Improving quality of care and outcome at very preterm birth: the Preterm Birth research programme, including the Cord pilot RCT

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Scientific summary

The Preterm Birth research programme

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Scientific summary

Background

Preterm birth has major impact on survival and quality of life, psychosocial and emotional stress for the family, and costs for health services and society. Mortality and morbidity are highest for infants born very preterm, before 32 weeks' gestation, and impairment may persist into early adulthood. This programme focused on care in the delivery room at very preterm birth.

Aims

Our aims were to improve the quality of immediate care at preterm birth, enhance family-centred care, and improve outcome for babies born very preterm and their families.

Methods

Our range of methods were delivered through five interconnected work packages.

- Work package 1: James Lind Alliance Priority Setting Partnership between service users and health-care professionals to identify and prioritise the top research questions in preterm birth –
  - with an ethnographic analysis of partnership working.
- Work package 2: two systematic reviews –
  - umbrella review to identify effective interventions in the delivery room for babies born very preterm
  - framework synthesis addressing ethics issues in recruiting preterm or sick babies to clinical trials.
- Work package 3: strategies for providing initial neonatal care beside the mother at preterm birth, with umbilical cord intact –
  - survey of neonatal care
  - qualitative interviews with parents: (1) comparative review of tools to assess experiences of care at birth; and (2) developing a new questionnaire for use after very preterm birth
  - measuring umbilical cord flow before cord clamping
  - developing and evaluating a mobile trolley to support neonatal care at birth beside the mother, with cord intact: (1) service evaluation; and (2) qualitative interviews with parents and clinicians
- Work package 4: pilot randomised controlled trial evaluating timing of cord clamping, including –
  - qualitative interviews with women and clinicians about consent
  - 1-year follow-up of women
  - 2-year follow-up of children (corrected for gestation).
- Work package 5: protocol for an individual participant data meta-analysis.

Results

Work package 1

We identified and distributed for public voting 104 unanswered research questions. The 30 most popular were ranked at a workshop. The top 15 were:

1. Which interventions are most effective to predict or prevent preterm birth?
2. How can infection in preterm babies be better prevented?
3. How best to prevent necrotising enterocolitis in premature babies?
4. What is the best treatment for lung damage in premature babies?
5. What should be included in packages of care to support families when a premature baby is discharged from hospital?
6. What is the optimum milk-feeding guidance for premature babies?
7. What is the best way to judge whether a premature baby is feeling pain?
8. Which treatments are best to prevent early-onset pre-eclampsia?
9. What emotional and practical support improves outcomes for premature babies and their families?
10. Which treatments are most effective for preterm premature rupture of membranes?
11. When is the best time to clamp the umbilical cord in preterm birth?
12. What support is most effective at improving breastfeeding for premature babies?
13. How best to treat necrotising enterocolitis in premature babies?
14. Does specialist antenatal care for women at risk of preterm birth improve outcomes?
15. What are the best ways to optimise the environment (such as light and noise) to improve outcomes?

Future prioritisations should endeavour to anticipate potentially differing perspectives, mitigate any imbalance where possible, and report voting by 'service users' and health-care professionals separately.

Work package 2

Our systematic review (umbrella review) identified 18 Cochrane reviews covering four topics:

1. *Delivery room interventions for airway management, respiratory or circulatory support (four reviews).* Two reviews found no eligible trials and one included one small trial. The fourth concluded that there is no evidence that routine endotracheal intubation reduces mortality or morbidity in vigorous term babies with meconium staining, compared with standard resuscitation.
2. *Surfactant replacement therapy for preterm infants with or at risk of respiratory distress syndrome (eight reviews).* The strongest evidence supported type and timing of surfactant administration: for very preterm infants surfactant reduced the risk of death by about 40%, and natural surfactant was more effective than synthetic. Early surfactant administration with brief ventilation reduced mechanical ventilation, but delivery room administration was no better than delayed selective administration. Uncertainty remains about the comparative effects of newer synthetic surfactants, and novel non-invasive administrations.
3. *Supplemental oxygen or other drugs for infants compromised at birth (five reviews).* There was insufficient evidence for reliable recommendations about using air or 100% oxygen for newborn resuscitation, about using adrenaline or sodium bicarbonate, and about using naloxone for infants exposed in utero to opiates. Various measures for keeping newborn very preterm infants warm reduced the risk of hypothermia, but effects on morbidity and mortality remain unclear.
4. *Strategies for influencing placental transfusion (one review).* Deferring cord clamping for between 30 and 120 seconds, rather than clamping before 30 seconds, possibly reduced blood transfusions and intraventricular haemorrhage. Effects on death and long-term neurodevelopment remained unclear.

Our framework synthesis addressing ethics issues in recruitment identified two types of study:

1. *Empirical (49 studies).* Revealed themes about parents' attitudes, clinicians' attitudes, validity of consent, different consent processes and miscellaneous topics. Empirical research confirmed that there are difficulties for some parents giving valid consent.

2. *Analytical (30 studies).* Revealed themes about the ethical basis of parental informed consent for neonatal research, parental consent validity, other options for seeking consent, risk and the double standard between consent for treatment versus research.

There was agreement that it is important for parents give or decline consent for neonatal trial participation. However, none of the existing consent processes reviewed was satisfactory. Clinicians have concerns that research participation is dropping because of problems with consent, and they may face ethical difficulties in discharging conflicting duties to research, neonates and parents.

We identified three important gaps:

1. evaluation of a process for obtaining emergency consent in perinatal research
2. studies on trials where both the mother and the fetus or neonate are participants
3. studies that report the views of bereaved parents on the consent process.

We developed a two-stage oral assent consent pathway and included this in our pilot trial (work package 4), which addressed the first two research gaps. The third research gap has been addressed elsewhere.

Work package 3

Our survey showed variation in delivery room practice for infants born very preterm. In tertiary units, the care provided was more consistent with current international guidance than in non-tertiary units. There was variation in how policies for cord clamping at very preterm birth were implemented, both between and within units. No unit provided neonatal care with cord intact, and staff were anxious about this practice. Implementation of deferred cord clamping seemed more successful if there was strong local interdisciplinary support, with agreement on a single technique and the eligibility criteria. Clinical leadership and training in the practical techniques also appeared helpful.

Parents' views and experiences of very preterm birth

Almost half of the parents interviewed described difficulty remembering aspects of the birth. The anticipation before seeing and touching their baby for the first time was characterised by contrasting and rapidly changing emotions. Parents who talked about touching and holding their baby described immediate bonding. Visiting the neonatal unit was initially overpowering, especially for those who had not been before or were seeing their baby for the first time. Parents referred to the awkwardness and exclusion felt by fathers.

Overall parents' experiences of care were positive. We identified four determinants of parents' experience: staff professionalism, staff empathy, involvement of the father, and the birth environment. These are consistent with research on term births. Two factors unique to very preterm birth were the importance of staff appearing calm and staff taking control during the birth. Two areas where parents felt that care could have been improved were staff not believing the women, or appearing not to listen to them, and fathers not being involved.

Our comparative review of measures of parents' satisfaction with care during childbirth identified nine questionnaires, none of which evaluated care at very preterm birth. Therefore, we developed a questionnaire to measure this. There were 17 items, with subscales on 'staff professionalism and empathy', 'information and explanations', 'confidence in staff' and 'involvement of the partner'. The total scores may be useful to compare satisfaction across hospitals, whereas individual aspects of care can be evaluated using the subscales. We used this questionnaire in our pilot trial. Further research should explore whether or not there is variation in experiences for parents from different backgrounds and in different settings.

Neonatal care at birth beside the mother

We developed a small trolley to support newborn resuscitation at birth beside the mother, marketed as LifeStart™ (Inditherm Medical, Rotherham, UK), and conducted a service evaluation within a busy tertiary hospital. Common delivery room resuscitation procedures were performed successfully on the trolley,

including with cord intact. Compared with conventional resuscitation equipment, for most aspects of care clinicians rated the trolley as 'the same', 'better' or 'much better'. Reported problems included difficulty in getting close to the operating table at caesareans and trip hazard from gas hoses.

When interviewed, parents said that they liked having their baby close and they felt reassured knowing what was going on. Some felt that their watching helped staff communicate with them. Others said that they would have liked more explanation. No parent whose baby received intensive intervention, such as intubation and cardiac massage, expressed regrets about watching.

Clinicians interviewed were also largely positive about care beside the mother, and felt that allowing parents to see and touch their baby at birth was especially important if the baby was subsequently admitted to the neonatal unit. They reported positive comments from parents about being close to their baby, and none mentioned negative comments. Most clinicians had no reservations about parents watching them, but some thought that staff with less experience might feel insecure. Practical challenges at caesarean sections were that parents were sometimes unable to see their baby, scrubbing for the sterile field took time and the trolley controls were under sterile drapes.

We also showed that neonatal care can be provided beside the mother using standard resuscitation equipment. This has advantages of being already available and staff being familiar with its use. Further research should assess experiences in other hospitals, using a trolley or standard equipment, and including parents from more diverse backgrounds and babies requiring advanced resuscitation.

Work package 4

This pilot trial assessed the feasibility of conducting a large UK multicentre randomised controlled trial comparing deferred cord clamping (after at least 2 minutes) and immediate neonatal care with the cord intact, with immediate clamping (within 20 seconds) and immediate neonatal care after cord clamping for very preterm births. Initially, recruitment was for 1 year but, as feasibility was demonstrated, the study continued while funding for the main trial was sought, but it closed when the application was unsuccessful.

Recruitment was above target, largely because of the two-stage consent pathway that allowed women to be offered participation when birth was imminent. Overall, 261 women were randomised and gave birth to 276 babies. Randomisation was across the range of gestation. Compliance with the allocated interventions was good. Fewer babies allocated to cord clamping after at least 2 minutes died than those allocated to cord clamping within 20 seconds, but the difference was not statistically significant. Three-quarters of deaths were in infants born before 28 weeks' gestation. For live births, there was no clear difference in intraventricular haemorrhage, or other outcomes at discharge for baby or mother.

Women's experiences of the two consent pathways were similar. Those recruited following oral assent reported having less information about the trial, but felt that it was sufficient to make their decision. Irrespective of the consent pathway, there were gaps in women's understanding. Clinicians were supportive of the two-stage consent pathway in time-critical situations and thought that providing information on a 'need-to-know' basis was an advantage over the usual process. They emphasised the importance of a team approach to inviting participation, regardless of the consent pathway. In the questionnaires at 1 year, women were largely positive about the trial. Suggestions about what could have been improved included being approached earlier in labour and better communication about the study from staff.

At the age of 2 years (corrected for gestation at birth), we found no clear difference in the composite of death or adverse neurodevelopment between the allocated groups after adjusting for missing data using multiple imputation.

Work package 5

A key challenge here was unpredictability of the time scale for analysis. The number of new trials has increased (29 registered in the past 2 years) but many are small and had begun data analysis before being

contacted. Therefore, we expanded the protocol to include a retrospective individual participant data meta-analysis. Currently, we know of 53 trials involving 11,811 infants (3020 for long-term outcomes). This meta-analysis will inform future trial design.

Conclusions

Central to the success of the programme was service user representatives being equal partners throughout. Parent experiences were heard and explored throughout. This allowed us to tackle emotive issues at very preterm birth, such as neonatal care in the delivery room and seeking consent for participation in an intrapartum trial.

Our work on neonatal care beside the mother brings family-centred care to the delivery room and has major implications for maternity services. Although this is a relatively simple change in practice, it requires a change in culture to multidisciplinary teamworking. Both parents and clinicians felt that this improved communication. The trolley was important in providing 'proof of concept' for care beside the mother, but existing equipment can be used. Hospitals can use the questionnaire we developed on parents' experiences.

Limitations of our work include participants in the prioritisation process not being representative of those most affected by preterm birth, the small sample for the qualitative interviews about preterm birth, evaluation of neonatal care beside the mother being conducted at a single hospital, and the randomised trial being a pilot.

Key implications for future research for funders and researchers:

- Consider the top 30 research priorities, ranked by those affected by preterm birth and by health-care professionals.
- Improve understanding of parent experiences at preterm birth through further research involving parents (including fathers) from a wider range of backgrounds and settings.
- Evaluate neonatal care beside the mother in a wider range of settings, using standard equipment or the mobile trolley (e.g. in a multicentre randomised controlled trial).
- Evaluation of interventions around the time of preterm birth in large multicentre NHS trials is feasible and should be considered.
- The two-stage consent pathway should be included in future intrapartum clinical research trials, and merits evaluation in other emergency or time-critical trials.
- Design of future clinical research trials comparing alternative policies for cord clamping should take account of results from our trial and the planned individual participant data meta-analysis.

Study registration

The study is registered as PROSPERO CRD42012003038 and CRD42013004405. The Cord pilot trial is registered as ISRCTN21456601.

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