

## REVIEW

# Perinatal pathology in the context of a clinical trial: a review of the literature

C Snowdon, D R Elbourne, J Garcia

*Arch Dis Child Fetal Neonatal Ed* 2004;**89**:F200–F203. doi: 10.1136/adc.2003.012740

Perinatal postmortem rates are declining world wide. In the United Kingdom, perinatal pathology has recently been seriously undermined by controversy. There are important consequences for perinatal trials that include pathology studies. This review looks at the reasons for the decline in perinatal postmortem examinations and the effects on research.

the past it would be unusual for anybody to refuse."<sup>13</sup> Pathology studies with inadequate numbers are unreliable, and so this decline clearly has important consequences for the quality and integrity of data.

Low rates of perinatal PMs are likely to be a product of highly interrelated factors. A number of studies have examined clinical and other characteristics of babies and mothers to assess any links with PM rates. It has been shown that prematurity,<sup>7 10 14 15</sup> lower birth weight,<sup>10</sup> and a specific diagnosis—for example, birth asphyxia<sup>16</sup> and congenital anomaly<sup>15</sup>—are all associated with a PM not being performed. Separation of mother and baby through hospital transfer<sup>14</sup> is also associated with no PM. Studies found no significant association between no PM and basic characteristics of the infant (birth hospital, age at death, birth and death weight, race, sex, year of death)<sup>10</sup> or of the mother (age, religion, gravidity),<sup>7</sup> except for lower parity<sup>10</sup> and fewer perinatal losses.<sup>15</sup> These studies have not addressed the contribution of parental and professional views.

In recent times several important social and political factors are also likely to have exacerbated the problem. Perinatal pathology as a specialty is said to be undergoing a period of crisis. There are now few experienced perinatal pathologists in post, insufficient numbers of PMs to retain specialised skills, and few new recruits to the specialty.<sup>13 17</sup> Furthermore, two relevant areas of concern have been raised in the United Kingdom; firstly, there have been governmental inquiries after revelations about the lack of consent for retention of children's organs after PMs at Bristol Royal Infirmary<sup>18</sup> and Alder Hey Children's Hospital in Liverpool<sup>19</sup> and secondly, there have been accusations<sup>20 21</sup> and refutations<sup>22</sup> of misconduct with reference to consent for procedures in perinatal research in the CNEP Trial at North Stafford Hospital.<sup>23</sup> It is against this highly sensitive background, in "a time of unprecedented mistrust between the medical profession, the public, and the media",<sup>24</sup> that all UK discussions about PMs are taking place.

Despite the widely acknowledged value of the postmortem examination (PM), there has been a sustained decline in PM rates around the world.<sup>1–6</sup> Although perinatal PM rates are higher than rates of PM in other contexts,<sup>7</sup> they are considered to be suboptimal<sup>8</sup> and are following this downward trend.<sup>9 10</sup> This is in spite of the fact that they are of particular value in several ways. As well as offering parents information about the cause of death of a baby and so a degree of closure, their value lies in giving information for subsequent pregnancies, their role in audit, and in being an important research tool.<sup>11 12</sup>

"A degree of altruism is required of parents who are in the most stressful of circumstances, and benefits to research may not seem important at that time."

As perinatal PMs can provide crucial empirical data, in research terms this decline is worrisome. Without pathology studies, perinatal trials cannot assess the possible impact an intervention has had on those who have died. With assessment incomplete, potentially serious consequences of an experimental treatment could go undetected. It is therefore important that, when babies who have been enrolled in a trial do go on to die, parents should be asked about the possibility of a PM. This is, however, a complicating element in an already difficult situation. A degree of altruism is required of parents who are in the most stressful of circumstances, and benefits to research may not seem important at that time. Their doctors may be uncomfortable requesting such altruism from them. Given declining consent rates for perinatal PMs generally, it does seem that most parents are either declining or are not being approached for permission. This is already having a tangible effect on research.<sup>12a</sup> A UK consultant perinatal histopathologist is quoted as saying "Consent for the use of tissues for research is about 10%. In

"An obvious tension lies between informing the parents of difficult details and managing the request with the sensitivity it deserves."

These concerns have contributed to the recent shift in clinical practice towards detailed consent forms, which now explicitly request permission for aspects of the PM that parents may not previously have considered. Requests for removal

See end of article for authors' affiliations

Correspondence to:  
C Snowdon, Centre for Family Research,  
University of Cambridge,  
Free School Lane,  
Cambridge CB2 3RF, UK;  
cms1000@cam.ac.uk

Accepted 2 October 2003

and retention of whole organs, decisions over methods of sampling, and decisions over subsequent disposal of body parts, has rendered the consent process “a legalistic and clerical business”.<sup>25</sup> An obvious tension lies between informing the parents of difficult details and managing the request with the sensitivity it deserves. Recent discussions about the management of consent for PMs have focused on who should raise the issue of the PM with newly bereaved parents and how those discussions should be handled.<sup>25 26 26a</sup>

In attempts to improve PM rates generally, there has been much interest in charting knowledge of, and reactions to, PMs outside of the perinatal context. There have been various surveys of the attitudes of professionals, such as hospital doctors,<sup>6 26–29</sup> junior doctors,<sup>30 31</sup> general practitioners,<sup>28</sup> medical students,<sup>32 33</sup> and nurses.<sup>34</sup> Perceptions of difficulties with the consent process have been shown to be an important block to offering a PM,<sup>6 27 29</sup> as is degree of certainty over the cause of death<sup>26 29</sup> and increasing age of the patient.<sup>27 29</sup> Although hospital clinicians, general practitioners,<sup>28</sup> junior doctors,<sup>31</sup> and nurses<sup>34</sup> are shown to have positive views of the value of the PM, junior staff in one study were unaware of the benefits.<sup>30</sup>

“Clarifying the cause of death was also important, as was gaining reassurance from the results.”

The views of bereaved relatives<sup>33–36</sup> have also been sought. When relatives had consented to a PM, the most common reasons given were altruistic, that is the advancement of science<sup>33 34</sup> and to help others.<sup>35</sup> Clarifying the cause of death was also important,<sup>33–35</sup> as was gaining reassurance from the results.<sup>33 36</sup> Reasons for refusal were concerns over disfigurement,<sup>33 34 36</sup> a sense that the relative had “suffered enough”,<sup>34 35</sup> and unease with the PM itself.<sup>34 35</sup> Difficulties with the process of giving permission for a PM was cited by one study<sup>33</sup> as a reason for refusal.

Less attitudinal research has been carried out in the perinatal context and none with particular reference to perinatal trials. As trial participation can alter the grounds on which consent is sought, and could significantly alter the experiences of those involved, this is an important omission. There are, however, elements of the existing empirical literature in the perinatal and paediatric field that can shed some light on the complexity of professional and parental determinants of PM rates.

## PROFESSIONAL VIEWS

The literature on professional views is useful in highlighting attitudes to the use of PMs in different clinical circumstances and for different groups of professionals. Four papers<sup>15 37–39</sup> report findings on attitudes to PMs.

VanMarter and colleagues<sup>15</sup> report a records based review supplemented by a questionnaire based study. In the review, they found an important association between rates of PM and presumed cause of death, with extremely premature babies being least likely, and those affected by a congenital anomaly being most likely, to undergo PM. They also found that giving permission for a PM was associated with repeated perinatal loss. Both findings seem to suggest that a parental wish for an explanation of events is important. It is, however, unclear from a review of records whether actual parental views, or professional perceptions of those views, are the most influential in this matter. In the questionnaire based element of the study, only professional views were sought. PMs were seen as more important by senior staff than by junior staff. In general, the sample saw the importance of the PM as being strongly related to the cause of death; whereas only 31% felt that they were very important when the cause

of death was extreme prematurity, when the cause of death was congenital anomaly or an indeterminate cause, 94% and 91% respectively felt that they were very important.

The views of paediatricians and paediatric residents were surveyed by Stolman and colleagues.<sup>37</sup> Respondents indicated on a multiple choice questionnaire that, although most felt PMs provide valuable information, 20% felt that they are unnecessary if the disease was known before death. When consent is not sought for a PM, this related to concerns not to distress the family and respondents’ belief that little information would be obtained. Seventeen percent of the sample indicated that they do not approach families who are upset.

In assessing the views of neonatologists, obstetricians, midwives, and neonatal nurses, Khong and colleagues<sup>38</sup> found that the most influential factor in the offer of a PM was perceptions of parental desire for a PM; when the diagnosis was clear and the parents did not desire a PM and planned no further pregnancies, there was least inclination to offer a PM. They argue that the determinant of PM rates in their sample was parental refusal, as the neonatologists and obstetricians did not generally show reluctance to make an approach for consent.

Cottreau and colleagues<sup>39</sup> considered the views of pathologists and other clinicians. Although most clinicians saw PMs as useful, 50% felt that they should not be offered when the cause of death is known. Younger clinicians and younger pathologists saw PMs as less useful than their senior colleagues. There was greater discomfort in discussing PMs amongst paediatric staff compared with those dealing with adults.

## PARENTAL VIEWS

Data are available on parental attitudes in a small number of studies<sup>33 40 41</sup> that provide some information on perceived advantages and disadvantages of PMs. A positive view of contributing to research is mentioned in two studies.

McPhee and colleagues<sup>33</sup> included parents in a general sample of bereaved relatives who had or had not permitted a PM. Although most likely to show concern over disfigurement, bereaved parents were singled out as the group especially likely to see benefits of a PM (listed in order of importance as advancement of medical knowledge, knowing the cause of death, and reassurance that all appropriate care was given). As 45% of those who did not permit a PM stated that they had not been approached, the authors argue, in contrast with the study by Khong and colleagues,<sup>38</sup> that reluctance of clinicians to offer PMs is likely to be more important than reluctance of relatives to sanction procedures.

Rankin and colleagues<sup>40</sup> found from a postal questionnaire of parents using a bereavement service that 81% of responding parents had taken up the offer of a PM. This is a high acceptance rate and may be due to the source of the sample, and the fact that the study included women who had miscarried or had terminated a pregnancy because of an abnormality. Although most of those accepting a PM did so for their own benefit—for example, wanted more information, wanted closure—24% wanted to contribute to research. Most of the refusers felt that their baby had “suffered enough”, and that a PM would not help them.

McHaffie and colleagues<sup>41</sup> found that 38% of their sample of bereaved parents refused permission for a PM, with concerns over disfigurement of the baby as “a major preoccupation”. Such concerns were also identified in relatives in non-paediatric settings.<sup>33 34 36</sup> Crucial to decision making was whether or not there was any further information that the parents, rather than the medical team, felt they needed.

## DISCUSSION

The available literature sheds some light on attitudes to PMs generally and to perinatal and paediatric PMs outside of a trial context. This can be used as a first step towards understanding some of the issues likely to affect the management of PMs within a trial context. It describes some of the pre-existing concerns about PMs, on which the complicating factor of the request for PM information for a randomised controlled trial is superimposed.

“...it is not clear whether actual parental views or professional perceptions of parental views are most influential”

These papers give some insight into ways in which parental views may intersect with those of professionals. Although they appear to show that, in usual clinical practice, PM rates are driven by parental inclination or disinclination towards further information, it is not clear whether actual parental views or professional perceptions of parental views are most influential.

The professional literature does suggest quite clearly that perinatal PMs appear to be valued only in certain circumstances. There is a strong theme that they are justified only if they have something important to offer parents—that is, if there is a query over the cause of death or if further information might be made available. If the likely cause of death appears to be clear, as in many cases of prematurity, then PMs are seen as inappropriate. As doctors decide whether or not to approach parents, there is clearly a process by which certain parents can be screened out. It is therefore likely that the subject of a PM is often not raised with parents of premature babies, or those who are thought to have no need for further information. It may be that those who are highly stressed, or who are thought to have suffered greatly, are also subject to a similar screening process. This is in spite of the fact that various studies have shown that PMs can provide unexpected findings that do not support the initially stated cause of death,<sup>7 11 42</sup> leading the Royal College of Pathologists to recommend that “relatives must be informed of the probability that a certified cause of death is wrong”.<sup>43</sup>

Given this apparently dominant view that PMs are only warranted in certain circumstances, it is likely that requesting a PM in a trials context will further complicate the situation. If a PM is thought to have nothing to offer parents, the request to carry out a PM for a pathology study for a clinical trial would be seen as being only for the benefit of the wider community. Rather than having family welfare at the heart of the request, essentially newly bereaved parents could be asked to consent for altruistic reasons. With professional concerns to offer PMs only where there appears to be strong grounds, this may be seen as an inappropriate request. Although some parents have a strong desire not to have a PM, the literature does suggest that some parents may wish to make a contribution to research. It is, however, inadequate to assess whether parental reactions to these particular circumstances are similar to or different from their professional counterparts in this setting.

In addition to assessing attitudes to trial related PMs, it is important to determine what actually happens when parents are approached for consent, and what are the consequences, if any, of the approach. The offer of a PM, and the request that samples should be used for specific research purposes, raise particular issues for both professionals and parents. The combination of the dynamics between parental and professional views, and a fraught political setting, produce a complicated and multilayered encounter. As yet there are no descriptive data to afford a greater understanding of this

situation, and no detailed information on reactions of the various parties. As the experiences of the offer and the decision making process could be very different from the usual clinical situation for all parties involved, the current literature is inadequate to aid understanding of experiences of perinatal pathology in a research context.

It is clear that further research is needed to explore this specialised area of consent and its consequences for those involved. A first step is taken in two linked papers, which report a qualitative study of the views of neonatologists and pathologists involved in two neonatal randomised controlled trials<sup>44</sup> and interview data from a small number of bereaved parents of babies enrolled in both trials.<sup>45</sup>

## ACKNOWLEDGEMENTS

The Nuffield Foundation funded this study. JG worked on this study at the National Perinatal Epidemiology Unit where she was funded by the Department of Health. CS was accommodated by CFR and assisted by Sally Roberts. Project coordination was facilitated by senior staff at the centres involved. Nina Hallowell, John Allison, David Field (and other members of the project's advisory group) commented on drafts of the paper.

## Authors' affiliations

C Snowdon, D R Elbourne, J Garcia, Medical Statistics Unit, London School of Hygiene and Tropical Medicine, University of London, Keppel Street, London WC1E 7HT, UK

C Snowdon, Centre for Family Research, University of Cambridge, Free School Lane, Cambridge CB2 3RF, UK

## REFERENCES

- 1 **Joint Working Party of representatives from the Royal College of Pathologists, Royal College of Physicians of London and the Royal College of Surgeons.** *Report of the Joint Working Party on the Autopsy and Audit.* London: Royal College of Pathologists, 1991.
- 2 **Sanner MA.** In perspective of the declining autopsy rate. Attitudes of the public. *Arch Pathol Lab Med* 1994;**118**:878–83.
- 3 **Wlodaver CG.** Why have autopsies grown so unpopular and what can we do about it? The clinical-pathological conference. *J Okla State Med Assoc* 1994;**87**:351.
- 4 **McPhee SJ.** Maximizing the benefits of autopsy, both for clinicians and families. What needs to be done? *Arch Pathol Lab Med* 1996 Aug;**120**:743–8.
- 5 **Chariot P, Witt K, Pautot V, et al.** Declining autopsy rate in a French hospital: physician's attitudes to the autopsy and use of autopsy material in research publications. *Arch Pathol Lab Med* 2000;**124**:739–45.
- 6 **Loughrey MB, McCluggage WG, Toner PG.** The declining autopsy rate and clinician's attitudes. *Ulster Med J* 2000;**69**:83–9.
- 7 **Brodie M, Laing IA, Keeling JW, et al.** Ten years of neonatal autopsies in tertiary referral centre: retrospective study. *BMJ* 2002;**324**:761–3.
- 8 **Joint Working Party of the Royal College of Obstetricians and Gynaecologists and the Royal College of Pathologists.** *Report on fetal and perinatal pathology.* London: RCOG, 1988.
- 9 **Kumar P, Angst DB, Taxy J, et al.** Neonatal autopsies: a 10-year experience. *Arch Pediatr Adolesc Med* 2000;**154**:38–42.
- 10 **Okah FA.** The autopsy: experience of a regional neonatal intensive care unit. *Paediatr Perinat Epidemiol* 2002, **16**:4:350–4.
- 11 **Carlidge PHT, Dawson AT, Stewart JH, et al.** Value and quality of perinatal and infant postmortem examinations: cohort analysis of 400 consecutive deaths. *BMJ* 1995;**310**:155–8.
- 12 **Chiswick M.** Perinatal and infant postmortem examination. *BMJ* 1995;**310**:141–2.
- 12a **Furness P.** Consent to using human tissue. Implied consent should suffice [editorial]. *BMJ* 2003;**327**:759–60.
- 13 **Kmietowicz Z.** Paediatric pathology service close to collapse. *BMJ* 2001;**322**:1270.
- 14 **Maniscalco WM, Clarke TA.** Factors influencing neonatal autopsy rate. *Am J Dis Child* 1982;**136**:781–4.
- 15 **VanMarter LJ, Taylor F, Epstein MF.** Parental and physician-related determinants of consent for neonatal autopsy. *Am J Dis Child* 1987;**141**:149–53.
- 16 **Landers S, Kirby R, Harvey B, et al.** Characteristics of infants who undergo neonatal autopsy. *J Perinatal* 1994;**14**:204–7.
- 17 **Cox P, Scott R.** Perinatal pathology in 2001. *Arch Dis Child* 2001;**84**:457–8.
- 18 **Bristol Royal Infirmary Inquiry.** *Learning from Bristol: the report of the public inquiry into children's heart surgery at the Bristol Royal Infirmary, 1984–1995.* London: HMSO, 2001(Cmnd 5207.).
- 19 **Department of Health.** *The removal and retention and use of human organs and tissue from post-mortem examinations: advice from the Chief Medical Officer.* London: DoH, 2001.

- 20 **Hall C**, Pook S. No one told us our babies were in a trial. *The Daily Telegraph* 1999 February 19:4.
- 21 **Wilson E**. They used our babies and never told us. *Daily Mail* 1999 February 19:1.
- 22 **Hey E**, Chalmers I. Investigating allegations of research misconduct: the vital need for due process. *BMJ* 2000;**321**:752.
- 23 **NHS Executive West Midlands Regional Office**. *Report of a review of the research framework in North Staffordshire Hospital NHS Trust* [Griffiths report]. Leeds: NHS Executive, 2000.
- 24 **Jones R**. Declining altruism in medicine [editorial]. *BMJ* 2002 March 16;**324**:624–625.
- 25 **Sayers GM**, Mair J. Getting consent for autopsies: who should ask what, and why? *BMJ* 2001;**323**:521.
- 26 **Grunberg SM**, Sherrad A, Muellenbach R, *et al*. Analysis of physician attitudes concerning requests for autopsy. *Cancer Invest* 1994;**12**:463–8.
- 26a **McDermott MB**. Obtaining consent for autopsy. *BMJ* 2003;**327**:804–6.
- 27 **Birdi KS**, Bunce DJ, Start RD, *et al*. Clinicians beliefs underlying autopsy requests. *Postgrad Med J* 1996;**72**:224–8.
- 28 **Midelfart J**, Aase S. The value of autopsy from a clinical point of view. A survey of 250 general practitioners and hospital clinicians in the county of Sor-Trondelag, Norway. *APMIS* 1998;**106**:693–8.
- 29 **Start RD**, Hector-Taylor MJ, Cotton DW, *et al*. Factors which influence necropsy requests: a psychological approach. *J Clin Pathol* 1992;**45**:254–7.
- 30 **Hinchliffe SA**, Godfrey HW, Hind CR. Attitudes of junior medical staff to requesting permission for autopsy. *Postgrad Med J* 1995;**71**:60.
- 31 **Lund JN**, Tierney GM. Hospital autopsy: standardised questionnaire survey to determine junior doctor's perceptions. *BMJ* 2001;**323**:21–2.
- 32 **Dziobon MD**, Roberts SD, Benbow EW. Attitudes of nursing staff to the autopsy. *J Adv Nurs* 2000;**32**:969–74.
- 33 **McPhee SJ**, Bottles K, Lo B, *et al*. To redeem them from death. Reactions of family members to autopsy. *Am J Med* 1986;**80**:664–71.
- 34 **Solomon SA**, Adams KH. Attitudes of relatives to autopsies of elderly patients. *Age Ageing* 1993;**22**:205–8.
- 35 **Start RD**, Sherwood SJ, Kent G, *et al*. Audit study of next of kin's satisfaction with clinical necropsy service. *BMJ* 1996;**312**:1516.
- 36 **Oppewal F**, Meyboom-De-Jong B. Family members' experiences of autopsy. *Family Pract* 2001;**18**:304–8.
- 37 **Stolman CJ**, Castello F, Yorio M, *et al*. Attitudes of pediatricians and pediatric residents toward obtaining permission for autopsy. *Arch Pediatr Adolesc Med* 1994;**148**:843–7.
- 38 **Khong TY**, Turnbull D, Staples A. Provider attitudes about gaining consent for perinatal autopsy. *Obstet Gynecol* 2001;**97**:994–8.
- 39 **Cottreau C**, McIntyre L, Favara BE. Professional attitudes towards the autopsy. A survey of clinicians and pathologists. *Am J Clin Pathol* 1989;**92**:673–6.
- 40 **Rankin J**, Wright C, Lind T. Cross sectional survey of parents' experiences and views of the postmortem examination. *BMJ* 6 April 2002;**324**:816–18.
- 41 **McHaffie HE**, Fowlie PW, *et al*. Consent to autopsy for neonates. *Arch Dis Child Fetal Neonatal Ed* 2001;**85**:F4–7.
- 42 **Porter HJ**, Keeling JW. Value of perinatal necropsy examination. *J Clin Pathol* 1987;**40**:180–4.
- 43 **The Royal College of Pathologists**. *Human bodies, human choices*. Response from The Royal College of Pathologists. November 2002. [www.rcpath.org](http://www.rcpath.org).
- 44 **Snowdon C**, Elbourne DR, Garcia J. Perinatal pathology in the context of a clinical trial: attitudes of neonatologists and pathologists. *Arch Dis Child Fetal Neonatal Ed* 2004;**89**:F204–7.
- 45 **Snowdon C**, Elbourne DR, Garcia J. Perinatal pathology in the context of a clinical trial: attitudes of bereaved parents. *Arch Dis Child Fetal Neonatal Ed* 2004;**89**:F208–11.