OBSTETRICS

Term induction of labor and subsequent preterm birth

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OBJECTIVE: Although the rate of inductions continues to rise, there is a paucity of data investigating subsequent pregnancy outcomes after induction. Our objective was to compare term inductions with term spontaneous labor and evaluate the rate of subsequent spontaneous preterm birth (sPTB).

STUDY DESIGN: A retrospective cohort study of women with 2 consecutive deliveries from 2005 through 2010 was performed. Term inductions or term spontaneous labor in the index pregnancy was included, and those with a prior sPTB were excluded. Data were obtained through chart abstraction. The primary outcome was sPTB (<37 weeks) in a subsequent pregnancy. Categorical variables were compared with χ^2 analyses, and logistic regression was used to calculate odds.

RESULTS: Eight hundred eighty-seven women were included (622 inductions, 265 spontaneous labor). The overall subsequent sPTB rate was 7.2%. Term inductions were less likely to have a subsequent sPTB compared with term spontaneous labor (6% vs 11%; odds ratio [OR], 0.49; 95% confidence interval, 0.29—0.81; $P = .005$). This remained after adjusting for confounders (adjusted OR, 0.55; $P = .04$). The sPTB risk depended on gestational age of index delivery. At 37-38.9 weeks, the sPTB rate after spontaneous labor was 24% vs 9% after induction (OR, 3.0; 95% confidence interval, 1.44—6.16; $P = .003$). This was not significant for 39-39.9 weeks ($P = .2$) or 40 weeks or longer ($P = .8$).

CONCLUSION: Induction is not a risk factor for subsequent sPTB. Spontaneous labor, however, in the early term period is associated with subsequent sPTB. Further investigation among early term deliveries is warranted to evaluate the risk of sPTB and target interventions in this cohort.

Key words: induction of labor, spontaneous early term labor, subsequent preterm birth

Cite this article as: Levine LD, Bogner HR, Hirshberg A, et al. Term induction of labor and subsequent preterm birth. Am J Obstet Gynecol 2014;210:354.e1-8.

The percentage of women undergoing an induction of labor is estimated to be greater than 20% and continues to rise.[1] Cervical ripening agents such as vaginal prostaglandin and mechanical dilators have been used to help increase the rate of successful induction and decrease the rate of cesarean deliveries. Previous investigations have examined the efficacy of cervical ripening agents for success of vaginal delivery[2,3]; however, there is a paucity of data looking at the potential effects these agents may have on a subsequent pregnancy, specifically on the risk of subsequent preterm birth (PTB).

Although the rate of PTB has decreased since 2006,[4,5] the decline has been marginal, and it still remains a large public health concern and a large contributor to the burden of neonatal morbidity. The overall PTB rate in the United States is currently 11.7%,[4-6] with spontaneous PTB (sPTB) accounting for 60% of the total preterm births.[7,8] There are many known risk factors for PTB including prior history of PTB[9], shortened cervix,[10-12] African American race,[4,5,8,9] low prepregnancy body mass index (BMI),[13] and smoking.[14] The majority of women, however, present in spontaneous preterm labor without an identified risk factor.

Because we have observed that the induction rate has been increasing and the PTB rate only marginally decreasing, it is plausible that an induction of labor may affect cervical integrity, altering it for future pregnancies. Cervical ripening and induction agents are used to prime and dilate the cervix with the intent of achieving labor prior to the spontaneous labor process. An iatrogenic initiation of labor may disrupt the cervical stroma and affect its normal integrity and strength. If such a change in the cervix did occur, this process might alter a woman's risk for preterm birth in a future pregnancy. Therefore, it is possible that induction may be a predisposing risk factor for sPTB. Given the number of women affected by an induction of labor, this is an important public health question to evaluate.

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Received June 14, 2013; revised Sept. 4, 2013; accepted Oct. 29, 2013.

This study was supported by Reproductive Epidemiology Training grant 5T32HD007440-15 from the National Institutes of Health.

The authors report no conflict of interest.

Presented as a poster at the 60th Annual Scientific Meeting of the Society for Gynecologic Investigation, Orlando, FL, March 20-23, 2013.

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0002-9378/$36.00 • © 2014 Mosby, Inc. All rights reserved. • http://dx.doi.org/10.1016/j.ajog.2013.10.877

There are numerous studies looking at second-trimester induced abortions and the risk of early loss or PTB in a subsequent pregnancy. The studies have looked at both the use of misoprostol and dilation and evacuation[15-17] and have found varying and inconsistent results when looking at the risk of PTB in a subsequent pregnancy, with many of them suggesting an increased risk.[16,17] These results are limited to the effects of second-trimester induction. The impact of induction agents on subsequent pregnancy outcome has never been studied among women undergoing third-trimester induction.

Our objective was to first compare women who underwent an induction of labor and those who went into spontaneous labor and evaluate their rates of sPTB in a subsequent pregnancy. As part of this objective, we evaluated the various methods of induction to assess whether a specific method, such as mechanical dilation, may place a woman at increased risk of sPTB in a subsequent pregnancy. Our hypothesis was that induction, specifically mechanical dilation, disrupts the integrity of the cervical stroma, placing a woman at risk for cervical incompetence and PTB in a subsequent pregnancy.

Materials and Methods

This was a retrospective cohort study of all women with 2 consecutive deliveries at the Hospital of the University of Pennsylvania during the years 2005-2010. The starting year was chosen as 2005 because this was the start of the electronic medical record at our institution. Approval from the University of Pennsylvania Institutional Review Board was obtained prior to initiation of the study.

Our objective was to evaluate the risk of sPTB among women undergoing a term induction compared with those presenting in term spontaneous labor. Our exposed group was women who underwent a term induction in their index pregnancy. Our unexposed group was women who presented in spontaneous labor at term in their index pregnancy.

Methods of induction included mechanical induction and pharmacological induction. Mechanical induction was via cervical Foley, and its use was defined by women who had a cervical Foley catheter placed at any time during their induction. Pharmacological induction was defined by women who had the following: (1) prostaglandin only, (2) oxytocin only, or (3) prostaglandin and oxytocin.

Outcome

The primary outcome for the study was spontaneous PTB in a subsequent pregnancy defined as spontaneous labor and delivery prior to 37 weeks' gestation or preterm premature rupture of membranes prior to 37 weeks' gestation. Secondary outcomes included mode of delivery in the subsequent pregnancy and PTB in the subsequent pregnancy less than 34 weeks and less than 28 weeks' gestational age.

Estimated gestational age at the time of delivery was based on standard obstetric dating.[18] For both the index pregnancy and subsequent pregnancy, if a patient presented with unknown dating (n = 12, 1.4%), an ultrasound was obtained prior to delivery to confirm if preterm or term. In those patients in whom an ultrasound was unable to be performed prior to delivery (n = 4), a birthweight greater than 3000 g confirmed a term gestation. Gestational age was then subsequently confirmed by a pediatric examination in all patients with unknown dating.

Sample size

For this study, we wanted to compare overall term induction to term spontaneous labor as well as compare mechanical induction with term spontaneous labor and pharmacological induction to term spontaneous labor. We therefore calculated our sample size based on the least prevalent exposure, mechanical induction. Of women undergoing an induction, approximately 20% have a mechanical induction and 80% have a pharmacological induction at our institution. We assumed an sPTB rate of 7%[7,8] for women presenting in spontaneous labor.

To have enough induction patients to enable subdivision into mechanical and pharmacologic inductions, we chose, a priori, to evaluate 2.5 times more induction patients than spontaneous labor patients. Using an alpha of 0.05 and a 2-sided test, we estimated that we would need a total of 887 patients (622 in the induction group and 265 in the spontaneous labor group) to give us 80% power to see a 2.5-fold increase risk in sPTB when comparing mechanical induction with spontaneous labor. With this sample size, we would have 85% power to see a 2-fold increase risk in sPTB when comparing overall induction (mechanical and pharmacological combined) to spontaneous labor.

Patient selection

Using our electronic database, we were able to obtain a list of patients who had more than 1 delivery between 2005 and 2010. The first pregnancy during this time period was considered their index pregnancy. The index pregnancy may or may not equate to the patient's first pregnancy because multiparous women were included among index pregnancies. The second pregnancy during this time period was then considered a subsequent pregnancy. Patients were included in the study only once.

Only women whose index pregnancy was a singleton pregnancy at term (gestation of $\geq$37 weeks) and who had a consecutive subsequent delivery of a gestational age of 16 weeks or longer at our institution were included in the study. Women with a prior cesarean section were included. Women undergoing an induction prior to 37 weeks' gestation, women presenting in spontaneous labor prior to 37 weeks, and women with a prior history of sPTB were excluded from the study, given the high a priori risk of a preterm birth in a subsequent pregnancy.

By using the *International Classification of Disease*, 9th edition (ICD-9) and undergoing a detailed chart review, we were able to identify which patients underwent an induction, which ones presented in spontaneous labor, and which ones had their subsequent pregnancy at our institution. The ICD-9 codes for induction (73.01, 73.1, 73.4) helped to

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