

Institution: University of Brighton		
Unit of Assessment: A3 Allied Health Professions, Dentistry, Nursing and Pharmacy		
Title of case study: Reducing risks of preterm death and improving developmental outcomes with delayed cord clamping		
Period when the underpinning research was undertaken: 2012 – to date		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Heike Rabe	Professor of Perinatal Medicine /Honorary Consultant Neonatologist	2012 – to date
Period when the claimed impact occurred: 2014 – 2020		
Is this case study continued from a case study submitted in 2014? N		
<p>1. Summary of the impact</p> <p>Prematurity is a leading cause of death worldwide for children up to the age of five. Rabe's systematic Cochrane Review showed that delayed cord clamping in preterm babies reduces in-hospital deaths by 27%. Recommendations from the review have contributed to 17 national and international guidelines, including the WHO Care of the Newborn Infant and NICE Preterm Labour and Birth guidelines, and the British Association of Perinatal Medicine Optimal Cord Management Toolkit. Rabe's evidence on delayed cord clamping has been the key driver of change in all 12 maternity and neonatal units in the West and South West of England, leading to their delayed cord clamping rate rising from 30% to 85% of their preterm births in one year.</p>		
<p>2. Underpinning research</p> <p>Early clamping of the umbilical cord has traditionally been standard practice, allowing preterm babies to be transferred quickly to neonatal care. Yet, delayed clamping for 30 seconds to three or more minutes allows vital placental transfusion which may improve the baby's health. In 2012, delayed cord clamping (DCC) was highlighted as a priority review topic by the Cochrane Pregnancy and Childbirth Stakeholder Group, which includes consumer organisations, professional bodies, guideline developers and policy makers.</p> <p>Professor Heike Rabe led a Cochrane Review that addressed the need for research-based evidence on the effects of delayed versus early cord clamping at preterm birth on infant outcomes [reference 3.1, 3.2]. Using evidence from 15 trials involving more than 700 mother and baby pairs, it was proved that delaying cord clamping for 30 to 120 seconds led to preterm health benefits such as a reduced need for blood transfusion and risk of brain haemorrhage [3.1]. In 2019, Cochrane Reviews commissioned Rabe to update the 2012 review to include guidance on ways to implement DCC at preterm birth while providing essential neonatal care [3.2]. This updated review included 40 studies undertaken in 19 countries providing data on 4,884 babies and their mothers. The review found that preterm babies have the added benefit of a 27% increase in survival rate if they receive DCC at birth (54:1000 vs 74:1000) and that fewer babies experience any brain haemorrhage (155:1000 vs 187:1000).</p> <p>This review is published under the Cochrane Pregnancy and Childbirth Review Group, which is one of 53 Cochrane Review Groups. Cochrane Reviews have a high authoritative role in informing clinical guidelines on a national and international level, particularly in neonatology. In contrast to adult medicine, most trials in preterm and term babies have a small sample size. It is therefore important to synthesise research evidence using stringent criteria for selection of primary research on preterm/term health to produce unambiguous and up-to-date recommendations that inform decisions by healthcare professionals and policy makers. Rabe has been first author for the Cochrane Reviews on the benefits of placental transfusion published in 2004, 2012 [3.1] and 2019 [3.2].</p>		

With more guidelines recommending delaying clamping of the cord at birth as part of routine care for infants, more studies emerged on the best way to enhance redistribution of placental blood into the baby at birth. A leading study was the NIHR *Research for Patients Benefit* project led by Rabe in collaboration with Professor Ayers at City University London [3.4]. This study compared the neurodevelopmental outcome at 2 and 3.5 years in preterm babies benefiting from DCC and cord milking, another alternative to increase placental blood transfer [3.3]. In this first follow-up study looking at the outcomes of both methods to increase placental transfusion on preterm babies over their first 3.5 years, Rabe and colleagues showed that both methods did not induce any long-term adverse effect on neurodevelopmental outcome at 2- and 3.5-years follow-up.

3. References to the research

[3.1] Rabe, H., Diaz-Rossello, J. L., Duley, L., and Dowswell, T. (2012). Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes. *Cochrane Database of Systematic Reviews*, 8. <https://doi.org/10.1002/14651858.CD003248.pub3> [Quality validation: leading peer-reviewed journal].

[3.2] Rabe, H., Gyte, G. M., Díaz-Rossello, J. L., and Duley, L. (2019). Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes. *Cochrane Database of Systematic Reviews*, 9. <https://doi.org/10.1002/14651858.CD003248.pub4> [Quality validation: leading peer-reviewed journal].

[3.3] Rabe, H., Sawyer, A., Amess, P., and Ayers, S. (2016). Neurodevelopmental outcomes at 2 and 3.5 years for very preterm babies enrolled in a randomized trial of milking the umbilical cord versus delayed cord clamping. *Neonatology*, 109(2), 113–119. <https://doi.org/10.1159/000441891> [Quality validation: leading peer-reviewed journal].

Key research grants

[3.4] Heike Rabe [PI], NIHR RfPB. PB-PG-1208-18244, 2010 – 2012. 'What is the neurodevelopmental outcome of preterm infants at 2 years of age, who received placental transfusion at delivery?', Total funding GBP49,849.

4. Details of the impact

Rabe's Cochrane Review on the optimal timing of the umbilical cord clamping has been instrumental in changing UK and international policy (EU, Canada and USA) on the use of delayed cord clamping in preterm births. In doing so, it has led to a shift in the understanding and acceptance on the importance and benefit of DCC, with these results filtering through to a reactive shift in practice to realise these benefits.

4.1 Informed national and international healthcare policies and guidelines on optimal cord management

Since its original publication in 2012, Rabe's Cochrane Review on DCC has been adopted in 17 national and international guidelines [Source 5.1a; as recorded on the Cochrane Review website on 20 Oct 2020] including the WHO 2014 Guideline on Delayed Umbilical Cord Clamping [5.2], the European Consensus Guidelines on the Management of Respiratory Distress Syndrome 2016 Update [5.3], and the National Institute for Health and Care Excellence Preterm Labour and Birth Guideline [5.4a and b; 2015 updated 2019].

4.1.1 WHO Maternal and Infants' Health: The WHO 2014 guideline on DCC [5.2] was developed following a request from Member States for the WHO to provide guidance on the effects of DCC to improve maternal and infant nutrition and health as a public health strategy. The Guideline Development Group (GDG) evaluated updated evidence from two existing WHO guidelines (both published in 2012) on optimal timing of the umbilical cord clamping. Rabe's 2012 Cochrane Review was one of three Cochrane Reviews assessed by the WHO 2014 DCC GDG and the only one that considered optimal timing of cord clamping in preterm babies. The GDG considered the benefits of DCC for preterm to be critical and concluded with a strong recommendation that DCC should form part of the essential neonatal care provision and be applied equally to preterm and term births [5.2]. Adherence to this recommendation is a reasonable measure of good-quality care. For policymakers, it

means that it can be adapted as an instruction for most clinical situations. The 2014 WHO guideline on DCC in preterm births has since been used as a key reference in the WHO 2018 recommendation on Intrapartum care for a positive childbirth experience [5.5], as well as the WHO recommendation on '*Optimal timing of cord clamping for the prevention of iron deficiency anaemia in infants*' [5.6].

4.1.2 American College of Obstetricians and Gynecologists/American Academy of Paediatrics Guideline: Rabe's 2012 Cochrane Review informed the latest American College of Obstetricians and Gynecologists (ACOG) Committee opinion on cord management which now '*recommends a delay in umbilical cord clamping in vigorous term and preterm infants for at least 30-60 seconds after birth [...] given the benefits to most newborns*' [5.7a]. Professor Tonse Raju, Medical Officer of the National Institute of Child Health and Human Development (NICHD) of the National Institutes of Health USA (NIH) contacted Rabe requesting a draft of her 2012 Cochrane Review to support the development of neonatal care policies with the Committee on Foetus and Newborn of the American Academy of Pediatrics (AAP):

'Thanks to the cumulative research data from Prof. Rabe and her colleagues and the strong message from their systematic review, the committee's approval accepting my draft was unanimous. The ACOG/AAP members were particularly impressed by the strength of the evidence related to lower rates of anemia, improved blood pressure, and reduced rates for all grade of intraventricular hemorrhage – the last one being the most important, prevention of which could improve long-term outcomes of preterm infants. Interestingly, the above paragraph is still retained in the ACOG Committee Opinion #684 published in January 2017 [5.7c] along with the citation for Prof. Rabe's 2012 publication' [5.7b].

4.1.3 The European Consensus Guidelines on the Management of Respiratory Distress Syndrome (RDS): The 2016 update [5.3] provides a set of recommendations for the optimal management of preterm babies with, or at risk of, RDS to achieve the best outcomes for neonates in Europe. Developed by European neonatologists, this guideline is endorsed by the European Association of Perinatal Medicine. Rabe's 2012 Cochrane Review has informed the 2016 updated recommendation on optimal cord clamping which states, citing Rabe's Review: '*if possible, [to] delay clamping the umbilical cord for at least 60 s to promote placentofetal transfusion.*' [5.3]. The European Consensus Guidelines provide a strong recommendation to use the intervention listing its benefits as reported in Rabe's 2012 Review (higher haematocrit, transiently higher blood pressure with less need for inotropic support and fewer intraventricular haemorrhages).

4.1.4 NICE Guidance on Preterm Labour and Birth: Both the original 2015 and the updated 2019 versions of the NICE Guidance on Preterm Labour and Birth [5.4a and b] recommends waiting for at least 30 seconds, but no longer than 3 minutes, before clamping the cord of preterm babies if the mother and baby are stable. Among the 3 evidence sources cited for these recommendations, Rabe's 2012 Cochrane Review is the only one noted as presenting no major limitations and providing research-based evidence on the timing of cord clamping ranging from 30 to 180 seconds.

4.1.5 British Association of Perinatal Medicine Optimal Cord Management Toolkit: The national rollout of the DCC practice to all maternity and neonatal units in England is supported by several interventions and organisations such as the British Association of Perinatal Medicine (BAPM) Perinatal Optimisation Care Pathway. Rabe was part of a four-nation team of obstetricians, midwives and neonatologists with parent representation leading on the BAPM Optimal Cord Management Toolkit development [5.8]. This toolkit, which draws significantly on Rabe's research-based evidence review, is one of four produced by the BAPM for their Perinatal Optimisation Care Pathway. Its implementation in maternity and neonatal units across NHS England will be supported throughout England by the Maternity and Neonatal Safety Improvement Programme (MatNeoSIP). One of the MatNeoSIP key drivers to improve the optimisation and stabilisation of the very preterm infant mandates the recording of the proportion of babies less than 34 weeks who received DCC at the time of delivery [5.9]. To justify this mandate, MatNeoSIP refers to the NICE 2015 Preterm Labour and Birth [5.4] which based their DCC recommendations on Rabe's 2012 Cochrane Review.

4.2 Produced change in health practitioners' attitudes towards DCC resulting in its increased adoption in clinical practice in the UK and the USA

The ACOG/AAC policy endorsement of Rabe's Cochrane Review recommendations has had a significant effect on the practice of cord clamping in the USA:

'A 2012 survey (published in 2014) showed that 88% of respondents of ACOG member-hospitals did not have a policy on cord clamping. But, a small 2014 survey showed that the policy implementation is improving—between 50% to 80% of preterm infants are getting the benefits from delayed cord clamping by adapting the ACOG/AAP policy' [5.7b].

This uptake of the DCC practice, following its endorsement by the ACOG, is reflected in a 2017 survey of the American College of Nurse-Midwives concerning their umbilical cord clamping practices [5.10]. The survey (1,050 responses analysed) revealed that DCC was performed in 65% of preterm births and that the existence of guidelines on the timing of cord clamping was associated with two-fold increased odds of practicing DCC for preterm newborns. A survey conducted in the same year on USA Obstetricians (n=137) following the recommendation of the ACOG showed that 73% waited at least 30 seconds before clamping the cord for preterm births and showed that employing strategies to implement the full uptake of this practice could prove vital [5.11].

In the UK, Rabe's 2012 Cochrane Review formed the basis of DCC practice guidelines developed and implemented by regional maternity and neonatal units as part of their contribution to the MatNeoSIP. Delivered through a network of 15 regionally based Patient Safety Collaboratives (PSC), one of the MatNeoSIP primary drivers for change to the maternal and neonatal care is the optimisation and stabilisation of the very preterm infant. In the West and South West England PSC, the delivery model developed and implemented for this primary driver is PERIPrem, a perinatal care bundle to improve the outcomes for premature babies across the 12 maternity units in the region. Launched in May 2020, PERIPrem is formed of ten interventions designed to improve preterm health, one of them being DCC [5.12]. The Operational Clinical Lead for PERIPrem, Dr Sarah Bates [5.13] explained the importance of Rabe's Cochrane Reviews in driving change in maternity units as part of PERIPrem:

'Including the clear findings of Prof Rabe's work on DCC and in particular, its mortality statistics (reduction by a third of preterm death following DCC), in the PERIPrem message has been one of the key drivers for change in the units.'

The maternity units were performing well in nine of the ten PERIPrem interventions (eg steroid and magnesium administrations); however, all of them needed support to improve their rates of DCC for their preterm population. For the majority, their baseline rates in DCC were about 30-40% of babies born at less than 34 weeks. Six months after its launch, the latest data received from Nov 2020, showed that 85% of all babies born before 34 weeks across the region now have their cord clamped following a delay of at least a minute [5.13].

Dr Bates credits this most significant growth area for PERIPrem to Rabe's research-based evidence on the effects of DCC on preterm mortality rates, which was used by Bates and colleagues to influence clinicians' attitude to change [5.13]:

'Prof Rabe's Cochrane Reviews provided the research-based evidence used in DCC training materials to educate teams to be able to overcome barriers to implementation of this practice.'

Rabe's research on DCC was also a pivotal source to Dr Donna Winderbank-Scott, Quality Improvement Lead for the Neonatal Department at the University Hospitals Southampton. The consultant neonatologist used Rabe's work to develop a new clinical guideline for DCC, and educate colleagues about the benefits of DCC on preterm babies [5.14]:

'Southampton has a busy maternity unit (>5,500 births/year) with the Neonatal Unit admitting 15-20 inborn preterm babies per month. [...] in 2016, the Trust had a significant variability in the implementation of DCC in term babies and very little implementation in preterm babies. [...] I developed a new guideline for DCC [...], I used Prof Rabe's 2012 Cochrane Review and her 2016 publication on neurodevelopmental outcomes to convince

the local team of the benefits of DCC to preterm babies, and thus the need for a change to the current working practices. [...] This proved to be invaluable in overcoming resistance to implementation from some clinicians who had not seen the latest research on the topic and who held beliefs or concerns which had been proven to be unsubstantiated.'

Following formal approval of the new clinical guideline on DCC in May 2018, the Unit has seen a steady increase in DCC rates in preterm babies, measured via correct adherence to the guideline raising from 50% in Oct 2018 to 100% in Oct 2019 [5.14]. Since the implementation of the new clinical guideline, informed by Rabe's research-based evidence on the topic, the overall DCC rate in the Unit for preterm babies (<32 weeks) has increased from 35% in 2016 to 48% in 2020 – a relatively high rate for a tertiary centre with a significant proportion of complicated births [5.14]. DCC teaching sessions are now included during induction and on mandatory study days to reach the entire midwifery team and to train junior medical staff within the Trust [5.14].

5. Sources to corroborate the impact

- [5.1a] Cochrane Database of Systematic Reviews 2012, 10.1002/14651858.CD003248.pub3; used in 17 guidelines including sources 5.2, 5.3, and 5.4a. [5.1b] Cochrane Database of Systematic Reviews 2019, 10.1002/14651858.CD003248.pub4; used in 3 guidelines [PDFs available].
- [5.2] WHO Guideline: Delayed umbilical cord clamping for improved maternal and infant health and nutrition outcomes. 2014. [PDF available].
- [5.3] European Consensus Guidelines on the Management of RDS – 2016 Update. Sweet et al. Neonatology, 2017; 111:107-125. 10.1159/000448985 [PDF available].
- [5.4a] NICE 2015 Guideline on Preterm Labour and Birth NG25 [PDF available].
- [5.4b] NICE 2015 NG25 Evidence Tables (Appendix H) [PDF available]
- [5.5] WHO recommendations: intrapartum care for a positive childbirth experience. 2018 (see p160, Recommendation 44) [PDF available].
- [5.6] WHO Optimal timing of cord clamping for the prevention of iron deficiency anaemia in infants (last updated Sept 2019) [PDF available].
- [5.7a] American College of Obstetricians and Gynecologists (ACOG) endorsement statement Dec 2016 [PDF available].
- [5.7b] Statement from Adj. Professor of Pediatrics at the School of Medicine Uniformed Services University USA, confirming the importance of Rabe's Cochrane Review 2012 in shaping the 2016 ACOG/AAP guidelines, and changing clinical practices in the USA. [PDF available]
- [5.7c] Committee Opinion No. 684: Delayed Umbilical Cord Clamping After Birth. Obstet Gynecol. 2017 Jan. 10.1097/AOG.0000000000001860 [PDF available].
- [5.8] BAPM Optimal Cord Management Toolkit (Dec 2020) [PDF available].
- [5.9] MatNeoSIP Driver Diagram and Change Package - Optimisation and stabilisation of the very preterm infant [PDF available].
- [5.10] Mayri Sagady Leslie and Debra Erickson-Owens. J. Midwifery and Women's Health. 2020; 10.1111/jmwh.13071 [PDF available]. Survey reporting the umbilical cord clamping practice of the members of the American College of Nurse-Midwives.
- [5.11] Mayri Sagady Leslie et al. J. Neonatal Perinatal Medicine 2018; 10.3233/NPM-181729 [PDF available]. Survey reporting the umbilical cord clamping practice of the members of the American College of Obstetricians and Gynecologists.
- [5.12] PERIPrem DCC Bundle, West of England AHSN [PDF available].
- [5.13] Statement from PERIPrem Operational Clinical Lead confirming the importance of Rabe's Cochrane Review, and the DCC recommendation as key intervention for very preterm infants care at birth in the West and South West of England. [PDF available]
- [5.14] Statement from the Quality Improvement Lead for the Neonatal Department at University Hospitals Southampton reporting the successful implementation of the DCC practice at the maternity unit. This quality improvement project was mainly based on Rabe's Cochrane Review on DCC. [PDF available]