An externally validated model to predict prolonged induction of labor with an unfavorable cervix: a retrospective cohort study

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Abstract

Objective: To develop and externally validate a prediction model to calculate the likelihood of prolonged induction of labor (induction start to delivery time >36 hours). Design: A retrospective cohort study Setting: Academic centers in the United States Population: Nulliparous women with singleton pregnancies and vertex presentation at term who underwent induction of labor and had a vaginal delivery at a single academic center. Methods: Analyses were limited to women with an unfavorable cervix. A backward stepwise logistic regression analysis was used to identify the factors associated with prolonged induction of labor. The final model was validated using an external dataset of the Consortium on Safe Labor after applying the same inclusion and exclusion criteria. We developed a receiver observer characteristic curve with area under the curve (AUC). Main outcomes of measures: Prolonged induction of labor Results: Of 2,118 women, 364 (17%) had prolonged induction of labor. Factors associated with prolonged induction of labor included body mass index, hypertension, fetal conditions, and epidural. Factors including younger maternal age, prelabor rupture of membranes, and a more favorable simplified Bishop score were associated with a decreased likelihood of prolonged induction of labor. In the external validation cohort, 4,418 women were analyzed, of whom 188 (4%) had prolonged induction of labor. The AUC of the final model was 0.76 (95%CI 0.73-0.80) for the external validation cohort. The online calculator was created and is available at https://medstarapps.org/obstetricriskcalculator. Conclusion: Our externally validated model was efficient in predicting prolonged induction of labor with an unfavorable cervix.

Introduction:

Induction of labor is one of the most common obstetrical procedures, accounting for more than 22% of deliveries.[1]Induction of labor often requires a long time to achieve vaginal delivery especially when the initial cervix is unfavorable. Previous studies showed mean induction to a vaginal delivery interval of 18-26 hours.[2-6] Factors that can be associated with longer induction to vaginal delivery interval include nulliparity, gestational age [?]41 weeks' gestation, higher maternal age, and higher body mass index (BMI kg/m^2).[7-9] However, previous studies did not develop a mathematical model that calculates the probability of prolonged induction of labor nor externally validate a model.

Studies showed that elective induction of labor was not associated with an increased risk of cesarean delivery.[10-14] Some researchers suggest that induction of labor at 39 weeks of gestation is no longer elective.[15] In fact, a population-based retrospective cohort study showed that there were more inductions of labor and deliveries at 39 weeks' gestation after the ARRIVE trial was published.[16] More induction of labor at 39 weeks' of gestation and beyond have been performed electively or for soft indications such as advanced maternal age and morbid obesity even if the initial cervix is unfavorable. Previously, our group developed a prediction model that calculates the likelihood of vaginal delivery in nulliparous women undergoing induction of labor at term.[17] Given that elective induction of labor is associated with 6 hours longer duration of stay in the labor and delivery unit compared to expectant management,[10]identifying individuals who are at risk for prolonged induction of labor may help hospitals with bed management. In addition, the prediction model

would provide pregnant individuals with a reasonable expectation regarding the duration of induction of labor. Therefore, we sought to develop and externally validate a predictive model to calculate the likelihood of prolonged induction of labor for nulliparous women who went induction of labor at term.

Materials and Methods

We conducted a retrospective study of nulliparous women with a singleton gestation with cephalic presentation who underwent induction of labor from 37 0/7 to 41 6/7 weeks of gestation using data from a single academic center from January 2009 to June 2018. We focused on nulliparous women with unfavorable cervix undergoing induction of labor because these women were at high risk for prolonged induction of labor.[7-9] The Institutional Review Board approved this analysis (Protocol Number 2018-039).

We excluded women with contraindications for vaginal delivery including placenta previa, placenta accreta spectrum, and active herpes simplex virus infection. We also excluded women with prior uterine scar (myomectomy or cesarean), antepartum stillbirth, congenital abnormalities, and chromosomal abnormalities since labor management could be different in these conditions. The analysis was limited to women with an unfavorable cervix at admission (both simplified Bishop score less than 6 and cervical dilation less than three centimeters). A simplified Bishop score was obtained from cervical dilation, effacement, and station (range 0-9). We also excluded women with any missing information on maternal age, gestational age at delivery, maternal race/ethnicity, height, maternal weight, and cervical exam at admission. We excluded women who underwent cesarean delivery. We only focused on women who had vaginal delivery after induction of labor because we have previously developed a model that predicts vaginal delivery after induction of labor.[17] Finally, we excluded outlier cases that required more than 72 hours of induction of labor.

The electronic medical record was used to identify all women with a singleton gestation who underwent induction of labor from 37 0/7 to 41 6/7 weeks of gestation. A chart review was conducted to obtain outpatient and inpatient data. We abstracted data on a broad variety of maternal demographic and clinical factors.

We defined the duration of induction of labor as the time interval from induction start time to delivery. We defined prolonged induction of labor as the duration of induction (induction start time to delivery) longer than 36 hours. We chose 36 hours as the cut-off because there were various definitions of prolonged induction of labor in the literature from 24 hours to 48 hours.[18-22] At our institution, we do not have a protocol for cervical ripening. However, we generally use Misoprostol for cervical ripening, followed by oxytocin for labor augmentation.

For potential predictors, we examined maternal age, gestational age, BMI at admission, height (meter), weight (kg), race and ethnicity, simplified Bishop score, and pregnancy conditions including hypertensive disorders (preexisting hypertension, gestational hypertension, preeclampsia, hemolysis, elevated liver enzyme, low platelet syndrome, and eclampsia), diabetes (gestational and pregestational diabetes), premature rupture of membranes, fetal conditions (oligohydramnios and growth restriction), abruption, and type of anesthesia.

The association between the prolonged induction of labor and predictors was examined using the student's t-test, Mann-Whitney U test, chi-square test, and Fisher's exact test as appropriate. Variables with P-value $<.05$ based on bivariable analyses were considered in the development of our prediction model. A multivariable logistic regression with backward elimination approach was then used to identify significant predictors with a threshold of P-value=0.05. For the included continuous variables after the backward selection, we performed the linearity test using restricted cubic spline analysis. Since the variable of maternal age was detected to be nonlinear (P=0.02) in the logistic model in the process of model development, we compared different forms of nonlinear transformation to obtain the one with the best overall predictive performance. Eventually, we adopted a cubic polynomial transformation for the variable of maternal age. No significance of non-linearity was obtained for the variable of BMI at admission (P=0.48).

An external validation cohort was derived from the Consortium on Safe Labor (CSL) database.[23] The CSL included all women delivering at 23 weeks of gestation or greater in 12 clinical centers with 19 hospitals

across nine American College of Obstetricians and Gynecologists (ACOG) districts between 2002 and 2008.[23] Predefined variables were abstracted from the obstetric and newborn electronic medical records, which were supplemented by hospital discharge codes. Using the same inclusion and exclusion criteria, a total of 4,425 women remained for external validation. A calibration plot was developed by grouping observations into five quintiles based on the probability of prolonged induction of labor and then connecting the scatter plots of the predicted and observed prolonged induction of labor to form a curve. The ideal curve is a 45-degree straight line. The receiver operating characteristic curve (ROC), with an area under the curve (AUC) was used to assess the classification ability of the model in the CSL cohort. Data analysis was performed using SAS Studio (SAS Institute Inc., Cary, NC).

Results

Of 34,498 women in the training cohort, 2,118 women were included in the analysis. Of these women, 364 (17%) had prolonged induction of labor (Figure 1). The maternal demographics of the training cohort are presented in Table 1. Women who had prolonged induction of labor compared to those who did not were more likely to be older and taller, delivered at earlier gestational age, and have higher BMI, higher weight, lower simplified Bishop score, chronic hypertension, gestational hypertension, preeclampsia or HELLP syndrome, pregestational diabetes, fetal conditions, and epidural during labor, and were less likely to have prelabor rupture of membranes (P <.05).

The final model is presented in Table 2. Factors associated with prolonged induction of labor included older maternal age, BMI at admission, hypertension, fetal conditions, and epidural. Factors including prelabor rupture of membranes and a more favorable simplified Bishop score were associated with a decreased likelihood of prolonged induction of labor. The online calculator was created and is available at https://medstarapps.org/obstetricriskcalculator (select "Prolonged Induction" tab).

The comparison of maternal characteristics between the training and the validation cohort is presented in Table 3. Women in the validation cohort compared to those in the training cohort were more likely to be older and taller, were more likely to deliver at later gestational age, have lower BMI, lower weight, more favorable simplified Bishop score, and abruption, and were less likely to have chronic hypertension, gestational hypertension, prelabor rupture of membranes, and fetal growth restriction (P <0.05). Compared to the training cohort, the validation cohort was associated with a higher rate of prolonged induction of labor (17.2% vs. 4.3%; P <0.01). The ROC in the validation cohort is presented in Figure 2. The final model had an AUC of 0.76 (95% confidence interval 0.73-0.80) in the validation cohort. The calibration plot for the validation cohort is presented in Figure 3. Finally, we have created a calculator in Excel format (Supplemental material).

Discussion

Principal Findings

In this cohort of nulliparous women who underwent term induction of labor with an unfavorable cervix, we identified factors associated with prolonged induction of labor. Our model allows healthcare providers to incorporate multiple factors and calculate the individualized likelihood of prolonged induction of labor. Our model was externally validated using the geographically diverse data from the CSL, suggesting that the model was generalizable. We have created a calculator in Excel format that provides the likelihood of prolonged induction of labor.

Results in the Context

In 2018, a large, well-designed randomized controlled trial found that elective induction of labor at 39 weeks 0 days to 39 weeks 4 days gestation in nulliparous low-risk women compared with expectant management was associated with decreased risks of cesarean delivery, hypertensive disorder of pregnancy, higher perceived control in labor, less pain, and shorter postpartum stay without increasing neonatal complications.[10] A policy of induction of labor in low-risk women at 39 weeks' gestation would prevent 883 stillbirths per year in the United States.[24] Some authors argue that induction of labor at 39 weeks' gestation without medical

indications should not be called "elective" given elective means "permitting a choice".[15] As a result of the ARRIVE trial, the number of induction of labor at 39 weeks' gestation and beyond has been increasing.[16]

Clinical Implications

Induction of labor at 39 weeks' gestation is associated with 6 hours longer duration of stay in the labor and delivery unit compared to expectant management.[10] Common questions that are asked by pregnant women include "What is the chance of successful vaginal delivery?" and "How long does the induction of labor take?". Many researchers including us previously developed models to predict vaginal delivery after induction of labor.[17, 25, 26]These models are helpful because the probability of vaginal delivery can be calculated based on individual information. Our study further provides providers and pregnant women with additional information on prolonged induction of labor. Specifically, our model can be used to identify individuals who are at risk for prolonged induction of labor so hospitals can be prepared for prolonged bed usage. In addition, our model would provide pregnant individuals with a reasonable expectation regarding the duration of induction of labor.

Research Implications

Women who had prolonged induction of labor longer than 36 hours had increased risks of cesarean delivery, chorioamnionitis, endometritis, and postpartum hemorrhage compared to those who did not have prolonged induction of labor.[18] Although our model was efficient in predicting prolonged induction of labor in nulliparous women at term, it would be useful to examine whether the final model could also predict adverse pregnancy outcomes. Studies that examine whether expectant management would decrease adverse pregnancy outcomes compared to induction of labor if the predicted probability of prolonged induction of labor is high would be also useful.

Strengths and Limitations

Our study has many strengths. Our model was externally validated using a large cohort from nine ACOG districts, making our model generalizable. The CLS cohort was diverse in age, race, and maternal medical comorbidities. Our sample size of more than two thousand women in the training cohort and four thousand women in the validation cohort was large enough to develop and validate the prediction model. We used only factors that were available before induction of labor was started. Our model incorporates individual information from pregnant women and calculates an individualized probability of prolonged induction of labor. We believe our model provides healthcare providers and pregnant women with useful information when considering induction of labor. Finally, developing the online application makes our model easier to apply to clinical practice.

Our study is not without limitations. We did not consider induction methods as we generally used Misoprostol as the first-line agent for cervical ripening. However, it is reassuring our model had a good AUC in the CSL cohort, which used a wide variety of induction methods. The rate of prolonged induction was much higher in the training cohort compared to the CSL cohort (18% vs. 4.3%). We postulated that the rate of prolonged induction was higher in the training cohort because women in the training cohort compared to those in the CSL cohort were at higher risks in terms of higher BMI, lower height, greater weight, unfavorable cervix, chronic hypertension, gestational hypertension, and fetal growth restriction. In addition, the rate of prolonged induction of labor in the training cohort was similar to that of a retrospective cohort study performed in Michigan (20%).[18]

Conclusions:

In conclusion, we developed a predictive model for prolonged induction of labor in nulliparous women undergoing term induction of labor. Our model identifies women who are more likely to have prolonged induction of labor. The prediction model is available as a web application form at https://medstarapps.org/obstetricriskcalculator (select "Prolonged Induction" tab). Further study is needed to examine the optimal cut-off of the likelihood of prolonged induction of labor to achieve optimal maternal, neonatal, and economical outcomes.

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References:

1. Martin JA, Hamilton EB, Osterman JK, Curtin SC, and Mathews TJ. Centers for Disease Control and Prevention National Center for Health Statistics National Vital Statistics System. Births: final data for 2013. Natl Vital Stat Rep. 2015;64(1):1-68.

2. Cromi A, Ghezzi F, Uccella S, Agosti M, Serati M, Marchitelli G, et al. A randomized trial of preinduction cervical ripening: dinoprostone vaginal insert versus double-balloon catheter. Am J Obstet Gynecol. 2012 Aug;207(2):125.e1-7.

3. Dällenbach P, Boulvain M, Viardot C, Irion O. Oral misoprostol or vaginal dinoprostone for labor induction: a randomized controlled trial. Am J Obstet Gynecol. 2003 Jan;188(1):162-7.

4. Delaney S, Shaffer BL, Cheng YW, Vargas J, Sparks TN, Paul K, et al. Labor induction with a Foley balloon inflated to 30 mL compared with 60 mL: a randomized controlled trial. Obstet Gynecol. 2010 Jun;115(6):1239-45.

5. Salim R, Zafran N, Nachum Z, Garmi G, Kraiem N, Shalev E. Single-balloon compared with double-balloon catheters for induction of labor: a randomized controlled trial. Obstet Gynecol. 2011 Jul;118(1):79-86.

6. Schoen CN, Grant G, Berghella V, Hoffman MK, Sciscione A. Intracervical Foley Catheter With and Without Oxytocin for Labor Induction: A Randomized Controlled Trial. Obstet Gynecol. 2017 Jun;129(6):1046-1053.

7. Cheng YW, Delaney SS, Hopkins LM, Caughey AB. The association between the length of the first stage of labor, mode of delivery, and perinatal outcomes in women undergoing induction of labor. Am J Obstet Gynecol. 2009 Nov;201(5):477.e1-7.

8. Greenberg MB, Cheng YW, Sullivan M, Norton ME, Hopkins LM, Caughey AB. Does length of labor vary by maternal age? Am J Obstet Gynecol. 2007 Oct;197(4):428.e1-7.

9. Hirshberg A, Levine LD, Srinivas S. Labor length among overweight and obese women undergoing induction of labor. J Matern Fetal Neonatal Med. 2014 Nov;27(17):1771-5.

10. Grobman WA, Rice MM, Reddy UM, Tita ATN, Silver RM, Mallett G, et al. Labor induction versus expectant management in low-risk nulliparous women. N Engl J Med. 2018;379(6):513-523.

11. Cheng YW, Kaimal AJ, Snowden JM, Nicholson JM, Caughey AB. Induction of labor compared to expectant management in low-risk women and associated perinatal outcomes. Am J Obstet Gynecol 2012;207(6):502.e1-502.e8.

12. Bailit JL, Grobman W, Zhao Y, Wapner RJ, Reddy UM, Varner MW, et al. Nonmedically indicated induction vs expectant treatment in term nulliparous women. Am J Obstet Gynecol. 2015;212(1):103.e1-7.

13. Walker K, Bugg GJ, Macpherson M, McCormick C, Grace N, Wildsmith C, et al. Randomized trial of labor induction in women 35 years of age or older. N Engl J Med 2016;374:813-22.

14. Kawakita T, Iqbal SN, Huang CC, Reddy UM. Nonmedically indicated induction in morbidly obese women is not associated with an increased risk of cesarean delivery. Am J Obstet Gynecol. 2017 Oct;217(4):451.e1-451.e8.

15. Berghella V, Al-Hafez L, Bellussi F. Induction for 39 weeks' gestation: let's call it what it is. AJOG MFM. 2020;2(2):100098

16. Gilroy LC, Al-Kouatly HB, Minkoff HL, McLaren RA. Changes in obstetrical practices and pregnancy outcomes following the ARRIVE trial. Am J Obstet Gynecol. 2022;226(5):716.e1-716.e12.

17. Kawakita T, Reddy UM, Huang CC, Auguste TC, Bauer D, Overcash RT. Predicting Vaginal Delivery in Nulliparous Women Undergoing Induction of Labor at Term. Am J Perinatol. 2018;35(7):660-668.

18. Triebwasser JE, VanArtsdalen J, Kobernik EK, Seiler K, Langen ES. Assessing Maternal and Fetal Risks Associated with Prolonged Induction of Labor. Am J Perinatol. 2019 Apr;36(5):455-459.

19. Bahn SA, Jacobson J, Petersen F. Maternal and neonatal outcome following prolonged labor induction. Obstet Gynecol. 1998 Sep;92(3):403-7.

20. Ferrazzi E, Brembilla G, Cipriani S, Livio S, Paganelli A, Parazzini F. Maternal age and body mass index at term: Risk factors for requiring an induced labour for a late-term pregnancy. Eur J Obstet Gynecol Reprod Biol. 2019 Feb;233:151-157.

21. Blackwell SC, Refuerzo J, Chadha R, Samson J. Duration of labor induction in nulliparous women at term: how long is long enough? Am J Perinatol. 2008 Apr;25(4):205-9.

22. Highley LL, Previs RA, Dotters-Katz SK, Brancazio LR, Grotegut CA. Cesarean delivery among women with prolonged labor induction. J Perinat Med. 2016 Oct 1;44(7):759-766.

23. Zhang J, Troendle J, Reddy UM, et al. Contemporary cesarean delivery practice in the United States. Am J Obstet Gynecol. 2010;203:323.

24. Po' G, Oliver EA, Reddy UM, Silver RM, Berghella V. The impact of induction of labor at 39 weeks in low-risk women on the incidence of stillbirth. Am J Obstet Gynecol 2020;222:88–90.

25. Tolcher MC, Holbert MR, Weaver AL, McGree ME, Olson JE, El-Nashar SA, et al. Predicting Cesarean Delivery After Induction of Labor Among Nulliparous Women at Term. Obstet Gynecol. 2015 Nov;126(5):1059-1068.

26. Levine LD, Downes KL, Parry S, Elovitz MA, Sammel MD, Srinivas SK. A validated calculator to estimate the risk of cesarean after induction of labor with an unfavorable cervix. Am J Obstet Gynecol.

2018 Feb;218(2):254.e1-254.e7.

Figure legend:

Figure 1. Cohort diagram of the training cohort

Abbreviations: GA (gestational age)

Figure 2. Receiver operating curve in the validation cohort

Area under the curve 0.76 (95% confidence interval 0.73-0.80).

Figure 3. Calibration plot

The ideal curve would be a 45-degree straight line (dashed line). The X-axis shows the predicted probability of prolonged induction of labor. The Y-axis shows the observed proportion who had prolonged induction of labor with corresponding 95% confidence intervals (vertical bars).

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