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Early infant male circumcision: Systematic review, risk-benefit analysis, and progress in policy

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Abstract

AIM

To determine whether recent evidence-based United States policies on male circumcision (MC) apply to comparable Anglophone countries, Australia and New Zealand.

METHODS

Articles in 2005 through 2015 were retrieved from PubMed using the keyword "circumcision" together with 36 relevant subtopics. A further PubMed search was performed for articles published in 2016. Searches of the EMBASE and Cochrane databases did not yield additional citable articles. Articles were assessed for quality and those rated 2+ and above according to the Scottish Intercollegiate Grading System were studied further. The most relevant and

representative of the topic were included. Bibliographies were examined to retrieve further key references. Randomized controlled trials, recent high quality systematic reviews or meta-analyses (level 1++ or 1+ evidence) were prioritized for inclusion. A risk-benefit analysis of articles rated for quality was performed. For efficiency and reliability, recent randomized controlled trials, meta-analyses, high quality systematic reviews and large well-designed studies were used if available. Internet searches were conducted for other relevant information, including policies and Australian data on claims under Medicare for MC.

RESULTS

Evidence-based policy statements by the American Academy of Pediatrics (AAP) and the Centers for Disease Control and Prevention (CDC) support infant and later age male circumcision (MC) as a desirable public health measure. Our systematic review of relevant literature over the past decade yielded 140 journal articles that met our inclusion criteria. Together, these showed that early infant MC confers immediate and lifelong benefits by protecting against urinary tract infections having potential adverse long-term renal effects, phimosis that causes difficult and painful erections and "ballooning" during urination, inflammatory skin conditions, inferior penile hygiene, candidiasis, various sexually transmissible infections in both sexes, genital ulcers, and penile, prostate and cervical cancer. Our risk-benefit analysis showed that benefits exceeded procedural risks, which are predominantly minor, by up to 200 to 1. We estimated that more than 1 in 2 uncircumcised males will experience an adverse foreskin-related medical condition over their lifetime. Wide-ranging evidence from surveys, physiological measurements, and the anatomical location of penile sensory receptors responsible for sexual sensation strongly and consistently suggested that MC has no detrimental effect on sexual function, sensitivity or pleasure. United States studies showed that early infant MC is cost saving. The evidence supporting early infant MC has further strengthened since the positive AAP and CDC reviews.

CONCLUSION

Affirmative MC policies are needed in Australia and New Zealand. Routine provision of accurate, unbiased education, and access in public hospitals, will maximize health and financial benefits.

Key words: Male circumcision; Evidence-based policy; Infants; Adults; Urinary tract infections; Adverse events; Sexually transmitted infections; Genital cancers; Risk-benefit analysis; Cost-benefit

Core tip: Australia and New Zealand should follow the lead of the American Academy of Pediatrics and the United States Centers for Disease Control and Prevention in facilitating education, provider training, patient access and affordability of circumcision of male infants and boys. Our systematic review of the current scientific evidence finds the protection afforded by early infant male circumcision against infections and other adverse medical conditions exceed risks by 200 to 1 and that over their lifetime over 1 in 2 uncircumcised males will suffer an adverse medical condition caused by their foreskin. Strong evidence shows no adverse effect on penile function, sexual sensitivity or pleasure. Circumcision is a desirable public health intervention. It is moreover cost-saving.

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INTRODUCTION

Early infant male circumcision (MC) is a simple, safe procedure that was performed in Anglophone countries for much of the 20th century. A substantial downturn in prevalence occurred after 1950 in the United Kingdom and in the 1970s in Australia and Canada. In the United States, however, only recently has there been a slight downturn[1]. Paradoxically such declines were accompanied by an increase in the quantity and quality of medical scientific findings attesting to numerous health and medical benefits. A decade ago the American Academy of Pediatrics (AAP) began an extensive review of the accumulated evidence to 2010. This led to the formulation and release of a new affirmative early infant MC policy statement in 2012 which concluded that, based on the evidence: (1) the benefits of early infant MC exceed risks; (2) parents should be given factually correct, nonbiased information on MC before conception or early in a pregnancy; (3) access to MC should be provided routinely for those families who choose it; (4) education and training should be provided to practitioners to enhance their competency; (5) the procedure should be performed by trained competent practitioners using sterile techniques and effective pain management; and (6) the preventive and public health benefits warrant third-party reimbursement[2]. The American College of Obstetricians and Gynecologists endorsed these recommendations. The American Urological Association has on its website a brief statement that presents benefits and risks of infant MC[3].

In 2014, after extensive deliberations stemming from a consultation in 2007 in Atlanta with stakeholders[4], the Centers for Disease Control and Prevention (CDC) released its draft recommendations on MC[5]. These endorsed the AAP's policy but went further by recommending MC of adolescents and men, especially those in populations in the United States in which prevalence of HIV and other sexually transmitted infections (STIs) is high. In 2015, the Canadian Paediatric Society (CPS) released a policy

statement on newborn MC that recommended MC only for boys in "high risk populations " or "circumstances"[6]. The basis for its deviation from the AAP and CDC policies was a faulty risk-benefit analysis that failed to include all common conditions that MC protects against and that inflated risk data[7].

What then has been the response of authorities in other countries outside of North America, especially those with Anglophone populations having socio-cultural roots and current practices similar to the United States? In this regard, perhaps the most comparable countries are Australia and New Zealand. Australia is the only non-United States country in which an evidence-based policy statement has been produced (by the Circumcision Academy of Australia; CAA)[8]. The authors of the policy included fellows of the Royal Australasian College of Physicians (RACP), as well as fellows of other Colleges and medical bodies. The conclusions reached were similar to those of the AAP and CDC.

Historically, the most influential policy statements for Australia and New Zealand have been ones emanating from the RACP's Division of Paediatrics and Child Health. The most recent of these was placed on the RACP's website in 2010[9]. This was evaluated in detail by authors of the CAA policy, who identified numerous flaws that led them to conclude the RACP's policy opposing "routine" early infant MC was not evidence-based[10]. By failing to adequately evaluate all of the evidence, and selectively citing small low-quality studies, the RACP policy falsely concluded that risks exceed benefits. This has led to a general perception that the RACP is opposed to infant MC. It may explain the subsequent withdrawal of parent-approved early infant MC and elective MC by men as allowable procedures in Australian public hospitals, as well as a proposal currently being considered by the Australian federal government to abolish the Medicare rebate for MC. The RACP policy nevertheless stated that, "it is reasonable for parents to weigh the benefits and risks of circumcision and to make the decision whether or not to circumcise their sons". The policy recommended that, "when parents request a circumcision for their child the medical attendant is obliged to provide accurate unbiased and up to date information on the risks and benefits of the procedure". It also stated that "parental choice should be respected" and that, the operation, "should be undertaken in a safe, child-friendly environment by an appropriately trained competent practitioner, capable of dealing with the complications, and using appropriate analgesia".

Other countries do not have evidence-based policy statements. A brief statement placed on the Internet by the Royal Colleges covering surgeons, nurses, paediatricians and anaesthetists in the United Kingdom in 2000[11] did not claim to be evidence-based and only mentions MC for treatment of phimosis, balanoposthitis and "some rare conditions". The policy of the Royal Dutch Medical Association in 2010 states that, "non-therapeutic circumcision of male minors is a violation of children's rights to autonomy and physical integrity", refers only to "complications" of the procedure, and urges, "a strong policy of deterrence"[12]. The recent policy statements by the AAP, CDC, CAA and even the CPS have raised the bar, meaning statements by other bodies should now be expected to similarly consider the evidence rather than rely on opinions.

Here we: (1) systematically evaluate the current evidence on MC, including findings subsequent to reviews by the AAP and CDC; (2) perform a risk-benefit analysis of early infant MC; and (3) determine whether other countries, in particular the comparable countries Australia and New Zealand, should follow the lead of the United States in translating MC science into policy and practice.

MATERIALS AND METHODS

Literature search

Articles dating from January 1 2005 until January 1 2016 were retrieved from PubMed using the keyword "circumcision" together with one of 36 other relevant subtopics (see Supplementary material). This yielded 10609 publications. To ensure no relevant publications were missed as of the date of submission a further search was performed using "circumcision 2016". This yielded 133 more publications. Any pertaining to "circumcision" of women were excluded. The publications were assessed for quality and those rated 2+ and above by conventional criteria[13] were studied further; the most relevant and representative of the topic were then cited. Bibliographies were examined to retrieve further key references. In instances in which a MC-related topic had been the subject of recent high quality systematic reviews or meta-analyses (level 1++ or 1+ evidence), these were cited for efficiency instead of all the individual studies on that topic. Internet searches were conducted for other relevant information, including policies and, in Australia, data on claims under Medicare for MC.

Risk-benefit analysis

Data from RCTs, meta-analyses, large observational studies in the United States and United Kingdom in particular and high quality systematic reviews were compiled and risk reduction conferred by MC was calculated in order to determine individual benefit of the various conditions that MC protects against. In the case of sexually transmitted infections and genital cancers, the prevalence of these in Australia was taken into account in order to determine risk reduction in the population. If data for Australia was not available data for the United States, United Kingdom, Canada or European countries was used. Findings for each condition were then summated to determine the overall benefit. The percentage of individuals who experience an adverse events arising from infant MC was determined from high quality studies and from this an overall prevalence of these was calculated.

RESULTS

Articles retrieved and included

We identified 115 journal articles that met our inclusion criteria, including 6 in 2016. Another 25 journal articles were identified from the bibliographies of these. The latter also revealed 9 relevant online documents, mostly by authoritative paediatric or medical bodies. A further 4 were articles "in press".

Prevalence of MC

The global prevalence of MC is approximately 38%[14]. In the United States, estimates by the CDC indicate 81% of males aged 14 to 59 years are circumcised, the prevalence having increased in the decade to 2010 to 91% in white, 76% in black and 44% in Hispanic males aged 14-59 years[15]. Figures for early infant MC are difficult to determine, although, after correction for under-reporting, the percentage appears to have declined from 83% in the 1960s to 77% by 2010[1]. Hospital discharge data, which under-estimate the true prevalence, indicated a decline from 61% in 2000 to 57% in 2010[16]. Despite MC prevalence having risen in Hispanic males, the greater rise in the Hispanic population as a proportion of the total American population may account in part for a likely fall, overall, in MC prevalence in the United States[1]. Another reason contributing to a decline in MC in the United States is the withdrawal of Medicaid coverage for elective or parent-approved MC by 18 United States states during the past decade[16]. Medicaid de-funding poses a barrier to access by poor families, a situation criticized by the CDC[15] and others[17]. This resembles the withdrawal of access to elective MC in Australian public hospitals starting in 2006.

In Australia large surveys found 66%-70% of males aged 50-59 years in 2001-2002[18] and in 2005[19] were circumcised, whereas prevalence in males aged 16-19 years was 32% in 2001-2002[18] and 27% in 2005[19]. Since most circumcisions in Australia occur early in infancy, these data suggest an early infant MC prevalence of 66%-70% in the 1960s but a fall to 27% by 1990[19]. The decline in infant MC is likely to have been accelerated, at least in part, by the negative RACP paediatric policy statements from the 1970s onwards.

Australian Medicare claims provide a lower bound for prevalence of MC. Claims data do not capture all religious MCs, nor MCs for which a claim is not made. Given the substantial rise in cost of infant and later MC in private practice in Australia to A$500-1000 (10-20 times the scheduled fee), some parents may forego making a claim for the Medicare rebate, which is less than A$40. In the most populous state, New South Wales, 14.3% of boys aged under 6 mo attracted a Medicare rebate in 2000, rising to 18.5% in 2007[20]. Nationwide, claims have stabilized over the past decade at 16433-19981[21]. This represents 12% of boys aged under 6 mo. For boys aged 0.5-10 years there were 893 claims in 2005 and 834 in 2014, while for males aged 10 years or more claims for specialist MC rose 54%, from 1906 in 2005 to 2941 in 2014[21]. Medicare only covers MC for treatment of medical conditions, so after adding MCs for parental preference, cosmetic or religious reasons the actual number of procedures will be higher than Medicare figures. Another large survey similar to those above[18,19] would help provide information on current MC prevalence in males older than 16 years of age. Publicity about health benefits in recent years and the increase in the number of Muslim families might have contributed to a rise in MC. On the other hand, as in the United States[16], reduced access and affordability has likely contributed to a decline, especially amongst the poor.

Benefits of male circumcision

Urinary tract infection (UTI): A UTI is an infection that affects part of the urinary tract. Of any year of life, UTI in males is most common in the first year, affecting 1%-2% of uncircumcised boys compared to 0.1%-0.2% of boys who are circumcised[22,23]. Risk reduction continues, however, beyond infancy. The most recent meta-analysis (in 2013) noted that over the lifetime 1 in 12 circumcised males experience a UTI compared with 1 in 3 uncircumcised males[22]. Recurrent UTI in particular may lead to renal parenchymal disease[24,25]. While treatment by oral antibiotics can be used for older children and men, an infant with a UTI presents with fever, often leading to blood collection, lumbar puncture, and if UTI is diagnosed, hospitalization to enable intravenous antibiotic administration[26]. Emergence of resistance to most or all antibiotics, including methicillin, will make treatment of UTI more challenging[27-29], including in Australia[30]. Swabs taken under the foreskin of boys aged 7 d to 11 years identified 50 bacterial isolates, most of which were multi-drug-resistant strains[31]. Maternal antibiotic use during pregnancy also increases the risk of resistant pathogens causing early infant UTI[32].

Phimosis: Phimosis is a penile condition where the foreskin cannot be fully retracted over the glans penis. Phimosis affects approximately 10% of uncircumcised adolescent and adult males[33-47]. Even though regular application of steroid creams, which may cause undesirable systemic absorption of glucocorticoids, can be used to alleviate this condition, the definitive treatment is MC. Paraphimosis (a condition in which the foreskin cannot be returned after retraction) is less common, but when it occurs represents a medical emergency because of haemostasis and risk of gangrene[48].

Inflammation: Inflammation of the glans (balanitis) or the foreskin and/or the underlying glans (balanoposthitis) is also common in uncircumcised males and can contribute to secondary phimosis[49-53]. A meta-analysis found circumcised males are at reduced risk of balanitis [odds ratio (OR) = 0.32; 95%CI: 0.20-0.52][54]. A form of penile inflammation, lichen sclerosis, is diagnosed in up to 40% of foreskins removed for phimosis and

peaks at around 10 years of age[51,52]. Early infant MC virtually eliminates the risk of lichen sclerosis[53,55]. MC is, moreover, the definitive cure.

Hygiene: Hygiene is less easily attained for an uncircumcised penis[56]. In the more highly populated east coast states of Australia, MC prevalence increases from south to north[20], correlating with the greater frequency of inflammatory conditions and skin irritation in an uncircumcised penis in hotter more humid climates. Candidiasis (thrush) is 60% lower in circumcised Australian men[19].

STIs in men: Several STIs are more prevalent in uncircumcised males[57,58]. These include oncogenic types of human papillomavirus (HPV)[59-65], that are the most common STIs in Australia and New Zealand, just as in the United States, and HSV-2[62,66-69] that is also common. There is a disproportionate burden of these STIs among adolescents and young adults[66].

Randomized controlled trials (RCTs) showed MC reduced infection of men by high-risk HPV by approximately 40%[61-63,70-72]. A meta-analysis in 2012 of 21 observational studies and 2 RCTs of MC found risk reductions in high-risk HPV of 43% and 33%, respectively[73]. A similar result was obtained in an earlier meta-analysis[65]. In one RCT circumcision of heterosexual men was found to reduce flat penile lesions, which typify oncogenic HPV, by 98%[63], and in another RCT viral load was reduced by 95%[72]. In those Australian homosexual men who predominantly practice insertive anal intercourse, protection afforded by MC against the major oncogenic type, HPV16, was 57%[74].

In the case of HSV-2, RCTs have shown MC reduces infection by approximately 30%[68,69,75,76] and a meta-analysis of older observational studies found infection to be 15% lower in circumcised men[67].

Other STIs against which MC affords protection include *Trichomonas vaginalis*[77], *Mycoplasma genitalium*[78], syphilis[67,79,80], chancroid[67], genital ulcer disease[81,82] and HIV[83-90]. Coital injuries, which increase risk of HIV infection, are higher in uncircumcised men[91]. In comparable developed countries in which HIV prevalence is low, the prevalence of heterosexually acquired HIV in those with low MC prevalence (the Netherlands and France) was 6 times higher in men and 10 times higher in women compared with Israel, a country having a very high MC prevalence[92].

National HIV statistics for Australia show that after excluding cases from a high prevalence country, the number of cases whose exposure to HIV was attributed to heterosexual contact has increased by 28% over the past decade. In 2013 there were 1236 new diagnoses, 313 (25%) of these being attributed to heterosexual contact (29% of the latter involving individuals born in Australia)[93].

HIV prevalence is high amongst Australian men who have sex with men, but a Sydney study found those adopting an exclusively insertive role during anal intercourse exhibit 89% protection if circumcised[94,95].

In the United States the latest data show approximately 10% of new HIV cases were in men infected heterosexually, with one estimate suggesting that universal infant MC could prevent 2500 HIV infections annually[96]. The increase in HIV infections in African Americans, however, has been faster than in all other groups in the United States[97]. The CDC has recommended MC for HIV prevention in such groups[90]. Such findings indicate an important public health role for early infant MC in developed countries, including Australia and New Zealand[98,99].

It is anticipated that a steep increase in multiple morbidities and drug interactions in aging HIV-infected patients on combination antiretroviral therapy is looming and will lead to a major medical burden[100], suggesting a flow-on of benefits resulting from the ability of MC to reduce HIV cases.

STIs in women: Circumcision of males also partially protects their female sexual partners from oncogenic types of HPV[59,60,101], HSV-2[102], *Trichomonas vaginalis*[103], bacterial vaginosis[103], *Chlamydia trachomatis*[104] and syphilis[79]. MC, by reducing HIV prevalence in heterosexual men, will help reduce HIV prevalence in women[105] and children[106]. Other STIs that MC protects against include ones that exacerbate HIV risk[107-110].

The impact of condoms on STIs: Condoms are 80% protective against HIV infection, but must be used consistently and correctly[111,112]. A Cochrane systematic review and meta-analysis of RCTs of condom use (two in the United States, one in England and four in Africa) found, however, "little clinical evidence of effectiveness" and no "favorable results" for HIV prevention[113]. This study did, however, find condoms exhibited 42% effectiveness against syphilis[113]. Unlike condoms, MC is a one-off procedure that does not require future voluntary compliance each time a man has sexual intercourse. In this respect MC can thus be compared with vaccination. However, the only vaccines currently in widespread use for STIs are those that protect against certain types of HPV (discussed below). Nevertheless both MC and condom use should be advocated[98].

Genital cancers: Penile cancer affects approximately 1 in 1000 uncircumcised men over the lifetime, thus making it uncommon, but not rare[2,114,115]. Infant MC reduces penile cancer later in life by 95%-99%[116-118]. Prevalence was 22-fold higher in uncircumcised men in a United States study[116]. MC appeared to afford lesser protection in a meta-analysis[119], although the inclusion of men circumcised as part of their treatment for penile cancer meant the level of protection was underestimated. Oncogenic HPV is found in one-quarter to one-half of penile cancers[73,114,120], prevalence varying with type of penile lesion[121]. Based on meta-analyses of risk factors, phimosis increases risk of penile cancer 12.1-fold (95%CI: 5.57-26.2), balanitis increases risk 3.82-fold (95%CI: 1.61-9.06) and smegma is associated with a 3.04-fold (95%CI: 1.29-7.16) increase in risk[114]. Each of

these conditions is much more common in uncircumcised males. Vaccination of boys against HPV16 and HPV18 may, under the most optimistic of scenarios, reduce penile cancer by 35%[115]. Vaccination, MC, consistent condom use and monogamy should all be advocated to achieve maximum protection.

For prostate cancer, MC prior to sexual debut reduces prevalence by 15%-50%[115,122-124]. The significant protective effect was confirmed in a recent meta-analysis[125]. In countries globally in which MC prevalence is greater than 80%, prostate cancer-related mortality, corrected for potential confounding factors, is half that of countries with a low or intermediate MC prevalence[126].

Cervical cancer is 10 times more common than penile cancer. This malignancy is up to 5 times more prevalent in women whose male partner is uncircumcised[59,60]. Since virtually all cases of cervical cancer are caused by oncogenic types of HPV, the ability of MC to reduce transmission of high-risk HPV to women[59,60,101] accounts for its protective effect against this commonly fatal and difficult to treat cancer. While prophylactic HPV vaccination of 12-13 years old girls can attenuate, but not eliminate, their future risk, vaccine uptake has not been universal. Current vaccines do not protect against all oncogenic HPV types, but only types HPV16 and HPV18 seen in approximately 70% of cervical cancers. Vaccination has a smaller effect against vulval epithelial neoplasia[127], oncogenic HPV types being present in only half of cases. There is uncertainty about the long-term durability of the benefits of vaccination. Although introduction of a nonavalent HPV vaccine, which will protect against additional high-risk types 31, 33, 45, 52 and 58 (meaning approximately 90% coverage), should further reduce cervical cancer prevalence, concerns about breadth of protection, adherence and long-term immunity will remain.

Therefore a benefit from MC remains, both for males and for their female sexual partners, in partial protection against genital cancers. In Australia, universal MC would prevent 2800-8400 cancers, comprising 2400-8000 of the prostate, 67 of the penis and 350 of the cervix annually[115].

Prevalence of adverse events of MC

The literature review by the AAP[2] and a large detailed study by CDC researchers of 1.4 million MCs from 2001-2010 (93% in newborns)[128] have determined that adverse events from MC occur in less than 0.5% of newborn infants and are almost all minor and immediately treatable, with complete resolution. In the CDC study, serious adverse events arising from early infant MC were extremely rare (one penile stricture, 4 penile replantations, 16 cases of artery suture and 3 partial, but no complete, penile amputations). In uncircumcised males incidence of infections, surgical procedures, pneumothorax, penile disorders and gangrene were each significantly higher than in circumcised males[128]. In older boys and men, prevalence of adverse events was, however, 10-20 times higher than in newborn males[128]. Meatal stenosis has been reported in 0.01%-1% of males during post-circumcision follow-up[128-131]. The CDC study was not able to identify any deaths from early infant medical MC in recent times, as also documented in a large series of 100157 MCs in United States hospitals from 1980-1985 [132], that the CDC cited. That study noted that amongst 35929 uncircumcised boys 88 developed a UTI in the first month of life, resulting in 32 cases of bacteremia, 3 cases of meningitis related to the same organism that caused the UTI, 2 cases of renal failure and 2 deaths[132].

MC, sexual function, sensitivity and pleasure

Medical MC does not adversely affect sexual function, sensitivity or pleasure, as shown by a detailed systematic review of all studies (totalling 40473 men) rated by quality[133] and by a meta-analysis of common forms of sexual dysfunction[134]. The conclusions were confirmed in a recent United Kingdom study of 6293 men and 8869 women[135] and a systematic review by Danish researchers[136].

A systematic literature review of histological correlates of sexual sensation showed that the sensory receptors responsible (genital corpuscles) reside in the glans, not the foreskin, meaning loss of the foreskin by MC should not diminish sexual pleasure[137]. In fact, by exposing the glans, MC should increase sexual pleasure[137]. The foreskin, just as other skin on the body, contains sensory receptors that respond to touch, temperature and pain. Since the density of Meissner's corpuscles (touch receptors) in the prepuce diminishes at puberty when male sexual activity is increasing these are unlikely to be involved in sexual sensation[137]. Moreover, free nerve endings (that also respond to touch) show no correlation with sexual response. Sensitivity of the glans to touch decreases with sexual arousal so further ruling out touch receptors in sexual sensation[138]. Sensitivity of the penis to vibration, which is able to elicit arousal and ejaculation, is not related to MC status[137].

Risk-benefit

Table 1 lists the conditions that early infant MC protects against and the adverse events that can occur as a result of the procedure. Also shown are the degree of protection against each condition and the frequency of procedural risk of each adverse event. When the frequency of each were summated, we found that over their lifetime up to 80% of uncircumcised males may be affected by a medical condition related to the presence of their foreskin, whereas only 0.4% of early infant circumcisions are associated with an adverse event, most of these being minor, easily and immediately treatable with complete resolution (Table 1). Comparing benefits to risk we calculated that lifetime benefit exceeded procedural risk by 200:1. Moreover, in contrast to the sum of virtually all risks of an adverse event during infant MC, conditions resulting from lack of MC can be serious, and in the case of genital cancers, syphilis and HIV infection potentially fatal. A recent risk-benefit analysis

Table 1 Risk-benefit analysis for newborn male circumcision

Condition	Decrease in risk[1]	Percent affected[2]	Study type and ref	Quality score[3]
A: Conditions avoided and risk reduction				
Pyelonephritis (infants)	–	0.6	OS[24,25]	2+
With concurrent bacteremia	–	0.1		
Hypertension in early adulthood	–	0.1		
End-stage renal disease in early adult	–	0.06		
Urinary tract infections: Age 0-1 yr	90%	1.3	Meta[22]	1+
Urinary tract infections: Age 1-16 yr	85%	2.7	Meta[22]	1+
Urinary tract infections: Age > 16 yr	70%	28	Meta[22]	1+
Urinary tract infections: lifetime	72%	27	Meta[22]	1+
Phimosis[4]	> 90%	10	OS[33-45,47]	2+
Balanitis	68%	10	Meta[54]	1+
Candidiasis (thrush)	60%	10	OS[19]	2+
High-risk HPV infection	56%	10	Meta[73]	1++
	53%-65%	4	Meta[65]	1++
	40%	6-10	RCT[61-63,70-72]	1++
HIV (acquired heterosexually)	60%	0.2	OS[90]	2+
	70%	0.1	Meta[87]	1++
Genital ulcer disease	50%	1	OS[81,82,160]	2+
Syphilis	47%	1	Meta[67]	1+
	40%-55%	1	OS[79,80]	2+
Trichomonas vaginalis	50%	1	RCT[77]	1+
Mycoplasma genitalium	40%	0.5	RCT[78]	1+
Herpes simplex virus type 2	30%	4	RCT[68,69,75,76]	1++
	15%	4	Meta[67]	1++
Chancroid	50%	< 1	Meta[67]	1+
Penile cancer (lifetime)	67%	0.07	Meta[119]	1+
	95%[5]	0.1	OS[116]	2+
	95%[6]	0.11	OS[117]	2+
	99%[7]	0.07	OS[118]	2+
Prostate cancer: Population-based	17%	2.1	Meta[125]	1+
Black race	42%	17	Meta[125]	1+
Total percentage of uncircumcised males affected = approximately 80%				
B: Risks of infant MC				
Excessive minor bleeding	0.1-0.2		OS[128,132]	2++
Infection, local	0.06		OS[128,132]	2++
Infection, systemic	0.03		OS[128]	2++
Need for repeat surgery	0.08		OS[128]	2++
Meatal stenosis	< 0.1		OS[128-131]	2++
Partial loss of penis	0.0002		OS[128]	2++
Death	< 0.000001		OS[132]	2++
Reduced penile function, sensitivity, sexual pleasure	0		SR[133,134,137]	2++
Reduced penile function	0		Meta[134]	1+
Total percentage of adverse events from infant circumcision: About 0.4%				
Risk: Benefit				
Thus, over the lifetime, the risk to an uncircumcised male of developing a foreskin-related condition requiring medical attention may be up to 80%. In comparison the procedural risk during infant MC of experiencing an easily treatable condition is approximately 1 in 250. The risk of a moderate or serious complication is approximately 1 in 3000. Thus benefit to risk = 1:200.				
C: Risks reduced by female partners				
Cervical cancer[6]	58%[7,8]		OS[59,60]	2++
	28%[7]		RCT[101]	1++
Herpes simplex virus type 2[6]	55%[7]		OS[102]	2+
Genital ulceration[6]	22%[7]		RCT[103]	1+
Trichomonas vaginalis[6]	48%[7]		RCT[103]	1+
Syphilis[6]	75%[7]		OS[79]	2++
Bacterial vaginosis[6]	40%[7]		RCT[103]	1+
Chlamydia trachomatis[6]	82[7,9]		OS[104]	1++

[1]Based on data for circumcised vs uncircumcised males; [2]The percentage of males who will be affected as a result of the single risk factor of retention of the foreskin. Data for STIs were estimated after taking into account the external factor of heterosexual exposure, which is dependent on population prevalence of each STI in North America and risk reduction conferred by circumcision; [3]Quality rating was based on an international grading system[13]. Rating was 1++ or 1+ for well-conducted meta-analysis and RCTs, was 2++ for well-conducted systematic reviews, and was 2++ or 2+ for the original studies cited; [4]Phimosis (tight foreskin) is confined almost exclusively to uncircumcised males; [5]Penile cancer was 22 times more frequent in uncircumcised males in the Californian study cited[116]; [6]The last two entries for penile cancer are the references cited by the AAP[2] and CDC[5] in their respective circumcision policy statements; [7]For women with circumcised *vs* women with uncircumcised sexual partners; [8]For monogamous women whose male sexual partner has had ≥ 6 other female sexual partners; [9]Chlamydia trachomatis was 5.6 times more frequent in female partners of uncircumcised males in a large multinational study[104]. Shown are the reference(s) and type of study. The meta-analyses provide comprehensive lists of references to individual studies relevant to the topic. Meta: Meta-analysis; OS: Original study; RCT: Randomized controlled trial; SR: Systematic review; HPV: Human papillomavirus; HIV: Human immunodeficiency virus.

by the Canadian Paediatrics Society under-estimated benefits by failing to include several common conditions that MC protects against, confused annual incidence figures for penile cancer with lifetime prevalence and, by citing data from small out-dated studies of meatal stenosis rather than data from the large recent study of adverse events by CDC researchers[128], greatly overestimated procedural risk of MC in early infancy[6].

Cost-effectiveness

A Johns Hopkins study that considered just UTIs during infancy and STIs later in life found that if infant MC prevalence in the United States was to decrease from the current prevalence of 80%[15] to the levels of 10% typically seen in Europe (and Australia and New Zealand), the additional direct medical costs in infancy and later for treatment of these among 10 annual birth cohorts would exceed $4.4 billion, after accounting for the cost of the procedure (average $291; range $146-437) and treatment of complications [at an average cost of $185 each (range $130-235); prevalence 0.4% (range 0.2-0.6%)][139]. Each forgone infant MC was estimated to lead to an average of $407 in increased direct medical expenses per male and $43 per female[139]. The Johns Hopkins researchers stated that their, "cost increase outcomes (were) highly conservative". Just for HIV in the United States, the "associated indirect costs may be more than 4 times the total direct medical expenses" [140]. The study further estimated that if early infant MC decreased to 10%, lifetime prevalence of infant UTIs would increase by "211.8%", high- and low-risk human HPV by "29.1%", HSV-2 by "19.8%" and HIV by "12.2%". Among females, lifetime prevalence of bacterial vaginosis would increase by "51.2%", trichomoniasis by "51.2%", high-risk HPV by "18.3%" and low-risk HPV by "12.9%". Clearly, if other conditions such as genital cancers as well as the indirect costs were to be considered, the true cost would be considerably higher. For prostate cancer in the United States in the absence of MC there would be 24%-40% more cases and $0.8-1.1 billion extra in costs for treatment and terminal care per year[141]. The CDC found MC in the United States was cost-saving for HIV prevention in black and Hispanic males in whom HIV prevalence is highest[90]. Another analysis - of just genital cancer prevention in Australia - found that, after taking into account the Medicare rebate totalling A$9M, if early infant MC were universal, this would save the Australian Federal Government $80-160 million annually, not adjusted for inflation[115].

In the United States Medicaid coverage for the poor has parallels with the availability until recent years of parent-approved infant MC in public hospitals in Australia. A study of a Medicaid birth cohort consisting of 29316 males found that for every year of decreased infant MC due to Medicaid defunding there would be over 100 additional HIV cases in the United States and $30000000 in net medical costs as a result of these[142]. The cost to circumcise males in this birth cohort was $4856000, *i.e.*, 6% of the cost of treating only HIV. Modelling studies have, moreover, found cost savings initially generated by non-coverage of elective infant MC by Medicaid in Louisiana[143] and Florida[144] were mitigated by increases in rate and expense of medically indicated MC. The Louisiana study only considered the costs of later MC for boys aged 0-5 years. Lifetime costs would therefore represent a far greater financial impost on healthcare systems. The Florida study, of males aged 1-17 years undergoing MC from 2003-2008, found Medicaid defunding led to a 6-fold rise in publicly funded MCs (cost = $111.8 million)[144]. As a result of the findings, Medicaid coverage for parent approved MC was restored by the government of Florida. These findings have implications for costs to the Australian and New Zealand health care systems and research is needed to determine the exact figures.

Thus, as in the United States, barriers to availability of infant MC in Australia and New Zealand based on immediate cost-savings to the health system are, "penny-wise and pound-foolish"[17]. Costs for later MC for medical need and for treatment of foreskin-related conditions, infections and genital cancers add to the net cost burden for governments, insurers and individuals.

Parental responsibility

Because most parents and guardians value the wellbeing of their children they endeavour to do what is best for them. The AAP recommends unbiased educational material, as well as the routine discussion of early infant MC by medical practitioners with parents prior to conception or early in a pregnancy, to assist in their decision to circumcise a newborn son. When fully informed, evidence suggests that parents are likely to choose to have their baby boy circumcised[145]. Those parents who are opposed to infant MC, even after being fully informed of the benefits and low risks, would seem to place greater value on preserving the foreskin than in protecting their boy and his future sexual partners against the harms posed by the uncircumcised state[146]. Parental opposition could include respect for a cultural or religious tradition, or a philosophical ideology that is opposed to anything other than the natural state. Nevertheless, early infant MC and other interventions in childhood (such as vaccination) are not "routine", but require parental approval. MC is therefore a decision for the parent or guardian.

While the RACP also advocates information for parents, its current information brochure is not evidence-based, but rather is biased towards discouraging the procedure[147]. In contrast, the CAA provides evidence-based brochures on its website: http://www.circumcisionaustralia.org. Its guide for parents was recommended as a resource in the recent CPS position statement on newborn MC[6].

The ideal time for MC

The timing of MC is crucial. Medical and practical considerations point to the neonatal period as the ideal time[54]. A neonate is less mobile, is amenable to any intervention, surgical risk is minimal and the health benefits conferred begin immediately[2,54]. The CDC pointed to a study that

found the first week post-partum to be the best time for MC because pain using local anesthesia is negligible[148], possibly because this period precedes the foreskin growth, thickening and increased vascularization starting in week 4 and ending at 4 mo of age[149]. Failure to circumcise early in infancy means loss of the benefit of protection against UTIs that result in considerable pain and can cause kidney damage[22]. It is not correct to suggest that MC is comparable at any age[146]. Later circumcision is a more substantial, more expensive operation, carries a higher risk of complications, entails risk from general anesthesia (as is often used for older boys and men), healing time in longer and cosmetic outcome is diminished by use of sutures[2,54]. If the adolescent or adult male normally engages in sexual activity temporary sexual abstinence for 6 wk is required, which some males and their sexual partners find challenging. Education or employment is interrupted, and there is a delay in protection against STIs if the male is sexually active[2,54]. Such barriers in older males reduce the likelihood that MC will occur. Furthermore, an adult cannot consent in retrospect to his own MC as an infant[146].

Opposition to circumcision of boys

Arguments by opponents start with the premise that MC has no benefits, only harms, or that the benefits only apply later in life when the male can make the decision to get circumcised[150-152]. In reality, not only are the benefits considerable, they start in early childhood and extend over the lifetime[1,2,5,8]. As described above, MC later in life poses significant barriers to adolescent boys and men that usually mean it will not happen except for a medical reason[54]. Another claim is that MC diminishes sexual function, sensitivity and pleasure[150,152,153]. But the detailed systematic reviews[133,136,137] and meta-analysis[134] referred to above strongly suggest otherwise. If anything sexual pleasure improves after MC, as found in a RCT[154]. Those findings are supported by data on location of sensory receptors[137]. Legal and human rights and other arguments used by MC opponents in criticizing the policy statements of the AAP and CDC have been shown to be flawed[155-159].

Why is it that those who condemn parent-approved MC of boys are not as quick to condemn other procedures that provide no medical benefit to children[146]? For example, cosmetic orthodontia, correction of harelip, surgery for tongue-tie, treatment of dwarfism by growth hormone injections and surgery for removal of supernumerary digits[146]. All of these interventions, MC included, should be regarded by parents and physicians as being beneficial to the child. As one commentator remarked, it seems odd that infant MC is regarded by some as controversial[146]. In European countries rising anti-Semitic and anti-Islamic bias as well as anti-American sentiments appear to parallel the opposition to circumcision of boys.

Implications for public health

Based on the evidence, the fall in early infant MC prevalence in Australia and New Zealand poses a significant threat to public health and individual wellbeing. Despite the current RACP policy in 2010[9] being out-dated and not evidence-based[10], it continues to be cited in Australia as the national medical position on MC. The flow-on effect has been complacency or indifference by other Australian medical bodies. Failure to rigorously assess the evidence so as to arrive at the kind of recommendations made by the AAP, CDC and CAA has given license to state departments of health to remove prophylactic MC as allowable in public hospitals. Although doing so might reduce government expenditure in the short term, United States studies show that in the long-term costs will be substantially higher because of the need for later, more expensive, medically indicated MC[90,139,142-144], which carries a 10-20 fold higher risk of an adverse event[128], and for treatment of a wide array of conditions that early infant MC protects against[17,90,115,139,142-144,160]. An absence of elective MC in teaching hospitals in Australia is an impediment to training in the procedure. Lack of familiarity amongst younger medical graduates may lead to reticence in recommending it.

Early infant MC should no longer be regarded as a controversial procedure. The value placed on evidence-based medicine in clinical practice requires a dispassionate consideration of early infant MC as a desirable intervention in Australia and New Zealand. Past prejudice should be set aside in order that evidence-based recommendations similar to those of the AAP and CDC be adopted in Australia and New Zealand, as well as in other countries. Doing so will improve public health by reducing prevalence, suffering and deaths from highly prevalent foreskin-related conditions and diseases, and at the same time provide cost savings to governments and families.

COMMENTS

Background

There has been a significant shift in male circumcision (MC) policy in the United States over recent years. The American Academy of Pediatrics (AAP) and Centers for Disease Control and Prevention (CDC) each reviewed the scientific evidence and concluded that benefits exceed risks. The United States has a high rate of MC. In the light of the recent recommendations for the United States, should other wealthy countries follow suit and recommend MC as a desirable public health intervention?

Research frontiers

Since males who are uncircumcised are at increased risk of various infections from infancy through old age, as well as physical problems, penile inflammatory disorders, candidiasis, inferior hygiene and genital cancers, MC would appear to represent a worthwhile intervention. The best time to circumcise has been debated. The authors therefore performed a systematic evaluation of the scientific literature over the past 10 years. The authors then assessed this to see whether the evidence is applicable to the comparable Anglophone countries of Australia and New Zealand. As part of this (unlike the AAP and CDC), the authors performed a risk-benefit analysis using the strongest relevant data.

Innovations and breakthroughs

Similar to the AAP and CDC, the authors identified a wide array of medical conditions that MC protects against, but the evidence has become even stronger as a result of new studies and analyses that have been published since those United States policy reviews on MC appeared. The present study

revealed a high benefit-to-risk ratio and that over their lifetime a large proportion of males will be protected against adverse medical conditions and diseases caused by foreskin retention if they are circumcised soon after birth.

Applications

The dichotomy between the scientific evidence and pediatric MC policy in Australia and New Zealand, as well as various other wealthy countries, is striking. Clearly, Australia and New Zealand should follow the recent AAP and CDC policies by replacing outmoded non evidence-based pediatric recommendations opposing early infant MC with strong evidence-based affirmative policy recommendations in favor. Given the low risks and enormous lifetime benefits, doing so should improve public health considerably and be cost saving to the health system.

Terminology

MC is a simple procedure that involves the surgical removal of the foreskin. Early infancy is the ideal time for the procedure.

Peer-review

The reviewer commented that some of the terms used should be defined and provided a list of minor corrections. All of these suggestions were implemented.

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