Elective birth at 37 weeks of gestation versus standard care for women with an uncomplicated twin pregnancy at term: the Twins Timing of Birth Randomised Trial

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Objective To evaluate whether for women with an uncomplicated twin pregnancy, elective birth at 37 weeks of gestation was associated with reduced risk of death or serious outcomes for babies, without increasing harm.

Design Randomised controlled trial.

Setting Maternity hospitals across Australia, New Zealand and Italy.

Population A total of 235 women with an uncomplicated twin pregnancy at 36+6 weeks of gestation, with no contraindication to continuing their pregnancy.

Methods Using a computer-generated, central telephone randomisation service, 235 women were randomised to Elective Birth (birth at 37 weeks; n = 116) or Standard Care (continued expectant management, with birth planned from 38 weeks; n = 119). Outcome assessors were masked to treatment allocation.

Main outcome measure A composite of serious adverse outcome for the infant.

Results For women with an uncomplicated twin pregnancy, elective birth at 37 weeks of gestation was associated with a significant reduction in risk of serious adverse outcome for the infant (Elective Birth 11/232 [4.7%] versus Standard Care 29/238 [12.2%]; risk ratio [RR] 0.39; 95% CI 0.20–0.75; P = 0.005), reflecting a reduction in birthweight less than the third centile using singleton gestational age-specific charts (Elective Birth 7/232 [3.0%] versus Standard Care 24/238 [10.1%]; RR 0.30; 95% CI 0.13–0.67; P = 0.004). In a post hoc analysis using twin gestational age-specific charts, there was evidence of a trend towards a reduction in the primary composite of serious adverse infant outcome (Elective Birth Group 4/232 [1.7%] versus Standard Care Group 12/238 [5.0%]; RR 0.34; 95% CI 0.11 to 1.05; P = 0.06).

Conclusion The findings of our study support recommendations for women with an uncomplicated twin pregnancy to birth at 37 weeks of gestation.

Keywords Infant morbidity, low birthweight, randomised trial, timing of birth, twin pregnancy.

Introduction

There is a well-recognised increased occurrence of both maternal and fetal or infant complications associated with multiple pregnancy, particularly longer-term risks, including cerebral palsy and developmental delay. Although women with a twin pregnancy are more likely to give birth preterm, approximately 46% will give birth after 37 weeks of gestation. For women whose twin pregnancy continues beyond 37 weeks of gestation, there is a higher risk of perinatal mortality and morbidity with advancing gestational age. Multiple population-based studies worldwide consistently indicate the lowest risk of perinatal mortality and morbidity for births between 36 and 38 weeks of gestation. These findings have prompted some to consider redefining the concept of 'post-term' in multiple pregnancies.
to be 38 weeks of gestation,9 whereas others7 have suggested that more than 80% of the mortality observed in twin pregnancies may be reduced by attention to ensuring optimal gestation at birth.

Induction of labour for women with an uncomplicated singleton pregnancy has been recommended at or beyond 41 weeks of gestation as an intervention to reduce the risk of perinatal death.10 Although the increase in perinatal mortality and morbidity seen in twin pregnancies beyond 37 weeks of gestation parallels that seen in singleton pregnancies beyond 41 weeks, the role of planned early term birth for women with a twin pregnancy remains unclear.

This uncertainty led us to evaluate in the Twins Timing of Birth Randomised Trial, whether for women with an uncomplicated twin pregnancy, elective timing of birth at 37 weeks of gestation was associated with a reduction in the risk of serious outcomes for the infant (as indicated by the occurrence of perinatal death or serious infant morbidity), without an increase in harms for either the woman or her infants.

Methods

Trial design
We conducted a multicentre randomised controlled trial between February 2003 and August 2010. Ethics approval was obtained from each individual collaborating site, and women provided written informed consent to participate.

Participants
Women with a twin pregnancy at 36+6 weeks of gestation or more with no contraindication to continuing the pregnancy, who presented to a collaborating centre, were eligible to participate. Women with fetal demise of one or both twins at the time of trial entry, in active labour, with evidence of a non-reassuring fetal heart rate tracing, or with maternal or fetal compromise precluding continued antenatal surveillance were ineligible.

Interventions

Elective birth group
Women randomised to the Elective Birth Group were planned for elective birth from 37 weeks of gestation. Where there was a plan for vaginal birth, this involved induction of labour. Where there was a plan for caesarean birth, this involved an elective caesarean section. The planned mode of birth was assessed and determined by the woman and the obstetrician caring for her.

Standard care group
For women randomised to the Standard Care Group, birth was planned from 38 weeks of gestation, according to the practice of the hospital where the woman expected to give birth. Where there was a plan for vaginal birth, this involved either awaiting the spontaneous onset of labour, or induction of labour if required. Where there was a plan for caesarean birth, this involved an elective caesarean section (where possible booked after 38 weeks and as close to 39 weeks of gestation as possible). The planned mode of birth was assessed and determined by the woman and the obstetrician caring for her.

If earlier birth (before 38 weeks of gestation) was considered appropriate because of the development of complications, this was carried out either by induction of labour or by caesarean section, as determined by the woman and the obstetrician caring for her. However, the woman remained in the Standard Care Group for the purposes of analysis.

For all women participating in the study, the process of induction of labour was carried out according to the usual practices of the attending obstetrician and the hospital involved. Women were encouraged to have continuous fetal heart rate monitoring by cardiotocograph when in active labour. The presence of a nonreassuring fetal heart rate tracing was managed by performing fetal scalp pH sampling where possible, or emergency caesarean section as appropriate. The spectrum of analgesia and anaesthesia was available according to the woman’s choice. Care for the woman was managed by the obstetric team with care of the infant by the attending neonatologist. After birth, a research assistant, blinded to treatment allocation, obtained information relating to birth and infant outcomes from the woman’s case notes.

Outcome measures
Our primary outcome measure was a composite of serious adverse outcome for the infant, as prespecified in our published trial protocol, including the use of singleton growth charts.11 We defined this as:

- Death (any fetal death after study entry or death of a live-born infant before 28 days of life [excluding lethal congenital anomalies]); or
- previously defined measures of Serious Morbidity12,13 (one or more of the following, excluding lethal congenital anomalies, and reflecting either
  - Adverse outcomes at term (birth trauma [subdural or intracerebral haemorrhage, spinal cord injury, basal skull fracture, other fracture, peripheral nerve injury present at discharge from hospital]); birthweight less than third centile for gestational age at birth and infant sex;14 Apgar score <4 at 5 minutes; cord pH <7.0 [arterial or venous cord blood];15 seizures at <24 hours of age or requiring two or more drugs to control; neonatal encephalopathy grade 3 or 416) or
  - immaturity (use of ventilation >24 hours; admission to neonatal intensive care unit >4 days; severe respiratory distress syndrome [mean arterial pressure >10
and or fractional inspired \(O_2 > 0.8\) with need for ventilation; chronic lung disease [continued oxygen requirement at 28 days of life]; proven necrotising enterocolitis; proven systemic infection within 48 hours of birth treated with antibiotics).

Although there is controversy surrounding the use of singleton birthweight centiles for twin infants,\textsuperscript{17} the clinical practice of centres participating in this study, was to use singleton reference standards for ultrasound estimates of fetal weight, birthweight and early infant growth, regardless of the plurality of the pregnancy, and a post hoc analysis was performed to consider the effect of twin-specific growth standards.\textsuperscript{18}

Our secondary study endpoints related to recognised maternal and infant complications\textsuperscript{19,20} including maternal antenatal medical and obstetric complications; labour and birth complications; and adverse infant outcomes.

The maternal antenatal medical and obstetric complications were defined as: pre-eclampsia or eclampsia (systolic blood pressure \(\geq 140\) mmHg and diastolic \(\geq 90\) mmHg on two occasions 4 hours apart or more, plus one of proteinuria (\(\geq 2000\) mg/24 hours or spot urine creatinine ratio \(\geq 30\) mg/mmol), renal insufficiency (serum plasma creatinine \(\geq 0.09\) mmol/l or oliguria), liver disease (elevated serum transaminases or right upper quadrant pain), neurological disturbances (convulsions, hyper-reflexia with clonus, severe headache with hyper-reflexia, persistent visual disturbances), or haematological disturbances (thrombocytopenia, disseminated intravascular coagulopathy, haemolysis);\textsuperscript{19} antepartum haemorrhage requiring hospitalisation; and abnormal umbilical artery Doppler study (absent or reversed end diastolic flow as detected by ultrasound examination).

Labour and birth complications were defined as: induction of labour for medical or obstetric complications; meconium-stained liquor; cardiotocogram abnormality during labour [fetal tachycardia [fetal heart rate >160 beats/minute]; fetal bradycardia [fetal heart rate <110 beats/minute]; reduced variability [<5 beats/minute]; decelerations of the fetal heart rate [early, late or variable]]; emergency caesarean birth; and severe maternal morbidity (defined as one or more of maternal death; uterine rupture [defined as a clinically significant rupture involving the full thickness of the uterine wall and requiring surgical repair]; severe haemorrhage [blood loss >1500 ml or requiring blood transfusion]; hysterectomy for any complications resulting from birth; vulvar or perineal haematoma requiring evacuation; deep vein thrombosis or thrombophlebitis requiring anticoagulant therapy; pulmonary embolus requiring anticoagulant therapy; pneumonia due to infection, aspiration or other causes; adult respiratory distress syndrome; wound infection [requiring prolongation of hospital stay or readmission] or wound dehiscence; damage to the bladder, ureter or bowel requiring repair, or cervical laceration extending to the lower uterine segment, or abnormal extension of the uterine incision; occurrence of a fistula involving the genital tract; bowel obstruction or paralytic ileus; pulmonary oedema; stroke [defined as acute neurological deficit >24 hours]; cardiac arrest; respiratory arrest].

Adverse infant outcomes were defined as the individual components of the composite morbidity and mortality outcome.

**Sample size**

We estimated the incidence of our composite outcome of serious adverse outcome for infants of a twin pregnancy at or beyond 37 weeks of gestation to be 16.3%.\textsuperscript{5} To reduce this to a rate of 6.7% seen in singleton infants at the same gestational age, and adjusting for clustering of twin infants within mothers, a sample size of 460 women was required (two-tailed \(z\) 0.05; power 80%). After recruitment of 235 women to the trial, the Trial Steering Committee decided to stop the trial because of a lack of ongoing funding.

**Randomisation and blinding**

The randomisation sequence was computer generated using balanced variable blocks, with stratification for planned mode of birth (planned caesarean birth or planned vaginal birth) and collaborating centre. Consenting, eligible women were randomised to timing of birth using a central telephone randomisation service. To maximise the likelihood that women received the care allocated at randomisation, women were randomised from 36\textsuperscript{48} weeks of gestation. Outcome assessors were blinded to allocated treatment group.

**Statistical analysis**

We adopted intention-to-treat principles, and conducted an initial analysis to examine the baseline characteristics of each treatment group as an indication of comparability. Primary and secondary outcomes were analysed according to allocated treatment group at randomisation. Continuous outcomes were analysed using linear regression models. Binary outcomes were analysed using generalised linear models with a log-link function and a binomial distribution. Generalised estimating equations were used to account for clustering of babies from multiple births. Clustering due to collaborating centre was investigated using multilevel models. Clustering was negligible as expected,\textsuperscript{21} given the randomisation sequence was stratified by centre, and we therefore present the results accounting for clustering due to multiple births only using generalised estimating equations. Results are presented as risk ratios (RR) or difference in means, comparing the elective birth group with the standard care group, with 95% confidence intervals (CI). The level of significance was 0.05 and all \(P\) values.
were two-sided. Interaction tests were performed to assess whether the effect of treatment on infant outcomes varied by pregnancy chorionicity. Post hoc tests comparing the treatment groups within the monochorionic and dichorionic pregnancies were not performed unless the interaction test was significant. Post hoc analyses were also conducted to evaluate the effect of twin-specific growth charts.18

Results

During the study period, approximately 45% of the eligible women approached consented to participate, with 55% declining. In all, 235 eligible women provided written informed consent and were randomised to the trial, 116 women to the Elective Birth Group and 119 women to the Standard Care Group (Figure 1). Outcome data were available for all of the 235 women randomised and their 470 infants.

Maternal baseline demographics were similar between the two treatment groups at trial entry (Table 1). Infants in the Elective Birth Group were at significantly lower risk of serious adverse infant outcome when compared with infants in the Standard Care Group (Elective Birth Group 11/232 [4.7%] versus Standard Care Group 29/238 [12.2%]; RR 0.39; 95% CI 0.20–0.75; \( P = 0.005 \)) (Table 2). There were no perinatal deaths among infants in the Elective Birth Group, and one in the Standard Care Group (Elective Birth Group 0/232 [0.0%] versus Standard Care Group 1/238 [0.4%]), in an infant 27 days after birth due to acquired Group B streptococcal infection. This infant was a second twin, born following elective caesarean section. Infants in the Elective Birth Group were at statistically significantly lower risk of morbidity due to adverse outcomes at term (Elective Birth Group 10/232 [4.3%] versus Standard Care Group 28/238 [11.8%]; RR 0.37; 95% CI 0.18–0.73; \( P = 0.004 \)) when compared with infants in the Standard Care Group. The reduction in risk of serious adverse infant outcome and morbidity due to adverse outcomes at term was the result of a statistically significant reduction in the risk of birthweight less than the third centile for gestational age and infant sex (Elective Birth Group 7/232 [3.0%] versus Standard Care Group 24/238 [10.1%]; RR 0.30; 95% CI 0.13–0.67; \( P = 0.004 \)). There were no other statistically significant differences identified in the individual components of the morbidity outcomes between the two treatment groups.

Infants in the Elective Birth Group were born at a mean gestational age of 37.3 ± 0.4 weeks (range 37\(^{00}\)–40\(^{12}\) weeks), whereas infants in the Standard Care Group were born at a mean gestational age of 37.9 ± 0.5 weeks (range 37\(^{00}\)–39\(^{13}\) weeks). As outlined in Figure 2, within the Elective Birth Group 86% of women birthed between 37\(^{10}\) and 37\(^{14}\) weeks of gestation, whereas among women in the Standard Care Group, 55% gave birth after 38 weeks of gestation as specified in the trial protocol. The 45% of women who gave birth between 37 and 38 weeks of gestation reflects both the reality of scheduling induction of labour and caesarean section procedures in a busy

Table 1. Baseline characteristics at the time of trial entry

<table>
<thead>
<tr>
<th></th>
<th>Elective birth group (n = 116)</th>
<th>Standard care group (n = 119)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age* (years)</td>
<td>28.6 (5.6)</td>
<td>29.2 (5.3)</td>
</tr>
<tr>
<td>Gestational age at randomisation** (weeks)</td>
<td>36.9 (36.9–36.9)</td>
<td>36.9 (36.9–36.9)</td>
</tr>
<tr>
<td>Body Mass Index** (kg/m²)</td>
<td>26.6 (23.8–31.0)</td>
<td>25.9 (23.3–30.3)</td>
</tr>
<tr>
<td>Public patient***</td>
<td>114 (98.3)</td>
<td>118 (99.2)</td>
</tr>
<tr>
<td>Race***</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>99 (85.3)</td>
<td>105 (88.2)</td>
</tr>
<tr>
<td>Asian</td>
<td>5 (4.3)</td>
<td>2 (1.7)</td>
</tr>
<tr>
<td>Other</td>
<td>12 (10.3)</td>
<td>12 (10.1)</td>
</tr>
<tr>
<td>Smoker***</td>
<td>31 (26.7)</td>
<td>30 (25.2)</td>
</tr>
<tr>
<td>Chorionicity***</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monochorionic</td>
<td>19 (16.4)</td>
<td>21 (17.6)</td>
</tr>
<tr>
<td>Dichorionic</td>
<td>95 (81.9)</td>
<td>98 (82.4)</td>
</tr>
<tr>
<td>Conception***</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous</td>
<td>88 (75.9)</td>
<td>93 (78.2)</td>
</tr>
<tr>
<td>Assisted Conception</td>
<td>17 (14.7)</td>
<td>19 (16.0)</td>
</tr>
<tr>
<td>Planned mode of birth***</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal birth</td>
<td>71 (61.2)</td>
<td>78 (65.5)</td>
</tr>
<tr>
<td>Caesarean birth</td>
<td>45 (38.8)</td>
<td>41 (34.5)</td>
</tr>
</tbody>
</table>

*Mean and standard deviation.
**Median and interquartile range.
***n (%).
maternity environment at close to 38 weeks of gestation, as well as individual clinician decisions to initiate earlier birth based on their clinical judgement.

Women in the Elective Birth Group were more likely to require induction of labour (Elective Birth Group 59/116 [50.9%] versus Standard Care Group 45/119 [37.8%]; RR 1.35; 95% CI 1.00–1.80; \( P = 0.046 \)), this was not associated with a statistically significant difference in the woman's chance of achieving a vaginal birth (Elective Birth Group 50/116 [43.1%] versus Standard Care Group 57/119 [47.9%]; RR 0.90; 95% CI 0.68–1.19; \( P = 0.51 \)), or of requiring a caesarean section (Elective Birth Group 66/116 [56.9%] versus Standard Care Group 62/119 [52.1%]; RR 1.09; 95% CI 0.86–1.38; \( P = 0.51 \)) (Table 3). The risk of serious adverse maternal outcome did not differ significantly between women in the Elective Birth Group and women in the Standard Care Group (Elective Birth Group 2/116 [1.7%] versus Standard Care Group 7/119 [5.9%]; RR 0.29; 95% CI 0.06–1.38; \( P = 0.12 \)), with all caused by severe haemorrhage defined as blood loss ≥1500 ml, and/or haemorrhage requiring blood transfusion.

Prespecified subgroup analyses did not indicate statistically significant differences in risk of infant health outcomes by treatment group between monochorionic and dichorionic twin pregnancies. Post hoc analysis using twin-specific growth standards identified a trend towards a reduction in the primary composite of serious adverse infant outcome (Elective Birth Group 4/232 [1.7%] versus Standard Care Group 12/238 [5.0%]; RR 0.34; 95% CI 0.11–1.05; \( P = 0.06 \)), with no statistically significant differences in the components morbidity from adverse outcomes at term (Elective Birth Group 3/232 [1.3%] versus Standard Care Group 9/238 [3.8%]; RR 0.34; 95% CI 0.09–1.23; \( P = 0.10 \)), or birthweight less than the third centile (Elective Birth Group 0/232 [0.0%] versus Standard Care Group 4/238 [1.7%]; RR not estimable) (Table 4).

### Table 2. Primary infant outcome and morbidity components by treatment group

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Elective Birth Group (n = 232 infants) n (%)</th>
<th>Standard Care Group (n = 238 infants) n (%)</th>
<th>Risk ratio (95% CI)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serious adverse infant outcome</strong>*</td>
<td>11 (4.7)</td>
<td>29 (12.2)</td>
<td>0.39 (0.20–0.75)</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>Perinatal death</strong></td>
<td>0 (0.0)</td>
<td>1 (0.4)</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td><strong>Stillbirth</strong></td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td><strong>Neonatal death</strong></td>
<td>0 (0.0)</td>
<td>1 (0.4)</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td><strong>Morbidity from adverse outcomes at term</strong>*</td>
<td>10 (4.3)</td>
<td>28 (11.8)</td>
<td>0.37 (0.18–0.73)</td>
<td>0.004</td>
</tr>
<tr>
<td><strong>Morbidity from immaturity</strong>*</td>
<td>2 (0.9)</td>
<td>2 (0.8)</td>
<td>1.03 (0.15–7.16)</td>
<td>0.98</td>
</tr>
<tr>
<td><strong>Birth trauma</strong></td>
<td>0 (0.0)</td>
<td>1 (0.4)</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td><strong>Seizures</strong></td>
<td>1 (0.4)</td>
<td>0 (0.0)</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td><strong>Apgar &lt;4 at 5 minutes</strong></td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td><strong>Cord pH &lt;7.0</strong></td>
<td>2 (0.9)</td>
<td>4 (1.7)</td>
<td>0.51 (0.10–2.75)</td>
<td>0.43</td>
</tr>
<tr>
<td><strong>Birthweight &lt;3rd centile</strong></td>
<td>7 (3.0)</td>
<td>24 (10.1)</td>
<td>0.30 (0.13–0.67)</td>
<td>0.004</td>
</tr>
<tr>
<td><strong>Stage 3 encephalopathy</strong></td>
<td>1 (0.4)</td>
<td>0 (0.0)</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td><strong>NICU admission &gt;4 days</strong>*</td>
<td>2 (0.9)</td>
<td>2 (0.8)</td>
<td>1.03 (0.15–7.16)</td>
<td>0.98</td>
</tr>
<tr>
<td><strong>Severe lung disease</strong>*</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td><strong>Ventilation &gt;24 hours</strong>*</td>
<td>2 (0.9)</td>
<td>1 (0.4)</td>
<td>2.05 (0.19–22.32)</td>
<td>0.56</td>
</tr>
<tr>
<td><strong>Chronic lung disease</strong>*</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td><strong>Necrotising enterocolitis</strong>*</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td><strong>Systemic infection</strong>*</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>Not estimable</td>
<td></td>
</tr>
</tbody>
</table>

*Serious adverse infant outcome includes: Death—any fetal death after study entry or death of a liveborn infant before hospital discharge (excluding lethal congenital anomalies); or Serious Neonatal Morbidity11,12—defined as one or more of the following, excluding lethal congenital anomalies, and reflecting either adverse outcomes at term (birth trauma [subdural or intracerebral haemorrhage, spinal cord injury, basal skull fracture, other fracture, peripheral nerve injury present at discharge from hospital]; birthweight less than third centile for gestational age at birth and infant sex;13 Apgar score <4 at 5 minutes; cord pH <7.0 [arterial or venous cord blood];14 seizures at <24 hours of age or requiring two or more drugs to control; neonatal encephalopathy grade 3 or 415) or immaturity (use of ventilation >24 hours; admission to neonatal intensive care unit [NICU] >4 days; severe respiratory distress syndrome [mean arterial pressure >10 and or fractional inspired O2 > 0.8 with need for ventilation]; chronic lung disease [continued oxygen requirement at 28 days of life]; proven necrotising enterocolitis; proven systemic infection within 48 hours of birth treated with antibiotics).

**Adverse Outcomes at Term—as defined above, including one or more of birth trauma, infant birthweight less than third centile for gestational age at birth and infant sex, Apgar score <4 at 5 minutes, cord pH <7.0, seizures, neonatal encephalopathy grade 3 or 4.

***Outcomes due to Immaturity—as defined above, including one or more of use of ventilation, NICU admission, severe respiratory distress syndrome, chronic lung disease, proven necrotising enterocolitis, proven systemic infection.
Discussion

The results of this randomised trial indicate that elective birth at 37 weeks of gestation for women with an uncomplicated twin pregnancy is associated with a statistically significant reduction in the risk of serious adverse outcomes for the infant when compared with continued expectant care. In particular this reflected a reduction in adverse outcomes at term, predominantly associated with a reduction in risk of birthweight less than the third centile. Whereas infants born to women in the Elective Birth Group were born significantly earlier than infants in the Standard Care Group, this was not associated with any increased risk of adverse infant outcomes related to immaturity. Elective birth was associated with an increased need for induction of labour but this did not decrease a woman’s chance of vaginal birth, or increase the risk of serious maternal health outcomes.

The Cochrane Systematic Review assessing elective birth from 37 weeks of gestation for women with an uncomplicated twin pregnancy identified a single randomised controlled trial from Japan. This trial, recruited 36 women with a twin pregnancy who gave birth after 37 weeks of gestation, where the first twin was in a cephalic presentation. Nineteen women were randomised to the expectant management group, which involved daily evaluation by non-stress cardiotocograph and twice weekly ultrasound examination. Provided no complications developed, the spontaneous onset of labour was awaited. Seventeen women were randomised to elective birth involving induction of labour with intravaginal prostaglandin E2 followed by amniotomy and oxytocin infusion as required. In this trial, the average gestational age at birth in infants from the induction of labour group was 37.5 ± 0.4 weeks, significantly earlier than infants born following expectant management (39.0 ± 1.1 weeks; P < 0.05). No statistically significant differences were identified between the two treatment groups with regards to mode of birth, birthweight <2500 g or Apgar score <7 at 5 minutes.

Infants of a multiple pregnancy are recognised to be at increased risk of intrauterine growth restriction, which may manifest as growth and birthweight discordance, with well-described limitations in antenatal diagnosis by ultrasound, particularly for the second twin. A number of authors have constructed plurality-specific growth charts by week of gestational age, involving populations from Australia, the USA, Canada and Belgium. Using these twin-specific growth charts, gestational-age-specific birthweight in twins diverges from singletons from between 29 and 34 weeks of gestation. Therefore, the use of singleton reference standards for twin infants is likely to underestimate growth at earlier gestational ages and overestimate growth at later gestational ages. Despite recommendations for using twin-specific gestational age growth standards, it is unclear how widely this occurs in clinical practice.

The variation in diagnosis and definitions of growth restriction in twin pregnancies has been highlighted in the recent National Institute for Health and Clinical Excellence (NICE) guidelines for the antenatal management of women with a multiple pregnancy, which considered that ‘no evidence-based growth charts specific to twin and triplet pregnancies (were) available for use in the diagnosis of intrauterine growth restriction’ were available. Furthermore, the identified research priorities indicate the need for the prospective development of specific twin fetal growth charts both to evaluate fetal growth in healthy twin pregnancies and to identify infants at risk of growth restriction.

There are extensive population-based data indicating that for women whose twin pregnancy continues beyond 37 weeks of gestation, there is a higher risk of perinatal mortality and morbidity with advancing gestational age. However, these studies have not differentiated between monochorionic diamniotic and dichorionic twin pregnancies. Whereas the risk of adverse neonatal outcomes for late preterm dichorionic twin infants may approach those seen in singleton infants of similar gestational age, there is increasing recognition that both mortality and morbidity for monochorionic diamniotic twin infants is greater than in

![Figure 2. Gestational age at birth by treatment group: A, elective birth; B, standard care.](image-url)
Although we detected no differences in outcomes based on chorionicity, the proportion of monochorionic twins in this randomised trial was 17%, and therefore we were underpowered to reliably detect differences in timing of birth between relatively late mean gestational ages of 37 and 38 weeks.
There are several limitations to our findings. The current trial was stopped before completion of the estimated sample size for a lack of ongoing funding. We are therefore relatively underpowered to assess our primary outcome of serious adverse outcome for the infant, as well as uncommon maternal labour and birth complications. To detect a 66% reduction in adverse outcome at term as suggested using plurality-specific data would require a sample size of approximately 1100 women with an uncomplicated twin pregnancy at term. Such a trial would certainly require considerable scale funding and a commitment from clinicians internationally to complete. Recent recommendations from NICE advocate birth for women with a monochorionic twin pregnancy at 36 + 0 weeks of gestation, and for women with a dichorionic twin pregnancy at 37 + 0 weeks of gestation.31 These recommendations have used population-based data and economic considerations,31 but it is unlikely that sufficient equipoise exists in current clinical practice to randomise women to a later timing of birth.

Despite our trial protocol specifying birth for women in the Standard Care Group being after 38 weeks of gestation, and as close to 39 weeks as possible, 45% of women in this group gave birth between 37 and 38 weeks of gestation, reflecting the practicalities of scheduling induction of labour and caesarean section procedures in a busy maternity environment at close to 38 weeks of gestation. The resultant mean difference of 4 days in gestational age at birth is consistent with the identified difference of 90 g in mean birthweight. However, these identified differences do not explain the significant reduction in the risk of birthweight less than the third centile observed in the Elective Birth Group, raising the possibility that this was a chance finding.

In current Western obstetric practice, outcomes such as maternal and perinatal mortality are rare. The difficulty for researchers of these declining event rates has led to the use of composite outcomes focusing on measures of infant morbidity.35 Many authors have highlighted the difficulties often encountered in the clinical interpretation of composite outcomes,35–37 as stated by Ross35 they represent an inevitable compromise between ‘what is possible in trial design versus what would be ideal’. The primary composite outcome used in this trial was prespecified a priori, the components reflective of adverse neonatal outcome.38 Identification of the small-for-gestational-age (SGA) infant was included,38 in recognition of the association between SGA (including both growth restriction and low birthweight infants) and impact on future health and disease, including cardiovascular disease, diabetes and obesity.39 Although these findings were described initially in singleton infants with SGA, there is increasing recognition in the literature of a similar association among twin infants.40

The findings of our randomised trial support the recent NICE recommendations.31 For women with an uncomplicated twin pregnancy at 37 weeks of gestation, elective birth was associated with a significant reduction in the risk of birthweight below the third centile, with no identified increase in the risks associated with early birth for either women or their infants.

Disclosure of interests
We declare that we have no conflict of interest.

Contribution to authorship
All authors contributed equally to the study concept and design, analysis and interpretation of data, and in obtaining funding. JMD was responsible for drafting the manuscript, with all authors contributing to revisions of the manuscript and approving the final version for submission. Statistical expertise was obtained from HO and LY. The study conduct was supervised by JMD and CAC.

Details of ethics approval
Ethics approval was obtained from all participating centres.

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Twins Collaborative Group
The following persons and institutions participated in the Twins: Timing of Birth Study Group:

**Steering Group:** JM Dodd, CA Crowther, RR Haslam, JS Robinson; **Co-ordinating Team:** JM Dodd, CA Crowther, RR Haslam, JS Robinson, AR Deussen, E Christou, M Ewens; **Statistical Analyses:** JM Dodd, H Oakey, L Yelland; **Writing Group:** JM Dodd, CA Crowther, RR Haslam, JS Robinson.

Collaboration by hospital (total number of women recruited from each site in parentheses)
- Auckland City Hospital, New Zealand (8)
  - A Budden, K Groom, J McDougall
- Caboolture Hospital, Qld, Australia (13)
  - S Bradford, K Brown, L Cochrane, L Harris-Mann, K Law, M Ratnapala

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Elective birth at 37 weeks of gestation versus standard care for women with an uncomplicated twin pregnancy at term: the Twins Timing of Birth Randomised Trial

Background

- Describe the current NICE recommendations for the timing of delivery of monochorionic and dichorionic twin pregnancies, and whether they differ depending on chorionicity.\(^1\) Compare them with practice and local guidance in your area.
- For which conditions associated with maternal death is multiple pregnancy a risk factor?\(^2\)

Methods

- Compare central computer-generated randomisation by telephone with other random allocation methods, including those where allocation is determined locally within each unit. Describe their advantages and disadvantages, including, but not limited to, allocation concealment, selection bias and practical considerations.
- Singleton growth charts were used in the primary analysis for this study. Discuss the implications. When twin-specific charts were used, the reduction in adverse outcome for the intervention group had an RR of 0.34, and a P value of 0.06.
- Discuss this finding, including a Bayesian perspective; describe how the results would be useful for meta-analyses considering the size of the difference in risk between the two groups.
- Critically appraise compliance with the protocol in the intervention and control groups, with regards to gestational age at delivery.
- The proportion of cases where labour was induced was higher in the intervention group. Discuss its differential impact in the two groups, for example on postpartum haemorrhage.
- This study was terminated prematurely because of a lack of funding, and the results were analysed for available cases. Had more funding become available, would it be appropriate to continue randomising women to the two groups from both an ethical and a methodological point of view?

Results and implications

- The reduction in risk in the elective birth group was related to a reduction in the risk of a birthweight of less than the third centile for gestational age and infant gender. Based on your appraisal of the methods and these results, should we use this study to counsel women about timing of delivery?
- How would you design further studies to answer this question? What would you do differently and why?■
References
