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Prelabor cesarean delivery for twin pregnancies close to term is associated with reduced mortality

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ABSTRACT

Objectives: To examine short and longer term outcomes for twins born at or near term, comparing prelabor cesarean delivery (CD) to birth after trial of labor.

Methods: A retrospective cohort of twin pregnancies delivered ≥ 36 weeks gestation from 2000 to 2009. Pregnancies with an antenatal death, lethal anomaly, birthweight discordance ≥25% or birthweight <2000 grams or >4000 grams were excluded. Outcomes included severe hypoxia, stillbirth and neonatal death, and hospital admissions or death during the first 5 years of life.

Results: 45.3% of 7099 twin pregnancies were delivered by prelabor CD. Compared to delivery after labor, prelabor CD was associated with significantly reduced risks of adverse infant outcomes including severe birth hypoxia (0.08% vs. 0.75%, RR 0.10, 95% CI 0.04-0.26), neonatal death (0.00% vs. 0.15%, RR 0.05, 95% CI 0.00-0.82), and death up to 5 years of age (0.16% vs. 0.40%, RR 0.41, 95% CI 0.20-0.85). Whereas total mortality for first twins was similar after labor (0.15%) compared to prelabor CD (0.16%), total mortality was four times more common in second twins born after labor (0.64%) compared to second twins born after prelabor CD (0.16%).

Conclusions: Twin pregnancies at and beyond 36 weeks who are delivered after labor have increased risks for birth outcomes associated with hypoxia. These risks do not result in increased mortality in the first twin, but second twins have significantly increased mortality up to 5 years of age. However, the absolute mortality rate for relatively uncomplicated twin pregnancies born at or near term is low.

Introduction

Twin pregnancies have higher rates of perinatal morbidity and mortality compared to singleton pregnancies and different gestational age-associated morbidity.(1) The Twin Birth Study,(2) a randomised clinical trial, found no significant difference in risk of neonatal mortality or severe perinatal morbidity for planned cesarean delivery (CD) versus planned vaginal birth. The Twin Birth Study recruited women from 32 weeks gestation onwards; 34% of twins were born at <34 weeks and 52% of the primary outcome events occurred in this group,(2) giving these early preterm deliveries the largest contribution to the statistical power of the study. In contrast, most twins are born at or near term; 67.4% of twins in a population-based study were born at ≥36 weeks and only 16% before 34 weeks.(3) The Twin Birth Study did report a point estimate of reduced risk of the primary composite outcome (perinatal death or severe neonatal morbidity) for planned CD at term but with a very wide confidence interval (OR=0.30; 95% CI 0.06-1.43).(2)

Previous research has reported an increased risk of perinatal death for second twins delivered vaginally at term(4, 5) and an increased risk of other morbidity.(6, 7) Whether there are perinatal benefits for cesarean delivery for twin pregnancies that reach 36 weeks remains an open question. The aim of this study was to examine, among twin pregnancies allowed to continue to 36 weeks gestation, short and longer term infant outcomes for delivery by prelabor cesarean compared to delivery after onset of labor, both overall and by birth order.

Materials and Methods

The study utilised records of all births in the state of New South Wales (NSW) Australia, during the period 1 July 2000 to 31 December 2009, with follow-up to June 2012. Data were obtained from two population datasets maintained by the NSW Ministry of Health: the Perinatal Data Collection (PDC, referred to as 'birth records') which reports on all NSW births, and the Admitted Patient Data Collection (APDC) which has discharge summaries of all NSW hospitalisations (referred to as ‘hospital records’). The PDC records births of at least 20 weeks gestation or at least 400 grams birth weight. Information on maternal characteristics, pregnancy, labor, delivery, and infant outcomes are recorded by the attending midwife or doctor. The APDC is a census of all NSW inpatient hospital discharges from both public and private hospitals, and includes demographic and episode-related data; diagnoses and procedures are coded for each admission from the medical records according to the 10th revision of the International Statistical Classification of Diseases and Related Health Problems, Australian Modification (ICD-10-AM) and the affiliated Australian Classification of Health Interventions. The PDC and APDC were linked cross-sectionally and longitudinally using probabilistic linkage methods and were made available to the researchers as anonymised data. The validity of probabilistic record linkage is extremely high;(8) quality assurance data relevant to this study show false positive and negative rates of 0.3% and <0.5% respectively. Additionally, records of death from the NSW Registry of Births, Deaths and Marriages (RBDM, referred to as death registrations) and the Perinatal Death Review (PDR, referred to as ‘death reviews’)(9) were linked to the main data. The RBDM identifies fact of death and the PDR contains summaries of the cause and timing of stillbirths and neonatal deaths based on a comprehensive review by an expert clinical panel. The linkage and use of the data was approved by the NSW Population and Health Services Research Ethics Committee.

Study population- lower risk term and near term twin births

The selection of the study population is shown in the flow diagram Figure 1. Twin births were restricted to gestations ≥36 weeks where the records of both twins could be linked as an intact twin pair. Twin infants with missing or unlinked records and twin pairs with inconsistent gestational ages or dates of birth were excluded. As our intention was to examine outcomes of twin pregnancies where the mode of delivery was not dictated by a fetal death or antenatal fetal compromise, and where vaginal delivery was not contraindicated, additional exclusion criteria included: a fetal reduction procedure or fetal death <36 weeks; antepartum stillbirth ≥36 weeks; laser surgery for twin-twin-transfusion syndrome had been performed; a congenital malformation which resulted in perinatal death; a birthweight <2000 grams or >4000 grams; a birthweight discrepancy of >25% between twins;(10) twin 1 with non-vertex presentation and not delivered by prelabor CD; mother with ≥2 prior CD not delivered by prelabor CD. Follow-up for each child was until either their fifth birthday or 31 December 2012 (for death) or 30 June 2012 (for hospital admission); infants born in 2009 thus had a minimum of 2.5 years follow-up for admissions.

Study exposures

The exposures of interest were: 1) prelabor CD versus delivery after the onset of labor 2) second-born twin (twin 2) versus first-born twin (twin 1). The first comparison categorised pregnancies by exposure to labor. The birth record indicates spontaneous labor, labor induction or no labor in the case of a prelabor CD, but does not record length or stage of labor. The second exposure comparison compares the effect of birth order in twins; twin birth order is recorded based on delivery order. No pregnancies were missing data for either onset of labor or birth order.

Outcomes

The outcomes of interest were birth events potentially associated with intrauterine hypoxia and included intrapartum stillbirth, neonatal death (within the first 28 days), severe birth hypoxia, resuscitation requiring intubation and an Apgar score at 5 minutes (Apgar5) of <4.

Severe birth hypoxia comprised severe birth asphyxia or hypoxic-ischemic encephalopathy identified from any of 20 ICD-10 diagnosis fields in the hospital record or a hypoxic fetal or newborn death as identified from the death review. Stillbirths were identified from the birth records and death reviews. The death reviews provided information on timing of stillbirth (before labor, during labor or timing not known) and a summary cause of perinatal death.

To investigate long term consequences by labor status and birth order, hospital readmissions or deaths were examined during the first five years of life. Childhood outcomes included any hospital admission, any respiratory-related admission (respiratory-related diagnosis or a procedure indicating respiratory support), and any admissions for seizure, epilepsy or cerebral palsy. Diagnoses and procedures were identified from the hospital records. Childhood deaths were identified from hospital records and from death registrations, which included deaths outside of hospital.

Statistical analyses

For the comparison of infant birth outcomes, a multilevel logistic regression model (SAS NLMIXED procedure, with twin pair as the cluster factor) was used. The risks for prelabor CD versus labor are reported as relative risks (RR) and 95% confidence intervals as estimated from the model odds ratios. Included covariates (Table 1) were maternal age category, nulliparity, week of gestation, infant sex and size-for-gestational age <25th centile for twins(11). Where there were fewer than 60 events for an outcome model, covariates were backwards eliminated to maintain a minimum ratio of 10:1 for events to covariates (including the exposure of interest). Where there were less than twenty events for an analysis, the crude RR and 95% CI were calculated using contingency tables. Records were dropped from models if missing data for a covariate (records missing data were <1%); no records involving a perinatal or child death had missing data for a covariate.

For the comparison of childhood outcomes, Cox proportional hazards survival analysis (SAS PHREG) was performed using a random effect (shared frailty) model with twin pair as the level of the random effect.(12) Infants were censored at their fifth birthday or 31 December 2012, whichever came first. The risks for prelabor CD versus labor are reported as adjusted hazard ratios (HR). Covariates were the same as for the birth outcome models, and were handled similarly.

For the comparison of outcomes by twin birth order twin 1 was the reference group. Analyses were performed separately for twins delivered after onset of labor and for twins delivered by prelabor CD. Models were adjusted for infant sex and size $<25^{th}$ centile.(11) Maternal age, nulliparity and gestational age were not potential confounders of a birth order effect as they are matched at the twin pair (cluster) level.

Results

During the period July 2000 through December 2009, 26,120 twin infants of at least 20 weeks gestation were born. The derivation of the study population is shown in Figure 1. The requirement for pregnancies to have reached at least 36 weeks gestation excluded 34.5% of all twins. Two of the 17 excluded infants with lethal malformations were stillbirths and the remaining 15 died during the neonatal period; the types of malformations are noted in Figure 1. Eight pregnancies with a reduction procedure or a fetal death before 36 weeks were excluded. A further 13 pregnancies were delivered at ≥36 weeks where a fetal death occurred before prelabor CD (6 pregnancies, 7 deaths) or before labor (7 pregnancies, 7 deaths), a rate of less than one per thousand infants among the pregnancies undelivered as of 36^{+0} weeks. After the remaining exclusions, there were 14,198 infants (7099 twin pairs, 54% of all twin births) of relatively uncomplicated pregnancies who reached at least 36^{+0} weeks gestation and who were included in the analyses.

Of these, 45.3% of women were delivered by prelabor CD and 54.7% of women were delivered after the onset of labor (either spontaneous or after labor induction). Table 1 shows the maternity characteristics for the twin pairs, including mode of delivery. Among the 3883 women who labored, 22.9% of first twins and 27.0% of second twins were delivered by CD. The majority of deliveries occurred before 38 weeks gestation, for both prelabor CD (60.9%) and for those who labored (54.8%). The shift towards earlier birth among the twins delivered by prelabor CD was a statistically significant difference (Wilcoxon test P<0.001).

Table 2 shows the distribution of birth and childhood outcomes by labor status. Delivery by prelabor CD was associated with significantly reduced risks for the adverse birth outcomes, except for stillbirth. Two of the four stillbirths were attributed to peripartum hypoxia; both of these were intrapartum deaths of second twins. Eleven of the twelve neonatal deaths (92%) were associated with birth asphyxia or hypoxic- ischaemic encephalopathy; ten of these eleven were second twins. For childhood hospital admissions, twins delivered by prelabor CD had a slightly increased risk of respiratory-related admissions (HR=1.10, 95% CI 1.01-1.21) compared with twins exposed to labor. Those born following prelabor CD had a significantly decreased risk of total mortality (HR=0.41, 95% CI 0.20-0.85) over the full follow-up period. There was no evidence that the mortality risk differed by hospital size. The total mortality risk for infants born at hospitals which performed <10 twin deliveries per annum, compared to hospital with ≥10 twin deliveries per annum, was RR=1.18, 95% CI 0.60-2.31.

Table 3 shows the risk of adverse outcomes by birth order for twin pairs where the mother labored. Compared to first twins, second twins exposed to labor had significantly increased risks for all adverse birth outcomes, except stillbirth. However, for childhood admissions, there were no significant differences in risk by birth order. There were more childhood deaths among the second twins, and although not statistically significant on its own, this excess contributed to the greater total mortality (including perinatal deaths) of second twins delivered after labor compared to first twins. Three of the second twins who had been delivered after labor and who died in childhood had had an admission for either cerebral palsy or epilepsy; none of the childhood deaths in the other groups had a record of either condition.

Table 4 shows the risk of adverse outcomes by birth order for twin pairs delivered by prelabor CD. There was a tendency for the point estimates of risk for birth outcomes to be higher for second twins compared to first twins, but none of the risks for any of the adverse outcomes reached the level of statistical significance. The total mortality rate for first twins after prelabor CD was similar to that for first twins after onset of labor (from Tables 3 and 4), (0.16% vs. 0.15% RR=1.01, 95% CI 0.31-3.29), but differed for second twins (prelabor CD versus onset of labor: 0.16% vs. 0.64%, RR=0.24, 95% CI 0.09-0.63). For second twins, the total mortality absolute risk reduction from prelabor cesarean was 4.9 per 1000 deliveries. Much of this was due to the reduced risk of perinatal death: 0.03% for second twins delivered by prelabor CD compared to 0.36% after labor (RR=0.09, 95% CI 0.01-0.66).

Discussion

This population-based study provides evidence that twin pregnancies that continue to 36 weeks and beyond and are delivered after labor, compared to delivery by prelabor CD, have significantly increased risks for adverse outcomes including perinatal death and death up to 5 years of age. However, the absolute mortality rate was low overall, with 4 per 1000 infants of these relatively uncomplicated twin pregnancies dying at birth or before their 5th birthday. The increased rate of perinatal and childhood mortality was concentrated amongst second twins born after labor. The total mortality for second twins was four times higher if delivered after the onset of labor (0.64%) compared with prelabor CD (0.16%). Assuming that there is a direct causal link, the number of women needing to have a prelabor CD to avoid one perinatal or childhood death is estimated at 205, attributable entirely to excess mortality associated with delivery after labor for second twins. The 205 planned CD would be in lieu of an estimated 150 vaginal deliveries and 55 intrapartum CD, based on the 27% intrapartum CD rate for second twins in this study. There may be an increase in childhood respiratory-related admissions associated with planned cesarean delivery, so that 205 additional such deliveries could result in 4.6 additional children with a respiratory-related hospital admission. In a study from the Netherlands, twins born by planned cesarean delivery ≥35 weeks gestation have been shown to have rates of respiratory distress syndrome that continued to reduce from 35^{+0} weeks onwards.(13) Twins delivered by prelabor CD in our study were more often delivered before 38 weeks than those born after labor so earlier birth could explain at least part of the risk for respiratory-related admission.

Severe hypoxia was ten times more frequent in second twins born after labor (1.16%) compared to no labor (0.12%). Yet despite having increased rates of hypoxia and low Apgar score, there was no evidence that second twins subsequently had higher childhood hospital admission rates, including for seizures or cerebral palsy. Twins are known to have an increased risk of cerebral palsy,(14) which may be related to the risk of intrapartum hypoxia; an Apgar at 5 minutes of <4 has been reported to have an odds ratio=51 for the outcome of cerebral palsy.(14) The overall rate of hospital admission for cerebral palsy in our study population of relatively uncomplicated twin pregnancies at ≥36 weeks was 0.8 per thousand infants. This is comparable to the results of a Swedish population study, which reported a rate of cerebral palsy of 1.4 per thousand at ≥37 weeks.(15) For first twins, severe birth hypoxia was also more common after labor compared to prelabor CD but this had little effect relative to mortality or childhood outcomes.

A systematic review which examined neonatal morbidity by birth order and mode of delivery found similar morbidity rates for planned CD and trial of labor, but did not differentiate births by gestational age.(16) Most studies have not had sufficient power to compare mortality in term twin infants by intended method of delivery. A study which examined birth outcomes at ≥36 weeks by delivery intention had 1175 pregnancies, with no stillbirths and only two neonatal deaths(7). The investigators reported an increased risk of the composite birth outcome only among dichorionic second twins with planned vaginal delivery. A study from France of 758 pairs of twins at >35 weeks, where the mean intertwin delivery interval was 4.9 minutes, reported no neonatal deaths and no difference in composite neonatal morbidity by planned mode of delivery.(17) A study of 1542 twin pairs from Nova Scotia found that term second twins planned for vaginal delivery had a 3.6 times higher rate of morbidity than second twins delivered by prelabor CD, primarily due to birth asphyxia, but had no perinatal deaths.(6) The Twin Birth Study had only 9 occurrences of the primary composite outcome in term infants; the effect was not statistically significant but tended towards favouring planned CD (OR=0.30; 95% CI 0.06-1.43).(2) Two population studies from the United Kingdom did report increased mortality for second twins close to term delivered vaginally(5, 18) and a related study reported that 264 planned cesareans would be needed to prevent one perinatal death.(4)

The strength of the study is the large study population drawn from validated datasets. By removing twins at greater risk of adverse perinatal outcomes because of congenital anomaly, growth restriction, or birth trauma because of large size, our study created a population of relatively uncomplicated term and near term twin pregnancies. Our results report outcomes that occurred across a range of hospitals and obstetric care providers. Differences in outcomes by mode of delivery and birth order might be reduced if all twin deliveries were performed by clinicians highly experienced in twin vaginal delivery in hospitals that deliver many twins per year, with ready access to operating theatres and experienced paediatricians.

In practice, that may not be possible due to geographical constraints and/or sudden onset of labor or pregnancy complications.

The limitations of the study include the lack of information on placental chorionicity. It is accepted that monochorionic (MC) twins are at higher risk of perinatal mortality at all gestations, partly due to twin to twin transfusion syndrome and growth restriction.(19) Twin pregnancies where photocoagulation had been performed were excluded from the study population, and the study only included pregnancies allowed to continue to at least 36^{+0} weeks. Further, although acute twin to twin transfusion syndrome has been reported with MC twins in labor this risk is low.(20) Another limitation is that the study exposure was labor or prelabor cesarean rather than delivery intentions at 36^{+0} weeks; delivery intentions are not recorded in the dataset used for the study. Women intending a vaginal birth at 36^{+0} may have had a prelabor CD subsequently recommended because of antenatal fetal complications. Women who developed acute pregnancy complications would be expected to have higher rates of emergency prelabor CD, and higher rates of adverse perinatal outcomes.(21) However this study did not demonstrate any apparent increase in adverse birth outcomes associated with prelabor CD; indeed, the neonatal outcomes tended to favour prelabor CD. We found no difference in the hospitalisation outcomes to age 5 years, but other long term outcomes, such as educational or behavioural outcomes, were not available.

A randomised trial with sufficient power to compare mortality for planned CD versus intended vaginal birth in term twins is unlikely to happen. The results from our cohort are consistent with the magnitude and direction of the primary outcome reported for the subgroup of term twin pregnancies in the Twin Birth Study: a protective effect associated with prelabor CD. This evidence can help quantify the risks for delivery options as twin pregnancies approach term.

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Table 1. Characteristics of the twin pregnancies, by labor status

	Prelabor cesarean delivery (CD) N=3216 n (%)	After onset of labor (any delivery mode) N=3883 n (%)
Maternal age		
<25 years	290 (9.0)	446 (11.5)
25-29 years	638 (19.8)	1017 (26.2)
30-34 years	1195 (37.1)	1407 (36.3)
35-39 years	878 (27.3)	857 (22.1)
≥ 40 years	215 (6.7)	156 (4.0)
Nulliparous	1326 (41.4)	1416 (36.5)
Prior cesarean (CD)	784 (24.4)	144 (3.7)
Gestational age at birth		
36 weeks	627 (19.5)	825 (21.3)
37 weeks	1333 (41.4)	1303 (33.6)
38 weeks	1091 (33.9)	1316 (33.9)
≥ 39 weeks	165 (5.1)	439 (11.3)
Hospital with ≥10 twins per annum	2382 (74.1)	2876 (74.1)
Spontaneous labor	NA	1664 (42.8)
Induced	NA	2225 (57.2)
Twin 1 instrumental delivery	NA	802 (20.7)
Twin 1 CD after labor	NA	888 (22.9)
Twin 2 breech or instrumental	NA	1470 (37.9)
Twin 2 CD after labor	NA	1050 (27.0)
Twin 1 median weight (grams)	2775	2730

Twin 2 median weight (grams)	2735	2710
Twin 1 <25th centile size(11)	459 (14.3)	631 (16.2)
Twin 2 <25th centile size(11)	603 (18.7)	755 (19.4)

Table 2. Adverse events for 14,198 twin infants delivered at ≥36 weeks gestation by labor status

Outcome	Prelabor cesarean delivery (CD) N=6432	Labor (any delivery mode) N=7766	Adjusted risk of outcome for prelabor CD vs. labor
Birth admission	n (%)	n (%)	*RR (95% CI)**
stillbirth	1 (0.02)	3 (0.04)	0.40 (0.04-3.87)†
severe birth hypoxia	5 (0.08)	58 (0.75)	**0.10 (0.04-0.26)**
intubated for resuscitation	22 (0.34)	62 (0.80)	**0.45 (0.28-0.73)**
Apgar 5 min <4	6 (0.09)	24 (0.30)	**0.30 (0.13-0.68)A**
neonatal death	0 (0.00)	12 (0.15)	**0.05 (0.00-0.82)**‡
Readmission for			*HR (95% CI)§*
any hospital admission	2121 (32.98)	2597 (33.44)	0.99 (0.94-1.03)
respiratory admission	988 (15.36)	1106 (14.24)	**1.10 (1.01-1.21)**
seizure	102 (1.59)	131 (1.69)	0.94 (0.73-1.22)
epilepsy	19 (0.30)	20 (0.26)	1.20 (0.64-2.24)B
cerebral palsy	5 (0.08)	6 (0.08)	1.00 (0.30-3.30)†
Childhood mortality			*HR (95% CI)*
to fifth birthday (excluding perinatal)	9 (0.13)	16 (0.21)	0.68 (0.30-1.54)C
any (including perinatal)	10 (0.16)	31 (0.40)	**0.41 (0.20-0.85)D**

* Relative risk (RR) as estimated from the logistic regression model odds ratio, adjusted for maternal age category, nulliparity, gestational age, <25th centile size and infant sex, except where noted separately

† RR from contingency table;

‡ RR from contingency table, using value of 0.5 added to each event count due to zero cell

§ Hazard ratio (HR), adjusted for maternal age, nulliparity, gestational age, <25th centile size and infant sex

A: adjusted for gestational age, infant sex; B: adjusted for infant sex, <25th centile size; C: adjusted for maternal age; D: adjusted for maternal age, nulliparity, <25th centile size

Table 3. Adverse events at birth and during first five years of life, for 7766 twins (3883 pairs) whose mother labored before delivery

Outcome	Twin 1 N=3883	Twin 2 N=3883	Adjusted risk of outcome (95% CI) Twin 2 vs. Twin 1
Birth admission	n (%)	n (%)	*RR (95% CI)**
stillbirth	0 (0.00)	3 (0.10)	not calculated
severe birth hypoxia	13 (0.33)	45 (1.16)	**3.57 (1.93-6.61)**
intubated for resuscitation	13 (0.33)	49 (1.26)	**4.00 (2.12-7.52)**
Apgar 5 min <4	7 (0.18)	17 (0.44)	**2.46 (1.04-5.81)A**
neonatal death	1 (0.03)	11 (0.28)	**11.00 (1.42-85.2)**†
Readmission for			*HR (95% CI)*‡
any hospital admission	1311 (33.76)	1286 (33.12)	0.98 (0.92-1.04)
respiratory admission	547 (14.09)	559 (14.40)	1.02 (0.91-1.14)
seizure	68 (1.75)	63 (1.62)	0.95 (0.67-1.35)
epilepsy	9 (0.23)	11 (0.28)	1.17 (0.48-2.82)B
cerebral palsy	1 (0.03)	5 (0.13)	5.00 (0.58-42.8)†
Childhood mortality			*HR (95% CI)*‡
to fifth birthday (excluding perinatal)	5 (0.13)	11 (0.28)	2.20 (0.77-6.33)†
any (including perinatal)	6 (0.15)	25 (0.64)	**4.24 (1.74-10.3)**

* Relative risk (RR) as estimated from the logistic regression model odds ratio, adjusted for <25th centile size and infant sex, except where noted

† RR from contingency table;

‡ Hazard ratio (HR), adjusted for <25th centile size and infant sex, except where noted

A: adjusted for infant sex; B: adjusted for <25th centile size

Table 4. Adverse events at birth and during first five years of life, for 6432 twins (3216 pairs) delivered by prelabor cesarean delivery

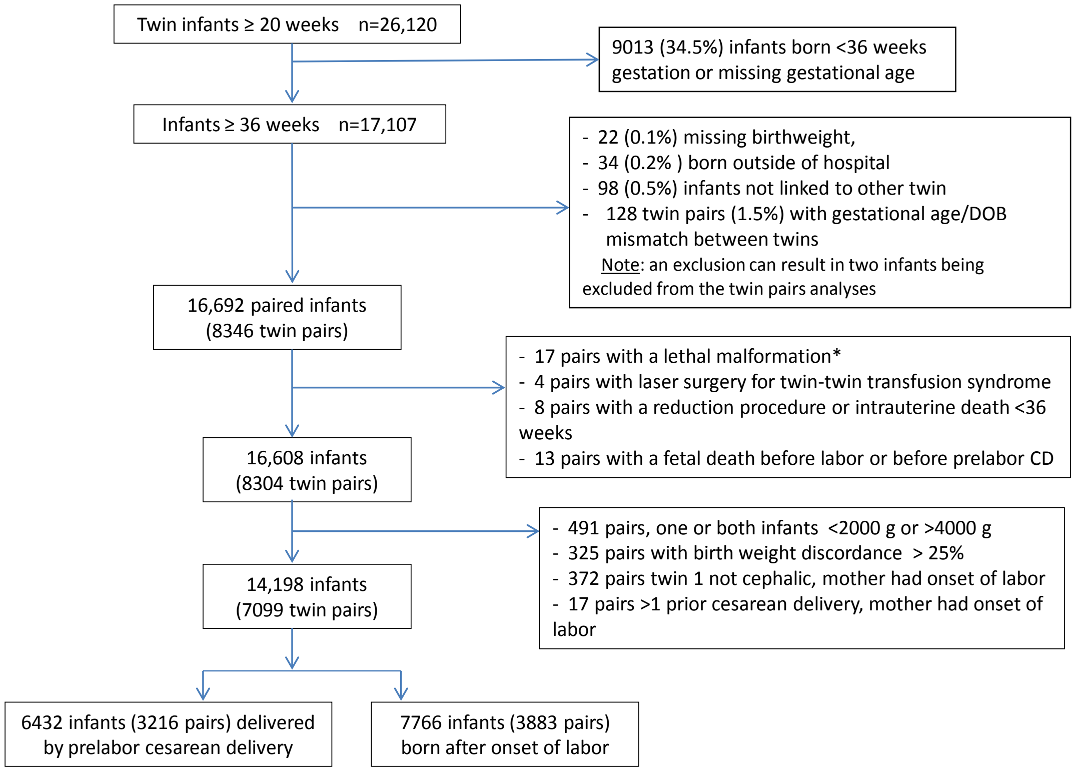
Outcome	Twin 1 N=3216	Twin 2 N=3216	Adjusted risk of outcome (95% CI) Twin 2 vs. Twin 1
Birth admission	n (%)	n (%)	*RR (95% CI)*
stillbirth	0 (0.00)	1 (0.03)	not calculated
severe birth hypoxia	1 (0.03)	4 (0.12)	4.00 (0.45-35.8)*
intubated for resuscitation	11 (0.34)	11 (0.34)	1.00 (0.43-2.31)†
Apgar 5 min <4	2 (0.06)	4 (0.12)	2.00 (0.37-10.9)*
neonatal death	0 (0.00)	0 (0.00)	not calculated
Readmission for			*HR (95% CI)* ‡
any hospital admission	1048 (32.59)	1073 (33.36)	1.03 (0.94-1.12)
respiratory admission	481 (14.96)	507 (15.76)	1.05 (0.93-1.19)
seizure	47 (1.46)	55 (1.71)	1.17 (0.80-1.72)
epilepsy	10 (0.31)	9 (0.28)	0.90 (0.37-2.21)*
cerebral palsy	3 (0.09)	2 (0.06)	0.67 (0.11-3.99)*
Childhood mortality			*RR (95% CI)*
to fifth birthday (excluding perinatal)	5 (0.16)	4 (0.12)	0.80 (0.22-2.98)*
any (including perinatal)	5 (0.16)	5 (0.16)	1.00 (0.29-3.45)*

* Relative risk (RR) from contingency table

† RR as estimated from the logistic regression model odds ratio, adjusted for <25th centile size

‡ Hazard ratio (HR), adjusted for <25th centile size, infant sex, except where noted

Figure 1. Flow chart for twin study (twins born 1 July 2000 to 31 December 2009)



* Lethal malformations: anencephaly, diaphragmatic hernia, spina bifida, cardiovascular defects, renal dysplasia, exomphalos, metabolic disorder, Potter's syndrome, chromosomal syndrome