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Association of Induction of Labor and Uterine Rupture in Women attempting Vaginal Birth After Cesarean: A Survival Analysis

Lorie M. Harper, M.D., M.S.C.I.¹, Alison G. Cahill, M.D., M.S.C.I.¹, Sarah Boslaugh, Ph.D.¹, Anthony O. Odibo, M.D., M.S.C.E.¹, David M. Stamilio, M.D., M.S.C.E.¹, Kimberly A. Roehl, M.P.H.¹, and George A. Macones, M.D., M.S.C.E.¹

¹Department of Obstetrics and Gynecology, Washington University in St. Louis

Abstract

Objective—To estimate the risk of uterine rupture associated with labor induction in women attempting trial of labor after cesarean (TOLAC) accounting for length of labor.

Methods—Nested case-control study of women attempting TOLAC within a multicenter retrospective cohort study of women with a prior cesarean. Time-to-event analyses were performed with time zero defined as the first cervical exam of 4-cm. Subjects experienced the event (uterine rupture) or were censored (delivered).

Results—One-hundred-eleven cases of uterine rupture were compared to 607 controls. When accounting for length of labor, the risk of uterine rupture in induced labor was similar to spontaneous-onset labor (hazard ratio (HR) 1.52, 95% confidence interval (CI) 0.97-2.36). An initial unfavorable cervical exam was associated with an increased risk of uterine rupture compared to spontaneous (HR 4.09, 95% CI 1.82-9.17).

Conclusion—After accounting for labor duration, induction is not associated with an increased risk of uterine rupture in women undergoing TOLAC.

With the rates of cesarean delivery and labor induction on the rise,¹ physicians frequently encounter the dilemma of whether or not to induce labor in a patient with a prior cesarean delivery. Although trial of labor after cesarean (TOLAC) in women with one prior low transverse cesarean (LTCS) is considered safe, the risk of uterine rupture associated with induction of labor may be increased. Most estimate the risk of uterine rupture in women with one prior LTCS during a trial of labor as less than 1%,^{2–4} but this may be increased to as high as 2–3% with an induction of labor.^{5–7} The increased risk has not been attributed to a single induction agent. In fact, studies are conflicting on whether or not prostaglandins^{3, 4, 6, 8, 9} and oxytocin^{10–12} are independently associated with uterine rupture. Given concerns regarding increased risks of uterine rupture, physicians may opt to perform an elective repeat cesarean rather than induce labor in patients with a prior LTCS.

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Corresponding Author: Lorie M. Harper, M.D. –Department of Obstetrics and Gynecology, Washington University School of Medicine, St. Louis, MO, Phone: 314 362 7139; Fax: 314 362 0041, harperl@wudosis.wustl.edu.

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However, women who undergo an induction of labor may have longer time spent in active labor, particularly if they require cervical ripening.^{13, 14} Longer time spent in active labor may translate into a greater amount of time at risk than women who labor spontaneously. The increased risk of uterine rupture attributed to labor induction may be a surrogate for a long and difficult labor. We therefore sought to estimate the independent association of induction of labor on the risk of uterine rupture while accounting for the time spent in labor.

Methods

This is a nested case-control study conducted from 1996–2000 within a 17-center retrospective cohort study of pregnant women with at least 1 previous cesarean delivery. To identify factors associated with uterine rupture, all cases (women who attempted TOLAC and experienced uterine rupture) were matched on hospital site with 5 control subjects, chosen by a random number generator, who attempted TOLAC but did not suffer a uterine rupture. Institutional review board approval was obtained from all study sites. A detailed description of the parent study has been published previously,⁴ but a brief description follows.

International Classification of Disease, 9th Revision (ICD-9) codes for “previous cesarean delivery, delivered,” were used to identify subjects at each site and data were extracted from medical charts by trained research nurses using standardized, closed-end data collection forms. Three percent of charts were re-extracted for quality control. Data collected included maternal demographics, medical and obstetric history, antepartum course, labor and delivery events, complications, and maternal outcomes. Data for patients selected for the case-control study were re-extracted in further detail, including all procedures, medications, and examination details in 15-minute time increments throughout labor. Only women with one or more low transverse cesareans were included in the parent cohort; patients were excluded if their prior cesarean was not low transverse.

Uterine rupture was explicitly defined *a priori* as a full-thickness disruption of the uterine wall accompanied by at least one of the following clinical signs: non-reassuring fetal heart rate tracing immediately preceding surgery, hemoperitoneum, or signs of maternal hemorrhage (systolic blood pressure <70 mm Hg, diastolic blood pressure <40 mm Hg, or heart rate >120 beats/minute). This definition was used to distinguish a clinically significant uterine rupture from an asymptomatic or incidental finding of uterine scar separation or “uterine window.”

For this analysis, women who attempted TOLAC were identified as having a labor induction by a directly extracted dichotomous variable for “induce.” Subjects were excluded if they had more than one prior LTCS. Cases (uterine rupture) were compared with control subjects (no uterine rupture) with respect to baseline characteristics: χ^2 or Fisher’s exact tests, as appropriate, for dichotomous variables and Student’s *t* test or Mann-Whitney *U* test, as appropriate, for continuous variables. Additionally, a sensitivity analysis of sociodemographics was performed, comparing the controls used for this analysis with the group of patients who did not experience a uterine rupture in the larger cohort to ensure that the controls chosen at random were representative (data available upon request). Because controls for this analysis were representative of the larger cohort, weights for the final covariates were not used.

For the time-to-event analysis, patients were classified as having the event of interest (uterine rupture) or censored (delivered). Imputed values were not used because data were nearly complete; <2% of data points were missing for any given variable. Subjects were grouped according to induction of labor (exposure) or spontaneous-onset of labor. We

anticipated that the admission exam would typically be a smaller cervical dilation for subjects admitted for induction compared to those admitted in labor, which would introduce left-censoring for those presenting in spontaneous labor. Therefore, time zero was defined as the first exam at 4-cm to minimize left censoring. An exam of 4-cm was chosen as a cutoff, not as a surrogate marker for labor, but because the majority of laboring subjects were admitted with an initial exam ≤ 4 -cm. In this study 12 uterine ruptures occurred prior to 4-cm, 7 in the induction group and 5 in the spontaneous-onset of labor group. As these uterine ruptures were evenly distributed between the exposed and unexposed groups, we feel that the exclusion of these subjects did not significantly bias our results.

Because some women who present in spontaneous labor eventually require oxytocin augmentation and because oxytocin has been linked in some studies to an increased risk of uterine rupture, a secondary analysis was performed defining labor as induced, augmented, or spontaneous. An additional secondary analysis was performed to examine the effect of cervical dilation (the extent of cervical ripening) at initiation of induction. As Bishop score was not routinely available for all subjects, cervical dilation at the time of starting oxytocin was used as a surrogate marker. Cervical dilation at the time of starting oxytocin was categorized as less than 2-cm, 2–3.9-cm, 4–5.9-cm, and greater than or equal to 6-cm.

Kaplan-Meier plots were used to graphically illustrate the risk of uterine rupture over time by whether or not labor was induced. Log-rank tests were used to compare the plots. Univariable analyses were used to identify potentially confounding factors in the labor induction-uterine rupture risk relationship. Cox proportional hazard regression was used to model the effect of induction of labor on the risk of uterine rupture; adjustment was made for potentially confounding effects identified in the univariable analysis and those historically proposed, such as prior vaginal delivery, race, and oxytocin dosing. The proportional hazards assumption was tested using cumulative martingale residuals and the Kolmogorov-based supremum test.¹⁵ All statistical analyses were completed with SAS (version 9.2, SAS Institute Inc, Cary, NC) and STATA (version 10 Special Edition, College Station, TX).

Results

Within the retrospective cohort of 25,005 patients with a history of at least one prior cesarean delivery, 13,706 attempted TOLAC, and of those who attempted TOLAC, 134 experienced a uterine rupture (cases). At random, 670 of the 13,572 patients who attempted TOLAC but did not experience a uterine rupture were selected as controls. For this analysis of patients with only one prior cesarean, 112 cases and 612 controls were included. Cases and controls were similar with respect to maternal age, gravidity, gestational age at delivery, birth weight, presence of any hypertensive disorder or diabetes, and delivery hospital type (Table 1). Cases were less likely to be black or have a prior vaginal delivery and more likely to be induced or exposed to oxytocin or prostaglandins. Also, cases were more likely to be in labor longer or have an unfavorable (< 2 -cm) initial cervical exam.

A Kaplan-Meier plot displays the survival curves for risk of rupture in women who underwent labor induction and those who labored spontaneously (Figure 1). In unadjusted analysis, the difference between the two curves is not statistically significant (log-rank $p=0.06$). A Cox proportional hazards model was built to better estimate the risk of uterine rupture associated with labor induction. After adjusting for important confounding factors (prior vaginal delivery and maternal race), the risk of uterine rupture was not statistically different between women who attempted TOLAC by labor induction compared to those who presented in spontaneous labor (hazard ratio (HR) 1.52, 95% confidence interval (CI) 0.97-2.36) (Table 2).

In subgroup analyses, an unadjusted time-to-event analysis demonstrated that the risk for uterine rupture in the spontaneous labor group was significantly different than the induced and augmented labor groups (log-rank $p < 0.01$ and $p = 0.03$, respectively) (Figure 2). However, the survival curves for induced versus augmented labor do not differ significantly (log-rank $p = 0.45$). After adjusting for prior vaginal delivery and maternal race (Table 3), the risk of uterine rupture remains similar between induced and augmented labor (HR 1.24, 95% CI 0.78-1.99). Compared to women who labored with no oxytocin, women with induced (HR 2.63, 95% CI 1.33-5.78) and augmented (HR 2.12, 95% CI 1.05-4.76) labor were at increased risk of uterine rupture.

A secondary analysis was performed to estimate the effect of cervical dilation at the time oxytocin was started. The greatest risk was seen in women with a cervical exam of less than 2-cm and 2–3.9-cm at the initiation of oxytocin. Women who received oxytocin starting at 4-cm or greater had a similar risk of uterine rupture as women who labored spontaneously.

Discussion

When considering labor duration, we determined that women with one prior LTCS who undergo induction of labor are at similar risk of uterine rupture compared to women who present in spontaneous labor. When oxytocin exposure is considered, induction of labor and augmentation of labor have similar risks of uterine rupture, although both induction and augmentation of labor are associated with increased risk of uterine rupture compared to women who labor spontaneously. The initial cervical exam impacts this finding; an unfavorable initial cervical exam (< 4 -cm dilation) results in an increased risk of uterine rupture compared to spontaneous labor.

Prior to this, several studies have examined the impact of induction of labor on uterine rupture. Landon et al explored the risk of uterine rupture in induced versus spontaneous labor using a prospective cohort study and found that labor induction was associated with a nearly 3-fold increase in the odds of uterine rupture.³ This increase was seen in women receiving prostaglandins with or without oxytocin and in women receiving oxytocin alone. A retrospective cohort of over 2500 patients was examined by Zelop et al and induction of labor was also found to be associated with a statistically significant increased risk of uterine rupture in women with no prior vaginal delivery.⁵ Weimar et al performed a case control study and concluded that 44% of uterine ruptures could be explained by induction of labor.¹⁶ When exposure to oxytocin and prostaglandins were examined individually, the risk of uterine rupture compared to spontaneous labor was not statistically significant. Conversely, Grobman et al determined that women with a prior vaginal delivery and one prior cesarean were not at increased risk of uterine rupture when their labor was induced.¹⁷

Prior studies do not take into account the amount of time a subject was in labor or being induced. As induction of labor may take days, particularly in those with an unfavorable cervix, subjects exposed to an induction of labor may experience an increase in uterine rupture because they are at risk for a longer period of time compared to those who rapidly deliver. By using a time-to-event analysis, we were able to examine the effect of induction while controlling for the length of active labor. As a result, we were able to more precisely estimate the association between induction of labor and uterine rupture risk.

Our study is unique in the detailed patient-level data available that enable us to conduct the time-dependent analyses necessary to estimate the relationship between labor induction and uterine rupture. The nested case-control design enabled us to examine the risk of a rare outcome (uterine rupture), which was strictly defined a priori as a clinically significant event. A power analysis demonstrates that we had greater than 90% power to detect a 2-fold

increase in the odds of uterine rupture, a difference which would be clinically significant. The risk of selection bias, inherent in case control studies, was minimized by randomly selecting controls nested within a large, well-characterized retrospective cohort, the same source cohort as our cases. Furthermore, a sensitivity analysis was performed to confirm that our control patients did not differ from the larger cohort in baseline demographic characteristics.

One important limitation to consider when interpreting these results is left-censoring. Patients admitted for induction of labor are observed for the entire length of time at risk of uterine rupture, while patients in active labor presumably were at risk for some undefined period of time prior to admission. The length of time spontaneously laboring subjects were unobserved is likely to be short because most people are unlikely to labor at home for long periods of time, particularly as patients with a prior hysterotomy are typically counseled to present early in labor. We attempted to minimize left-censoring by defining time-zero of the analysis as 4-cm as the majority of laboring patients were admitted with a cervical exam ≤ 4 -cm; the 12 uterine ruptures that occurred in our study prior to this dilation were evenly distributed between induced and spontaneously laboring subjects. However, some subjects in spontaneous labor were admitted with an initial cervical exam greater than 4-cm. These differences would likely bias our findings towards the null hypothesis.

Also, as Bishop scores were not routinely documented prior to induction, a surrogate of cervical dilation was used to define a favorable versus unfavorable cervix. Cervical dilation of less than two centimeters was defined as unfavorable as these patients are more likely to have required cervical ripening (prostaglandins, transcervical foley catheter) compared to women with a cervical exam of two centimeters or more. Using cervical dilation alone rather than Bishop score may have misclassified some patients, however, this misclassification was likely random and would have biased our findings towards the null. Method of induction was not included in the model for several reasons. First, relatively few subjects were exposed to prostaglandins, and only 1 included subject was exposed to foley balloon. Additionally, all induction agents have been associated with uterine rupture to some degree, although the mechanism is unclear. Consequently, initial cervical exam was considered as a marker for the need for cervical ripening.

Despite these limitations, we feel that clinically useful conclusions can be drawn. When considering the time at risk, induction of labor does not appear to increase the risk for uterine rupture compared to women who enter labor spontaneously. Additionally, when labor is induced with a favorable initial cervical exam, the risk of uterine rupture is not increased compared to spontaneous labor. Patients may be counseled that an induction of labor from a favorable cervix carries similar risks of uterine rupture as spontaneous labor; induction of labor from an unfavorable cervix has slightly increased risks of uterine rupture compared to spontaneous labor. Rather than absolutely avoiding labor induction in general, clinicians may choose to restrict labor induction to patients with a more favorable cervical exam to minimize uterine rupture risk.

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Figure 1.
Kaplan Meier plot of uterine rupture risk by spontaneous or induced labor

Figure 2.
Kaplan Meier plot of risk for uterine rupture by spontaneous, augmented or induced labor

Table 1

Baseline characteristics of cases and controls

Variable	Cases (n=111)	Controls (n=607)	p
Maternal age (yr)	31.6 ± 4.9	30.6 ± 5.5	0.09
Gravidity	3.1 ± 1.5	3.5 ± 1.7	0.02
Gestational Age at Delivery (wks)	39.2 ± 1.5	38.6 ± 2.8	0.01
Birth Weight (g)	3506 ± 591	3380 ± 698	0.08
Black Race (%)	31 (27.9%)	270 (44.5%)	<0.01
Prior Vaginal Delivery (%)	17 (15.3%)	236 (38.8%)	<0.01
Induction of Labor (%)	47 (42.3%)	177 (29.2%)	<0.01
Oxytocin Exposure (%)	73 (65.8%)	244 (40.2%)	<0.01
Prostaglandin Exposure (%)	27 (24.3%)	41 (6.7%)	<0.01
Hypertensive Disorder of Pregnancy (%)	6 (5.4%)	20 (3.3%)	0.27
Any Diabetes (%)	4 (3.6%)	33 (5.4%)	0.63
University Hospital (%)	56 (61.5%)	322 (60.5%)	0.86

Table 2

Final Cox model for induction of labor versus spontaneous-onset of labor.

	Hazard Ratio	95% Confidence Interval
Induction of Labor	1.52	0.97–2.36
Prior Vaginal Delivery	0.78	0.42–1.37
Black Race	0.62	0.34–1.08

Table 3

Effect of oxytocin exposure

Exposure Group	HR* (95% CI)
Induced	2.63 (1.33–5.78)
Augmented	2.12 (1.05–4.76)

* Adjusted for prior vaginal delivery and black race

Table 4

The effect of cervical dilation at time of starting oxytocin on the risk of uterine rupture, as compared to spontaneous labor (n=200)

Cervical Exam at Time of Starting Oxytocin	HR [*]	95% CI	p
<2 cm (n=56)	4.09	1.82–9.17	<0.01
2–3.9 cm (n=94)	4.91	2.29–10.51	<0.01
4–5.9 cm (n=74)	1.67	0.71–3.91	0.24
≥6 cm (n=56)	1.28	0.51–3.20	0.59

* Adjusted for prior vaginal delivery and black race