ORIGINAL ARTICLE

# A Randomized Trial of Planned Cesarean or Vaginal Delivery for Twin Pregnancy

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Because of assisted reproductive technologies, twin pregnancy occurs more frequently now than in the past, and it complicates 2 to 3% of all births.[1,2] Twins are at higher risk for an adverse perinatal outcome than singletons.[3,4] Planned cesarean section, as compared with planned vaginal delivery, may reduce this risk.[5] Although a small, randomized, controlled trial did not show better perinatal outcomes with planned cesarean section than with planned vaginal delivery,[6] several cohort studies have shown a reduced risk of adverse perinatal outcomes for both twins, or for the second twin, when twins at or near term were delivered by means of elective cesarean section.[7-10] Despite the lack of evidence to support a policy of planned cesarean section for twins at or near term, the rates of elective cesarean section for twins have increased in North America and worldwide.[11,12]

Video

Cesarean or Vaginal Delivery for Twins.

We conducted the Twin Birth Study to compare the risk of fetal or neonatal death or serious neonatal morbidity with two delivery strategies — planned cesarean delivery or planned vaginal delivery with cesarean delivery only if indicated — for twin pregnancies between 32 weeks 0 days and 38 weeks 6 days of gestation, if the leading twin was in the cephalic presentation.

## METHODS

### Study Design

Women were eligible for the study if they had a twin pregnancy between 32 weeks 0 days and 38 weeks 6 days of gestation, the first twin was in the cephalic presentation, and both fetuses were alive with an estimated weight between 1500 g and 4000 g, confirmed by means of ultrasonography within 7 days before randomization. We enrolled women with pregnancies as early as 32 weeks of gestation because many women with twins wish to begin planning the method of delivery at this time and because many twin births are preterm.

Exclusion criteria were monoamniotic twins, fetal reduction at 13 or more weeks of gestation, lethal fetal anomaly, contraindication to labor or vaginal delivery (e.g., fetal compromise, first twin substantially larger than the second twin, fetal anomaly or condition that might cause mechanical problems at delivery, and previous vertical uterine incision or more than one previous low-segment cesarean delivery), and previous participation in the Twin Birth Study.

### Study Oversight

The research ethics committee at each participating center approved the study protocol, which is available with the full text of this article at NEJM.org. The first, second, and last authors take

responsibility for the accuracy and completeness of the reported data and for the fidelity of the report to the study protocol. All the women provided written informed consent before being enrolled.

**Treatment Protocol**

Women were randomly assigned to planned cesarean section or planned vaginal delivery. Randomization was centrally controlled at the Centre for Mother, Infant, and Child Research at Sunnybrook Health Sciences Centre in Toronto with the use of a computerized randomization program stratified according to parity (0 vs. ≥1) and gestational age (32 weeks 0 days to 33 weeks 6 days, 34 weeks 0 days to 36 weeks 6 days, or 37 weeks 0 days to 38 weeks 6 days), with the use of random block sizes.

Data were abstracted from the medical records at participating centers by trained study staff and were recorded, after delivery, on standardized data-collection forms. Participating centers assessed fetal growth and well-being with the use of ultrasonography at least every 4 weeks and with the use of nonstress or biophysical profile tests twice weekly if needed; were prepared to perform a cesarean section within 30 minutes if necessary; and had anesthetic, obstetrical, and nursing staff available in the hospital at the time of planned vaginal delivery.

Elective delivery by means of either cesarean section (for women in the planned-cesarean group) or labor induction (for women in the planned-vaginal-delivery group) was planned between 37 weeks 5 days and 38 weeks 6 days of gestation, because evidence suggested that perinatal outcomes would be best during this gestational-age window.[13-15] If the first twin was delivered vaginally in a woman in the planned-cesarean group, a cesarean section was attempted for the second twin, if logistically possible. For women with a planned vaginal delivery, we anticipated that more than 60% would deliver both twins vaginally.[16] The pregnancy was reassessed at the time of labor, and if there was a contraindication to labor or vaginal delivery, a cesarean delivery was undertaken. If labor was induced, standard methods were used, but prostaglandins were not recommended for women who had previously undergone a cesarean section.

Continuous electronic monitoring of the fetal heart rate was recommended during active labor. The use of oxytocin to augment labor and the use of epidural analgesia were left to the discretion of the obstetrician. After the delivery of the first twin, the use of ultrasonography was encouraged in order to check the presentation of the second twin. If the second twin was in the cephalic presentation, amniotomy was delayed until the fetal head was engaged and spontaneous vaginal delivery was anticipated, unless a nonreassuring fetal status required the use of forceps or vacuum extraction. If the second twin was not in the cephalic presentation, the obstetrician decided on the best delivery option (spontaneous or assisted vaginal breech delivery, total breech extraction with or without internal podalic version, external cephalic version and vaginal cephalic delivery, or intrapartum cesarean section).

Women having a vaginal delivery were attended by a qualified obstetrician who was experienced at vaginal twin delivery, defined a priori as an obstetrician who judged himself or herself to be experienced at vaginal twin delivery and whose department head agreed with this judgment.[17,18] Before beginning recruitment at each center, we assigned a code number to qualified obstetricians who were considered to be experienced at vaginal twin delivery, and we recorded information about their qualifications and years of experience with vaginal twin delivery. Similar information was collected for other clinicians who were present at delivery.

Infants received positive-pressure ventilation with endotracheal intubation, oxygen, intravenous therapy, blood transfusion, surfactant, or a combination of these therapies if needed at the time of birth. Intracranial pathological findings were assessed with the use of neonatal ultrasonography if clinically indicated.

**Outcomes**

For the present analysis, mothers and infants were followed until 28 days after delivery. The primary outcome was a composite of fetal or neonatal mortality or serious neonatal morbidity. Neonatal mortality was assessed for the period from 0 to 27 days after birth. Serious neonatal morbidity was defined as one or more of the following: birth trauma (spinal cord injury, basal or depressed skull fracture, fracture of a long bone [humerus, radius, ulna, femur, tibia, or fibula]; injury to a peripheral nerve [brachial plexus or phrenic or facial nerve] present at 72 hours of age or at discharge from the hospital; subdural or intracerebral hemorrhage confirmed by mean of ultrasonography, computed tomography [CT], or magnetic resonance imaging [MRI]); Apgar score of less than 4 at 5 minutes; coma, stupor, or decreased response to pain; seizures on at least two occasions before 72 hours of age; need for assisted ventilation with the use of an endotracheal tube, inserted within 72 hours

after birth and remaining in place for at least 24 hours; septicemia confirmed by means of blood culture or meningitis confirmed by means of cerebrospinal fluid culture within 72 hours after birth; necrotizing enterocolitis, defined as intestinal perforation, pneumatosis intestinalis, or air in the portal vein diagnosed by means of surgery or radiography; bronchopulmonary dysplasia, defined as the need for supplemental oxygen at a postnatal gestational age of 36 weeks and confirmed by means of radiography; grade III or IV intraventricular hemorrhage confirmed by means of ultrasonography; or cystic periventricular leukomalacia confirmed by means of ultrasonography. Data for infants with the primary outcome events were adjudicated, with masking of the assigned group and (if possible) the method of delivery, by an adjudication committee.

Another outcome was a composite of maternal death or serious maternal morbidity before 28 days post partum, defined as one or more of the following: death; hemorrhage (blood loss ≥1500 ml, need for blood transfusion, or need for dilation and curettage after delivery); laparotomy; genital tract injury (need for hysterectomy; vulvar or perineal hematoma requiring evacuation; broad-ligament hematoma confirmed by means of ultrasonography, CT, or MRI; intraoperative damage to the bladder, ureter, or bowel requiring repair; fistula involving the genital tract; or third-degree or fourth-degree perineal laceration involving the anal sphincter or mucosa); thromboembolism (deep-vein thrombosis, thrombophlebitis, or pulmonary embolism) requiring anticoagulant therapy; systemic infection (temperature ≥38.5°C on two or more occasions at least 24 hours apart, not including the first 24 hours after delivery, or pneumonia confirmed by means of radiography or, if there was sepsis, confirmed by means of blood culture); major medical life-threatening illness (the acute respiratory distress syndrome, amniotic-fluid embolism, disseminated intravascular coagulation, bowel obstruction, or paralytic ileus requiring the use of nasogastric suctioning); wound infection requiring prolongation of the hospital stay, readmission to the hospital, or repeated treatment as an outpatient; wound dehiscence or breakdown; or other serious maternal complication. Adverse events other than predefined measures of morbidity were to be reported to the independent data and safety monitoring board.

Secondary outcomes to be reported subsequently included death or a poor neurodevelopmental outcome among the children at 2 years of corrected age and problematic urinary, fecal, or flatal incontinence among the mothers at 2 years postpartum. Other maternal outcomes included satisfaction with the method of delivery, breast-feeding, quality of life, fatigue, and depression (see the Supplementary Appendix, available at NEJM.org).

**Statistical Analysis**

We calculated that a sample of 2800 pregnancies (5600 twins) was required in order to detect a reduction in the risk of the composite primary outcome of fetal or neonatal death or serious neonatal morbidity from 4% (on the basis of data from the Nova Scotia Atlee Perinatal Database regarding rates of adverse outcomes for twins with vaginal delivery or emergency cesarean section) to 2% with a policy of planned cesarean delivery, with 80% power and a two-sided type I error of 0.05, allowing for a 10% rate of crossover between groups.

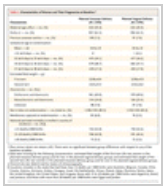
Two interim analyses were performed and reviewed by the data and safety monitoring board. The first interim analysis included data from the first 1000 women who underwent randomization, and the second included data from the first 1800 women who underwent randomization.

Fetal or neonatal death and maternal death were excluded from the analyses of neonatal and maternal morbidity, respectively. Odds ratios and 95% confidence intervals for the composite primary outcome with planned cesarean delivery, as compared with planned vaginal delivery, were calculated with the use of a logistic model with the fetus or infant as the unit of analysis and generalized estimating equations to account for the correlation between the two fetuses or infants from the same pregnancy.[19,20]

Two models were fitted: one with treatment group alone and another with treatment group and the stratification variables of parity and gestational age at randomization. A two-sided P value of 0.05 or less was considered to indicate statistical significance for the composite primary outcome. Since a very stringent level of significance (a two-sided P value of <0.002) was used for the interim analyses, no adjustment for the final analysis was deemed necessary. Standard logistic-regression models were used to compare treatment groups with respect to the maternal composite outcome. Statistical significance was set at a two-sided P value of less than 0.01 for the maternal composite outcome. Although not planned a priori, two-sample t-tests were used to compare treatment-group means with respect to gestational age at delivery, time from randomization to delivery of the first twin, and the interval between the twin deliveries. For these analyses, a two-sided P value of less than 0.05 was considered to indicate statistical significance.

Planned subgroup analyses for the primary outcome were conducted by testing the interaction term between the treatment group and the following baseline variables: parity (0 vs. ≥1), gestational age at randomization (32 weeks 0 days to 33 weeks 6 days, 34 weeks 0 days to 36 weeks 6 days, or 37 weeks 0 days to 38 weeks 6 days), maternal age (<30 years vs. ≥30 years), presentation of the second twin (cephalic vs. noncephalic), chorionicity (dichorionic vs. monochorionic), and the national perinatal mortality in the mother's country of residence (<15 deaths per 1000 births, 15 to 20 deaths per 1000 births, or >20 deaths per 1000 births)[21] (Table 1).

TABLE 1



Characteristics of Women and Their Pregnancies at Baseline.

## RESULTS

### Characteristics of the Participants

Between December 13, 2003, and April 4, 2011, we enrolled 2804 women at 106 centers in 25 countries. A total of 1398 women were randomly assigned to planned cesarean section and 1406 to planned vaginal delivery. The numbers of women recruited in each country are provided in the Supplementary Appendix. Outcome data were available for 1392 women (2783 fetuses or infants) in the planned-cesarean-delivery group and for 1392 women (2782 fetuses or infants) in the planned-vaginal-delivery group (Figure 1).

FIGURE 1

Randomization, Enrollment, and Outcome Data.

Baseline characteristics were similar in the two study groups (Table 1). Most women (82.4%) underwent randomization between 32 weeks 0 days and 36 weeks 6 days of gestation.

Table 2 shows the labor and delivery outcomes for all women. Of the 1393 women randomly assigned to planned cesarean section, 89.9% had a cesarean section for the delivery of both fetuses or infants, 0.8% had a combined vaginal–cesarean delivery, and 9.3% delivered both twins vaginally. Of the 1263 cesarean sections (90.7% of women) in this group, 748 (59.2%) were performed before labor. For women randomly assigned to planned vaginal delivery, 56.2% delivered both twins vaginally, and 4.2% had a combined vaginal–cesarean delivery. The remaining women (39.6%) had a cesarean section for both twins. Of the 610 cesarean sections (43.8% of women), 412 (67.5%) were performed during labor.

TABLE 2

Characteristics of Labor and Delivery for All Pregnancies.

The time from randomization to delivery was shorter in the planned-cesarean-delivery group than in the planned-vaginal-delivery group (mean days, 12.4 vs. 13.3; P=0.04). The mean gestational age at delivery was lower in the planned-cesarean-delivery group than in the planned-vaginal-delivery group (P=0.01).

The characteristics of labor and delivery for women having labor and for women having a vaginal delivery are provided in Table S4 in the Supplementary Appendix. For 95.2% of the women who were assigned to the planned-vaginal-delivery group and who had a vaginal delivery for the first twin, an experienced obstetrician, according to our a priori definition, was present at the time of vaginal delivery.

Table 3 shows the outcomes involving fetal and neonatal death and serious neonatal morbidity. The frequency of the composite primary outcome did not differ significantly between the planned-cesarean-delivery group and the planned-vaginal-delivery group (2.2% and 1.9%, respectively; odds ratio with planned cesarean delivery, 1.16; 95% confidence interval [CI], 0.77 to 1.74; P=0.49). Adding the stratification variables to the model did not materially change the result (odds ratio, 1.16; 95% CI, 0.77 to 1.74; P=0.49). The only stratification variable that was significantly related to the primary outcome was gestational age at randomization (odds ratio for 35 weeks 0 days to 36 weeks 6 days vs. 37 weeks 0 days to 38 weeks 6 days of gestation, 1.83; and odds ratio for 32 weeks 0 days to 33 weeks 6 days vs. 37 weeks 0 days to 38 weeks 6 days, 3.36; P<0.001 for the overall comparison).

TABLE 3

Fetal or Neonatal Outcomes.

There was no significant difference between the planned-cesarean-delivery and planned-vaginal-delivery groups in the frequency of the maternal composite outcome (7.3% and 8.5%, respectively; P=0.29) (Table 4). All adverse events documented during the trial were among the predefined measures of morbidity composing the morbidity component of the primary outcome; no other adverse outcomes were

TABLE 4

reported to the data and safety monitoring board.

Maternal Outcomes.

**Subgroup Analyses**

There were no significant interactions for the primary outcome between treatment group and parity (0 vs. ≥1; P=0.23), gestational age at randomization (32 weeks 0 days to 33 weeks 6 days, 34 weeks 0 days to 36 weeks 6 days, or 37 weeks 0 days to 38 weeks 6 days; P=0.18), maternal age (<30 years vs. ≥30 years; P=0.63), presentation of the second twin (cephalic vs. noncephalic; P=0.51), chorionicity (dichorionic vs. monochorionic; P=0.15), or the national perinatal mortality in the mother's country of residence (<15 deaths per 1000 births, 15 to 20 deaths per 1000 births, or >20 deaths per 1000 births; P=0.50).

The second twin was more likely than the first twin to have the primary outcome (odds ratio, 1.90; 95% CI, 1.34 to 2.69, P<0.001). However, the interaction between treatment group and birth order was not significant (odds ratio for the first twin, 1.30; odds ratio for the second twin, 1.09; P=0.63).

## DISCUSSION

In this large, randomized trial comparing delivery strategies for twins between 32 and 38 weeks of gestation, planned cesarean section did not reduce the risk of fetal or neonatal death or serious neonatal morbidity, as compared with planned vaginal delivery (with cesarean section if medically indicated). We found a higher risk of an adverse perinatal outcome for the second twin than for the first twin, as others have found[8-10]; however, planned cesarean section did not reduce this risk.

There has been controversy regarding the safest method for the delivery of twins at or near term. A policy of planned cesarean section for the delivery of twins gained support after the publication of the Term Breech Trial, which showed that planned cesarean delivery was associated with a reduced risk of an adverse perinatal outcome in the case of a full-term pregnancy with the fetus in the breech presentation.[17,22] Further support for planned cesarean section has come from large cohort studies of twins showing a reduced risk of an adverse perinatal outcome with elective cesarean section, as compared with vaginal delivery or emergency cesarean section.[7,8,10] There are several possible reasons why our results differ from previous observational data: we avoided selection bias, we ensured the presence of an experienced obstetrician at delivery, and many of the twins in our study were born preterm.

We did not find any significant interactions between treatment group and baseline variables, suggesting no significant benefit of planned cesarean delivery for any subgroup tested. However, our study was not powered for these subgroup analyses. Further study may be warranted for the gestational-age subgroup of 37 to 38 weeks, particularly given the limited number of infants in this subgroup.

We did not find that planned cesarean delivery was associated with a higher or lower risk of maternal death or serious maternal morbidity than planned vaginal delivery. This finding may be explained in part by the high rate of cesarean section (>40%) in the planned-vaginal-delivery group, with most of these deliveries occurring during labor.

The strengths of our trial include the randomized design and use of central randomization, the large size of the study (106 participating centers in 25 countries), and a high rate of follow-up. Any possible unblinding of outcome assessors is unlikely to have introduced bias because the criteria for the morbidity outcomes were clearly defined. However, our findings are generalizable only to centers that can provide the obstetrical management specified by the protocol, including the ability to perform an emergency cesarean section within 30 minutes if necessary. On the basis of the 95% confidence interval around the odds ratio for the primary outcome, our results are consistent with no more than a 23% reduction and no more than a 74% increase in the odds of fetal or neonatal death or serious neonatal morbidity with planned cesarean delivery, as compared with planned vaginal delivery.

In conclusion, we found no benefits of planned cesarean section, as compared with planned vaginal delivery, for the delivery of twins between 32 and 38 weeks of gestation, if the first twin was in the cephalic presentation.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

No potential conflict of interest relevant to this article was reported.

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## SOURCE INFORMATION

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The members of the Twin Birth Study Collaborative Group are listed in the Supplementary Appendix, available at NEJM.org.