

Pre-labor Cesarean delivery or induction of labor in twin gestation

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Abstract

BACKGROUND: We aimed to compare neonatal and maternal outcomes of twin gestations without spontaneous onset of labor, which underwent induction of labor or pre-labor cesarean section.

METHODS: In the Twin Birth Study (TBS), women at 32^{0/7}-38^{6/7} weeks of gestation, in whom the first twin was in cephalic presentation, were randomized to planned vaginal delivery or cesarean section. In this secondary analysis of the TBS we focused on the outcomes of the subset of women who did not have a spontaneous onset of labor. We compared those who had an induction of labor with those who had a pre-labor cesarean section. The primary outcome was a composite of fetal or neonatal death or serious neonatal morbidity. Secondary outcome was a composite of maternal morbidity and mortality.

RESULTS: Of the 2,804 women included in the TBS, a total of 1,347 (48%) women did not have a spontaneous onset of labor: 568 (42%) in the planned vaginal delivery arm and 779 (58%) in the planned cesarean arm. Induction of labor was attempted in 409 (30%), and 938 (70%) had a pre-labor cesarean section. The rate of intrapartum cesarean section in the induction of labor group was 41.3%. The rate of the primary outcome was comparable between the pre-labor cesarean section and induction of labor groups (1.65% vs. 1.97%; p=0.61; OR 0.83; 95% CI 0.43-1.62). The maternal composite outcome was found to be lower with pre-labor cesarean section compared to induction of labor (7.25% vs. 11.25%; p=0.01; OR 0.61; 95% CI 0.41-0.91).

CONCLUSION: In women with twin gestation between 32^{0/7}-38^{6/7} weeks of gestation with the first twin in cephalic presentation, induction of labor and pre-labor cesarean section have similar neonatal outcomes. Pre-labor cesarean section is associated with favorable maternal outcomes.

Background

The prevalence of twin gestations is approximately 3% of all pregnancies, and they carry a higher risk profile compared to singleton gestations¹. Some of which may necessitate delivery prior to the spontaneous onset of labor, or the pre-scheduled elective cesarean section (CS).

In attempt to limit perinatal mortality and other adverse neonatal outcome, elective delivery at 37 to 39 weeks of gestation has been widely recommended in twin gestations¹⁻⁶.

There is a paucity of information concerning the outcomes of pre-labor deliveries using induction of labor (IOL) compared to pre-labor CS in twins. Published studies have compared IOL in twin and singleton gestations (rather than IOL in twins versus CS in twins) or limit their analysis to specific subgroups, such as monochorionic twin pregnancies⁷⁻⁹. The Twin Birth Study (TBS) is the largest multicenter, randomized controlled trial, in which women with twin pregnancies between 32^{0/7} and 38^{6/7}, with the first twin in cephalic presentation, were randomized to planned vaginal delivery (VD) or planned CS. Results demonstrated that planned VD had similar neonatal and maternal outcomes compared to a planned CS¹⁰. As the study compared planned modes of delivery, the population included both those who had a

spontaneous onset of labor and those who required delivery by IOL or pre-labor CS (PrICS). Thus, when facing the need to counsel a patient with twins who requires pre-labor obstetrical intervention, there is still a knowledge gap.

This secondary analysis sought to evaluate and compare fetal, neonatal and maternal outcomes in the subset of women who required IOL or PrICS.

Methods

A total of 106 centers in 25 countries participated in the original TBS study between December 2003 and April 2011. A full detailed description of the study protocol is available elsewhere¹⁰, but in brief; Eligibility was limited to women between 32^{0/7} and 38^{6/7} weeks of gestation, with the first twin in cephalic presentation, an estimated fetuses weight between 1500g and 4000g, and two viable fetuses. Women with two or more previous low-segment CS, vertical uterine incision, mono-amniotic twins or any contraindication to vaginal birth were excluded. IOL or PrICS were performed for the indication of “advanced gestational age” in a twin pregnancy (defined as gestational age between 37^{5/7} weeks and 38^{6/7} weeks of gestation) or other obstetrical or medical indications (e.g. preeclampsia).

Method of IOL, oxytocin augmentation protocol, mode of analgesia and the management of the second twin were at the discretion of the attending obstetrician. Ability to perform a cesarean section within 30 minutes if necessary was a stipulation of trial participation.

The primary outcome of the TBS and of this secondary analysis was a composite of fetal or neonatal mortality or serious neonatal morbidity. Serious neonatal morbidity included the following: Birth trauma; Apgar score of less than 4 at 5 minutes; seizures before 72 hours of age; coma; need for assisted ventilation; confirmed septicemia; necrotizing enterocolitis; pneumoatosis intestinalis; bronchopulmonary dysplasia; grade III or IV intraventricular hemorrhage and cystic periventricular leukomalacia. The secondary outcome was a composite maternal outcome, which was defined as any of the following occurring up to 28 days postpartum: Death; severe hemorrhage; laparotomy; genital tract injury; thromboembolism requiring anticoagulation; systemic infection; major medical life-threatening illness; wound infection, dehiscence or breakdown. The full protocol and specific methods of identification of each of these outcomes is detailed in the original manuscript¹⁰.

Utilizing the data from the initial TBS, in this secondary analysis we compared neonatal and maternal outcomes in the subgroup of women who required delivery prior to onset of labor. As the aim of the study was to assess the impact of PrICS and IOL on maternal and neonatal outcomes, we did not follow the original randomization arms and the intention to treat analysis approach. Since, faced with the decision of IOL, some women randomized to the planned VD arm chose to undertake CS, we felt an analysis based on actual attempt of labor (IOL) versus no attempt (pre-labor CS) would be more appropriate.

Continuous outcomes compared between groups using mean \pm standard deviations. Categorical data are presented as percentages, odd ratios (OR) and corresponding 95% confidence intervals (CI). The unit of analysis was the infant when assessing neonatal outcomes. Generalized estimating equations were used to account for the correlation between infants from the same pregnancy. Statistical significance was set to 0.05, two-sided. A sub-analysis of women that required a delivery for “advanced gestational age” in a twin pregnancy (gestational age between 37^{5/7} weeks and 38^{6/7}) was performed as well. Since this analysis was secondary to a randomized clinical trial, no power calculations were performed. The original study and all secondary analyses were approved by the Research Ethics Board at the Sunnybrook Health Sciences Centre.

Results

In the original TBS, 2,804 women were included. A total of 1,347 (48.0%) women required delivery prior to the onset of spontaneous labor: 779 (57.8%) in the planned CS arm and 568 (42.2%) in the planned VD arm. Overall, 31 women (3.9%) in the planned CS arm and 190 women (33.4%) in the planned VD arm crossed over to the other group following a discussion regarding the need for delivery.

Of the 1,347 women who needed a delivery, 409 (30.4%) had an IOL and 938 (69.6%) PrlCS (Figure 1). The groups were significantly different with regards to maternal age, parity, previous cesarean section status, antenatal corticosteroids use, estimated fetal weight of the second twin, and gestational age and presentation at delivery (Table 1). In the IOL group, 155 women (37.9%) had an intrapartum CS for both twins, and 14 (3.4%) had a CS for the second twin.

The rate of the primary neonatal outcome was comparable between the PrlCS and IOL groups (1.65% vs. 1.97%; $p=0.61$; OR 0.83; 95% CI 0.43-1.62). The rates of the individual components of the neonatal composite outcome were similar between the groups as well (Table 2).

The maternal composite outcome was significantly lower in the PrlCS group: 7.25% vs. 11.25% ($p=0.01$; OR 0.61; 95% CI 0.41-0.91), and this difference stemmed primarily from the differences in hemorrhagic morbidity. Compared with women in the IOL group, women in the PrlCS group had significantly lower rates of hemorrhage (6.19% vs. 9.56%; $p=0.02$; OR 0.62; 95% CI 0.40-0.94), and required less postpartum uterine dilatation and curettage (0.32% vs. 1.47%; $p=0.03$; OR 0.21; 95% CI 0.05-0.86). The rate of severe perineal injury (3rd or 4th degree) in the IOL group was 0.98%. There were no significant differences between the two groups in respect to other individual maternal outcomes (Table 3).

We also performed a sub-analysis of women who had IOL or PrlCS for “advanced gestational age” in a twin pregnancy. The characteristics of these women were similar in terms of age, parity, gestational age at delivery, estimated fetal weight of each twin and antenatal steroid use. While the rate of the composite primary neonatal outcome was similar between the two sub-groups, maternal outcome was found to be significantly lower with PrlCS in comparison with IOL (0% vs. 9.41%; $p=0.03$; OR 0.15; 95% CI 0-0.7). Again, this was mainly due to differences in the rates of hemorrhagic episodes. There were no significant

differences between the two sub-groups with respect to individual neonatal or maternal outcomes (Table 4 & Table 5).

Table 1. Characteristics of women who underwent pre-labor cesarean section (PrLCS) or induction of labor (IOL).

Characteristic n (%)	PrICS (n=938)	IOL (n=409)	P
Maternal age (y) mean±SD	29.7 ±6.1	30.5±6.1	0.01
≥30	445 (47.4)	212 (51.8)	0.14
Parity ≥1	560 (59.7)	208 (50.9)	0.003
Previous cesarean section	95 (10.1)	18 (4.4)	0.0005
Estimated fetal weight			
First twin (g) mean±SD	2245±430	2284±420	0.12
Second twin (g) mean±SD	2225±422	2291±432	0.008
Mode of delivery			
Vaginal for both	0	240 (58.7)	
Cesarean for both	938 (100.00)	155 (37.9)	< 0.0001
Vaginal/cesarean	0	14 (3.4)	
Presentation at delivery			
Cephalic/Cephalic	503 (53.6)	276 (67.5)	
Cephalic/Non-cephalic	376 (40.1)	131 (32.0)	< 0.0001
First twin in non-cephalic	58 (6.2)	2 (0.5)	
Gestational age at delivery (wk) Mean±SD			
32 wk 0 days to 33 wk 6 days	37.01± 1.35	37.51± 1.17	< 0.0001
34 wk 0 days to 36 wk 6 days	30 (3.2)	3 (0.7)	
37 wk 0 days to 38 wk 6 days	328 (35.0)	115 (28.1)	< 0.0001
≥39 wk 0 days	560 (59.7)	270 (66.0)	
	20 (2.1)	21 (5.1)	
Interval between deliveries (min) Mean±SD			
	2.2±3.2	12.2±21.2	< 0.0001
Use of antenatal corticosteroids	274 (29.2)	78 (19.1)	< 0.0001
Chorionicity at birth			
Dichorionic- diamnionic	699 (74.5)	304 (74.3)	0.91
Monochorionic-diamnionic	214 (22.8)	92 (22.5)	
Monochorionic-monoamniotic	1 (0.1)	1 (0.2)	

Undocumented

24 (2.6)

12 (2.9)

PrICS- pre-labor cesarean section. IOL- induction of labor.

Table 2. Neonatal outcomes in women who underwent pre-labor cesarean section (PrICS) or induction of labor (IOL).

Outcome n (%)	PrICS (n=938)	IOL (n=409)	Odds Ratio (95% CI)	P
Composite primary outcome	31 (1.7)	16 (2.0)	0.8 (0.4-1.6)	0.61
Death	15 (0.8)	6 (0.7)	1.1 (0.4-3.3)	0.88
Serious neonatal morbidity	16 (0.9)	10 (1.2)	0.7 (0.3-1.6)	0.4
Birth trauma *	2 (0.1)	2 (0.2)	0.4 (0.0-4.8)	0.49
Apgar score <4 at 5 min	2 (0.1)	3 (0.4)	0.28 (0.0-1.7)	0.24
Abnormal level of consciousness †	0	0	-	
≥2 Seizures within 72 hr after birth	0	2 (0.3)		0.09
Assisted ventilation ‡	12 (0.7)	2 (0.3)	2.61 (0.6-11.9)	0.13
Neonatal sepsis within 72 hours after birth	0	0	-	
Necrotizing enterocolitis	0	1 (0.1)		0.30
Cystic periventricular leukomalacia	2 (0.1)	0		0.99

PrICS- pre-labor cesarean section. IOL- induction of labor.

*Birth trauma: Long-bone fracture, other bone fracture, facial-nerve injury at 72 hr of age or at discharge, intracerebral hemorrhage.

†Abnormal level of consciousness: Coma, stupor or decreased response to pain, hyperalert, drowsy, or lethargic.

‡Assisted ventilation for ≥24 hr by means of endotracheal tube, inserted within 72 hr after birth.

Table 3. Maternal outcomes in women who underwent pre-labor cesarean section (PrICS) or induction of labor (IOL).

Outcome n (%)	PrICS (n=938)	IOL (n=409)	Odds Ratio (95% CI)	P
Death or serious maternal morbidity	68 (7.3)	46 (11.3)	0.61 (0.4- 0.9)	0.01
Death	1 (0.1)	1 (0.2)	0.43 (0.0- 7.0)	0.55
Hemorrhage	58 (6.2)	39 (9.6)	0.62 (0.4- 0.9)	0.02
Blood loss \geq 1500 ml	19 (2.0)	14 (3.4)	0.58 (0.3- 1.2)	0.13
Blood transfusion	49 (5.2)	29 (7.1)	0.72 (0.4- 1.2)	0.17
D&C of uterus after delivery*	3 (0.3)	6 (1.5)	0.2 (0.1- 0.9)	0.03
Laparotomy	9 (1.0)	0 (0)	5.5 (1.10- Inf)	0.07
Genital tract injury \times	3 (0.3)	0 (0)	1.7 (0.25- Inf)	0.67
Perineal third- or fourth-degree tear involving anal sphincter	0 (0)	4 (0.98)	0.1 (0-0.5)	0.01
Thromboembolism requiring anticoagulant therapy	5 (0.5)	1 (0.3)	2.2 (0.3- 18.8)	0.47
Infection, excluding wound infection	16 (1.7)	5 (1.2)	1.40 (0.5- 3.9)	0.51
Wound infection †	20 (2.1)	4 (1.0)	2.20 (0.7- 6.5)	0.15
Wound dehiscence or breakdown	12 (1.3)	3 (0.7)	0.17 (0.5- 6.2)	0.38

PrICS- pre-labor cesarean section. IOL- induction of labor.

*D&C- Dilation and curettage.

\times 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.

†Wound infection: Infection requiring prolongation of hospital stay, infection requiring readmission to hospital, infection requiring repeated treatment as an outpatient.

Table 4. Neonatal outcomes in women whose indication for delivery was “advanced gestational age”.

Outcome n (%)	PrICS (n==46)	IOL (n=202)	Odds Ratio (95% CI)	P Value
Composite primary outcome	0 (0)	9 (2.2)		0.35
Death	0 (0)	3 (0.8)		0.99
Serious neonatal morbidity	0 (0)	6 (1.5)		0.36
Birth trauma *	0 (0)	2 (0.5)		0.99
Apgar score <4 at 5 min	0 (0)	2 (0.5)		0.99
Abnormal level of consciousness †	0 (0)	0 (0.0)	N/E	
≥2 Seizures within 72 hr after birth	0 (0)	1 (0.3)		0.99
Assisted ventilation‡	0 (0)	1 (0.3)		0.99
Neonatal sepsis within 72 hours after birth	0 (0)	0 (0)	N/E	
Necrotizing enterocolitis	0 (0)	0 (0)	N/E	
Cystic periventricular leukomalacia	0 (0)	0 (0)	N/E	

PrICS- pre-labor cesarean section. IOL- induction of labor.

*Birth trauma: Long-bone fracture, other bone fracture, facial-nerve injury at 72 hr of age or at discharge, intracerebral hemorrhage.

N/C- No Convergence. N/E- No Events.

†Abnormal level of consciousness: Coma, stupor or decreased response to pain, hyperalert, drowsy, or lethargic.

‡Assisted ventilation for ≥24 hr by means of endotracheal tube, inserted within 72 hr after birth.

Table 5. Maternal outcomes in women whose indication for delivery was “advanced gestational

Outcome n (%)	PrICS (n=46)	IOL (n=202)	Odds Ratio (95% CI)	P Value
Death or serious maternal morbidity	0 (0)	19 (9.4)	0.15 (0-0.7)	0.03
Death	0 (0)	1 (0.5)	4.39 (0-83.4)	0.99
Hemorrhage	1 (2.2)	17 (8.5)	0.23 (0.0-1.8)	0.17
Blood loss ≥1500 ml	0 (0)	6 (3.0)	0.52 (0-2.8)	0.58
Blood transfusion	1 (2.2)	13 (6.5)	0.32 (0.0-2.5)	0.28
D&C of uterus after delivery	0 (0)	2 (1.0)	1.81 (0-15.3)	0.99
Laparotomy	0 (0)	0 (0)	-	
Genital tract injury	0 (0)	0 (0)	-	
Perineal third- or fourth-degree tear involving anal sphincter	0 (0)	1 (0.5)	4.39 (0-83.4)	0.99
Thromboembolism requiring anticoagulant therapy	0 (0)	0 (0)	-	
Infection, excluding wound infection	0 (0)	2 (1.0)	1.81 (0-15.3)	0.99
Wound infection*	0 (0)	3 (1.5)	1.13 (0-7.6)	0.99
Wound dehiscence or breakdown	0 (0)	1 (0.5)	4.39 (0-83.4)	0.99

age”.

PrICS- pre-labor cesarean section. IOL- induction of labor.

*Wound infection: Infection requiring prolongation of hospital stay, infection requiring readmission to hospital, infection requiring repeated treatment as an outpatient.

Discussion

The initial TBS found no major differences in perinatal morbidity or mortality between planned vaginal delivery and planned cesarean section in women with twin gestations at 32^{0/7}-38^{6/7} with the first twin in cephalic presentation¹⁰. A recent secondary analysis of the TBS showed no change in neonatal or

maternal outcomes between the study arms in women who presented with spontaneous labor¹¹. In this secondary analysis we reviewed the outcomes of those women who did not have a spontaneous onset of labor, but had either IOL or PrICS. Analysis of this group comes with the difficulty of cross over between the original randomization groups. The high cross over rate from the original TBS planned vaginal delivery arm to the PrICS group may be partially explained by higher rate of non-cephalic presentation at delivery (either twin) found in the PrICS group in compare to the IOL group. An increased risk for intra-partum CS following IOL in twins⁸ is another possible factor affecting maternal decision to choose PrICS over IOL. An earlier gestational age at delivery at the PrICS group might represents higher risk fetuses with indications for delivery at an earlier stage of pregnancy. Hypothetically, higher risk fetuses are prone to increase rate of neonatal morbidity and mortality. Despite this, perinatal outcomes were comparable between the PrICS and IOL groups, which may represent an overall more favorable result for PrICS if the groups had been evenly matched in fetal risk level.

Our results correlate with the original TBS regarding neonatal outcomes, but differ in showing lower risk of adverse maternal outcomes in PrICS, compared with IOL. The composite maternal outcome was higher in the IOL group mainly due to differences in hemorrhagic morbidity. This held true among the subset of women whose delivery was indicated due to “advanced gestational age” in a twin pregnancy.

We are aware of the high rate of intra-partum CS in the IOL group, compared to what has been reported in singleton pregnancies following IOL^{12,13}. We postulate that a prior higher risk for CS in twins¹⁴ in addition to late maternal age and increased rate of nulliparity (both has been associated with an intra-partum CS following IOL) can explain this finding^{15,16}. The increased maternal morbidity in the IOL group may be explained by the high rate of intra-partum CS in these women (41.3%).

There is minimal evidence regarding the relative safety of IOL versus CS of twins for women not in labor. Previous studies compared IOL in twins with IOL in singletons^{7,8}, or compared IOL in twins with expectant management¹⁷. Our finding of fewer maternal adverse outcomes with CS is in contrast to studies performed by Drassinower et al¹⁸ and Ylilehto et al¹⁹. Drassinower’s study of 1009 twin pregnancies found no significant difference in maternal hemorrhage or need for blood transfusion between cases of trial of labor or CS¹⁸. Similarly, Ylilehto et al, in a single center cohort study of 495 twin gestations, found fewer adverse maternal outcomes in the trial of labor group compared to elective CS group¹⁹. Of note, both studies included spontaneously laboring women and pre-labor women requiring IOL in the same group, and had small study groups compared to the TBS population. An argument can be made concerning safety of IOL in twins, and the various methods of IOL in twins. A secondary analysis by our group showed that there was no difference in maternal or fetal outcomes between methods of labor induction²⁰.

The strength of this secondary analysis lies in its size, multiple site recruitment and high rate of follow up on which to base results. It is a pioneer study to compare maternal outcomes in twin gestations that required delivery while not in labor. One might consider loss of intention to treat as a study weakness, as

intention to treat analysis aims to give an unbiased estimate of treatment effect and preserves prognostic balance^{21,22}. However, an analysis where attempted vaginal delivery (IOL) was compared to no attempt at vaginal delivery (PrICS) gives results more akin to true life. This garners more representative results for clinical application and is beneficial when counseling patients with twins facing IOL. The main limitations of this study include the secondary analysis nature, not planned a priori, and therefore not powered to detect significant change between attempted modes of delivery in those who did not labor spontaneously. Lastly, neonatal complications found in this study may be impacted by confounding factors, such as gestational age at delivery or other obstetric complications, and not be exclusively related to mode of delivery.

Conclusion

In twin pregnancies between 32^{0/7} and 38^{6/7} weeks of gestation who require delivery prior to onset of labor, our limited data suggests no fetal or neonatal benefit in either IOL or CS but possible maternal benefit with CS.

Abbreviations

CS- Cesarean section; IOL -Induction of labor; TBS- Twin Birth Study; VD- Vaginal delivery; PrICS- Pre-labor Cesarean section; OR- odd ratios; CI- confidence intervals.

Declarations

Ethics approval and Consent to participate:

The Twin Birth Study and all secondary analyses were approved by the Research Ethics Board at the Sunnybrook Health Sciences Centre.

Availability of data and materials:

The data that support the findings of this study are available from Twin Birth Study but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Twin Birth Study.

Competing interest:

The authors declare that the authors Nir Melamed and Amir Aviram are members of the editorial board of the BMC Pregnancy and Childbirth.

Authors' contributions:

MDE - Conceived the idea for the study and conducted the analysis.

AA, WAR - Analyzed and interpreted the patient data.

DC, AA, MN, GL, AEV, AS, BJFR, MDE- Major contributor in writing the manuscript, oversaw drafting and revision of the manuscript for submission.

All authors read and approved the final manuscript.

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Consent for publication:

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Figures

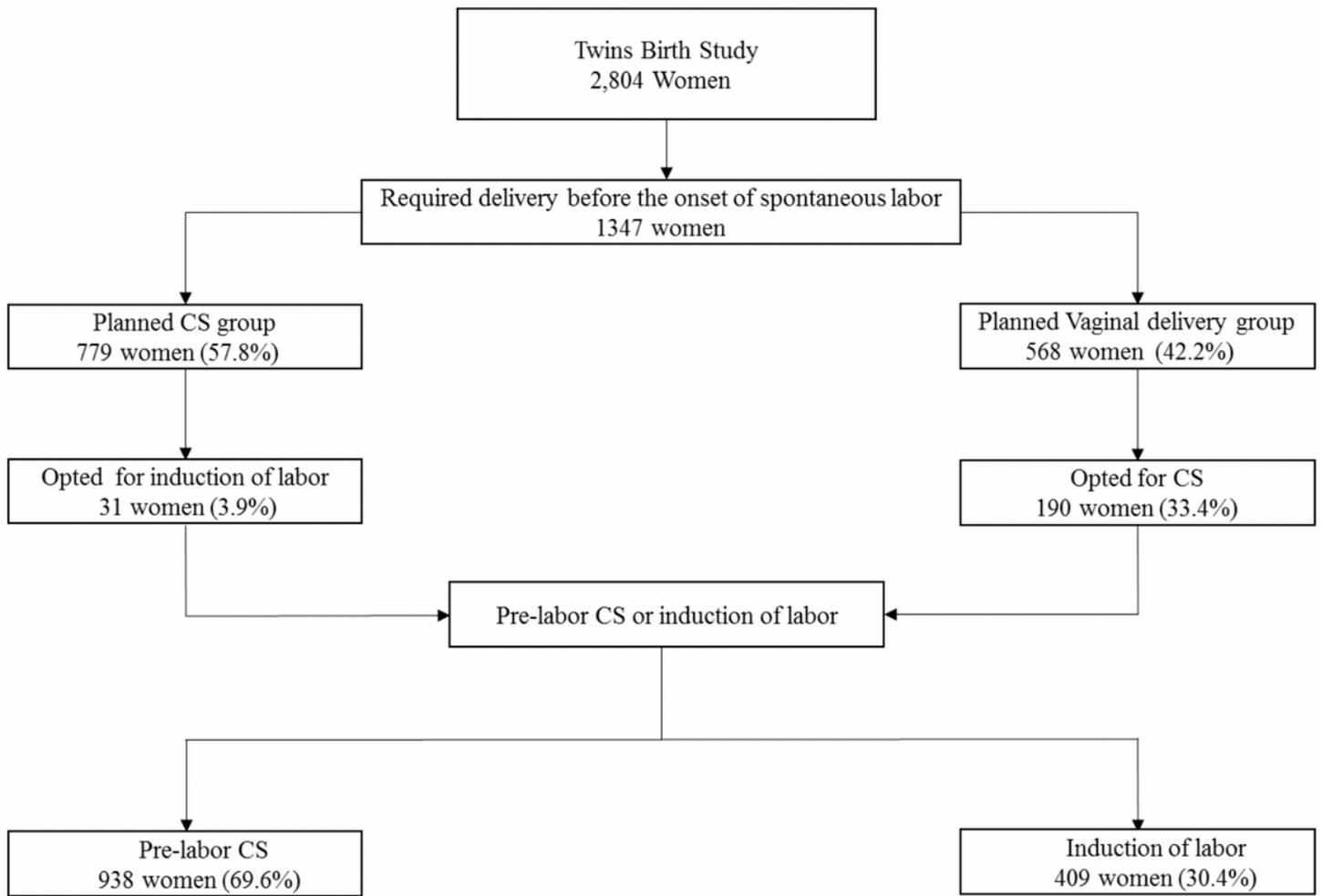


Figure 1

Flow chart of women who underwent pre-labor cesarean section (CS) or induction of labor