Induction of labor in twin gestation: lessons from a population based study

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Abstract

Introduction: The route of delivery and the role of induction of labor in twin gestations are controversial. The aim of this study was to determine the efficacy of induction of labor in twin gestations.

Methods: This retrospective population based cohort study included 4605 twin gestations divided into following groups: 1) spontaneous parturition (n = 2937, 63.78%); 2) induction of labor (n = 653, 14.2%) and 3) elective cesarean delivery (n = 1015, 22.04%).

Results: The rate of vaginal delivery in the labor induction group was 81% (529/653). In comparison to the other study groups, induction of labor in twins was independently associated with a 77% reduction in the risk of cesarean delivery (OR 0.23; 95% CI 0.18–0.31) and a 78% reduction in the risk of postpartum death for the second twin (OR 0.22; 95% CI 0.05–0.94). The rate of nulliparity, term delivery and labor dystocia was higher in the induction of labor group (p < 0.001 in all comparisons).

Conclusions: Our results suggest that induction of labor in twin gestation is successful and is independently associated with substantial reduction in the risk of cesarean delivery and postpartum death of the second twin.

Keywords

Cesarean delivery, Foley catheter, oxytocin, prostaglandins, term pregnancy

Introduction

Twin pregnancies account for approximately 3% of all gestations [1]. The incidence of these pregnancies in the western world increased by approximately 100% during the past three decades. Indeed, the rate of twin deliveries, out of all US live births, increased from 2.2% in 1990 to 3.2% in 2005 [2] and reached a steady state thereafter [3,4]. This observation is in contrast to the expected frequency of twins and triplets by Hellin’s law [5] (twin’s gestation to be 1/90 and triplets 1/8100 pregnancies). Two factors have contributed substantially to the increased incidence of twin gestations: the delay of childbirth to advance maternal age and the increased use of assisted reproduction technologies [6–8].

Multiple pregnancies are associated with increased maternal and neonatal morbidity. Indeed, the prevalence of pregnancy complications (i.e. preeclampsia, gestational diabetes and preterm birth) occurs three to seven times more often in these gestations [9]. In addition, perinatal morbidity is increased from 4- to 10-fold in multiple as compared to singleton gestations [9]. Aside the common perinatal morbidity described above, twin’s pregnancies have specific complications [10,11].

In addition, the higher risk of stillbirth in twin pregnancies than in singleton has been long recognized, as described in the early report by the Dublin Lying-in Hospital dating to 1784: “one-half more twins die and near one-third more are stillborn, than of single children” [12]. Collectively, these data led to a controversy regarding the route of delivery and the role of induction of labor in twin gestations. The latter is one of the most common procedures in modern obstetrics, which assist the physician in addressing maternal and/or fetal conditions necessitating delivery. The incidence of induction of labor in singleton rose between 1983 and 1996 from 7.5% to 26% [13], and it is approximately 20% today [1]. Similar findings were reported for twin
gestations, in which the proportion of labor induction increased by 136% (from 5.8% in 1989 to 13.8% in 1999) together with a concomitant decrease in the rates of stillbirth [14]. Currently with the growing number of cesarean deliveries, there is a controversy regarding the utilization of induction of labor as an effective tool for delivering twin gestations. Data regarding the safety and efficacy of induction of labor in twin gestation are lacking. Therefore, the current study was designed as a population based cohort that aims to address this gap in the obstetrical literature.

Materials and methods

This is a population based retrospective cohort study including all pregnant women with twin gestation who delivered at the Soroka University Medical Center since 1988–2010 (n = 4605). The Department of Obstetrics and Gynecology at our medical center has a computerized database of all the deliveries; the information is captured from the patient’s medical records and is coded according to the International Classification of Diseases 9th Revision diagnosis into the database by trained secretaries. The use of the database was feasible since Soroka University Medical Center is a tertiary medical center that is exclusively serving the population of the Negev, and all the deliveries of the region take place in its labor and delivery suites. The study was approved by the Soroka University Medical Center institutional review board committee (IRB 0097-12-SOR). Records/information were anonymized and de-identified prior to analysis.

All twin gestation who delivered after 24 complete gestation weeks were included. Women with fetuses who had congenital anomalies or chromosomal abnormalities were excluded. The women included in the study were divided into the following groups: (1) spontaneous parturition (n = 2937); (2) induction of labor (n = 653) and (3) elective cesarean delivery (n = 1015).

Data regarding demographic characteristics, medical and obstetric history and current pregnancy, as well as delivery and neonatal outcome were obtained from the computerized database. Our database is constantly tested and validated by the Department of Epidemiology at the Ben-Gurion University of the Negev (Beer Sheva, Israel). Clinical definitions are detailed in the Supplementary file.

Our Institution has a policy to allow induction of labor in all monochorionic/biamniotic and dichorionic twin pregnancies where the leading twin is in vertex presentation, and internal podalic version and total breech extraction was performed in cases of non-vertex second twin. After delivery of the first vertex twin, the delivery of the second vertex twin is performed according to clinical judgment arising from fetal conditions. As a consequence, either expectant management (leaving the membranes intact and without setting a maximum delay between the delivery of first and second twin) or active management in which the attending physician ruptures the membrane and actively delivers the patient by oxytocin administration is possible. In case of a non-vertex second twin, the delay until delivery of the second twin is kept minimum by performing internal podalic version.

All vaginal twin deliveries are assisted by a certified ob/gyn specialist.

Statistical analysis

Background characteristics, as well as medical history, pregnancy and outcome characteristics were compared among the three study groups using parametric or non-parametric tests, including Chi square, t-test and Mann–Whitney U tests, according to the their type and distribution. A value of p < 0.05 was considered statistically significant.

Our study is aimed to deal with the success rate of vaginal delivery following induction of labor in twins and for this the group of induction of labor was compared with that of spontaneous parturition. The second aim of the study was to assess the safety of the process and for that we included the comparison versus woman who had elective cesarean delivery (which are not eligible for the primary outcome of the study, which is a successful vaginal delivery, but are part of the reference group for the safety of the process of induction in relation to the maternal and neonatal complications of the leading as well as the second twin). Multivariable logistic models were used to assess the risk of adverse pregnancy outcomes that were associated with the induction of labor. Variables that reached statistical significance of p < 0.1 at the univariate level were adjusted for. In order to control the pregnancies occurring in the same woman, we used Generalized Estimating Equation (GEE) multivariate models [15], in which multiple pregnancies of the same woman were entered as nonhierarchical clusters and similarities within the clusters were controlled for. Statistical analysis was performed with the SPSS package 19th edition (SPSS Inc., Chicago, IL).

Results

Maternal characteristics of the study groups are presented in Table 1. Maternal age distribution differed among the study group. The rate of teenage pregnancies was the highest in the spontaneous labor group, and advanced maternal age was more prevalent in the elective cesarean delivery group (p < 0.001). The rate of nulliparity was higher in the induction groups than in the other study groups (p < 0.001). The rates of assisted reproduction, obesity and Jewish origin were higher in women who had elective cesarean than those who had spontaneous delivery or induction of labor (Table 1).

Overall the combination of surgical induction and oxytocin administration was the most common form of induction (73.4%, 479/653). One hundred and seventy-four (26.6%) patients needed ripening of the cervix prior to induction in the labor floor. Two methods for cervical ripening were used: Foley catheter was used in 130 (74.7%, 130/174) women and prostaglandins were employed in the remaining [n = 44 (25.3%)] as the primary method for cervical ripening.

Among all inductions, 50% were performed at term, while only 35% of the spontaneous delivery and 46.9% of the elective cesarean deliveries were performed after 37 weeks (Figure 1).

Table 2 describes the clinical characteristics of the study groups. The rate of anemia and diabetes differed among the groups being the highest in the elective cesarean delivery.
The rate of mild preeclampsia was lowest in the spontaneous parturition group as compared to the other study groups. The rate of placental abruption was significantly lower in the induction group compared to the spontaneous delivery group (1.2% versus 2%, \( p < 0.001 \)), while labor dystocia was more prevalent in women undergoing induction of labor (10.8% versus 2.1%, \( p < 0.001 \)).

The rate of cord prolapse and non-reassuring fetal heart rate did not differ between the spontaneous parturition and induction of labor groups neither for the first twin nor for the second one.

The overall rate of cesarean births was 44.3% in the spontaneous parturition group (1300/2937) and 14.4% in the induction group (94/653) \( p < 0.001 \). Of interest, the rate of cesarean deliveries of the second twin was similar between the two groups (5.2% versus 4.6%, \( p < 0.001 \)). The rate of vaginal delivery in the induction group was 81.0% (Table 2).

In contrast, the rate of vacuum extraction was significantly higher in the induction of labor group both for first and second twin \( p < 0.0001 \) for first twin, \( p = 0.002 \) for second twin) (Table 3).

The rate of total perinatal mortality differed among the study groups being the highest in the spontaneous delivery group. The rate of antepartum death was higher in the induction of labor group versus the other study groups while the rate of neonatal death was higher in the spontaneous delivery group in comparison to the other study group \( p < 0.001 \) (Table 4).

The rate of very low birth weight was substantially higher in the first and second twin of the spontaneous delivery group as compared to the other study groups (Figure 2).

The rate of Apgar score \( 5 \) at 1 and 5 min of the first and second twin was significantly higher in the spontaneous delivery group (Table 5).

**Table 1. Maternal demographic characteristics.**

| Maternal characteristics | Elective cesarean \( n = 1015 \) | Spontaneous delivery \( n = 2937 \) | Induction of labor \( n = 653 \) | \( p \) values |
|-------------------------|---------------------------------|---------------------------------|-----------------------------|-------------|
| Ethnicity               |                                 |                                 |                             |             |
| Jews                    | 625 (61.6)                      | 1417 (48.2)                     | 384 (58.8)                  | \( p < 0.001 \) |
| Bedouins                | 390 (38.4)                      | 1520 (51.8)                     | 269 (41.2)                  |             |
| Maternal age            |                                 |                                 |                             |             |
| \( \leq 20 \)           | 24 (2.4)                        | 123 (4.2)                       | 21 (3.2)                    | \( p < 0.001 \) |
| 21–35                   | 751 (74.0)                      | 2239 (76.2)                     | 548 (83.9)                  |             |
| \( \geq 36 \)           | 240 (23.6)                      | 575 (19.6)                      | 84 (12.9)                   |             |
| Gravidity               |                                 |                                 |                             |             |
| 1                       | 242 (23.8)                      | 659 (22.4)                      | 178 (27.3)                  | \( p < 0.001 \) |
| 2–4                     | 473 (46.6)                      | 1307 (44.5)                     | 314 (48.2)                  |             |
| \( \geq 5 \)            | 300 (29.6)                      | 970 (33.0)                      | 160 (24.5)                  |             |
| Parity                  |                                 |                                 |                             |             |
| 1                       | 314 (30.9)                      | 807 (27.5)                      | 226 (34.6)                  | \( p < 0.001 \) |
| 2–4                     | 481 (47.4)                      | 1370 (46.6)                     | 313 (47.9)                  |             |
| \( \geq 5 \)            | 220 (21.7)                      | 760 (25.9)                      | 114 (17.5)                  |             |
| Smoking                 | 12 (1.2)                        | 38 (1.3)                        | 6 (0.9)                     | 0.3         |
| Obesity                 | 27 (2.7)                        | 29 (1.0)                        | 7 (1.1)                     | \( p < 0.001 \) |
| Infertility treatment   | 365 (36.0)                      | 692 (23.6)                      | 171 (26.2)                  | \( p < 0.001 \) |

Data is presented as number (percentage).
The rate of meconium stained amniotic fluid in the first twin was the highest in the induction of labor group in comparison to the two other study groups \( (p = 0.01) \). This difference was not significant for the second twin. When considering mortality according to twin order, the overall mortality was higher in the spontaneous labor group for both first and second twin \( (p < 0.001) \). In addition, the rate of antepartum death was higher in the labor induction group in comparison to the other study groups, while patients delivering spontaneously had a significantly higher rate of postpartum death, for both twins (Table 6).

The median time interval between delivery of the twins was three minutes with a minimum interval of one minute and a maximum of 24 h.

### Table 2. Maternal clinical characteristics and pregnancy outcomes.

| Maternal characteristics and pregnancy outcomes | Elective cesarean \( n = 1015 \) | Spontaneous delivery \( n = 2937 \) | Induction of labor \( n = 653 \) | \( p \) values |
|-------------------------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|----------------|
| Anemia                                          | 541 (53.3)                        | 1309 (44.6)                       | 305 (46.7)                        | <0.001         |
| Diabetes                                        | 121 (11.9)                        | 235 (8.0)                         | 63 (9.6)                          | <0.001         |
| Mild preeclampsia                               | 74 (7.3)                          | 149 (5.1)                         | 49 (7.5)                          | 0.002          |
| Severe preeclampsia                             | n/a                               | 138 (4.7)                         | 22 (3.4)                          | 0.13           |
| Postpartum hemorrhage                           | 62 (6.1)                          | 186 (6.3)                         | 40 (6.1)                          | 0.958          |
| Cord prolapse                                   |                                   |                                   |                                   |                |
| 1st twin                                        | n/a                               | 59 (2.0)                          | 8 (1.2)                           | 0.116          |
| 2nd twin                                        | n/a                               | 53 (1.8)                          | 8 (1.2)                           | 0.195          |
| Non reassuring fetal heart rate                 |                                   |                                   |                                   |                |
| 1st twin                                        | n/a                               | 103 (3.5)                         | 28 (4.3)                          | 0.197          |
| 2nd twin                                        | n/a                               | 84 (2.9)                          | 19 (2.9)                          | 0.514          |
| Placental abruption                             | n/a                               | 59 (2.0)                          | 8 (1.2)                           | <0.001         |
| Arrest of dilation                              | n/a                               | 30 (1.0)                          | 46 (7.0)                          | <0.001         |
| Arrest of descent                               | n/a                               | 32 (1.1)                          | 25 (3.8)                          | <0.001         |
| Wound infection                                 | 6 (0.5)                           | 5 (0.2)                           | 0                                 | 0.026          |
| Preterm birth <37                                | 539 (53.1)                        | 1909 (65.0)                       | 323 (49.5)                        | <0.001         |
| Preterm birth <34                                | n/a                               | 773 (26.3)                        | 68 (10.4)                         | <0.001         |
| Mode of delivery                                |                                   |                                   |                                   |                |
| Both vaginal                                    | n/a                               | 1485 (50.6)                       | 529 (81)                          | <0.001         |
| Cesarean section on 2nd twin                    | n/a                               | 152 (5.2)                         | 30 (4.6)                          | 0.958          |
| Cesarean section                                | 1015 (100)                        | 1300 (44.3)                       | 94 (14.4)                         | <0.001         |

Data is presented as number (percentage); n/a, not available.

### Table 3. Characteristics of the delivery, according to twin order.

| Characteristics of the delivery | Elective cesarean \( n = 1015 \) | Spontaneous delivery \( n = 2937 \) | Induction of labor \( n = 653 \) | \( p \) values |
|---------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|----------------|
| Breech presentation             |                                   |                                   |                                   |                |
| 1st twin                        | 501 (49.4)                        | 701 (23.9)                        | 15 (2.3)                          | <0.001         |
| 2nd twin                        | 399 (39.3)                        | 1033 (35.2)                       | 158 (24.2)                        | <0.001         |
| Assisted breech delivery        |                                   |                                   |                                   |                |
| 1st twin                        | n/a                               | 58 (2.0)                          | 4 (0.6)                           | 0.007          |
| 2nd twin                        | n/a                               | 490 (16.7)                        | 135 (20.7)                        | 0.01           |
| Vacuum extraction               |                                   |                                   |                                   |                |
| 1st twin                        | n/a                               | 45 (1.5)                          | 26 (4.0)                          | <0.001         |
| 2nd twin                        | n/a                               | 46 (1.6)                          | 22 (3.4)                          | 0.002          |

### Table 4. Neonatal characteristics and outcomes, without identification of twin order.

| Neonatal characteristics and outcomes | Elective cesarean \( n = 1015 \) | Spontaneous delivery \( n = 2937 \) | Induction of labor \( n = 653 \) | \( p \) values |
|--------------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|----------------|
| Gender, Male                         | 1050 (51.7)                       | 2954 (50.4)                       | 658 (50.4)                        | 0.714          |
| LBW                                  | 1117 (55.0)                       | 4045 (68.9)                       | 713 (54.6)                        | <0.001         |
| VLBW \( \leq 1500 \)                 | 42 (2.1)                          | 865 (14.7)                        | 62 (4.7)                          | <0.001         |
| IUGR                                 | 96 (4.7)                          | 132 (2.2)                         | 30 (2.3)                          | <0.001         |
| Mortality (total)                    | 21 (1.0)                          | 323 (5.5)                         | 45 (3.4)                          | <0.001         |
| APD                                  | 14 (0.7)                          | 74 (1.3)                          | 30 (2.3)                          | 0.034          |
| IPD                                  | 0 (0.0)                           | 11 (0.1)                          | 1 (0.1)                           | 0.67           |
| PPD                                  | 7 (0.3)                           | 238 (4.1)                         | 14 (1.1)                          | <0.001         |
| Meconium stained amniotic fluid      | 37 (1.8)                          | 161 (2.7)                         | 43 (3.3)                          | <0.001         |

Data is presented as number (percentage). LBW, low birth weight; VLBW, very low birth weight; IUGR, intrauterine growth restriction; APD, antepartum death; IPD, intrapartum death; PPD, postpartum death.
Table 5. Neonatal characteristics, according to twin order.

| Neonatal characteristics | Elective cesarean | Spontaneous delivery | Induction of labor | p values |
|--------------------------|-------------------|----------------------|-------------------|----------|
|                         | n = 1015          | n = 2937             | n = 653           |          |
| Gender 1st twin          |                   |                      |                   |          |
| Male                     | 527 (51.9)        | 1499 (51.0)          | 328 (50.2)        | 0.79     |
| Female                   | 488 (48.1)        | 1438 (49.0)          | 325 (49.8)        |          |
| Gender 2nd twin          |                   |                      |                   |          |
| Male                     | 523 (51.5)        | 1455 (49.5)          | 330 (50.5)        | 0.54     |
| Female                   | 492 (48.5)        | 1482 (50.5)          | 323 (49.5)        |          |
| SGA                      |                   |                      |                   |          |
| 1st twin                 | 122 (12.0)        | 392 (13.3)           | 99 (15.2)         | 0.045    |
| 2nd twin                 | 185 (18.2)        | 515 (17.5)           | 100 (15.3)        | 0.21     |
| Apgar 1<7                |                   |                      |                   |          |
| 1st twin                 | 102 (10.0)        | 477 (16.2)           | 43 (6.6)          | <0.001   |
| 2nd twin                 | 121 (11.9)        | 669 (22.8)           | 91 (13.9)         | <0.001   |
| Apgar 5<7                |                   |                      |                   |          |
| 1st twin                 | 9 (0.9)           | 177 (7.6)            | 19 (2.9)          | <0.001   |
| 2nd twin                 | 27 (2.7)          | 208 (7.1)            | 36 (5.5)          | <0.001   |

Data is presented as number (percentage). SGA, small for gestational age.

Table 6. Neonatal outcomes, according to twin order.

| Patients characteristics | Elective cesarean | Spontaneous delivery | Induction of labor | p values |
|--------------------------|-------------------|----------------------|-------------------|----------|
|                         | n = 1015          | n = 2937             | n = 653           |          |
| Meconium stained amniotic fluid |                   |                      |                   |          |
| 1st twin                 | 30 (3.0)          | 139 (4.7)            | 39 (6.0)          | 0.01     |
| 2nd twin                 | 7 (0.7)           | 22 (0.7)             | 4 (0.6)           | 0.93     |
| Total mortality          |                   |                      |                   |          |
| 1st twin                 | 5 (0.5)           | 158 (5.4)            | 19 (2.9)          | <0.001   |
| 2nd twin                 | 16 (1.6)          | 165 (5.6)            | 26 (4.0)          | <0.001   |
| APD                      |                   |                      |                   |          |
| 1st twin                 | 3 (0.3)           | 33 (1.1)             | 12 (1.8)          | 0.008    |
| 2nd twin                 | 11 (1.1)          | 41 (1.4)             | 18 (2.8)          | 0.016    |
| IPD                      |                   |                      |                   |          |
| 1st twin                 | 0 (0.0)           | 7 (0.2)              | 1 (0.2)           | 0.29     |
| 2nd twin                 | 0 (0.0)           | 4 (0.1)              | 0 (0.0)           | 0.32     |
| PPD                      |                   |                      |                   |          |
| 1st twin                 | 2 (0.2)           | 118 (4.0)            | 6 (0.9)           | <0.001   |
| 2nd twin                 | 5 (0.5)           | 120 (4.1)            | 8 (1.2)           | <0.001   |

Data is presented as number (percentage). APD, antepartum death; IPD, intrapartum death; PPD, postpartum death.
A multivariable logistic model was constructed to study the probability of cesarean delivery in women attempting labor with twin gestation. The model was adjusted for the possible confounding variables: gestational age at delivery, maternal age, labor dystocia, preeclampsia, abnormal presentation, assisted reproductive technique and non-reassuring fetal heart rate. Women who had induction of labor had a protective effect and an independently lower risk of cesarean delivery in comparison to the spontaneous parturition group (adj. OR 0.233, 95% confidence interval (CI) 0.176–0.308) (Table 7).

Additional logistic regression models were built, separately for each of the twins, to study the association between induction of labor and neonatal death. The models were adjusted for gestational age at delivery, birthweight, lack of prenatal care and maternal age. No association was found between first twin neonatal death and labor induction as compared to elective cesarean (Table 8). Regarding the mortality of the second twin, induction of labor seems to have a protective effect in comparison to elective cesarean delivery (adj. OR 0.22, 95% CI 0.05–0.94) (Table 8).

**Discussion**

**Principle findings of the study**

1. Induction of labor is associated with a high rate of success in vaginal delivery; (2) it is associated with a lower rate of cesarean deliveries than those who come with spontaneous labor; (3) the rate of neonatal death is lower in women undergoing induction of labor than spontaneous labor.

**When to deliver twin gestation?**

The timing of delivering twin gestations is under constant debate. Some studies have suggested that it is prudent to intervene in twin pregnancies between 37 and 38 weeks of gestation and that due to an increased risk of mortality and morbidity, twin pregnancies should not continue beyond 39 weeks of gestation [16,17]. Moreover, Warner et al. reported that the optimal pregnancy outcomes occur earlier in twin versus singleton gestations [17]. The association between advancing gestational age and the risk of morbidity and mortality in multiple pregnancies is well established [16,18–22]. Cincotta and colleagues [19] studied the gestational age-specific stillbirth risk for twins and singleton gestations. They concluded that while the gestation-specific rise in stillbirth rate occurs in singletons pregnancies at 40 weeks and beyond, in twins this risk increases from 36 weeks of gestation and onwards [19]. Minakami and Sato [22] suggested that the estimated date of confinement in twin pregnancies is between 37 and 38 weeks of gestation. This is based on retrospective information obtained from almost 89,000 infants born to Japanese women with twin pregnancy. This study found a mean gestation at birth for twins of 37 weeks, with the risk of stillbirth and early neonatal death increasing after 38 weeks of gestation [22]. The lowest risk of perinatal death in twin pregnancies at 38 weeks of gestation corresponded to that observed in singleton pregnancies at 43 weeks of gestation [22]. Similar reports from Sweden [18] and the USA [16] supported the findings that the lowest gestational age specific risk for unexplained intrauterine death is between 37 and 38 weeks of gestation [16,18–21].

Collectively, the results of these studies lead to the development of the current recommendation regarding the time of delivery of twin gestation. These recommendations vary among the different societies around the world, the National Institute of Child Health and Human Development (NICHD) and the Society for Maternal-Fetal Medicine (SMFM) suggested delivery at 38 weeks for uncomplicated dichorionic twins and 34–37 weeks for uncomplicated monochorionic diamniotic twins [23]. The National Institute for Health and Clinical Excellence (NICE) recommends elective delivery of dichorionic twin pregnancies from 37 weeks of gestation and monochorionic twin pregnancies from 36 weeks (after a course of corticosteroids) [24]. The American College of Obstetricians and Gynecologists (ACOG) recommends delivery of uncomplicated dichorionic twins at 38+0/7 to 38+6/7 weeks and uncomplicated monochorionic twins at 34+0/7 to 37+6/7 weeks of gestation [25]. As of today, the general recommendation is to deliver dichorionic twins between 38 and 39 weeks of gestation and monochorionic around 37 weeks. The gestational age at delivery varied in our study among the groups. Almost 25% of the spontaneous twin deliveries occurred prior to 34 weeks of gestation and about 10% of the inductions that

Table 7. Generalized Estimated Equation (GEE) model for the identification of risk factors for cesarean section.

| Co-variables | Adj. OR (95% CI) | p values |
|--------------|-----------------|---------|
| Spontaneous labor | 1 (reference group) |         |
| Induction of labor | 0.233 (0.176–0.308) | <0.001 |
| Gestational age (weeks) | 0.909 (0.888–0.932) | 0.001 |
| Maternal age | 1.04 (1.023–1.055) | <0.001 |
| Arrest of dilatation | 143.56 (43.19–477.12) | <0.001 |
| Arrest of descent | 2.01 (1.08–3.73) | 0.027 |
| Preeclampsia | 4.198 (0.53–33.22) | 0.174 |
| Abnormal presentation | 19.09 (14.87–24.52) | <0.001 |
| Infertility treatment | 2.48 (2.04–3.02) | <0.001 |
| Non reassuring fetal heart rate | 5.65 (3.59–8.89) | <0.001 |

Table 8. Generalized Estimated Equation (GEE) model for the identification of risk factors for postpartum death in the twins.

| Co-variables | Adj. OR (95% CI) | p values |
|--------------|-----------------|---------|
| (a) First twin | | |
| Elective cesarean section | 1 (reference group) |         |
| Gestational age at delivery | 0.84 (0.75–0.95) | 0.005 |
| Birth weight | 0.997 (0.996–0.998) | <0.001 |
| LOPC | 1.13 (0.51–2.50) | 0.76 |
| Maternal age | 0.97 (0.94–1.01) | 0.14 |
| Spontaneous labor | 1.11 (0.23–5.31) | 0.895 |
| Induction of labor | 0.29 (0.04–2.02) | 0.211 |
| (b) Second twin | | |
| Elective cesarean section | 1 (reference group) |         |
| Gestational age at delivery | 0.72 (0.57–0.90) | 0.004 |
| Birth weight | 0.999 (0.997–1.00) | 0.095 |
| LOPC | 1.18 (0.59–2.35) | 0.63 |
| Maternal age | 0.98 (0.95–1.02) | 0.297 |
| Spontaneous labor | 0.68 (0.23–1.96) | 0.47 |
| Induction of labor | 0.22 (0.05–0.94) | 0.04 |

LOPC, lack of prenatal care.
were due to either maternal or neonatal complications necessitated delivery. Nevertheless, a substantial proportion of the induction and the elective cesarean delivery group occurred at term until 40 weeks representing also the change in management through time since the recommendation to deliver twins at 38 weeks comes from the last decade [25].

Of interest, Dodd et al. [26] performed a randomized trial comparing elective delivery at 37 weeks versus expectant management of uncomplicated twin pregnancy in 235 women who had no contraindication to the continuation of pregnancy. These authors found that delivery at 37 weeks was associated with a significant reduction in the risk of serious adverse neonatal outcomes, compared to expectant management (4.7% versus 12.2%; 95% CI 0.20–0.75; p = 0.005). In addition, Hack et al. [27] observed that in monochorionic twin pregnancies the incidence of intrauterine fetal death becomes lower that is ≥32 weeks of gestation and that neonatal morbidity rapidly declines from 32 weeks of gestation onwards with only a 1.7% incidence between 35 and 37 weeks of gestation. Therefore, a planned delivery before 36 weeks does not seem to be justified. Moreover, mortality at term was still three times higher in monochorionic twins than in singletons [28] and term dichorionic twins [29]. They suggest that planned delivery between 36 and 37 weeks of gestation should be considered, taking into consideration that a planned cesarean delivery in all monochorionic twin pregnancies is unlikely to have a large impact on perinatal mortality (number needed to treat 186).

What is the preferable mode of delivery in twins?

The rapid increase in the rate of cesarean deliveries in the USA and other western countries has been attributed in part to the growing proportion of multiple gestations in past few decades [30–32]. Several factors were suggested to be associated with this observation including: (1) the lack of experience in management of non-vertex deliveries especially of the second twin; (2) the fact that a large proportion of these pregnancies are the result of assisted reproduction and the treating physician felt it will be safer not to go through the trial of labor in order to assure a favorable neonatal outcome; (3) the concern for adverse outcome for the second twin even if it is in vertex presentation; and (4) the fear from litigation in cases of adverse neonatal outcome. Our study addresses three out of these four aspects. We demonstrated that a large proportion (52.5%) of the second non-vertex twin were delivered vaginally in assisted breech delivery without an increase in adverse neonatal outcomes or intra- and postpartum mortality. As for the second argument, indeed, in our study population, women who had an elective cesarean were more likely to conceive by assisted reproduction. Nevertheless, 26.2% of the pregnancies in the induction group were conceived through assisted reproduction and their outcome was favorable suggesting that this argument needs to be reassessed in light of the accumulating data regarding the safety of induction of labor in twins. As for the adverse outcome of the second twin, regardless of the mode of delivery, the immediate perinatal outcome of the second twin is less favorable than that of the first one. However, we address that concern in a specific logistic regression dealing with the direst consequences of delivery in twins which is neonatal death and in the second twin we demonstrated that after adjustment for confounding factors induction of labor actually had a protective effect against neonatal mortality even in comparison to elective cesarean. Therefore, our findings suggest that induction of labor is safe for the first as well as for the second twin in comparison to both spontaneous vaginal delivery and elective delivery by cesarean. Evidence in support of this approach is the randomized multicenter international study conducted by Jon Barrett et al. [33], this study included more than 2800 women from 26 countries, and compared 1398 planned C-section births to 1406 planned vaginal births. Vaginal births were induced and only twins 32–38 weeks – with the first twin situated head first – were eligible. Their research reveals no advantage in choosing cesarean births in these types of twins. In fact, planned cesarean birth did not affect perinatal/neonatal death or serious neonatal morbidity versus planned vaginal birth [33]. Thus, scheduling women with twin gestation and a first twin in vertex presentation for an elective cesarean delivery may not offer these patients the expected protective effect for her neonates along with the price of performing an unnecessary cesarean for the mother.

Who will benefit from induction in twin gestations?

Appropriate patient selection is a key factor in the success of labor induction in singleton as well as in twin gestation. In our population, patients who were induced were more likely to conceive spontaneously and to be at term.

In singleton gestations, induction of labor is an independent risk factor for cesarean delivery [34]. Indeed, Seyb et al. [35] in 1999 found on their study, that elective induction of labor in term nulliparous women was an important risk factor for cesarean delivery. Moreover, women undergoing elective induction had a 17.5% rate of cesarean delivery, whereas those in whom labor started spontaneously had a cesarean birth rate of 7.8%. Of interest, the success rate of labor induction in twins did differ than that of singleton, Taylor et al. [34] concluded that, patients with twin pregnancies undergoing induction of labor have a similar risk of cesarean delivery (19% in twins compared with 21% in singletons, p = 0.724) and a similar length of labor as patients with singleton pregnancies undergoing induction of labor [34].

However, in addition to these reports, our study brings an interesting observation in which induction of labor had a protective effect from cesarean delivery. This novel finding can be explained by the fact that induction was conducted in a selected population which is a priori at lower risk for cesarean delivery and has favorable chances to succeed in this process. This information is important since it brings to the attention of the readers that induction of labor is a feasible option in twin gestation and emphasizes the importance of a proper patient’s selection to the success of this process. The same principle might represent the explanation for the reduction in the risk of mortality of the second twin, in women undergoing induction of labor, since the underlying pathologic condition that influences the clinician’s decision to perform a cesarean delivery instead induction of labor in case of first vertex twin, may be by itself the cause for this finding.
Strength and limitations of the study

The retrospective nature of our study is its major weak point. All the groups included patients from a period of more than 20 years (1988–2011), in a tertiary medical center. As this is a long time period, it is reasonable to assume that changes in obstetrics practice (especially indication for induction of labor) occurred. An additional strength associated to the long time period covered by our study relies in the possibility to observe expectant management until a higher gestational age, compared to the indication for timing of delivery in twin pregnancies, according to modern guidelines. Unfortunately, our database cannot distinguish among types of balloon catheters or doses of prostaglandins. An additional potential pitfall in our study is the lack of information of twin’s chorionicity that may need to be addressed in a different study. Nevertheless, we present here a large cohort study that is population based and, therefore, is representative of the obstetrical outcome in our population and its sample size is such that it adequately represents even low prevalence phenomena and clearly presents the attributed risk for complications in the process of induction of labor in twin gestation regardless to the chorionicity.

Another point worthy of attention is that a major contributor to the adverse outcome observed in the spontaneous twin delivery is the fact that a large proportion of them (25%) occurred early preterm prior to 34 weeks of gestation. We tried to address this affect by adjusting to gestational age at delivery in our multiple logistic regression models. Even after that, induction of labor had a protective effect against urgent cesarean delivery compared to the spontaneous group after that, induction of labor had a protective effect against urgent cesarean delivery compared to the spontaneous group.

Conclusions

In a selected population of twin gestation; at term with spontaneous pregnancy, induction of labor is safe and may contribute to the reduction of cesarean birth rate in these pregnancies.

Future prospective research is needed to provide a better definition for the selection of patients who can fulfill the criteria as good candidates for induction of labor.

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Declaration of interest

The authors report no conflict of interest.

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Supplementary material available online