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18 July 2013

Dear Dr Borror,

Re: Plank et al. (2013) A Randomized Trial of Mogen Clamp Versus Plastibell for Neonatal Male Circumcision in Botswana. JAIDS 15 April 2013 - Volume 62 - Issue 5 - p e131–e137 doi: 10.1097/QAI.0b013e318285d449.

We wish to lodge a formal complaint about the behaviour of the Boston, Brigham and Woman's Hospital Institutional Review Board (IRB) which approved and monitored the above trial.

Our complaint has two elements.

(1) The IRB should not have approved the trial.
(2) Having approved it, their monitoring of adverse events was inadequate.

Background

The trial compared two methods of neonatal circumcision in Botswana. The subjects were new-born boys who were unable to give informed consent, i.e. a vulnerable group.

The research was designed to find out which method of circumcision was better. It was non-therapeutic. The babies were healthy, and the trial was performed in a setting where, according to the published report, "neonatal male circumcision is rarely performed". This means that had the research not been going on participants would not have been circumcised at all. The risks of participation were therefore not just those of randomisation and the potential difference between the two methods, but the total risks of neonatal circumcision.

The standard which the committee should have followed is the Declaration of Helsinki paragraph 27 which states (our emphasis):

> *"*For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only *minimal risk and minimal burden."*

Our complaints

(1) Unethical approval of the project

For the avoidance of doubt, we accept that informed consent was sought from the parents, although we have not seen the parent information sheet. We accept that the research was intended to promote the health of the population represented by the potential subject, and we accept that the research could not be performed with competent persons.

However, we contend that no reasonable person could argue that neonatal male circumcision in Botswana entailed "minimal risk and minimal burden".

The authors do not cite any primary research on the risks of neonatal male circumcision in Africa dating from before the trial started, i.e. before 2009. However, they quote two secondary sources, the WHO manual for neonatal circumcision and the UNAIDS review: Neonatal and child male circumcision: a global review. Both manuals have the explicit purpose of encouraging male neonatal circumcision. The WHO manual states in the sample parent information sheet.

> "Surgical risk. Complications during male circumcision are rare, being estimated to occur in 1 of every 500 procedures. These complications, which can be severe, include poor cosmetic outcome, bleeding, infection, injury to the penis and the removal of too much or too little skin."

The WHO manual also includes pictures and descriptions of a range of very rare but catastrophic injuries from circumcision, including amputation of the penis or glans, complete penile destruction with electro-cautery, bladder rupture from plastibell ring migration and death.

Referring to amputation of the penis the manual states:

> "This extremely rare complication can be minimized by using good surgical technique but is unlikely to be eliminated. Unfortunately, even under ideal circumstances and with experienced surgeons [it] continues to occur."

Referring to retained plastibells the manual states:

> "Some of the most serious complications ever seen [retention and bladder rupture] [...] have resulted from retained Plastibells. Educating the family to closely monitor the wound and the infant's urine output is paramount with the use of this device."

The UNAIDS review: Neonatal and child male circumcision: a global review, states p 35:

> "Serious complications can occur during the procedure, including death from excess bleeding and amputation of the glans penis if the glans is not shielded during the procedure.[29,81,103,150–152] Late (postoperative) complications include the formation of a skin bridge between the penile shaft and the glans, infection, urinary retention, meatal ulcer, impetigo,[153] fistulas loss of penile sensitivity, sexual dysfunction and oedema of the glans penis.
>
> Our literature search found many case reports and case series of circumcision-related complications, but relatively few studies that reported the proportion of circumcised males with a complication. For an accurate estimate of risks, active follow-up of circumcised boys is needed. Hospital-based studies of circumcision-related complications are usually retrospective and record based.[45,49,81] Complications in these studies are commonly recorded from discharge sheets, so tend to underestimate the true frequency of complications because events occurring after discharge are not captured. Furthermore, not all postoperative complications will be seen again at the same hospital. We therefore present results separately for prospective and retrospective studies. […]
>
> An additional problem in estimating complication risks is that precise definitions are not often given. For example, 'bleeding' may mean oozing, which is readily stopped by compression, or more severe bleeding requiring a blood transfusion. Therefore, to report complications as consistently as possible between studies, we excluded all cases of oozing or minor bleeding as well as some other minor complications (noted under the individual studies). Cases of excess residual foreskin or inadequate circumcision are also excluded—these are adverse outcomes of circumcision and may involve further surgery, but are not medical complications per se. We have also reported serious adverse events separately—these include complications defined as 'severe' or 'serious' by authors, or with long-term or life-threatening sequelae."
>
> The manual then cites 16 prospective studies (Table 5) which give serious adverse event rates of between 0 and 2.1%, and 10 retrospective studies (table 6) which give serious adverse event rates of between 0 and 1.3%. 'Serious' or 'severe' adverse events included long-term or life-threatening sequelae (partial amputation of glans, urethral laceration, and need for re-surgery or plastic surgery).

For a boy undergoing a research circumcision which he would not otherwise have undergone, such risks cannot reasonably be described as of minimal risk and minimal burden.

Note

We are not suggesting that a trial testing the relative safety of two widely used methods of circumcision would necessarily be unethical if performed in a setting where circumcision was the culturally normal practice. For the avoidance of doubt we accept that if the infants were going to be circumcised anyway, that the present trial would be ethical.

2. Failure to adequately monitor the research subject's safety

Three babies out of 300 died during the project. The published report is ambiguous as to whether all three deaths were reviewed contemporaneously by the Boston IRB. We ask the OHRP to investigate when these deaths were reviewed and what evidence was presented to the IRB.

However, the published report is clear that the baby who died at 3 days of age, 24 hours after the procedure, was reviewed. The IRB concluded that this death was not related to the circumcision procedure.

We have been sent the following statement from Dr Plank about the circumstances of this death.

> "The last death occurred in a baby who died of suspected sepsis on day of life 3. The baby was circumcised using a Mogen clamp on day of life 2 and discharged to home later that day. The following day he was brought to the local health center with respiratory distress, and was noted to be febrile. He was transferred to the district hospital in the evening where he was again found to be febrile. The study team was not notified of his admission until the next morning after he had died. No urinalysis, blood cultures, chest x-ray or lumbar puncture were performed. The circumstances of this baby's death were reviewed in great detail with several groups, in order to obtain independent assessment of the cause of death: the hospital staff, the Botswana Ministry of Health, the Botswana Health Research and Development Committee, the Partners Institutional Review Board and our own Data Safety Monitoring Committee. All parties agreed that based upon all of the clinical data available, the most likely cause of death was neonatal sepsis or pneumonia, and that it was extremely unlikely that the baby's death was related to the circumcision procedure.
>
> Autopsies are very rarely performed in Botswana, and were not performed in any of the three deaths in the study. Detailed diagnostic work-ups are also often not available in resource-limited settings, or are not performed (e.g. because a baby dies at home). Finally, prenatal screening for group B streptococcus is not routinely performed, and mothers do not receive prophylactic antibiotics."

In our opinion the conclusion that "it was extremely unlikely that the baby's death was related to the circumcision procedure" is irrational. This was a healthy newborn baby. The death occurred 24 hours post procedure. No investigations were done. Even if the baby had some unrecognised congenital heart disease, or streptococcal infection, as the direct cause of death, it would remain highly likely that the research circumcision was an aggravating factor.

We believe that the IRB's conclusion is unreasonable. We believe the IRB had ceased to protect the research participants, and was protecting itself and the researchers from criticism.

We have expressed our concerns to the IRB who declined to alter either their decision to approve the study, or their decision to classify the deaths as unrelated to the research procedure. When asked how they came to this decision Dr Hohmann replied "We don't publish our deliberations".

We request that you institute an enquiry into the functioning of the Boston IRB with respect to its approval of non-therapeutic research in children.

Yours sincerely

Jim Thornton MD, FRCOG
Professor of obstetrics and gynaecology

On behalf of:

Professor Susan Bewley, London.

Professor Arri Coomarasamy, Birmingham

Professor David Field, Leicester.

Mr Prasad Godbole, Sheffield

Professor Chisale Mhango, Malawi

Professor Lesley Reagan, London

Professor Daniel Sidler, South Africa

Enc. Checklist for the Office for Human Research Protections