Abstract

Objectives

To assess feasibility of a large trial comparing alternatives policies for umbilical cord clamping and immediate neonatal care for very preterm births, based on recruitment for one year.

Methods

Women were eligible if expected to have a livebirth before 32 weeks at eight tertiary maternity units. Recruitment was available via two consent pathways. Randomisation (1:1), using sealed opaque numbered envelopes, was to either cord clamping after at least two minutes and immediate neonatal care with cord intact, or clamping within 20 seconds and neonatal care after clamping. Feasibility outcomes were measures of recruitment, compliance, acceptability and retention.

Results

Overall, 125 women were randomised over one year; with 22% (121/550) of births before 32 weeks randomised, of whom one third were before 28 weeks (39/121). Over a quarter of recruitment (29%, 36/125) was via the two-stage consent pathway. Compliance with the allocated intervention was good, with median time to clamping 120 seconds (IQR 30 to 135 seconds) for the deferred arm and 10 (10 to 15) for the early arm. Neonatal care with cord intact was provided for babies using both the mobile trolley (n=32), and the usual equipment (n=35).

Conclusions

A large multicentre trial comparing cord clamping after at least 2 minutes and immediate neonatal care, if needed, with cord intact versus clamping within 20 seconds and neonatal care after clamping is feasible in the UK.

Introduction

We conducted a pilot randomised trial to assess the feasibility of conducting a large multicentre randomised trial in the UK comparing alternative policies for timing of cord clamping and immediate neonatal care at birth. Having demonstrated feasibility recruitment continued beyond the planned one year.[1] This paper presents the assessment of feasibility based on the first twelve months of recruitment.

Methods

This was a pragmatic multicentre pilot randomised trial comparing alternative policies for cord clamping at very preterm birth. Recruitment was at eight UK tertiary maternity units, five of which (in Nottingham, Leicester, Bradford and Liverpool) had contributed to development work, and therefore were not necessarily typical of all UK sites. To ensure an adequate assessment of feasibility, we included three sites (in Wolverhampton, London and Aberdeen) with no previous involvement.

Ethics approval was by Nottingham REC 2(NRES reference 12/EM/0283). The sponsor is Nottingham University Hospitals NHS Trust. Coordination was by the Nottingham Clinical Trials Unit (NCTU). The protocol[2] and an update[3] are published and summarised here.

Participants

Women were eligible if they were expected to have a livebirth before 32 weeks gestation, regardless of mode of birth or whether cephalic or breech presentation. Exclusion criteria were monochorionic twins (from an ultrasound scan) or clinical evidence of twin-twin transfusion syndrome; triplets or higher order multiple pregnancy; and known congenital malformation.

Interventions

We compared umbilical cord clamping after at least two minutes and immediate neonatal stabilisation and resuscitation, if needed, with the cord intact with usual care of clamping within 20 seconds and neonatal care after clamping. For the intervention group, babies were placed with the cord intact onto a firm surface with easy access to resuscitation equipment, either the usual equipment moved alongside the woman's bed[4] or a mobile trolley designed for this purpose.[5] At caesarean births the neonatal resuscitation equipment was covered with sterile drapes, and the neonatologist scrubbed and gowned. After cord clamping, neonatal

care continued either beside the mother or at the usual location (the side of the room or an adjacent room), at the discretion of the local clinicians. Until cord clamping, the baby was kept at the level of placenta (introitus or mothers' abdomen or, if a caesarean birth, the anterior thigh).

For the control group, babies were dried and/or wrapped at birth with all other neonatal care after cord clamping. For both groups other aspects of care, including administration of a prophylactic uterotonic drug, were at the discretion of the attending clinicians. Neonatal care was based on local unit policy and consistent with Resuscitation Council (UK) newborn life support guidelines.[6,7] Standard equipment was used according to local practice.

Outcome measures

Feasibility outcome measures were to:

- Estimate the number of potential recruits in each centre
- Measure the recruitment rate
- Describe reasons for non-recruitment
- Measure the spectrum of gestational age and neonatal outcome among recruits
- Measure compliance with the trial interventions and describe factors in non-compliance
- Measure the completeness of data collection for main outcomes
- Record views of parents on randomisation and treatment procedures
- Measure loss to follow-up after discharge from hospital.

Data collection included clinical outcomes for the women and babies.[1] For example, for the baby death before discharge; intraventricular haemorrhage; periventricular leukomalacia; hypothermia; blood transfusion; other measures of serious neonatal morbidity; and neurosensory outcome at age 2 years (corrected for gestation at birth). For the woman, complications of the third stage of labour; wellbeing and satisfaction with care at birth; and their about participation in the trial.

Initially, we collected data on intraventricular haemorrhage (IVH) and other brain injury using the case report form completed at site. However, as we planned that IVH would be a primary outcome for the full trial, we adjudicated cranial ultrasound scan images and

compared these with the scan reports, to assess whether this would be necessary for a large trial.[8] Adjudication was for all babies in the trial, not just those recruited during the first year, and is reported in detail elsewhere.[9]

Recruitment and consent pathways

Information about the study was available in the antenatal clinics and on antenatal wards. Women at risk of very preterm birth were invited to participate. They had the opportunity to ask questions, and whenever possible had at least 12 hours to consider participation. Those who agreed to participate gave written informed consent.

As very preterm birth can be rapid and unexpected, there may be insufficient time for the usual consent pathway. Therefore, we developed a two-stage oral assent consent pathway, in discussion with the National Childbirth Trust (NCT) and Bliss, the special care baby charity. This complies with recommendations from the Royal College of Obstetricians and Gynaecologists.[10] If birth was imminent and the attending clinician considered it appropriate, we offered women a brief explanation of the study and invited participation. Those who said 'yes' (i.e. gave oral assent) were randomised.

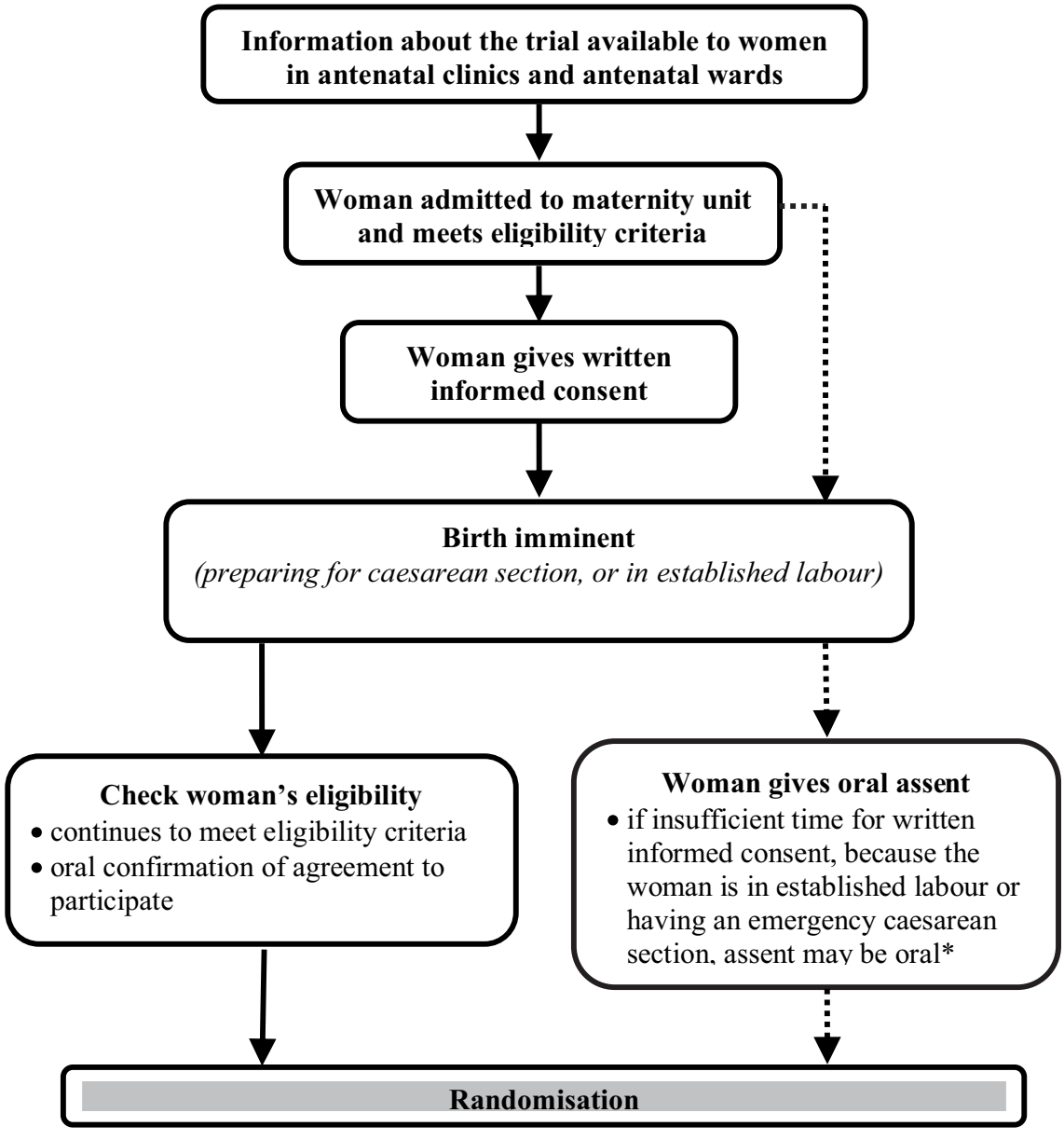
Randomisation

Randomisation was by attending clinicians, who took the next sealed consecutively numbered opaque envelope from a ringbinder folder. Each maternity unit kept a central log of envelopes. Sequence generation (1:1) was by computer, stratified by site with balanced blocks of randomly varying size, created by NCTU. On the envelope was a reminder to check eligibility criteria, and a label to record the date, time, woman's initials, her date of birth and gestation. Once this label was completed, she was considered randomised, even if the envelope was not opened. Inside the envelope was a yellow card instructing when to clamp the cord, and a 'Birth Record' (plus a second for twins) for clinical staff to record information about the third stage of labour and neonatal care at birth. Used envelopes and yellow cards were placed in a locked mailbox, which was emptied regularly and details from each envelope entered into the online randomisation log.

Sample size

For the assessment of feasibility it was planned that eight large maternity hospitals would recruit for one year. Based on a total of 43,600 livebirths per year at these eight hospitals (average annual livebirths per unit 5-6,000) we expected 610 (1.4%)[11] livebirths to be before 32 weeks gestation. Target accrual was 16% to 18% of eligible births so we anticipated 100 to 110 women randomised in one year. As this was planned as a pilot trial there was no formal power calculation.

Figure 1: The two consent pathways



** Women approached to give oral assent in established labour or at emergency caesarean section only if the attending clinicians considered it appropriate Women were not approached if there was insufficient time to give a brief verbal summary of the trial, or they did not speak fluent English and no translator was available. How long was required for oral assent depended on factors such as how much the woman already knew about the study, and her knowledge and wishes about care during the third stage.*

If recruitment was after oral assent:

- *women were approached before discharge to give written consent to participation in follow up*
- *Chief Investigator notified within 15 days, and monitoring by Trial Steering Committee*

Site training and initiation

To prepare for the trial launch, we held a collaborators' meeting with representatives from each site. Key challenges addressed during the meeting were training in deferring cord clamping and neonatal care with the cord intact, and in the two consent pathways. Short film clips of simulations supported training in deferred cord clamping and neonatal care with cord intact. Roleplaying various scenarios for recruitment, with two actresses playing the women, supported training in the consent pathways.

As success of the trial depended on engagement by clinicians, the chief investigator or another clinician (obstetrician or neonatologist) accompanied the trial manager (or senior trial manager) on site initiation visits. These included training in the protocol and trial procedures, and a walk through of the participant pathway including the antenatal clinic and wards, labour suite, obstetric operating theatres, and neonatal unit. This was helpful for integrating the trial into local processes, and for raising its profile. Before opening to recruitment, sites were encouraged to agree how they would deliver neonatal care with cord intact for vaginal and caesarean births. We suggested training staff using simulation and/or at low risk births. To support training we provided film clips of the recruitment scenarios from the collaborators meeting, and of simulations for neonatal care with cord intact (both usual equipment and the trolley).

As randomisation was by the clinical staff, the local investigator and research nurse provided regular study specific training to relevant staff. We encouraged sharing of experiences between sites by newsletters, site visits and collaborators meetings.

Statistical analysis

Continuous data were summarised as mean with standard deviation and/or median with lower and upper quartiles. Categorical data were summarised as frequency counts and percentages. We excluded women (and their babies) randomised who gave birth after 35^{+6} weeks, as outcomes for these babies are different from those born very preterm. For each site, the number of births before 32 weeks, the number of women approached, consenting and randomised were described, along with reasons why women did not give consent or were not randomised if they had given consent. Baseline characteristics were described, along with compliance with the allocated intervention and reasons for non-compliance. For IVH we derived the worst grade for each baby. As this was a feasibility study, no analysis of outcome

by allocated group was planned. Analyses were conducted in Stata v13.1. No formal interim analysis was planned. An independent Data Monitoring Committee Data monitored data in confidence.

Results

Recruitment opened in March 2013, and for the feasibility assessment ended after 12 months (on 28th February 2014). Four sites randomised women within a month of opening to recruitment, two within two months, one within 4 months, and one 5 months. The sites not involved in the development work took longer to recruit their first participant. Issues contributing to delays included: concerns about having the neonatal equipment close to the sterile field at caesarean section (which led to one site largely recruiting vaginal births); research staff having limited time as they were running multiple studies; difficulties in building the necessary agreement between the neonatologists and obstetricians; and engagement of the local investigator.

We randomised 125 women, four of whom gave birth after 32 weeks gestation. This was 22% of women who gave birth before 32 weeks gestation, varying from 43% to 9% between sites. Factors in this variation were whether women having a caesarean birth were offered participation, availability of the trolley in the two sites using this equipment, and availability of clinical staff trained in the trial. Four hundred and thirty four women were approached: of whom 389 were offered usual consent and 45 the two-stage oral assent consent pathway (table 1). For those offered the usual consent pathway, almost half (184/389, 47%) gave consent, of whom almost half (89, 48%) were randomised. For women offered oral assent, most (38/45, 84%) gave assent, of whom almost all (36, 95%) were randomised. Thirty five women were randomised following oral assent only, as one woman gave written consent before randomisation. Of the women offered participation who did not give consent, almost half (101/212, 48%) declined, and a quarter (53/212, 25%) were discharged home (figure 2). For the women who gave consent but were not randomised, the main reason was pregnancy continuing beyond 32 weeks (63/97, 65%).

Table 1: Consent and randomisation for women offered participation, by site

(i) usual written consent pathway

	Offered participation	Consent n (%)	Consent & randomised n (%)
Site 1	65	28 (43%)	10 (36%)
Site 2	58	37 (64%)	18 (49%)
Site 3	63	31 (49%)	12 (39%)
Site 4	66	21 (32%)	11 (52%)
Site 5	21	11 (52%)	6 (55%)
Site 6	92	42 (46%)	24 (57%)
Site 7	12	9 (75%)	4 (44%)
Site 8	12	5 (42%)	4 (80%)
Total	**389**	**184 (47%)**	**89 (48%)**

(ii) two-stage oral assent consent pathway

	Offered oral assent*	Gave oral assent**	Oral assent & randomised	Written consent after randomisation†
Site 1	7	6	6	6
Site 2	6	6	6	5
Site 3	9	5	5	5
Site 4	6	6	6	5
Site 5	2	2	2	2
Site 6	9	9	9	9
Site 7	1	1	1	1
Site 8	5	3	1	1
Total	**45**	**38 (84%)**	**36 (95%)**	**34 (95%)**

* Declined oral assent only recorded from July 2013

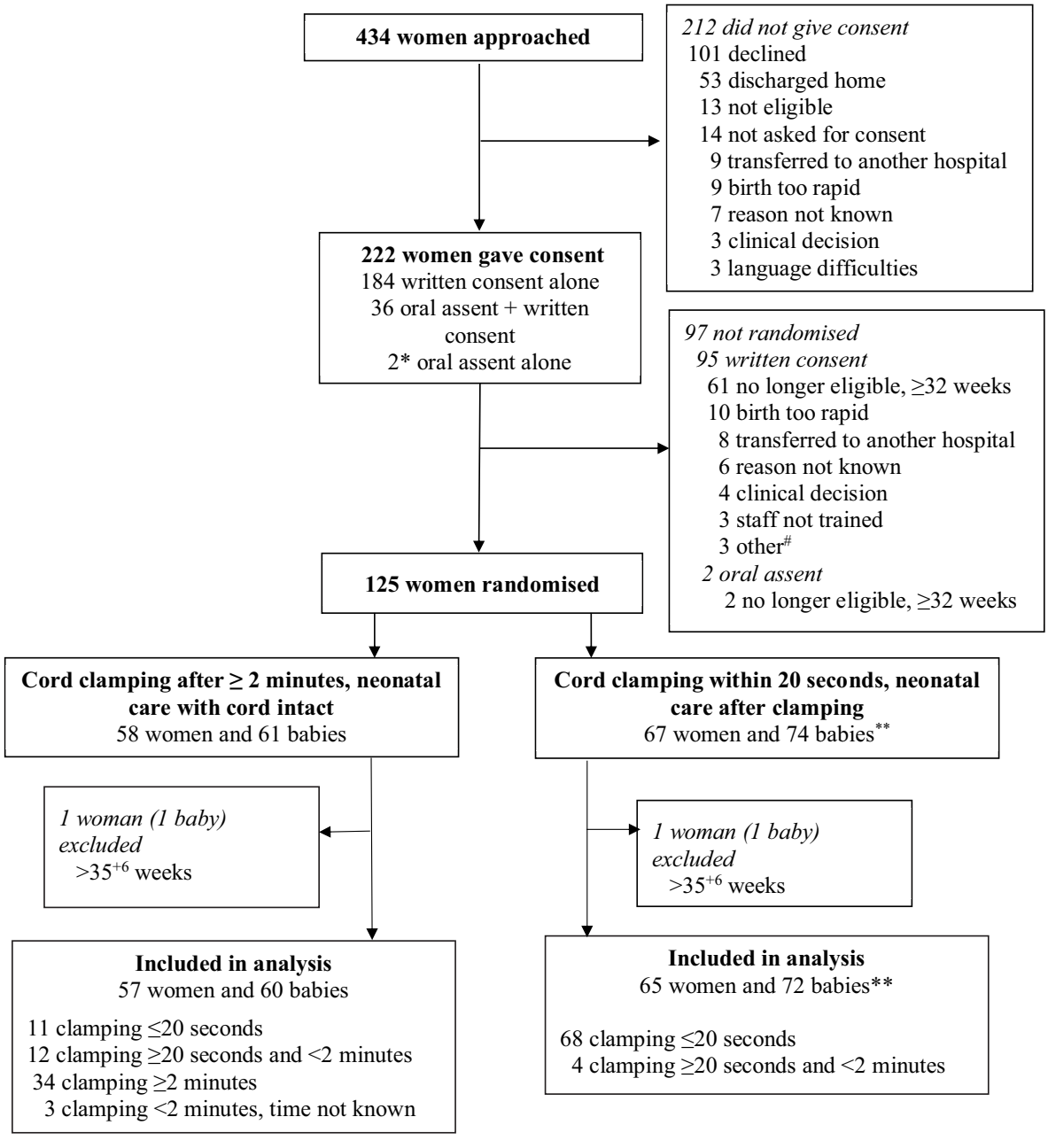
** 1 woman who gave oral assent also gave written consent before randomisation

† for 2 women written consent after randomisation was not obtained, as the baby died before discharge and they did not return for the counselling appointment

The 125 women randomised gave birth to 135 babies (figure 2). Two women randomised before 32 weeks gave birth at 38^{+2} and 39^{+2} weeks respectively, and were excluded from analysis. One woman withdrew the use of her and her baby's data, leaving 122 women and 132 babies for analysis (figure 2). Six sites used their usual resuscitation equipment (75 women randomised) and two the trolley (50 women).

The system of randomisation envelopes was popular at sites, and worked well. The only incorrect use was when a second envelope was taken in error for a second twin; data are presented according to the allocation in the first envelope. Five randomisation envelopes were taken from the folder but not used, reasons: second twin (2 women), birth too quick (1), gestation 35 weeks (1), and woman did not give birth and was discharged home (1).

Figure 2: Consort flow for the feasiblity assessment based on one year of recruitment



* baby died before discharge and written consent was not obtained;
** 1 woman and her baby withdrew, data reported for mortality only;
# intrauterine death (n=1), equipment failure (1), randomised after the end of the feasibility phase (1)

Baseline characteristics

The allocated groups were balanced at trial entry (table 2). Time from randomisation to birth was within half an hour for over a third of women, and within an hour for over half; three quarters of women gave birth within two hours of randomisation and eight gave birth more than one day after randomisation. Recruitment was across the range of gestational age with approximately one third before 28 weeks, one third 28 to 29 weeks, and one third 30 to 31 weeks. One women was randomised in error, at 33 weeks. The earliest gestation at randomisation was 23^{+1} weeks.

Table 2: Baseline characteristics for the women

	Clamp ≥2 minutes + neonatal care with cord intact	**Clamp ≤20 seconds + neonatal care after clamping**
	n= 57 (%)	**n=65 (%)**
Oral assent	19 (33%)	16 (25%)
Time from randomisation to birth		
<30 min	22 (39%)	22 (34%)
≥30 min to <1 hour	12 (21%)	13 (20%)
≥1 hour to <2 hours	8 (14%)	13 (20%)
≥2 hours to <5 hours	5 (9%)	7 (11%)
≥5 hours to <12 hours	3 (5%)	5 (8%)
≥12 hours to <24 hours	2 (4%)	2 (3%)
≥24 hours	5 (9%)	3 (5%)
Gestation at randomisation (weeks)		-
≥32	1 (2%)	
30 to 31^{+6}	19 (33%)	28 (43%)
28 to 29^{+6}	16 (28%)	19 (29%)
26 to 27^{+6}	10 (18%)	11 (17%)
<26	11 (19%)	7 (11%)

		Clamp ≥2 minutes + neonatal care with cord intact n= 57 (%)	Clamp ≤20 seconds + neonatal care after clamping n=65 (%)
Age (years), mean [sd]		30.5 [6.5]	29.4 [6.8]
Primiparous		31 (54%)	41 (63%)
Twin pregnancy		*4 (7%)	7 (11%)
Pregnancy complications			
prelabour rupture of membranes		22 (39%)	26 (40%)
antepartum haemorrhage/placenta previa		5 (9%)	12 (18%)
spontaneous onset of labour		12 (21%)	11 (17%)
chorioamnionitis		6 (11%)	10 (15%)
pre-eclampsia/pregnancy induced hypertension		14 (25%)	10 (15%)
CTG abnormalities/fetal distress		12 (21%)	10 (15%)
fetal growth restriction/small for gestational age		3 (5%)	5 (8%)
other		-	**5 (8%)
In last week received:	magnesium sulphate	28 (49%)	20 (31%)
	corticosteroids	52 (91%)	59 (91%)
Caesarean section		38 (67%)	36 (55%)
	before labour	31	28
	during labour	7	8
Vaginal birth		19 (33%)	29 (45%)
	breech presentation	4	5

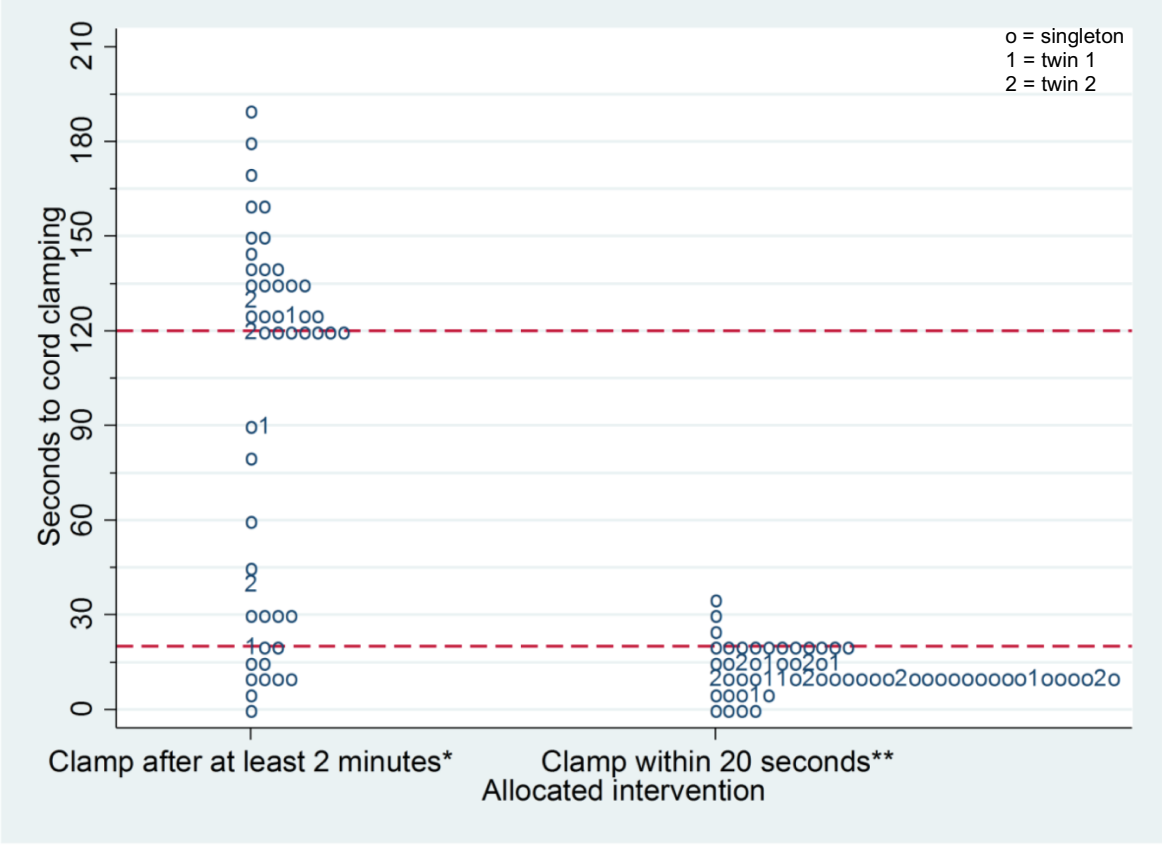
* For one woman, one twin known intrauterine death before randomisation. Data for this baby not included in any tables

**Abdominal pain (n=1), severe asthma (1), pyelonephritis (1), antiphosphate lipid syndrome (1) and not known (1).

Compliance with the allocated intervention

In the intervention group, cord clamping was after at least two minutes for 34 (56%) babies and after 20 seconds for 44 (77%) (Figure 3). Of the 27 babies in this group with cord clamping before two minutes, for 11 (42%) this was due to the cord being too short. For singleton births without a short cord, cord clamping was at two minutes or later for 69%, and after 20 seconds for 78%. Compliance in the control group compliance was high; for 68 babies (94%) cord clamping was within 20 seconds.

Figure 3: Time to cord clamping (seconds) for babies by allocated group



* 60 babies allocated to clamp cord after at least 2 minutes, seconds to cord clamping not known for 8 babies.
** 72 babies allocated to clamp cord within 20 seconds, seconds to cord clamping not known for 8 babies

In the deferred clamping group, there were no obvious differences in time to cord clamping according to equipment for providing immediate neonatal care (usual equipment or trolley), or whether vaginal or caesarean birth. As sites gained experience, compliance with deferred clamping seemed to improve, although numbers are small (data not shown). Three quarters of the babies were positioned level with the placenta. Almost all women (118/122, 97%) received a prophylactic uterotonic drug. Time of administering this, used to derive whether it was before or after cord clamping, was not recorded for 37 women.

Neonatal care was provided beside the mother for 67 babies, of whom 49 (82%) were allocated deferred clamping (table 3) (some were in the immediate clamping group, for whom neonatal care was after cord clamping). The usual resuscitation equipment was used for 35 babies, and the trolley for 32.

Table 3: Care given to the babies at birth, beside the mother and at the roomside

	Beside the mother	**At the roomside**	**Location not known**
baby in plastic bag/sheet	72*	39	-
airway suction	23	54	-
mask ventilation	44	54	1
CPAP	11	22	-
intubation attempted, but unsuccessful	12	22	-
intubation successful	28	55	-
supplemental oxygen	28	48	-
surfactant	22	48	-
cardiac massage	6	4	-
umbilical venous catheterisation	1	5	-

* some allocated to immediate clamping were placed in plastic bag beside mother, but received all other care at roomside

Outcomes at hospital discharge

Fifteen babies (11%) died before discharge; this included three stillbirths born extremely premature for whom resuscitation was attempted (table 4). Two thirds of deaths were of babies born before 26 weeks. One baby born at 30^{+4} weeks died during surgery for an undiagnosed abdominal mass (congenital anomaly).

Table 4: Death before discharge from hospital

		n=133* (%)
Died before discharge		15 (11%)
	stillbirth	3
	day 0-6	5
	day 7-27	6
	≥day 28	1

		n=133* (%)
Gestational age at birth (weeks)	$30^{+0} – 31^{+6}$	1
	$28^{+0} – 29^{+6}$	2
	$26^{+0} – 27^{+6}$	3
	$<26^{+0}$	9

* includes one woman who requested her data be removed from the analysis, data reported for death only

Of liveborn babies, 51 (40%) had an intraventricular haemorrhage of whom this was severe for eight (6%) (Table 5). Only one baby had a temperature below 35°C on admission to the neonatal unit. Almost half the babies had a blood transfusion, which was usually for anaemia.

Table 5: Outcome at discharge from hospital for livebirths

		n=129 (%)
*Brain injury**	any IVH (grade 1-4)	51 (40%)
	severe IVH (grade 3-4)	8 (6%)
	periventricular leukomalacia	9 (7%)
	other**	10 (8%)
Heart rate < 100 at 1 minute		40 (31%)
	not known	2 (2%)
Temperature on admission to neonatal unit (°C) mean [sd]		36.8 [0.7]
	≤36°C	9 (7%)
	<35°C	1 (1%)
Blood transfusion (any)		61 (47%)
	for anaemia	58
	for hypotension	3
	other†	8

		n=129 (%)
Jaundice requiring treatment		117 (91%)
	phototherapy	117
	exchange transfusion	-
Polycythaemia requiring treatment		1 (1%)
	intravenous fluids	1
Chronic lung disease‡		42 (36%)
Ventilation		97 (75%)
	duration (days) median (25th, 75th centile)	3 (1, 10)
Necrotising enterocolitis (≥grade 2)		4 (3%)
	x-ray with perforation or pneumatosis	4
	laparotomy	2
Clinical sepsis		71 (55%)
	positive culture + antibiotics ≥5 days	27
	negative culture + antibiotics ≥5 days	44
Treatment for:	patent ductus arteriosis	18 (14%)
	retinopathy of prematurity ‡††	6 (5%)
Duration of hospital stay (nights)[4] median (25th, 75th centile)		56 (36, 82)
Receiving mother's breast milk at discharge[ף]		67 (57%)

* 124 babies had cranial scan, adjudication results available for 112. For 12 with no scan adjudication, report review/CRF was used: IVH (n=6), severe IVH (2)

** prominent subarachnoid spaces suggestive of atrophy (n=3), ventriculomegaly (2), periventricular echodensities (1), increased echogenicity of deep white matter (1), periventricular cyst (1), mega cysterna (1), porencephalic cysts (1)

† thrombocytopenia (n=2), pulmonary haemorrhage (2) NEC clinically unwell (1), internal bleeding (1), haemorrhage and clotting anomaly (1), and bradycardia (1)

‡ for 118 babies who survived to 36 weeks postmenstrual age

†† information collected at 36 weeks postmenstrual age, discharge or death whichever happened first

ף n=118 alive at discharge

Overall, one in ten women had blood loss of 1,000ml or more, and five in ten of 500 ml or more (table 6). A quarter had postpartum infection requiring parenteral antibiotics. Most women whose babies were alive when they were discharged were breastfeeding at discharge.

Table 6: Outcome at discharge from hospital for the women

		n=122 (%)
Postpartum haemorrhage	≥500 ml	58 (48%)
	≥1000 ml	12 (10%)
Blood transfusion		4 (3%)
For vaginal births (n=48)	manual removal of placenta	2 (4%)
	length of third stage >30 minutes	1 (2%)
Postpartum infection treated with parenteral antibiotics		28 (23%)
	pyrexia >38°C	5
Duration of hospital stay (nights) median (IQR)		4 (2, 6)
Expressing breast milk/breast feeding at discharge*		106 (91%)

IQR = interquartile range
* for 117 women whose babies were alive at the time of their discharge

Overall assessment of feasibility objectives

The independent Trial Steering Group (TSC) assessed progress against the feasibility objectives and recommended progression to the full trial (table 7). They felt assessment of the feasibility of long-term follow up was not necessary at this point, as this should be comparable to other similar trials. They advised that recruitment in the pilot sites continue whilst seeking funding, in order to maximise efficiency and value for money. Progression was "strongly supported" by the DMC.

Table 7: Feasibility assessment based on one year of recruitment

Feasibility objective	Outcome
Recruit 100-110 women at 8 sites over 12 months	• Recruitment opened on schedule • 125 women randomised across 8 sites • 51% women approached gave consent (222/434) • 56% women with consent randomised (125/222)
Recruit 16%-18% of women with livebirth <32 weeks gestation	• 22% (121/550) births <32 weeks randomised • 4 women recruited gave birth >32 weeks
Describe main reasons for non-recruitment	• 23% approached declined participation (101/434), 12% discharged home (53/434) • 97 with consent not randomised, reasons: 65% progressed >32 weeks (63/97), 8% transferred or discharged (8/97), 10% birth too rapid (10/97), and 4% a clinical decision (4/97)
Generalisable spectrum of gestational age, and outcome	• 32% recruited <28 weeks (39/122) • 15% recruited <26 weeks (18/122) • 11% perinatal mortality
Compliance with trial interventions	• Good compliance, endorsed by DMC • Median time (seconds) to clamping 120 (IQR 30, 135) deferred arm vs 10 (10, 15) early arm • Neonatal care provided with cord intact, so same care in both groups
Describe reasons for non-compliance	• Deferred clamping: cord too short (11/60), clinical decision (7/60), staff error (2/60) • Early clamping: staff error (2/72), baby born membranes intact (1/72), natural sequence of events (1/72)
Assess feasibility of oral assent consent pathway	• Offered to 45 women, 84% (38/45) accepted • 2 not randomised, progressed >32 weeks • 36 randomised: 34 gave written consent. 2 not offered written consent, as baby died and they did not return for bereavement counselling appointment

Feasibility objective	Outcome
Assess acceptability of oral assent consent	• No issues reported in follow up questionnaires • Qualitative interviews with women and clinicians largely positive
Completeness of data collection for main outcomes	• 100% for death before discharge • 96% for IVH (124/129 livebirths with cranial ultrasound)
Women's view of participation	• 75% (91/122) response to questionnaire at 6-8 weeks • 94% (81/86 who completed this section) answered 'probably yes' or 'definitely yes' to *'if time suddenly went backwards, and you had to do it all over again, would you agree to participate in the Cord pilot trial'*

IQR=interquartile range

Discussion

The Cord pilot trial demonstrated feasibility of a large multicentre UK trial comparing deferred cord clamping and neonatal care, if needed, with the cord intact versus usual care. Nevertheless, we were unsuccessful in our attempt to transform this successful external pilot trial into an internal pilot, by continuing into the full trial.[12]

The trial was multicentre and conducted within existing clinical services, so widely generalizable to similar settings. Randomisation close to the time of birth was feasible, with over half the women giving birth within one hour of randomisation. We achieved good compliance with the allocated intervention. As this is a complex multidisciplinary intervention, maintaining compliance required regular training for clinical staff at sites, particularly following staff changes and rotations. We anticipate compliance would improve in a larger trial as, with sufficient units participating, a growing pool of trainees and other staff would have experience of deferring cord clamping and providing neonatal care with the cord intact. In addition, the cord being too short, a key reason for clamping before two minutes in the intervention arm, becomes less of a problem with more experience.

Mortality was 11.3% (15/133. As three babies were stillborn, livebirth mortality was 9.2% (12/130), comparable with UK data for 2012[13] and suggesting a generalizable spectrum of babies was recruited. Our two-stage consent pathway allowed recruitment of women for whom birth was imminent and was largely supported by parents and clinicians.[14,15] Resuscitation with the cord intact allowed us to recruit babies requiring resuscitation at birth. These two strategies mean high-risk women and infants were randomised.

Our independent adjudication of cranial ultrasound scans shows improved reliability of the diagnosis of IVH,[8] suggesting that for trials where IVH is a main outcome criteria for diagnosis should be standardised and adjudication considered.

A practical problem was that babies were sometimes transferred to another hospital not participating in the trial. Although we were able to adapt our trial procedures to allow data collection for these babies, this was time consuming. For a large trial with many sites this would be a less common problem.

In conclusion, this pilot trial demonstrates that a large multicentre trial in the UK would be feasible. The two-stage consent pathway merits further evaluation, although our data support its use in future trials of cord clamping at preterm birth. Similarly, our data support provision of neonatal care beside the mother, although further evaluation of neonatal care with cord intact is required.

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