the level of homogeneity in the effect across a variety of settings and the three different study designs. An OR of 0.13 reflects a substantial reduction and makes residual confounding an unlikely source of the observed association.

The temporal and biological plausibility of circumcision (by modifying preputial colonisation and thus decreasing the potential source of bacteria causing UTI) adds weight to the association being a genuine effect of circumcision on UTI. However, colonisation may also increase the risk of contamination of bag urine collections, leading to false positive urine cultures in uncircumcised boys. The method of urine collection was poorly defined or included bag urine collections, leading to false positive urine cultures in uncircumcised boys. The method of urine collection was poorly defined or included bag urine collections, leading to false positive urine cultures in uncircumcised boys. The method of urine collection was poorly defined or included bag urine collections, leading to false positive urine cultures in uncircumcised boys.

All studies
The summary OR across study types when all three were combined was 0.13 (95% CI, 0.08 to 0.20). There was no significant heterogeneity between the three subgroups ($\chi^2 = 0.16$, df = 2, $p = 0.9$). However, significant heterogeneity was observed between the individual studies ($\chi^2 = 90.63$, df = 11, $p < 0.00001$) owing to the inclusion of the To study. Without To there was no significant heterogeneity between the remaining studies ($\chi^2 = 10.92$, df = 10, $p < 0.4$).
controlled trial was identical to that of the other studies included, and to our combined result. Another shortcoming is that the majority of studies measured episodes of UTI rather than the number of patients experiencing UTI. Thus the prevalence of repeat UTI in these populations is not known and may have biased the observed results if the distribution of patients with repeat UTI was unequal between the two treatment groups. However, as seen in the To study,1 the number of recurrences is likely to be small and an unlikely explanation for the large difference observed between the circumcised and uncircumcised groups.

Existing systematic reviews on the association between circumcision and UTI by Amato in 19924 and Wiswell in 19936 also concluded that circumcision was associated with a protective effect on UTI, with ORs of 0.07 (95% CI, 0.06 to 0.09) and 0.08 (0.07 to 0.09), respectively, being obtained. These results imply a more protective effect than we found in our analysis. This difference may be explained by the fact that we included several additional studies4 21 23 24 26 published since the earlier meta-analyses. We also excluded duplicate data from our analysis and examined heterogeneity between the available data.

While circumcision is protective for UTI, the overall risk–benefit derived from circumcision in preventing UTI is not easily quantifiable, as the incidence of important sequelae of UTI (sepsis, permanent renal damage, hypertension, and chronic renal failure) are not known. The complication rate of circumcision is documented to be between 2% and 10%,11 12 and no data are available on the relative risks and benefits of circumcision. Thus we have used a conservative estimate of circumcision complications of 2% and assumed equal utility for benefits and harms in the following analysis.

Existing studies suggest that from 1% to 2% of boys can be expected to experience a UTI within the first 10 years of life.23 31 32 From the data included in this meta-analysis, the UTI rate in the uncircumcised group was approximately 0.5% and may reflect a shorter follow up period than other studies. Furthermore, studies15 33 have shown a recurrence rate of UTI in preschool children of around 10% in the absence of complications.

Table 4  Benefit versus harm for circumcision in preventing urinary tract infection in boys at different levels of risk for UTI per 1000 boys, assuming a complication rate of 2% and an odds ratio of 0.13

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Risk of UTI</th>
<th>UTI in uncircumcised (n)</th>
<th>UTI in circumcised (n)</th>
<th>UTI prevented by circumcision (n)</th>
<th>Complications of circumcision (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>1%</td>
<td>10</td>
<td>1</td>
<td>9</td>
<td>20</td>
</tr>
<tr>
<td>Past UTI</td>
<td>10%</td>
<td>100</td>
<td>13</td>
<td>87</td>
<td>20</td>
</tr>
<tr>
<td>High grade VUR</td>
<td>30%</td>
<td>300</td>
<td>39</td>
<td>261</td>
<td>20</td>
</tr>
</tbody>
</table>

OR, odds ratio; UTI, urinary tract infection; VUR, vesicoureteric reflux.
significant urinary tract abnormality. The recurrence rate increases to 30% in children with vesicoureteric reflux of grade 3 and above. 22 23 We have used these estimates of UTI incidence and circumcision complication rate to construct a table of harms and benefits of circumcision (table 4).

This shows that the benefit of circumcision on UTI only outweighs the risk in boys who have had UTI previously and have a predisposition to repeated UTI. As this analysis has used a conservative circumcision complication rate of 2%, if the complication rate were in reality higher the risk–benefit analysis may not favour circumcision even in the higher risk populations.

In conclusion, the data we present do not support the routine circumcision of normal boys with standard risk in order to prevent UTI. However, our data suggest that circumcision of boys with higher than normal risk of UTI should be considered. As there is no direct evidence of the effect of circumcision on UTI in this group, confirmation through a randomised trial of circumcision in high risk patients would be beneficial. Using an OR of 0.2 (the upper limit of the 95% CI of the combined OR found in this study) and a power of 80%, the sample size required to study this hypothesis would be 140 (70 in each treatment arm), assuming a recurrence risk of 10%.

Until this additional information is available, the present data do not support the routine circumcision of boys to prevent UTI. However, circumcision should be considered in those with recurrent UTI or significantly increased risk of UTI.

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