

LETTERS



IMPROVING OUTCOME IN VERY PRETERM INFANTS

Authors' reply to Page and Rafi

Jennifer Zeitlin *senior researcher*¹, Bradley N Manktelow *senior lecturer in medical statistics*², Aurelie Piedvache *statistician*¹, Marina Cuttini *perinatal epidemiologist*³, Elaine Boyle *senior lecturer in neonatal medicine*², Arno van Heijst *director*⁴, Janusz Gadzinowski *professor and chair of department*⁵, Patrick Van Reempts *professor of paediatrics and chair of department*⁶, Lene Huusom *consultant obstetrician and gynaecologist*⁷, Tom Weber *consultant obstetrician and gynaecologist*⁷, Stephan Schmidt *professor of obstetrics*⁸, Henrique Barros *professor of epidemiology*⁹, Dominico Dillalo *public health doctor*¹⁰, Liis Toome *head and researcher*¹¹, Mikael Norman *professor of paediatrics and neonatal medicine*¹², Beatrice Blondel *senior researcher*¹, Mercedes Bonet *researcher*¹, Elisabeth S Draper *professor of perinatal and paediatric epidemiology*², Rolf F Maier *director of the children's hospital and paediatrics chair*¹³

¹INSERM UMR 1153, Obstetrical, Perinatal and Pediatric Epidemiology Research Team (Epopé), Center for Epidemiology and Statistics Sorbonne Paris Cité, DHU Risks in pregnancy, Paris Descartes University, Paris, 75014, France; ²Department of Health Sciences, University of Leicester, Leicester, UK; ³Clinical Care and Management Innovation Research Area, Bambino Gesù Children's Hospital, Rome, Italy; ⁴Department of Neonatology, Radboud University Medical Centre, Nijmegen, Netherlands; ⁵Department of Neonatology, Poznan University of Medical Sciences, Poznan, Poland; ⁶Department of Neonatology, Antwerp University Hospital, Antwerp; Study Centre for Perinatal Epidemiology, Flanders, Brussels, Belgium; ⁷Department of Obstetrics, Hvidovre University Hospital, Hvidovre, Denmark; ⁸Department of Obstetrics, University Hospital, Philipp University of Marburg, Germany; ⁹EPIUnit-Institute of Public Health, University of Porto, Porto, Portugal; ¹⁰Health Department, Regione Lazio, Rome, Italy; ¹¹Unit of Neonates and Infants, Tallinn Children's Hospital, Tallinn, Estonia; University of Tartu, Tartu, Estonia; ¹²Department of Clinical Science, Intervention and Technology, Division of Paediatrics, Karolinska Institute, Stockholm, Sweden; Department of Neonatal Medicine, Karolinska University Hospital, Stockholm, Sweden; ¹³Children's Hospital, University Hospital, Philipp University of Marburg, Germany

We agree with Page and Rafi about the importance of identifying the key evidence based obstetric and neonatal interventions that can be monitored to assess quality of care for very preterm infants.^{1 2} As our study shows,³ evaluating the use and impact of four evidence based practices together sets higher standards and focuses attention on care processes. The EPICE (Effective Perinatal Intensive Care in Europe) project's international dimension is a strength, as it reveals underuse of evidence based care in many health systems and cultures.

But international studies are challenging. Despite universal access to evidence based knowledge, guidelines differ between countries. The all-or-nothing composite is a powerful concept when the selected interventions are based on widely accepted scientific evidence and clear, consensual guidelines. However, not many interventions for very preterm infants fulfil these requirements in a cross national perspective.

As part our project's objectives we reviewed recommendations in the 11 participating countries and the published literature.

We found many differences in the existence and content of recommendations and in evidence related to common interventions for the care of preterm infants, including caesarean section, antibiotics during labour, cord clamping, probiotics, management of persistent ductus arteriosus, and breastfeeding support. Our review also found inconclusive evidence for the use of tocolytics to improve outcomes, as noted in recent debates.⁴

Magnesium sulphate provides another good example of these challenges. Despite a 2009 Cochrane review concluding that magnesium sulphate is effective for neuroprotection,⁵ only a few countries, to our knowledge, have recommendations on its use for this indication.⁶⁻⁸ In Denmark—one of the EPICE countries—a randomised trial on the effectiveness of magnesium sulphate for neuroprotection is ongoing, reflecting concerns that the previous meta-analysis was underpowered.⁹ The absence of consensus may also relate to uncertainty about dose and regimen, as concluded by the Cochrane review.

To benchmark care across units, regions, and countries we need common international standards about what constitutes evidence based care for very preterm infants. Greater collaboration between national obstetric and neonatal societies would be one way of achieving this goal. Providing an international context for national guidelines would also allow national societies to clarify how their recommendations relate to those available elsewhere.

Finally, our composite measure of evidence based care was developed to show an effect on short term outcome. This led us to select practices that reduced mortality before discharge home or reduced severe morbidity at discharge. Many practices, including magnesium sulphate, aim primarily to improve the longer term development and health of the child. Using this approach to evaluate the use and impact of these interventions is more complex, but it should be a priority.

Competing interests: None declared.

1 Page A-S, Page G. Tocolysis may optimise outcomes in very preterm infants. *BMJ* 2016;354:i4632.

- 2 Rafi J. Introducing a preterm care bundle: magnesium sulphate can be the fifth component. *BMJ* 2016;354:i4658.
- 3 Zeitlin J, Manktelow BN, Piedvache A, et al. EPICE Research Group. Use of evidence based practices to improve survival without severe morbidity for very preterm infants: results from the EPICE population based cohort. *BMJ* 2016;354:i2976. doi:10.1136/bmj.i2976 pmid:27381936.
- 4 Walker KF, Thornton JG. Tocolysis and preterm labour. *Lancet* 2016;387:2068-70. doi: 10.1016/S0140-6736(16)00590-0 pmid:26944025.
- 5 Doyle LW, Crowther CA, Middleton P, Marret S, Rouse D. Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus. *Cochrane Database Syst Rev* 2009;1:CD004661. doi:10.1002/14651858.CD004661.pub3. pmid:19160238.
- 6 National Institute for Health and Care Excellence. Preterm labour and birth (NICE guideline 25). Nov 2015. www.ncbi.nlm.nih.gov/pubmedhealth/PMH0080792/pdf/PubMedHealth_PMH0080792.pdf.
- 7 Health Service Executive, Royal College of Physicians of Ireland. Antenatal magnesium sulphate for fetal neuroprotection (clinical practice guideline). Apr 2013. www.hse.ie/eng/about/Who/clinical/natclinprog/obsandgynaeprogramme/mgso.pdf.
- 8 Belgian Health Care Knowledge Centre (KCE). Prevention of preterm birth in women at risk: selected topics. 2014. https://kce.fgov.be/sites/default/files/page_documents/KCE_228Cs_Preterm%20birth_Synthesis.pdf.
- 9 Huusom LD, Secher NJ, Pryds O, Whitfield K, Gluud C, Brok J. Antenatal magnesium sulphate may prevent cerebral palsy in preterm infants--but are we convinced? Evaluation of an apparently conclusive meta-analysis with trial sequential analysis. *BJOG* 2011;118:1-5. doi:10.1111/j.1471-0528.2010.02782.x pmid:21197681.

Published by the BMJ Publishing Group Limited. For permission to use (where not already granted under a licence) please go to <http://group.bmj.com/group/rights-licensing/permissions>