

Effects of delayed versus immediate umbilical cord clamping in reducing death or major disability at 2 years corrected age among very preterm infants (APTS): a multicentre, randomised clinical trial



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Summary

Background Very preterm infants are at increased risk of adverse outcomes in early childhood. We assessed whether delayed clamping of the umbilical cord reduces mortality or major disability at 2 years in the APTS Childhood Follow Up Study.

Methods In this long-term follow-up analysis of the multicentre, randomised APTS trial in 25 centres in seven countries, infants (<30 weeks gestation) were randomly assigned before birth (1:1) to have clinicians aim to delay clamping for 60 s or more or clamp within 10 s of birth, both without cord milking. The primary outcome was death or major disability (cerebral palsy, severe visual loss, deafness requiring a hearing aid or cochlear implants, major language or speech problems, or cognitive delay) at 2 years corrected age, analysed in the intention-to-treat population. This trial is registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12610000633088).

Findings Between Oct 21, 2009, and Jan 6, 2017, consent was obtained for follow-up for 1531 infants, of whom 767 were randomly assigned to delayed clamping and 764 to immediate clamping. 384 (25%) of 1531 infants were multiple births, 862 (56%) infants were male, and 505 (33%) were born before 27 weeks gestation. 564 (74%) of 767 infants assigned to delayed clamping and 726 (96%) of 764 infants assigned to immediate clamping received treatment that fully adhered to the protocol. Death or major disability was determined in 1419 (93%) infants and occurred in 204 (29%) of 709 infants who were assigned to delayed clamping versus 240 (34%) of 710 assigned to immediate clamping, (relative risk [RR]) 0·83, 95% CI 0·72–0·95; $p=0\cdot010$). 60 (8%) of 725 infants in the delayed clamping group and 81 (11%) of 720 infants in the immediate clamping group died by 2 years of age (RR 0·70, 95% CI 0·52–0·95); among those who survived, major disability at 2 years occurred in 23% (144/627) versus 26% (159/603) of infants, respectively (RR 0·88, 0·74–1·04).

Interpretation Clamping the umbilical cord at least 60 s after birth reduced the risk of death or major disability at 2 years by 17%, reflecting a 30% reduction in relative mortality with no difference in major disability.

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Introduction

Worldwide, about 1 million babies are born before 30 weeks gestation annually. In high-income countries, about 25% die or face increased risks of impairment and disability in childhood; the burden of mortality and impairment is greater in low-income and middle-income countries.^{1–3} Global child mortality declined by almost 50% between 2000 and 2019, but progress is slower in neonates, and 65 (32%) of 204 countries, mostly in sub-Saharan Africa and south Asia, are not on track to meet Sustainable Development Goal targets by 2030.⁴ Focused improvements in perinatal and newborn care could substantially improve under-5 mortality rates. Given the effects of the COVID-19 pandemic, considerable effort will be required to maintain progress.⁴ Delaying clamping of the umbilical cord in very preterm infants is a simple,

universally affordable procedure that might improve in-hospital mortality rates^{5–7} and neurodevelopment in early childhood,⁸ but more evidence is needed. Recommended durations of delayed clamping vary from between 30–60 s to 3 min.^{6,9–12}

We have previously reported hospital outcomes at 36 weeks postmenstrual age in the Australian Placental Transfusion Study (APTS),¹³ a pragmatic randomised trial in 1566 infants born before 30 weeks gestation that compared aiming to delay clamping for 60 s or more with aiming to clamp the cord within 10 s of birth. Briefly, we found no difference in the primary outcome of death or major morbidity at 36 weeks postmenstrual age. Mortality differed at 36 weeks postmenstrual age (6·4% in the delayed clamping group vs 9·0% in the immediate clamping group; $p=0\cdot03$), but this difference was not

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Research in context

Evidence before this study

We searched PubMed, without language restrictions, between Jan 1, 2009, and May 10, 2021, for randomised trials in infants born before 32 weeks gestation comparing the effect of delayed versus immediate cord clamping on outcome between 18 months and 3 years, using the search terms “preterm”, “infant”, “newborn”, “prematu*”, “delayed cord clamping”, “clamp*”, “cord*”, “DCC or ICC or ECC or LCC”. We also searched Embase, MEDLINE and the Cochrane Central Register of Controlled Trials, with slight adaptations (appendix p 5). Our search returned one trial, which reported outcomes at 2 years of delayed clamping, with immediate neonatal care if needed, versus immediate clamping in 218 (81%) of 270 infants of less than 32 weeks gestation. After adjusting for missing values by multiple imputation, the effect of delayed clamping on death or adverse neurodevelopmental outcome was inconclusive (relative risk [RR] 0.69, 95% CI 0.44–1.09). Another trial comparing delayed versus immediate clamping reported mortality at 18–22 months in 161 (77%) of 208 infants of less than 32 weeks gestation, with inconclusive results (RR 0.41, 95% CI 0.11–1.54). Neither trial used cord milking. In a prospective cohort study in 15 563 healthy, self-breathing neonates in Tanzania, the risk of death or admission to the neonatal unit decreased by 20% for every 10 s delay in clamping after breathing, both in the whole cohort and in a subgroup of 813 neonates with low birthweight.

Added value of this study

In our trial, compared with immediate clamping, aiming to delay clamping for 60 s or more without milking the cord

reduced the relative risk of the primary outcome of death or major disability by 17% and reduced the relative risk of the secondary outcome of mortality by 30%, with no clear difference in the secondary outcome of major disability. The primary outcome was determined in 93% of all 1531 eligible infants. These findings provide the first clear evidence of an intervention at delivery that improves disability-free survival at 2 years, supporting WHO’s policy that, in newly born term or preterm babies who do not require positive-pressure ventilation, the cord should not be clamped earlier than 1 min after birth.

Implications of all the available evidence

In combination with two other trials, data from 1824 very preterm infants showed that aiming to delay clamping by up to 2 min after birth without cord milking reduced death or major disability in early childhood by a fifth and death before early childhood by a third. There was no increase in the risk of survival with major disability. It will be important in routine practice to record the time in seconds at first breath and when the cord is clamped and to undertake intensive staff training to improve adherence to new protocols. An individual participant network meta-analysis of all trials of umbilical cord management is ongoing to assess the best treatment option for key subgroups of participants. Delayed cord clamping could improve childhood outcomes in very preterm infants, helping to achieve Sustainable Development Goal 3.2 by substantially reducing neonatal and under-5 mortality.

significant after adjustment for multiple secondary outcomes.

The primary objective of this analysis, the APTS Childhood Follow Up Study, was to assess whether delayed clamping of the umbilical cord, versus immediate clamping, reduces mortality or major disability at 2 years.

Methods

Study design and participants

APTS is an international, open-label, parallel, pragmatic, randomised, controlled, superiority trial. Recruitment began with a pilot trial on Oct 21, 2009, registered in the Australian and New Zealand Clinical Trials Registry (ACTRN12609000248268). APTS was registered on Aug 2, 2010 (ACTRN12610000633088) and aimed to compare the effects of delayed versus immediate clamping on mortality or major morbidity at 36 weeks postmenstrual age in 1600 fetuses from women expected to deliver before 30 weeks of gestation. Fetuses were eligible if obstetricians or maternal–fetal medicine specialists considered that they might be delivered before 30 weeks of gestation. Exclusion criteria included fetal haemolytic disease, hydrops fetalis, twin–twin transfusion, genetic syndromes, and potentially lethal malformations. Enrolment closed on Jan 6, 2017, after

1634 fetuses were randomly assigned to one of two study groups in 25 centres in six high-income and one low-income country.¹³ Consent was obtained to collect data on long-term outcomes in 1531 infants. In July, 2014, before any trial outcomes were known, fetal death after discharge from the birth hospital or major disability in early childhood was specified as the primary outcome of this analysis—the APTS Childhood Follow-Up Study—for which funding began on Jan 1, 2015, and unblinding of investigators and data analysis began after Aug 27, 2020. Trial protocols, and details of all changes, are available in the appendix (pp 10–61).

An ethics committee approved the trial for each centre. Parents provided written informed consent to obtain follow-up data. All authors vouch for the accuracy and completeness of data from their centres and authors from the National Health and Medical Research Council Clinical Trials Centre (University of Sydney, Sydney, Australia) vouch for the analysis and fidelity of the trial to the protocol.

Randomisation and masking

Infants were randomly assigned (1:1) to either receive delayed clamping or immediate clamping of the umbilical cord. Infants of multiple births were individually

See Online for appendix

randomised. When vaginal delivery was considered imminent (within hours) and inevitable or the operating theatre was booked for caesarean section, randomisation was performed centrally by a clinician calling an automated telephone service. This telephone service used computer-based minimisation methods, stratified for gestation (<27 weeks *vs* \geq 27 weeks), centre, and multiple birth status (singleton *vs* multiple), thus ensuring allocation concealment. Parents and care providers in the delivery room were not blinded to the intervention because such masking was impracticable. However, researchers who assessed disability status were unaware of the randomised group.

Procedures

Infants were assigned to have clinicians aim to clamp the cord with the infant held as low as possible for 60 s or more (delayed clamping) or within 10 s from birth (immediate clamping). Both approaches had to be done without palpating or milking the cord. Clinicians had the discretion to clamp the cord promptly if the infant was non-vigorous with a heart rate below 100 beats per min, had low muscle tone, or was not breathing or crying. A clock in the resuscitation room was used for timing.

We assessed major disability between 18 and 27 months corrected age using a staged algorithm (appendix pp 3–4).^{14,15} The algorithm included information from (1) a Short Health Status Questionnaire, which records clinical data documented by medical professionals,^{14,15} and (2) parent-completed ASQ-3,¹⁶ which provides age-adjusted cutoff scores (with more than two SDs below the mean score indicating delay). If information from these stages was inconclusive, two paediatricians who were unaware of group assignment (IR and PS) determined the child's disability status after reviewing all data, including any formal examinations using the Bayley Scales of Infant and Toddler Development, third edition.

Outcomes

The primary outcome was death or major disability at 2 years corrected age. Survival was determined from birth up to 24 months corrected age. Infants who were known to be alive after 21 months were assumed to be alive at 24 months corrected age. Deaths after that age were not included.

Major disability was defined as one or more of the following conditions: cerebral palsy and unable to walk unassisted at or after 2 years corrected age; severe visual loss, defined as legally blind or having corrected acuity (<6/60) in both eyes; deafness requiring a hearing aid or cochlear implants; major language or speech problems at or after 24 months corrected age, defined as the inability to use more than 10 words (including signed words); or cognitive delay, defined as an Ages and Stages Questionnaire third edition (ASQ-3) score more than two SDs below the mean score for problem solving for

children at 24 months corrected age.¹⁶ Infants alive at 24 months corrected age without cerebral palsy, severe visual loss, deafness, or major language or speech problems, but who had missing information for cognitive delay were assumed to be alive and disability-free. Otherwise, infants were considered as having missing data for the primary analysis.

Secondary outcomes were the incidence at 2 years corrected age of death, major disability, the five components of major disability, and all five ASQ-3 domain scores.¹⁷

Statistical analysis

This study had 80% power, assuming a two-tailed significance level of 5% and 30% non-adherence to assigned treatment, to detect differences in the primary outcome ranging from 35.0% in the immediate clamping group to 25.4% in the delayed clamping group (a 27% reduction in relative risk [RR]) with 1350 infants, to a difference of 40% versus 30% (a 25% reduction in RR) with 1450 infants, as detailed in the statistical analysis plan (appendix p 75). No interim analyses were planned for the APTS Childhood Follow-Up Study.

Analyses were pre-specified before any follow-up results were unblinded or analysed in a statistical analysis plan (appendix pp 73–89). We planned to use all available data, and all analyses were done in the intention-to-treat population. Effects on primary and binary secondary outcomes were assessed by generalised estimating equations with a log-link function and compound symmetric correlation structure accounting for multiple births.¹⁸ Treatment effects were expressed as RRs and 95% CIs. The denominator for events was the number of infants for whom each outcome was known. For the five ASQ-3 domains, generalised estimating equations were used in a linear model to derive mean differences between treatments and 95% CI. We evaluated heterogeneity in effects on the primary outcome by tests for interaction in two pre-specified subgroups: gestation (<27 weeks *vs* \geq 27 weeks) and sex.

Sensitivity analyses of the primary outcome and 2-year mortality were adjusted for five descriptive variables: gestational age (<27 weeks *vs* \geq 27 weeks), sex, birth-weight (in quartiles), multiple birth status (singleton *vs* multiple), and mode of delivery (vaginal *vs* caesarean) using generalised estimating equations. The effect of missing data^{19,20} on the primary outcome was assessed by multiple imputation with chained equations^{21,22} using the same five descriptive variables as covariates (appendix p 4). No adjustment for multiplicity of inferences was planned. A p value was reported only for the primary outcome. All other analyses are reported as point estimates with 95% CI. Analyses were done in SAS software (version 9.4; SAS Institute) and in R.²³ Exploratory analyses relating the primary outcome to adherence to treatment and ASQ-3 to Bayley-III scores are outlined in the statistical analysis plan (appendix pp 82–84, 86), but are not reported here.

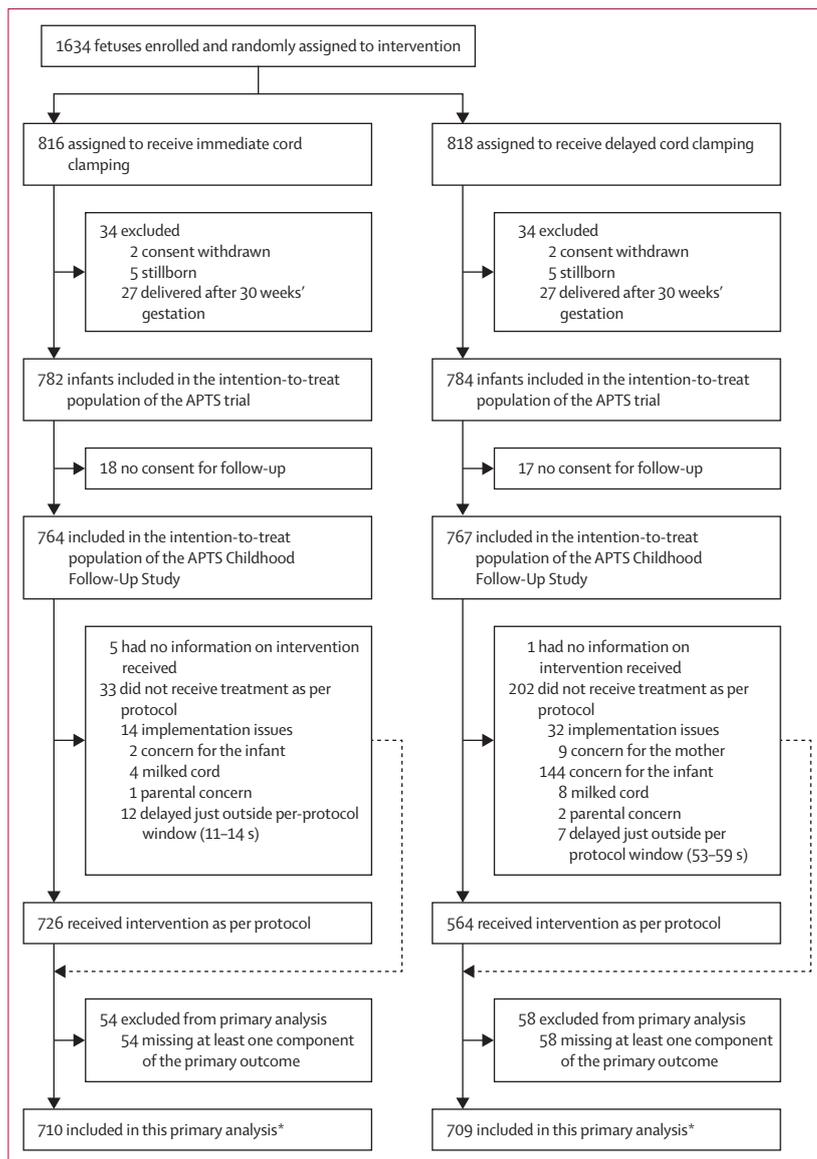


Figure 1: Trial profile for long-term follow-up

*710 (93%) of 764 infants assigned to immediate clamping and 709 (92%) of 767 infants assigned to delayed clamping in the intention-to-treat population were included in this primary analysis.

Meta-analysis

Using standard methods for searching and meta-analysis (appendix p 5), we identified additional trials comparing the effects of delayed versus immediate clamping on neonates (<32 weeks) for the outcomes death or major childhood disability up to 2 years old, or death up to 2 years corrected age. We performed a post-hoc synthesis updating all relevant evidence to place our results in context.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Of 1634 infants enrolled as fetuses between Oct 21, 2009, and Jan 6, 2017,¹³ 68 were excluded because consent was withdrawn (n=4) or because the infant was stillborn (n=10) or born after 30 weeks gestation (n=54). Of the 1566 infants remaining, 35 had no consent for follow-up, leaving 1531, of whom 767 were randomised to receive delayed clamping and 764 to immediate clamping (figure 1). Follow-up started in Feb 6 2012, and was completed in Aug 28, 2020. Baseline characteristics were well matched between groups (table 1).

The median time to clamping was 60 s (IQR 58–60) in infants assigned to delayed clamping and 5 s (3–8) in infants assigned to immediate clamping. The cord was milked in 21 (1.4%) of 1531 infants, of whom 17 of 767 were assigned to delayed clamping and four of 764 were assigned to immediate clamping. Full adherence to randomised treatment occurred in 564 (74%) infants assigned to delayed clamping and 726 (96%) infants assigned to immediate clamping. In those assigned to delayed clamping, partial adherence (>30 s) occurred in 609 (79%) infants and, in those assigned to immediate clamping, partial adherence (≤30 s) occurred in 753 (99%) infants. Non-adherence in those assigned to delayed clamping largely reflected clinical concern for the infant (144 [71%] of 202 infants). Non-adherence in those assigned to immediate clamping largely reflected implementation issues (14 [42%] of 33 infants) or clamping just beyond 10 s (range 11–14; 12 [36%] of 33; figure 1; appendix p 6).

The primary outcome of death or major disability was determined in 1419 (93%) of 1531 infants with consent for follow-up (the intention-to-treat population). The remaining 147 infants either lacked consent for follow-up (n=35) or were missing one or more components of the primary outcome (n=112); their baseline characteristics were similar to those with primary outcome data available (appendix p 7). Death or major disability at 2 years occurred in 29% (204/709) of infants assigned to delayed clamping versus 34% (240/710) of infants assigned to immediate clamping, with a RR of 0.83 (95% CI 0.72–0.95, p=0.010; table 2). After adjusting for gestation, sex, birthweight, multiple birth status, and mode of delivery, the RR of death or major disability in the delayed clamping group (referred to as the RR for delayed clamping) was 0.87 (0.76–0.99). After accounting for missing data using multiple imputation (n=1531), the treatment effect persisted, with a RR for delayed clamping of 0.87 (0.76–0.99). This effect did not differ according to sex or gestation (figure 2).

60 (8%) of 725 infants in the delayed clamping group and 81 (11%) of 720 infants in the immediate clamping group died by 2 years of age (RR 0.70, 95% CI 0.52–0.95). After adjustment for death by 2 years corrected age, the RR for delayed clamping was 0.78 (0.58–1.04) and, in a Cox regression for all 1531 infants adjusted for gestational age, the hazard ratio for delayed clamping was 0.71 (0.50–1.00,

	Delayed cord clamping (n=767)	Immediate cord clamping (n=764)
Sex		
Male	421 (55%)	441 (58%)
Female	346 (45%)	323 (42%)
Gestational age in weeks*	28 (2)	28 (2)
Aged <27 weeks gestation*	258 (34%)	247 (32%)
Presentation at birth		
Cephalic	467 (61%)	475 (62%)
Breech	267 (35%)	252 (33%)
Other, including transverse	26 (3%)	33 (4%)
Unknown	7 (1%)	4 (1%)
Mode of delivery		
Vaginal, with instruments	43 (6%)	38 (5%)
Vaginal, without instruments	216 (28%)	228 (30%)
Caesarean section, in labour	158 (21%)	163 (21%)
Caesarean section, not in labour	350 (46%)	335 (44%)
Multiple birth status†		
Singleton	574 (75%)	573 (75%)
Twin	173 (23%)	165 (22%)
Triplet	19 (2%)	23 (3%)
Quadruplet	1 (0%)	3 (0%)
Ethnicity of the mother‡		
White	554 (72%)	561 (73%)
Asian	131 (17%)	107 (14%)
Aboriginal or Torres Strait Islander	29 (4%)	36 (5%)
Pacific Islander and Maori	35 (5%)	52 (7%)
Other	18 (2%)	8 (1%)
Birthweight, g	1020 (282)	1004 (269)
Birthweight below 10th percentile for gestational age	93 (12%)	82 (11%)

Data are n (%) or mean (SD). *Estimated gestational age at randomisation. †Infants of multiple births underwent randomisation separately. ‡As reported by the mother.

Table 1: Baseline characteristics

appendix p 9). Between 36 weeks and 2 years postmenstrual age, there were 13 deaths in the immediate clamping group and 12 deaths in the delayed clamping group. Causes of death by treatment are given in the appendix (p 8).

Among infants who survived to 2 years corrected age, major disability at 2 years occurred in 23% (144/627) of those assigned to delayed clamping and 26% (159/603) of those assigned to immediate clamping (RR 0·88, 95% CI 0·74–1·04). Rates of individual components of major disability in those assigned to delayed versus immediate clamping are shown in table 2. Mean ASQ-3 scores did not differ by treatment group (appendix p 8).

Our meta-analysis found three trials, including ours, reporting childhood outcomes after delayed versus immediate clamping in 1824 very preterm infants

	Ascertainment of outcome	Delayed cord clamping group	Immediate cord clamping group	Relative risk with delayed cord clamping (95% CI)	p value
Primary outcome					
Death or major disability at 2 years	1419/1531 (93%)	204/709 (29%)	240/710 (34%)	0·83 (0·72–0·95)	0·010
Secondary outcomes					
Death at 2 years	1445/1531 (94%)	60/725 (8%)	81/720 (11%)	0·70 (0·52–0·95)	..
Major disability at 2 years*	1230/1390 (88%)	144/627 (23%)	159/603 (26%)	0·88 (0·74–1·04)	..
Cerebral palsy*	1299/1390 (93%)	10/660 (2%)	8/639 (1%)	NE	..
Severe visual loss*	1296/1390 (93%)	2/657 (<1%)	0/639	NE	..
Deafness*	1290/1390 (93%)	7/652 (1%)	4/638 (1%)	NE	..
Major problems with language or speech*	1281/1390 (92%)	115/651 (18%)	126/630 (20%)	0·89 (0·72–1·10)	..
Cognitive delay*	1217/1390 (88%)	62/618 (10%)	66/599 (11%)	0·92 (0·67–1·25)	..

Data are n/N (%), unless stated otherwise. Major disability was defined in individuals with one or more of the following: cerebral palsy, severe visual loss, deafness, major problems with language or speech, or cognitive delay. Primary outcome and death data were ascertained in APTS infants eligible for inclusion in the follow-up study (n=1531), while disability and its components are of infants known not to have died by 2 years corrected age (n=1390). NE=not estimable (due to fewer than 10 events in at least one treatment group). *Excluding those infants who had died at 2 years. To have complete data for major disability at 2 years (the composite of the five items), an infant must be assessed for at least one item as a yes to be considered an event, or all of the five items as a no to be considered a non-event.

Table 2: Outcomes by 2 years corrected age

(figure 3).^{8,24} Only our trial and one other⁸ reported death and major disability at about 2 years, in 1637 infants total. Combined, the findings of these studies suggest that aiming to delay clamping between 30 s and 2 min after birth might reduce death or major disability in early childhood (RR 0·81, 95% CI 0·70–0·92) and death by early childhood (RR 0·65, 0·49–0·86).

Discussion

In this randomised trial of 1531 infants of less than 30 weeks gestation, aiming to delay clamping of the umbilical cord for at least 60 s reduced the RR of death or major disability at 2 years corrected age (primary outcome) by 17%. The effect of delayed clamping is largely explained by the secondary finding of a 30% reduction in the RR of mortality at 2 years. The reduction in relative mortality at 2 years was similar in magnitude to the reduction in relative mortality at 36 weeks corrected age or before hospital discharge in our previous report of the APTS trial¹³ and in two systematic reviews of comparable trials.^{5,6}

This trial is the largest to study delayed versus immediate cord clamping, reporting outcomes at 2 years in over four times as many children as in comparable studies.^{8,24} Other strengths are its low risk of bias⁵ and its specification of death or major disability as primary outcome before any post-hospital discharge data were unblinded or analysed further minimising bias (appendix pp 73–89). The rate of ascertainment of the primary outcome (93%) in our trial is greater than recent similar

trials,^{8,24} and our analysis confirmed that the effect of delayed clamping in reducing the primary outcome persisted after accounting for missing data by multiple imputation. The intention-to-treat analysis, including infants in whom delayed cord clamping was thought to be inappropriate, was also a strength, as was the documentation of adherence to the study protocol. Our trial had a low rate (1.4%) of cord milking, the safety of which has been questioned in very preterm infants,^{25,26} and we also placed our findings in context with all other available evidence by way of a meta-analysis.

Our findings are consistent with those of Ersdal and colleagues,²⁷ who reported an observational study of 15 563 healthy, self-breathing neonates in a low-resource setting. Infants were more likely to die if cord clamping occurred before or immediately after onset of spontaneous respirations. The risk of death or admission to the neonatal unit in the whole cohort, and in a subgroup of 813 low birthweight infants, decreased by 20% for every delay of 10 s in clamping after breathing.

Our study had limitations. First, staff and parents were not blinded to the intervention and assessments of outcome, but researchers who assessed disability were

unaware of randomised group and death is an outcome at low risk of observer bias. Second, we did not record heart rate or time to first breath or to regular breathing. Finally, clamping occurred before 60 s in 26% of infants assigned to delayed clamping, largely reflecting clinical concerns for the infant. However, those concerns might not have reflected true clinical instability, given that about 80–90% of very preterm infants breathe spontaneously by 60 s without resuscitation, particularly if gently stimulated.^{28–30} Indeed, if those concerns largely reflected unfamiliarity with delayed clamping, greater adherence to protocol in future might further improve 2-year survival rates.

Does delayed clamping reduce mortality at 36 weeks postmenstrual age or before hospital discharge? Delaying clamping reduced this short-term outcome by about 30% in two systematic reviews of trials in nearly 3000 preterm infants, most of whom were born before 30 weeks gestation.^{5,6} By contrast, a recent systematic review of the effects of delayed clamping on mortality before hospital discharge in trials in about 3500 infants born before 34 weeks gestation was not conclusive.⁷ This discrepancy might, in part, have arisen because—unlike other reviews^{5,6}—the most recent systematic review⁷ included a trial in 461 infants over 30 weeks gestation,³¹ in whom 25% of those assigned to placental transfusion had cord milking and there were more deaths in those assigned to placental transfusion than to immediate clamping (38 vs 30 deaths).

The difference in mortality at 36 weeks postmenstrual age between delayed versus immediate clamping of 6.4% versus 9.0% in our original report,¹³ which represents a 31% reduction in RR, was not significant after adjustment for multiple secondary outcomes. This finding might have been a false negative result (type II error) owing to lack of power. Mortality for delayed versus immediate clamping at 2 years was 8% versus 11%, respectively (RR 0.70, 95% CI 0.52–0.95), with a similar 30% reduction in RR perhaps reflecting higher mortality rates at 2 years, thus

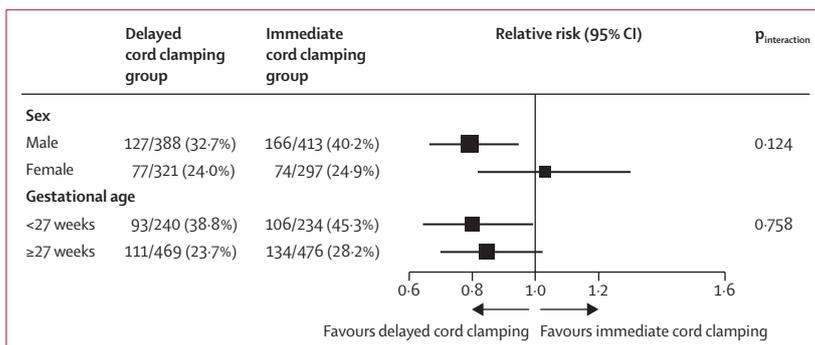


Figure 2: Subgroup analyses of the primary outcome of death or major disability by 2 years corrected age
Data are n/N (%) unless otherwise stated. $p_{\text{interaction}}$ denotes the interaction (treatment by subgroup) p value.

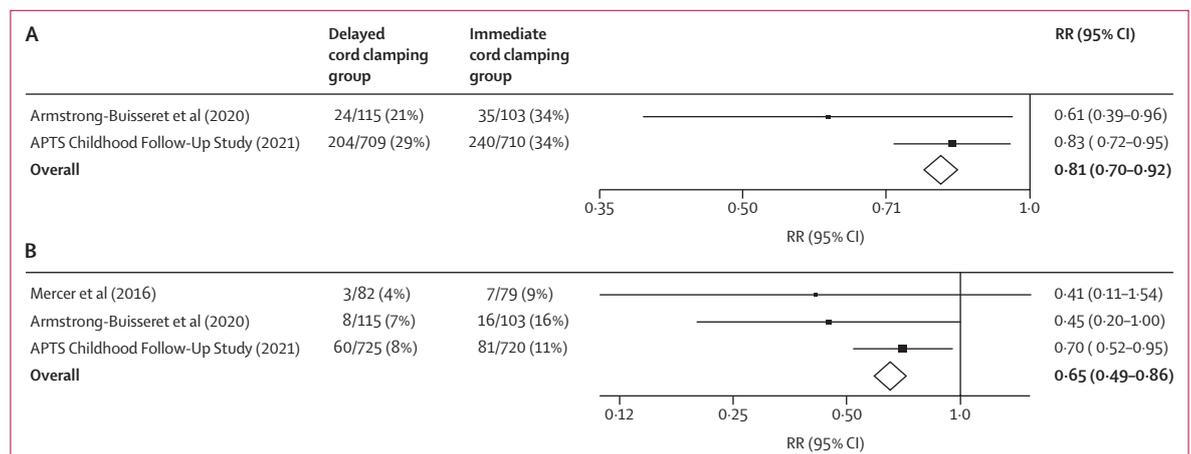


Figure 3: Post-hoc syntheses of trials of effects of delayed versus immediate cord clamping on death and disability (A) and death by 18–27 months (B)
Data are n/N (%) unless otherwise stated. The APTS trial accounted for correlation between multiple births. Effects in Armstrong-Buisseret et al⁶ and Mercer et al¹⁴ were not adjusted for covariates or by multiple imputation for missing data.

greater power. The ongoing individual participant data network meta-analysis being conducted by the iCOMP Collaboration³² in over 10 000 infants will have greater power to detect pairwise differences in mortality between randomised groups reliably. It might also clarify other questions by undertaking a sensitivity analysis excluding infants managed with cord milking and using generalised estimated equations to account for multiple births when analysing mortality at 36 weeks postmenstrual age.¹³

An added benefit of delayed cord clamping is its effect on haematological outcomes. In our previous report of the APTS trial, fewer infants in the delayed clamping group received red-cell transfusions (52·1%) than in the immediate clamping group (60·5%; $p=0\cdot001$).¹³ Systematic reviews of trials in very preterm infants indicate that, compared with immediate clamping, delayed clamping increases infant haemoglobin and reduces the rate of subsequent blood transfusions.⁵⁻⁷

What are the implications for practice? Given that aiming to delay cord clamping for 60 s or more improved 2-year outcomes and short-term haematological measures with no evidence of significant harm, it seems reasonable to conclude that delayed clamping is appropriate as standard care in very preterm infants, consistent with WHO policy on timing of cord clamping to prevent iron deficiency anaemia—which states that, in newly born term or preterm babies who do not require positive-pressure ventilation, the cord should not be clamped earlier than 1 min after birth.¹² Based on these recommendations and on evidence that delaying clamping until after breathing has started might stabilise heart rate and circulatory transition sooner,^{33,34} perhaps predisposing infants to improved outcomes,²⁷ it will be important in future to routinely record the time in seconds at first breath, the time when the cord is clamped, and heart rate at regular intervals, and to use intensive staff training to improve adherence to new protocols. This simple, highly affordable intervention could contribute to achieving Sustainable Development Goal 3.2 by substantially improving mortality in neonates and children under 5 years old.⁴

What are the implications for research? Very few perinatal interventions have reduced mortality by 30–35% and none which are as simple and affordable as delaying clamping. To reliably detect more moderate reductions in RR of mortality of 20% or less,³⁵ pairwise comparisons in future trials or prospective meta-analyses^{32,36} will need more than 11 000 patients if the control mortality rate is 8%, and tens of thousands of patients if the control mortality rate is 5% or less.³⁷ Reliable, cost-effective measures of disability are essential.^{33,38-40} Scales administered by trained assessors at a single evaluation (such as the Bayley-III) can become prohibitively expensive for perinatal trials large enough to change practice.^{14,41,42} Assessments by parents and linkage with long-term outcomes from national educational tests with parental consent might be more cost effective^{40,43} and represent infant behaviours more accurately, because they reflect more prolonged observations in more natural

settings. Guided by systematic reviews of individual patient data,³² adaptive platform trials might evaluate delayed clamping for more than 30 s, 60 s, or 90 s or until respiration and respiration are stable,³³ with infants randomly assigned to receive resuscitation, if required, with or without the cord intact. However, such studies would require intensive staff training, unlike large, simple drug trials.³⁵

The principal challenge for future research is how to enrol the numbers of infants required to find moderate, but clinically relevant, improvements in mortality.⁴¹ Through international partnerships, the ALPHA Collaboration^{5,37,44,45} will work with other organisations to identify questions of high priority to stakeholders worldwide for perinatal trials addressing mortality or survival as the primary outcome and to focus globally collaborative efforts on rapidly answering those questions in a new generation of low-cost, perinatal megatrials and prospective meta-analyses of two-arm or multi-arm, multi-stage trials enrolling more than 5000 patients. Such studies will need highly streamlined processes to facilitate fast recruitment with minimal data collection, as in the UK RECOVERY³⁵ and WHO SOLIDARITY trials.⁴⁶ Mega trials or prospective meta-analyses of trials of this size will also yield considerably more precise and reliable estimates of differences in disability in survivors.

In summary, compared with immediate clamping of the cord, aiming to delay clamping for at least 60 s in very preterm infants reduced death or major disability at 2 years, reflecting a reduced risk of death with no clear difference in disability.

Contributors

WTM, JS, AM, KL, MK, WH, IR, JM, KR, and AG conceived the trial and WOT-M is chief investigator. KPR, WOT-M, IR, PS, AM, CY, AG, HGL, DO, JM, WH, MK, KL, RS, MC, AKe, AKI, and JS contributed to the implementation of the study or data collection. IR and PS did the central clinical outcome review. KPR and AKI did the statistical analyses and verified the data. KPR and DO searched for articles for inclusion in the meta-analysis. KPR and WOT-M wrote the first version of the manuscript. All authors critically reviewed and approved the final version, and vouch for the accuracy and completeness of the data from their centres. Authors from the National Health and Medical Research Council Clinical Trials Centre vouch for the analysis and fidelity of the trial to the protocol. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

Individual de-identified participant data for findings reported in this Article will be available for 5 years after publication. Researchers wishing to gain access to data should provide a methodologically sound proposal to apts.study@sydney.edu.au, which will be reviewed by the trial management committee. Researchers will need to sign a data access agreement.

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For more on the ALPHA Collaboration see <https://www.alphacollaboration.com>

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