Prediction of cesarean delivery after induction of labor in twin pregnant women: a retrospective cohort study

Seung Hyun Bang[1], Seung Mi Lee[1], Sohee Oh[2], Su Jin Sung[1], Jeesun Lee[1], Jee Yoon Park[3], Chan-Wook Park[1], Joong Shin Park[1], and Jong Kwan Jun[1]

[1]Seoul National University College of Medicine
[2]Seoul National University Seoul Metropolitan Government Boramae Medical Center
[3]Seoul National University Bundang Hospital Department of Obstetrics and Gynecology

March 31, 2022

Abstract

Objective: The purpose of this study was to develop a predictive model for cesarean delivery after induction of labor (IOL) in twin pregnancy. Design: Retrospective cohort study Setting: University hospital. Population: Twin pregnancy who underwent IOL from 2005 to 2018 Methods: The study population was randomly divided into the training and test sets at a ratio of 2:1. Three-fold cross-validation (CV) with 100 times repetitions was applied to select the best model. Main outcome measure to develop and validate a prediction model for cesarean delivery after IOL in twin pregnancies. Results: A total of 1,703 twin pregnancies were analyzed, including 1,356 women in the development cohort of the SNUH database and 347 women in the external validation cohort of the SNUBH database. In the development cohort, the clinical variables that were different between the successful and failed IOL groups were included in the logistic regression analysis, and the final prediction model, composed of five variables (maternal age, maternal height, parity, cervical effacement, and summated birth weight of both twins), was selected with an AUROC of 0.742 (95% confidence interval [CI], 0.700-0.785) and 0.733 (95% CI, 0.671-0.794) in the training set and test set, respectively. A nomogram for predicting the risk of cesarean delivery after IOL in twin pregnancies was also developed. Conclusion: A prediction model to provide information and evaluate the risk of cesarean delivery after IOL in twin pregnancies was developed. Keywords Twin pregnancy, induction of labor, cesarean section, prediction model

Prediction of cesarean delivery after induction of labor in twin pregnant women: a retrospective cohort study

Seung Hyun Bang[1], Seung Mi Lee[1], Sohee Oh[2], SuJin Sung[1],Jeesun Lee[1], Jee Yoon Park[1,3],Chan-Wook Park[1],Joong Shin Park[1], Jong Kwan Jun[1]

1 Department of Obstetrics and Gynecology, Seoul National University College of Medicine, Seoul, Korea

[2]Department of Biostatistics, Seoul Metropolitan Government Seoul National University Boramae Medical Center, Seoul, Korea

[3]Department of Obstetrics and Gynecology, Seoul National University College of Medicine, Seoul National University Bundang Hospital, Seongnam, Korea

SH Bang and SM Lee contributed equally as the first authors of this study.

This study was presented at the 40th Annual Pregnancy Meeting in Society for Maternal-Fetal Medicine (7 February 2020) in Texas, United States

Conflicts of Interest: The authors report no conflicts of interest.

Correspondence to :

Jong Kwan Jun, MD, PhD

Department of Obstetrics and Gynecology, Seoul National University College of Medicine, Seoul, 110-744, Korea.

Tel: 82-2-2072-3744

Fax: 82-2-762-3599

E-mail: jhs0927@snu.ac.kr

Funding

This work was supported by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HI19C0213).

Abstract word count : 242

Text word count : 2,358

Abstract

Objective The purpose of this study was to develop a predictive model for cesarean delivery after induction of labor (IOL) in twin pregnancy.

Design Retrospective cohort study

Setting University hospital.

Population Twin pregnancy who underwent IOL from 2005 to 2018

Methods The study population was randomly divided into the training and test sets at a ratio of 2:1. Three-fold cross-validation (CV) with 100 times repetitions was applied to select the best model. Main outcome measure to develop and validate a prediction model for cesarean delivery after IOL in twin pregnancies.

Results A total of 1,703 twin pregnancies were analyzed, including 1,356 women in the development cohort of the SNUH database and 347 women in the external validation cohort of the SNUBH database. In the development cohort, the clinical variables that were different between the successful and failed IOL groups were included in the logistic regression analysis, and the final prediction model, composed of five variables (maternal age, maternal height, parity, cervical effacement, and summated birth weight of both twins), was selected with an AUROC of 0.742 (95% confidence interval [CI], 0.700-0.785) and 0.733 (95% CI, 0.671-0.794) in the training set and test set, respectively. A nomogram for predicting the risk of cesarean delivery after IOL in twin pregnancies was also developed.

Conclusion A prediction model to provide information and evaluate the risk of cesarean delivery after IOL in twin pregnancies was developed.

Keywords Twin pregnancy, induction of labor, cesarean section, prediction model

Introduction

Recent improvement in assisted reproductive technologies (ART) has led to an increase in the rate of twin pregnancies.[1,2] Compared to singleton pregnancies, twin pregnancies are at a higher risk for gestational hypertension, preeclampsia,[3,4] intrahepatic cholestasis,[5] and gestational diabetes.[6] Moreover, there is a higher risk of stillbirth with advancing gestational age even in uncomplicated twins,[3-8,] and elective delivery at 37-38 weeks of gestation is generally recommended.[9,10]

Regarding the mode of delivery, diamniotic twin pregnancies with the cephalic presentation of the fetus are candidates for vaginal delivery. Planned vaginal delivery was shown to have a similar risk of neonatal

mortality/morbidity and maternal morbidity compared to planned cesarean delivery in uncomplicated twin pregnancies.[11] The American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine recommend that women with twin pregnancies with either cephalic/cephalic twins or cephalic/non-cephalic twins should undergo counseling to attempt a vaginal delivery.[12]

Women with twin pregnancies who plan to give birth through vaginal delivery without labor pain may undergo labor induction for vaginal delivery. While several reports have shown that induction can be safely performed without increased risk[11,13,14], others have reported an increased risk.[15-19] Therefore, twin pregnant women should undergo counseling regarding the benefits and risks of labor induction. The prediction of successful induction is a clinically important issue. However, there are few studies on the risk factors for cesarean delivery after IOL in twin pregnancies.

To address this issue, we conducted this study to develop and validate a prediction model for cesarean delivery after IOL in twin pregnancies.

Methods

Study design

(1) Development cohort

In this retrospective cohort study, this group consisted of twin pregnant women underwent IOL at [?] 36 weeks of gestation at SNUH from 2005 to 2018. Twin pregnant women with the following inclusion criteria were included: 1) both viable fetuses; 2) the first baby in the cephalic presentation; 3) no contraindication for IOL (e.g., abnormal placentation, fetal compromise, fetal congenital anomaly, previous uterine surgery, or cesarean delivery); and 4) absence of spontaneous labor, which is defined as regular uterine contractions with cervical change. Women who gave birth through combined delivery (cesarean delivery of the second baby followed by vaginal delivery of the first baby) were excluded.

(2) Validation cohort.

In this validation cohort, the study population consisted of twin pregnant women who underwent IOL at [?] 36 weeks of gestation at SNUBH from 2005 to 2018. In SNUBH, it is routine practice to perform IOL only in cases with the cephalic presentation of both fetuses, therefore twin pregnancies with cephalic (1st baby) / non-cephalic (2nd baby) presentation are not candidates for IOL.

We collected clinical characteristics including maternal age, maternal height, maternal weight, pregestational body mass index (BMI, divided by weight in kilograms (kg) by the square of their height in meters (m^2)), parity, gestational age at IOL, gestational age at delivery, method of conception, cervical examination, chorionicity, presentation, and birth weight of each twin, and summated birth weight of both twins. The variables were compared between pregnant women who had a successful vaginal delivery and those who underwent cesarean delivery after IOL. This retrospective study was approved by the Institutional Review Board of SNUH and SNUBH.

Induction of labor

The clinical decision regarding IOL was made at the discretion of the attending physician. Induction was performed either by transvaginal prostaglandin (dinoprostone or misoprostol), intravenous oxytocin infusion, or a combination of both.[18,20-22] Electronic monitoring of the fetal heart rate was performed continuously. After the delivery of the first baby, use of ultrasonography was conducted to check the presentation and heart rate of the second baby. If the second baby was in the cephalic presentation, we waited for spontaneous engagement and vaginal delivery with or without the use of vacuum extraction. If the second baby had a non-reassuring fetal heart rate or was not in the cephalic presentation, the obstetrician determined the best delivery method (vacuum extraction, total breech extraction with or without internal podalic version, or combined intrapartum cesarean section). The diagnosis of failure to progress or fetal distress and the subsequent decision for cesarean delivery was made by the attending physician.

Statistical analysis

Categorical variables were compared with the chi-square test, and continuous variables were compared using the Student's t-test. To select the best prediction model for cesarean delivery in the development cohort, a three-fold CV with 100 repetitions was applied. CV is a statistical analysis method used to organize and evaluate study models. The study population in the development cohort was randomly divided into a training set and a test set with a ratio of 2:1. In the training set, the prediction model was developed by logistic regression analysis with clinical variables that were different between cases with vaginal delivery and those with cesarean delivery. In logistic regression analysis, a generalized estimating equation (GEE) was used to account for the familial correlation between twin pairs within a single mother. The developed model was evaluated using a test set. The model with the highest average test area under the receiver operating characteristic (AUROC) was selected as the best model. To validate the developed prediction model, AUROC was also calculated in the validation cohort. The model with the highest average AUROC in the test set was selected as the final prediction model and was then validated with the external validation group using the SNUBH database. A P-value of 0.05 was considered significant and statistical analyses were performed with IBM SPSS version 25 for Windows.

Results

(1) Development cohort

During the study period, a total of 1,356 twin pregnant women who met the inclusion criteria and delivered at SNUH, were assigned as the development cohort. The indications for IOL were maternal request (n=517), prolonged pregnancy (n=484), suspected intrauterine growth retardation (n=147), rupture of membrane (n=110), preeclampsia (n=60), gestational diabetes (n=13), suspected large for gestational age fetus (n=9), chronic hypertension (n=6), oligohydramnios (n=5) and other reasons for maternal medical condition (n=5).

Of these twin pregnant women, 17.0% (n=230) underwent cesarean delivery and 83.0% (n=1126) underwent vaginal delivery. The reasons for cesarean delivery were failure to progress (n=81), failed induction (n=64), maternal condition (such as medical reason or request, n=54), and non-reassuring fetal status (n=31). Failed induction was defined as failure to give birth after more than three days of serial induction without rupture of the membrane.[23,24]

Table 1 compares the clinical variables according to the final mode of delivery. The gestational age at labor induction and presentation of the second twin did not differ between the two groups. However, patients who underwent cesarean delivery were older, had shorter height, higher pregestational body mass index, less effaced and dilated cervix, and heavier birth weight of twins. In addition, patients who underwent cesarean delivery were more likely to become pregnant after assisted reproductive techniques and had a higher frequency of nulliparous and dichorionic twins.

To find the best prediction model for cesarean delivery with these clinical variables, we conducted a three-fold CV with 100 repetitions. The study population in the development cohort was randomly divided into a training set and a test set with a ratio of 2:1, and the prediction model was developed using logistic regression analysis in the training set, and the AUROC was calculated in the test set. Table S1 shows the mean AUROC for each prediction model. Among the possible models, the prediction model including maternal age, parity, maternal height, cervical effacement, and total birth weight of twins, had the highest average AUROC value in the test set and was selected as the best prediction model [AUROC, 0.742 (95% CI 0.700-0.785) in the training set and 0.733 (95% CI, 0.671-0.794) in the test set]. Table 2 summarizes the odds ratios of each variable in the best prediction model in the SNUH development cohort. In addition, a nomogram for predicting the risk of cesarean delivery after IOL in twin pregnancy (Figure 1) and a web-based predictive calculator (Figure 2) was developed.

(2) Validation cohort.

In SNUBH, a total of 347 twin pregnant women who met the inclusion criteria and delivered between 2005 and 2018 were assigned as the external validation cohort. In this validation cohort, 26.5% of women (n=92)

underwent cesarean delivery. External validation of the prediction model for cesarean delivery derived from the SNUH cohort was performed on this cohort. The AUROC in this cohort was 0.714 (95% CI, 0.650-0.777), which was similar to that of the development cohort (Figure 3).

Discussion

Main findings

The principal findings of this study were: (1) We developed a prediction model, composed of five variables (maternal age, maternal height, parity, cervical effacement, and total birth weight of twins), for cesarean delivery after IOL in twin pregnant women; (2) In addition, a nomogram for predicting the risk of cesarean delivery after IOL in twin pregnancies was developed; and (3) The developed prediction model showed good performance in both the development and external validation databases.

To predict the risk of cesarean delivery after IOL in twin pregnancies, we compared many clinical variables including maternal age, maternal height, maternal weight, pregestational BMI, parity, gestational age at IOL, gestational age at delivery, method of conception, cervical examination, chorionicity, presentation and birth weight of each twin, and total birth weight of twins. We found some independent risk factors that increased the risk of cesarean delivery, and the final prediction model included maternal age, parity, maternal height, cervical effacement, and total birth weight of twins. Maternal age, maternal height, and cervical effacement are also known risk factors in singleton pregnancies.[25,26] The birth weight-related variable retained in the final model was the total birth weight of twins.

To our knowledge, this is the first study to develop a prediction model for cesarean delivery after IOL in twin pregnancies. Several studies have reported many prediction models after IOL in singleton pregnancies.[25,27] The AUROC of the prediction model in the current study was 0.742 (95% CI 0.700-0.785) in the training set, 0.733 (95% CI 0.671-0.794) in the test set, and 0.714 (95% CI 0.650-0.777) in the validation cohort, which is similar to the reported AUROC of the prediction models in singleton pregnancies (AUROC 0.787 [95% CI 0.786-0.788] in the study by Rossi et al.[27], 0.79 [95% CI, 0.74-0.83] in the study by Levine et al.[25]).

Clinical implications

For clinical utility, a nomogram for the prediction of cesarean delivery after induction was constructed according to the final prediction model (Figure 1). In addition, a web-based calculator was created to estimate the likelihood of cesarean delivery after IOL in twin pregnancies (Figure 2, http://snuhtwin.com/). The nomogram and calculator will be useful when considering counseling for labor induction in twin pregnant women without contraindications for vaginal delivery. In particular, this predictive calculator can be used to provide clinical information for twin pregnant women who are considering IOL.

Research implications

Although we have developed a prediction model and validated the model in an independent study population, the developed model should be further evaluated in other institutions with different races/ethnicities to confirm the results of this current study. Moreover, through a prospective randomized trial, we may be able to establish new protocols regarding the usefulness of the developed prediction model. In addition, the maternal or neonatal outcomes in terms of morbidity/mortality after IOL in twin pregnancies need to be evaluated.

Strengths and limitations

The strength is that this is the first study to develop a prediction model for cesarean delivery after IOL in twin pregnancies. Some risk factors that increased cesarean delivery after IOL have been reported in previous studies.[24,28-30] However, we first developed a prediction model that can estimate the risk of cesarean delivery after IOL. Another strength of our study is the large sample size. A total of 1,772 twin pregnant women were analyzed. In addition to deriving a development model for cesarean delivery, we validated the model internally and externally to interpret the reliability of a model in a more generalized population.

Nevertheless, the current study has several limitations. Several other important clinical variables such as Bishop score and cervical length could not be evaluated as this was a retrospective study, although these variables might be associated with the risk of cesarean delivery.[24,25] In addition, the current study population included only Asian, mainly Korean women, and investigated only two tertiary hospitals. Finally, the current study did not evaluate maternal and neonatal morbidity and mortality, which are beyond the scope of the current study. Few previous studies have found that such outcomes were not significantly different between planned cesarean delivery and vaginal delivery after IOL in twin pregnancy.[11,14] Further studies are needed to evaluate the maternal and neonatal outcomes after IOL in twin pregnancies.

Conclusion

A prediction model for cesarean delivery after IOL was created for twin pregnancies. This model could be used to provide information and evaluate the risk of cesarean delivery after IOL in twin pregnant women.

Disclosure of interests

The authors declare no conflicts of interest. Completed disclosure of interest forms could be viewed online as supporting information.

Contribution to authorship

All authors were involved in the interpretation of the data. SHB, SML, JKJ were responsible for the conception and design of this study. SJS, JL, SO, JYP, CWP, JSP were responsible for data collection, data management, and analyses. SHB, SML, and JKJ drafted the initial manuscript, which was reviewed and critically revised by all authors. All authors approved the final manuscript as submitted.

Details of ethics approval

We follow the ethical standards for human experimentation established in the Declaration of Helsinki. We have obtained the approval of this study by The Institutional Review Board. And the patients provided their written consent for the collection and use of clinical information for research purposes.

Funding

This work was supported by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HI19C0213).

Acknowledgments

We are grateful to all the patients (twin pregnant women) for providing clinical data.

References

1. Martin JA, Hamilton BE, Osterman MJ. Three decades of twin births in the United States, 1980-2009. *NCHS Data Brief* 2012; (80): 1-8.

2. Chauhan SP, Scardo JA, Hayes E, Abuhamad AZ, Berghella V. Twins: prevalence, problems, and preterm births. *Am J Obstet Gynecol*2010; **203** (4): 305-15.

3. Krotz S, Fajardo J, Ghandi S, Patel A, Keith LG. Hypertensive disease in twin pregnancies: a review. *Twin Res* 2002; **5** (1): 8-14.

4. Sibai BM, Hauth J, Caritis S, et al. Hypertensive disorders in twin versus singleton gestations. National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. *Am J Obstet Gynecol* 2000; **182** (4): 938-42.

5. Liu X, Landon MB, Chen Y, Cheng W. Perinatal outcomes with intrahepatic cholestasis of pregnancy in twin pregnancies. *J Matern Fetal Neonatal Med* 2016; **29** (13): 2176-81.

6. Rauh-Hain JA, Rana S, Tamez H, et al. Risk for developing gestational diabetes in women with twin pregnancies. *J Matern Fetal Neonatal Med* 2009; **22** (4): 293-9.

7. Dodd JM, Deussen AR, Grivell RM, Crowther CA. Elective birth at 37 weeks' gestation for women with an uncomplicated twin pregnancy.*Cochrane Database Syst Rev* 2014; (2): CD003582.

8. Cheung YB, Yip P, Karlberg J. Mortality of twins and singletons by gestational age: a varying-coefficient approach. *Am J Epidemiol*2000; **152** (12): 1107-16.

9. Bateni ZH, Clark SL, Sangi-Haghpeykar H, et al. Trends in the delivery route of twin pregnancies in the United States, 2006-2013.*Eur J Obstet Gynecol Reprod Biol* 2016; **205** : 120-6.

10. Arabin B, Kyvernitakis I, Liao A, Zugaib M. Trends in cesarean delivery for twin births in the United States: 1995-2008. *Obstet Gynecol* 2012; **119** (3): 657-8; author reply 8-9.

11. Barrett JF, Hannah ME, Hutton EK, et al. A randomized trial of planned cesarean or vaginal delivery for twin pregnancy. *N Engl J Med* 2013; **369** (14): 1295-305.

12. American College of O, Gynecologists, Society for Maternal-Fetal M, et al. Safe prevention of the primary cesarean delivery. *Am J Obstet Gynecol* 2014; **210** (3): 179-93.

13. Harle T, Brun J, Leng J. Induction of labor in twin pregnancy after 36 weeks does not increase maternal–fetal morbidity.*International Journal of Gynecology & Obstetrics* 2002;**77** (1): 15-21.

14. Asztalos EV, Hannah ME, Hutton EK, et al. Twin Birth Study: 2-year neurodevelopmental follow-up of the randomized trial of planned cesarean or planned vaginal delivery for twin pregnancy. *Am J Obstet Gynecol* 2016; **214** (3): 371 e1- e19.

15. Smith GC, Pell JP, Dobbie R. Birth order, gestational age, and risk of delivery related perinatal death in twins: retrospective cohort study. *BMJ* 2002; **325** (7371): 1004.

16. Schmitz T, Carnavalet Cde C, Azria E, Lopez E, Cabrol D, Goffinet F. Neonatal outcomes of twin pregnancy according to the planned mode of delivery. *Obstet Gynecol* 2008; **111** (3): 695-703.

17. Fox NS, Silverstein M, Bender S, Klauser CK, Saltzman DH, Rebarber A. Active second-stage management in twin pregnancies undergoing planned vaginal delivery in a U.S. population. *Obstet Gynecol* 2010;**115** (2 Pt 1): 229-33.

18. Smith GC, Shah I, White IR, Pell JP, Dobbie R. Mode of delivery and the risk of delivery-related perinatal death among twins at term: a retrospective cohort study of 8073 births. *BJOG* 2005;**112** (8): 1139-44.

19. Haest KM, Roumen FJ, Nijhuis JG. Neonatal and maternal outcomes in twin gestations > or =32 weeks according to the planned mode of delivery. *Eur J Obstet Gynecol Reprod Biol* 2005;**123** (1): 17-21.

20. Taylor M, Rebarber A, Saltzman DH, Klauser CK, Roman AS, Fox NS. Induction of labor in twin compared with singleton pregnancies.*Obstet Gynecol* 2012; **120** (2 Pt 1): 297-301.

21. Bush MC, Csaba A, Eddleman KA, Saphier CJ. Is misoprostol safe for labor induction in twin gestations? *J Matern Fetal Neonatal Med*2006; **19** (1): 35-8.

22. Huber G, Schutz H, Seelbach-Gobel B. Induction of labor in twin pregnancies with oral misoprostol versus vaginal dinoprostone–is it effective and safe? *J Matern Fetal Neonatal Med* 2015;**28** (9): 1043-6.

23. Rouse DJ, Owen J, Hauth JC. Criteria for failed labor induction: prospective evaluation of a standardized protocol. *Obstet Gynecol*2000; **96** (5 Pt 1): 671-7.

24. Han BR, Park KH, Lee SY, Jung EY, Park JW. Prediction of the risk of cesarean delivery after labor induction in twin gestations based on clinical and ultrasound parameters. *J Obstet Gynaecol Res* 2016;**42** (9): 1125-31.

25. Levine LD, Downes KL, Parry S, Elovitz MA, Sammel MD, Srinivas SK. A validated calculator to estimate risk of cesarean after an induction of labor with an unfavorable cervix. *Am J Obstet Gynecol* 2018;**218** (2): 254 e1- e7.

26. Heffner LJ, Elkin E, Fretts RC. Impact of labor induction, gestational age, and maternal age on cesarean delivery rates. *Obstet Gynecol* 2003; **102** (2): 287-93.

27. Rossi RM, Requarth E, Warshak CR, Dufendach KR, Hall ES, DeFranco EA. Risk Calculator to Predict Cesarean Delivery Among Women Undergoing Induction of Labor. *Obstet Gynecol* 2020; **135** (3): 559-68.

28. Jonsson M. Induction of twin pregnancy and the risk of caesarean delivery: a cohort study. *BMC Pregnancy Childbirth* 2015;**15** : 136.

29. Fox NS, Gupta S, Melka S, et al. Risk factors for cesarean delivery in twin pregnancies attempting vaginal delivery. *Am J Obstet Gynecol* 2015; **212** (1): 106 e1-5.

30. Razavi AS, Chasen ST, Chambers F, Kalish RB. Induction of labor in twin gestation: can we predict success? *J Perinat Med* 2018;**46** (7): 771-5.

Hosted file

`3. Twin_Table_Final.docx` available at https://authorea.com/users/472112/articles/563176-prediction-of-cesarean-delivery-after-induction-of-labor-in-twin-pregnant-women-a-retrospective-cohort-study

Hosted file

`4. Twin_Figure_Final.docx` available at https://authorea.com/users/472112/articles/563176-prediction-of-cesarean-delivery-after-induction-of-labor-in-twin-pregnant-women-a-retrospective-cohort-study