Risk of Uterine Rupture With a Trial of Labor in Women With Multiple and Single Prior Cesarean Delivery

*Mark B. Landon, MD, Catherine Y. Spong, MD, Elizabeth Thom, PhD, John C. Hauth, MD, Steven L. Bloom, MD, Michael W. Varner, MD, Atef H. Moawad, MD, Steve N. Caritis, MD, Margaret Harper, MD, MS, Ronald J. Wapner, MD, Yoram Sorokin, MD, Menachem Miodovnik, MD, Marshall Carpenter, MD, Alan M. Peaceman, MD, Mary J. O'Sullivan, MD, Baha M. Sibai, MD, Oded Langer, MD, John M. Thorp, MD, Susan M. Ramin, MD, Brian M. Mercer, MD, and Steven G. Gabbe, MD, for the National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network**

OBJECTIVE: To determine whether the risk for uterine rupture is increased in women attempting vaginal birth after multiple cesarean deliveries.

See related editorial on page 2.

** For members of the NICHD Maternal-fetal Medicine Units Network, see the Appendix.*

From the Departments of Obstetrics and Gynecology at the Ohio State University, Columbus, Ohio; University of Alabama at Birmingham, Birmingham, Alabama; University of Texas Southwestern Medical Center, Dallas, Texas; University of Utah, Salt Lake City, Utah; University of Chicago, Chicago, Illinois; University of Pittsburgh, Pittsburgh, Pennsylvania; Wake Forest University, Winston-Salem, North Carolina; Thomas Jefferson University, Philadelphia, Pennsylvania; Wayne State University, Detroit, Michigan; University of Cincinnati, Cincinnati, Ohio, and Columbia University, New York, New York; Brown University, Providence, Rhode Island; Northwestern University, Chicago, Illinois; University of Miami, Miami, Florida; University of Tennessee, Memphis, Tennessee; University of Texas Health Science Center at San Antonio, San Antonio, Texas; University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; University of Texas Health Science Center at Houston, Houston, Texas; Case Western Reserve University, Cleveland, Ohio; Vanderbilt University, Nashville, Tennessee; and the National Institute of Child Health and Human Development, Bethesda, Maryland; and the George Washington University Biostatistics Center, Washington, DC.

Supported by grants From the National Institute of Child Health and Human Development (HD21410, HD21414, HD27860, HD27861, HD27869, HD27905, HD27915, HD27917, HD34116, HD34122, HD34136, HD34208, HD34210, HD40500, HD40485, HD40544, HD40545, HD40560, HD40512, and HD36801).

The following core committee members participated in protocol/data management and statistical analysis: Sharon Gilbert, MS; and protocol development and coordination between clinical research centers: Frances Johnson, RN, and Julia McCampbell, RN.

Corresponding author: Mark B. Landon, MD, the Ohio State University College of Medicine and Public Health, 1654 Upham Drive, Means Hall 5th Floor, Columbus, OH 43210-1228; e-mail: landon.1@osu.edu.

ISSN: 0029-7844/06

METHODS: We conducted a prospective multicenter observational study of women with prior cesarean delivery undergoing trial of labor and elective repeat operation. Maternal and perinatal outcomes were compared among women attempting vaginal birth after multiple cesarean deliveries and those with a single prior cesarean delivery. We also compared outcomes for women with multiple prior cesarean deliveries undergoing trial of labor with those electing repeat cesarean delivery.

RESULTS: Uterine rupture occurred in 9 of 975 (0.9%) women with multiple prior cesarean compared with 115 of 16,915 (0.7%) women with a single prior operation ($P = .37$). Multivariable analysis confirmed that multiple prior cesarean delivery was not associated with an increased risk for uterine rupture. The rates of hysterectomy (0.6% versus 0.2%, $P = .023$) and transfusion (3.2% versus 1.6%, $P < .001$) were increased in women with multiple prior cesarean deliveries compared with women with a single prior cesarean delivery attempting trial of labor. Similarly, a composite of maternal morbidity was increased in women with multiple prior cesarean deliveries undergoing trial of labor compared with those having elective repeat cesarean delivery (odds ratio 1.41, 95% confidence interval 1.02–1.93).

CONCLUSION: A history of multiple cesarean deliveries is not associated with an increased rate of uterine rupture in women attempting vaginal birth compared with those with a single prior operation. Maternal morbidity is increased with trial of labor after multiple cesarean deliveries, compared with elective repeat cesarean delivery, but the absolute risk for complications is small. Vaginal birth after multiple cesarean deliveries should remain an option for eligible women.

(Obstet Gynecol 2006;108:12–20)

LEVEL OF EVIDENCE: II-2

The cesarean delivery rate in the United States has risen over the past decade to the highest level recorded: 29.1% in 2004.[1] A major contributor to this evolution in obstetric practice has been a steady decline in vaginal birth after previous cesarean (VBAC) from a peak rate of 31% in 1998 to just 9.2% in 2004. The decreased use of VBAC has likely stemmed from 1) limited practice in smaller institutions as a result of specific personnel requirements for offering trial of labor and 2) increasing safety and medical-legal concerns regarding the risk of uterine rupture and its sequelae. Clinical guidelines continue to endorse the practice of offering VBAC while at the same time suggesting limiting this option to subgroups of women with perceived lower risk for uterine rupture.[2] Specifically, the American College of Obstetricians and Gynecologists (ACOG) has recommended that, for women with 2 prior cesarean deliveries, only those with a prior vaginal delivery should be considered candidates for a trial of labor.[2] Given that few large studies have attempted to address the safety of trial of labor after multiple prior cesarean deliveries, we conducted a multicenter study of women with prior cesarean delivery to determine whether additional risks exist for this group of women attempting VBAC compared with those with a single prior operation. We also compared outcomes for women with multiple prior cesarean deliveries undergoing trial of labor with those undergoing elective repeat cesarean delivery.

PARTICPANTS AND METHODS

The cesarean registry was a 4-year observational study (1999–2002) of the National Institute of Child Health and Human Development's Maternal–Fetal Medicine Units Network, which was designed to assess several specific contemporary issues related to cesarean delivery. The study was conducted at 19 academic medical centers; five participated only during the first 2 years, and six participated for part of the last 2 years. The study was approved by the institutional review board of each participating institution. Data were collected for all women undergoing repeat cesarean delivery or VBAC. The labor and delivery log book or computer database at each participating center was screened continuously to identify all women with a gestation of at least 20 weeks or with a birth weight of at least 500 g. Women with a singleton gestation and a history of cesarean delivery were included for analysis. Medical records for each woman and infant were reviewed by trained study nursing personnel. Demographic and obstetric data, as well as information concerning intrapartum and postpartum events, were obtained from completed medical records. Neonatal data were collected up to 120 days of life or at discharge. All uterine ruptures, maternal deaths, stillbirths, and cases of hypoxic ischemic encephalopathy of the newborn underwent secondary review by local study investigators and a final central review (C.Y.S., M.B.L., S.L.B.) to ensure the accuracy of these diagnoses. Data forms were entered at each clinical center using a distributed data entry system and transmitted weekly to the data coordinating center at The George Washington University Biostatistics Center where they were uploaded to a mainframe computer and merged with the existing database. The data were edited on a regular basis for missing, out-of-range, and inconsistent values.

This analysis represents the primary study hypothesis concerning the cohort of women with a history of cesarean childbirth as part of the Maternal–Fetal Medicine Units Cesarean Registry.[3] Maternal and perinatal outcomes were compared among women with a single prior cesarean delivery and multiple prior cesarean deliveries undergoing trial of labor. We also compared these outcomes among women with multiple prior cesarean deliveries who underwent a trial of labor and those undergoing elective repeat cesarean delivery without labor or other indications for cesarean delivery.

Uterine rupture was defined as a disruption of the uterine muscle and visceral peritoneum or a uterine muscle separation with extension to the bladder or broad ligament found at the time of cesarean delivery or laparotomy following VBAC. Postpartum endometritis was defined as a clinical diagnosis of puerperal uterine infection in the absence of findings suggesting another source.

To estimate sample size for the cesarean registry, we assumed a uterine rupture rate of 0.5% in women with a single prior cesarean delivery and the percentage of those women undergoing trial of labor with multiple prior cesarean deliveries to be 10–15%. A sample size of 12,000 women was deemed necessary to detect a relative risk (RR) of 2.5–3.0 for uterine rupture in women with multiple prior cesarean deliveries with type I error of 5% 2-sided and a power of 80%. The sample size was re-evaluated in 2001 because the rate of multiple prior cesarean deliveries among women undergoing trial of labor was lower than expected (5.4%). We estimated 17,000 trials of labor would be necessary to demonstrate a three-fold increased risk of uterine rupture (given an overall rupture rate of 0.66%). The present study of 17,898 women yields almost 85% power to show a three-fold

difference in rupture rate and almost 70% power to detect a RR of 2.5.

To assess further whether multiple prior cesarean delivery was associated with an increased risk for uterine rupture in the trial-of-labor group, three multivariable models were used to control various factors. All three models included oxytocin augmentation, induction, epidural use, and prior vaginal delivery as potential confounders. The years since last cesarean delivery and dilatation at admission were then entered sequentially. Two other multivariable logistic regressions were also used to confirm an increased risk in a maternal composite outcome with multiple prior cesarean deliveries in the trial-of-labor group as well as in women with multiple prior cesarean deliveries undergoing trial of labor compared with elective repeat cesarean delivery. These models controlled for maternal age, race, marital status, tobacco use, insurance status, birth weight, and prior vaginal delivery. Center-to-center variation was assessed but was not found to make a difference in our conclusions. Continuous variables were compared using the Wilcoxon rank-sum test and categorical variables using the χ^2 or Fisher exact test. Nominal two-sided P values are reported with statistical significance defined as a $P < .05$. No adjustments were made for multiple comparisons. SAS 8.2 (SAS Institute Inc, Cary, NC) was used for the analyses.

RESULTS

A total of 45,988 women with histories of cesarean delivery and singleton gestations were identified among 19 centers. A total of 17,898 (39%) underwent a trials of labor, whereas 15,801 (34%) had elective repeat operations, which included 6,035 women with multiple prior cesareans. The remaining 12,289 repeat cesarean deliveries included 9,013 with indications for repeat operations and 3,276 (7%) women who presented in early labor and whose intent to undergo trial of labor could not be determined. The trial of labor rate was 48% among women with a single prior cesarean delivery versus 9% among women with multiple prior cesarean deliveries ($P < .001$). Of 17,898 women undergoing trial of labor, 16,915 (95%) had a history of one cesarean delivery. Women with multiple prior cesarean deliveries (n = 975) included 871 (89%) with two prior, 84 (9%) with three prior, and 20 (2%) with four prior operations. Eight women had an unknown number of prior cesareans. Demographic and obstetric information concerning women with multiple versus single prior cesarean delivery undergoing trial of labor is presented in Table 1. Women with multiple prior cesarean were older, more likely to be African American, obese, and receiving public assistance. Earlier gestational age and lower birth weight were more likely among women with multiple prior cesarean deliveries. Women with multiple prior cesarean deliveries were less likely to undergo oxytocin augmentation and to receive epidural analgesia. A history of VBAC was more common in women with multiple prior cesarean deliveries.

The overall trial-of-labor success rate was 13,138 of 17,890 (73%). Women with a single prior cesarean delivery had a success rate of 12,490 of 16,915 (74%) compared with 648 of 975 (66%) in women with multiple prior cesarean deliveries ($P < .001$). The trial of labor success rates were 584 of 871 (67%) for two prior, 53 of 84 (63%) for three prior, and 11 of 20 (55%) for four prior cesarean deliveries ($P < .001$).

Uterine rupture occurred in 9 (0.9%) cases with multiple prior cesarean compared with 115 (0.7%) with a single prior operation; the difference was not statistically significant ($P = .37$) (Table 2). The rates of hysterectomy and transfusion were significantly higher in the multiple prior cesarean group. A composite of maternal morbidity consisting of uterine rupture, endometritis, hysterectomy, transfusion, thromboembolic disease, and operative injury revealed an increased risk for women with multiple prior cesarean deliveries compared with those with single prior cesarean delivery ($P = .001$). A multivariable model controlling for age, race, marital status, tobacco use, insurance status, birth weight, and prior vaginal delivery confirmed an increased risk for maternal morbidity in the multiple prior cesarean delivery group (odds ratio [OR] 1.35, 95% confidence interval [CI] 1.03–1.75). Among perinatal outcomes, the frequency of both term intrapartum stillbirth and term neonatal death were not statistically different among comparison groups. There were no cases of hypoxic ischemic encephalopathy in term infants of women with multiple prior cesarean delivery undergoing trial of labor compared with 12 such cases in women with a single prior cesarean delivery.

Risk factors for uterine rupture are presented in Table 3. Oxytocin augmentation, induction of labor, epidural anesthesia, and less than a 2-year interval from previous cesarean delivery were associated with higher rates of uterine rupture. Both prior vaginal delivery and prior successful VBAC were associated with a lower risk for this complication. Three multivariable models were constructed to control for confounding variables associated with uterine rupture (Table 4). In all adjusted models, multiple prior cesarean delivery was not associated with an in-

Table 1. Women With Multiple and Single Prior Cesarean Delivery Demographics

Characteristic	Multiple (n = 975)	Single (n = 16,915)	*P*
Age at delivery (y)	30 (26, 34)	28 (24, 33)	< .001
Race			< .001
African American	497 (51.0)	5,961 (35.2)	
White	285 (29.2)	6,167 (36.5)	
Hispanic	159 (16.3)	3,919 (23.2)	
Other/unknown	34 (3.5)	868 (5.1)	
Married	460 (47.2)	9,391 (55.5)	< .001
Tobacco use	252 (25.9)	2,627 (15.5)	< .001
BMI at deliver (kg/m^2)	32 (28, 37)	31 (27, 35)	< .001
30 or greater	533 (61.2)	8,610 (55.3)	
Private insurance at delivery	294 (30.2)	7,013 (41.5)	< .001
Birth weight (g)	3,110 (2,510, 3,555)	3,330 (2,957, 3,675)	< .001
Less than 2,500	242 (24.9)	1,670 (9.9)	
2,500–3,999	656 (67.6)	13,680 (80.9)	
4,000 or greater	73 (7.5)	1,556 (9.2)	
Gestational age at delivery (wk)	38.6 (36.0, 40.0)	39.4 (38.1, 40.3)	< .001
Less than 37	295 (30.5)	2,225 (13.2)	
37–40	569 (58.9)	12,554 (74.3)	
41 or greater	102 (10.6)	2,102 (12.5)	
Induction	231 (23.7)	4,473 (26.4)	.06
Oxytocin augmentation	244 (25.0)	5,414 (32.0)	< .001
Epidural anesthesia	571 (58.6)	12,014 (71.0)	< .001
Cervical dilatation at admission (cm)	3 (1, 5)	3 (2, 4)	.006
2 or less	390 (44.5)	6,139 (38.1)	
3–4	267 (30.4)	6,353 (39.5)	
5–6	123 (14.0)	2,357 (14.6)	
7 or greater	97 (11.1)	1,245 (7.7)	
Prior vaginal delivery	497 (51.4)	8,356 (49.7)	.30
Prior VBAC	363 (40.7)	5,403 (33.7)	< .001
2 years or fewer since last delivery	244 (27.4)	4,043 (25.1)	.12
Prior low vertical scar	9 (0.9)	95 (0.6)	.15
Prior unknown scar	273 (28.0)	2,961 (17.5)	< .001

Data are presented as median (25th, 75th percentile) or n (%).

Data on tobacco use were missing for one patient with previous multiple cesarean deliveries and 13 patients with a single previous cesarean delivery; data on body mass index at delivery were missing for 104 patients with previous multiple cesareans and 1,356 patients with single previous cesarean delivery; data on insurance at delivery were missing for one patient with previous multiple cesareans and 3 patients with a single previous cesarean; data on birth weight at delivery were missing for 4 patients with previous multiple cesareans and 9 patients with a single previous cesarean; data on gestational age at delivery were missing for 9 patients with previous multiple cesareans and 34 patients with a single previous cesarean; data on epidural anesthesia use were missing for 2 patients with a single previous cesarean; data on cervical dilatation at admission were missing for 98 patients with a previous multiple cesarean and 821 patients with a single previous cesarean; data on prior vaginal delivery were missing for 8 patients with previous multiple cesareans and 102 patients with a single previous cesarean; data on prior vaginal birth after a previous cesarean were missing for 84 patients with previous multiple cesareans and 861 patients with a single previous cesarean; data on interval between last delivery were missing for 85 patients with previous multiple cesareans and 805 patients with a single previous cesarean.

creased risk for uterine rupture. Oxytocin augmentation and induction remained significant risk factors, whereas a history of vaginal delivery remained protective against the risk for uterine rupture in two of the models. The rate of uterine rupture in women with multiple prior cesarean delivery and a prior vaginal delivery was 5 in 497 (1%) compared with 4 in 470 (0.85%) in women without a prior vaginal birth (P = 1.0).

Demographic information and obstetric features of women with multiple prior cesarean deliveries undergoing trial of labor versus elective repeat cesarean delivery is presented in Table 5. Women undergoing trial of labor were younger and more likely to be unmarried, African American, tobacco users, and receiving public assistance. Lower birth weight, earlier gestational age, history of vaginal delivery, and VBAC were more common in those undergoing trial of labor. Maternal morbidity, consisting primarily of uterine rupture and blood transfusion, was more commonly observed in women undergoing trial of labor (Table 6). Multivariable analysis controlling for age, race, marital status, tobacco use, insurance status, birth weight, and prior vaginal delivery confirmed an increased risk for a composite of maternal morbidity with trial of labor (OR 1.41, 95% CI 1.02–1.93). There

Table 2. Maternal and Perinatal Outcomes

Outcome	Multiple (n = 975)	Single (n = 16,915)	OR (95% CI)	*P*
Uterine rupture	9 (0.9)	115 (0.7)	1.36 (0.69–2.69)	.37
Endometritis	30 (3.1)	485 (2.9)	1.08 (0.74–1.56)	.70
Hysterectomy	6 (0.6)	35 (0.2)	2.99 (1.25–7.12)	.023
Transfusion	31 (3.2)	273 (1.6)	2.00 (1.37–2.92)	< .001
Thromboembolic disease*	1 (0.1)	6 (0.04)	2.90 (0.35–24.09)	.32
Operative injury†	4 (0.4)	60 (0.4)	1.16 (0.42–3.19)	.78
Maternal death	0 (0.0)	3 (0.02)	–	1.00
Maternal composite‡	71 (7.3)	829 (4.9)	1.53 (1.19–1.96)	.001
Term NICU admission§	75 (11.2)	1321 (9.0)	1.28 (1.00–1.63)	.05
Term intrapartum stillbirth§	0 (0.0)	2 (0.01)	–	1.00
Term neonatal death§	1 (0.15)	12 (0.08)	1.83 (0.24–14.08)	.44
Term HIE§	0 (0.0)	12 (0.1)	–	1.00

OR, odds ratio; CI, confidence interval; NICU, neonatal intensive care unit; HIE, hypoxic ischemic encephalopathy.
Data are presented as n (%).
* Thromboembolic disease includes deep vein thrombosis or pulmonary embolism.
† Maternal injury includes broad ligament hematoma, cystotomy, bowel injury, or ureteral injury.
‡ Maternal composite includes one or more of the above maternal outcomes.
§ There were 672 term deliveries of patients with previous multiple cesarean deliveries and 14,656 term deliveries of patients with a single previous cesarean delivery.

Table 3. Risk Factors for Uterine Rupture

Characteristic	Rupture Rate	OR (95% CI)	*P*
Multiple prior CD	9 (0.9)	1.36 (0.69–2.69)	.37
Oxytocin augmentation	50 (0.9)	1.46 (1.02–2.10)	.04
Induction	48 (1.0)	1.78 (1.24–2.56)	.002
Epidural anesthesia	100 (0.8)	1.76 (1.13–2.75)	.012
Birth weight 4,000 g or greater	12 (0.7)	1.09 (0.60–1.97)	.79
Prior vaginal delivery	47 (0.5)	0.62 (0.43–0.90)	.01
Previous VBAC	25 (0.4)	0.52 (0.34–0.82)	.004
2 years or fewer since last CD	48 (1.1)	2.05 (1.41–2.96)	< .001

OR, odds ratio; CI, confidence interval; CD, cesarean delivery; VBAC, vaginal birth after previous cesarean.
Data are expressed as n (%).

Table 4. Multivariable Analysis of Uterine Rupture Risk Factors

Variable	Model 1	Model 2	Model 3
Multiple prior CDs	1.55 (0.73–2.91)	1.51 (0.67–2.92)	1.69 (0.75–3.29)
Oxytocin augmentation	2.32 (1.43–3.87)	2.40 (1.45–4.07)	2.31 (1.35–4.05)
Induction	2.71 (1.67–4.49)	2.78 (1.68–4.69)	2.81 (1.56–5.22)
Epidural use	1.30 (0.82–2.15)	1.32 (0.82–2.22)	1.23 (0.76–2.10)
Prior vaginal delivery	0.66 (0.45–0.95)	0.67 (0.45–0.97)	0.82 (0.53–1.25)
Years since last CD		0.99 (0.97–1.01)	0.92 (0.86–0.98)
Dilatation at admission			0.96 (0.85–1.08)
Data missing (%)	0.6	5.4	10.3

CD, cesarean delivery.
Data are expressed as adjusted odds ratios (95% confidence intervals).

were no significant differences in perinatal outcomes among term infants of women undergoing trial of labor versus elective repeat cesarean delivery.

DISCUSSION

Our data indicate that the risk for uterine rupture is not significantly increased in women with multiple prior cesarean deliveries undergoing a trial of labor when compared with those with a single prior operation. The risks of other adverse maternal events (hysterectomy and transfusion) is increased in women with multiple prior cesarean deliveries, but the absolute level of these risks is small.

Our study also demonstrates that perinatal outcomes for this population are comparable to those observed in women with one prior cesarean delivery

Table 5. Population Characteristics of Women With Multiple Prior Cesarean Delivery

Characteristic	TOL (n = 975)	ERCD (n = 6,035)	*P*
Age at delivery (y)	30 (26, 34)	30 (26, 34)	.02
Race			< .001
African American	497 (51.0)	1,386 (23.0)	
White	285 (29.2)	2,338 (38.7)	
Hispanic	159 (16.3)	2,058 (34.1)	
Other/unknown	34 (3.5)	253 (4.2)	
Married	460 (47.2)	3,861 (64.0)	< .001
Tobacco use	252 (25.9)	806 (13.4)	< .001
BMI at delivery (kg/m^2)	32 (28, 37)	33 (29, 38)	< .001
BMI greater than 30	533 (61.2)	3,886 (68.3)	
Private insurance at delivery	294 (30.2)	2,514 (41.7)	< .001
Birth weight (g)	3,110 (2,510, 3,555)	3,398 (3,085, 3,720)	< .001
Less than 2,500	242 (24.9)	186 (3.1)	
2,500–3,999	656 (67.6)	5,188 (86.0)	
4,000 or greater	73 (7.5)	660 (10.9)	
Gestational age at delivery (wk)	38.6 (36.0, 40.0)	39.0 (38.4, 39.3)	< .001
Less than 37	295 (30.5)	352 (5.8)	
37–40	569 (58.9)	5,534 (91.8)	
41 or greater	102 (10.6)	142 (2.4)	
Epidural anesthesia	571 (58.6)	2,305 (38.2)	< .001
Prior vaginal delivery	497 (51.4)	805 (13.4)	< .001
Prior VBAC	363 (40.7)	332 (5.6)	< .001
2 years or fewer since last delivery	244 (27.4)	2,067 (35.6)	< .001
Prior low vertical scar	9 (0.9)	50 (0.8)	.76
Prior unknown scar	273 (28.0)	1,892 (31.4)	.04

TOL, trial of labor; ERCD, elective repeat cesarean delivery; BMI, body mass index; VBAC, vaginal birth after previous cesarean.
Data are presented as median (25th, 75th percentile) or n (%).
Data on tobacco use were missing for one trial of labor patient with previous multiple cesareans deliveries and 5 elective repeat cesarean delivery patients with multiple previous cesareans; data on BMI at delivery were missing for 104 trial of labor patients and 347 elective repeat cesarean delivery patients; data on insurance at delivery were missing for one trial of labor patient and 4 elective repeat cesarean delivery patients; data on birth weight at delivery were missing for 4 trial of labor patients with previous multiple cesareans and one elective repeat cesarean delivery patient with previous multiple cesareans; data on gestational age at delivery were missing for 9 trial of labor patients and 7 elective repeat cesarean delivery patients; data on prior vaginal delivery were missing for 8 trial of labor patients and 32 elective repeat cesarean delivery patients; data on prior vaginal birth after a previous cesarean were missing for 84 trial of labor patients and 91 elective repeat cesarean delivery patients; data on interval between last delivery were missing for 85 trial of labor patients and 221 elective repeat cesarean delivery patients.

Table 6. Maternal and Perinatal Outcomes of Women With Multiple Prior Cesarean Deliveries

Outcome	TOL (n = 975)	ERCD (n = 6,035)	OR (95% CI)	*P*
Uterine rupture	9 (0.9)	0 (0.0)	–	< .001
Endometritis	30 (3.1)	129 (2.1)	1.45 (0.97–2.17)	.07
Hysterectomy	6 (0.6)	27 (0.4)	1.38 (0.57–3.34)	.45
Transfusion	31 (3.2)	93 (1.5)	2.10 (1.39–3.17)	< .001
Thromboembolic disease*	1 (0.1)	4 (0.1)	1.55 (0.17–13.88)	.53
Operative injury†	4 (0.4)	36 (0.6)	0.69 (0.24–1.93)	.47
Maternal death	0 (0.0)	1 (0.02)	–	1.00
Maternal composite‡	71 (7.3)	252 (4.2)	1.80 (1.37–2.37)	< .001
Term NICU admission§	75 (11.2)	514 (9.1)	1.27 (0.98–1.64)	.07
Term intrapartum stillbirth§	0 (0.0)	0 (0.0)	–	–
Term neonatal death§	1 (0.1)	1 (0.02)	8.52 (0.53–136.29)	.20
Term HIE§	0 (0.0)	0 (0.0)	–	–

TOL, trial of labor; ERCD, elective repeat cesarean delivery; OR, odds ratio; CI, confidence interval; NICU, neonatal intensive care unit; HIE, hypoxic ischemic encephalopathy.
Data are expressed as n (%).
* Thromboembolic disease includes deep vein thrombosis or pulmonary embolism.
† Maternal injury includes broad ligament hematoma, cystotomy, bowel injury, or ureteral injury.
‡ Maternal composite includes one or more of the above maternal outcomes.
§ There were 672 term deliveries of TOL patients with previous multiple cesareans and 5,676 term deliveries of ERCD patients with a previous multiple cesareans.

attempting VBAC. This information is important for counseling women regarding their options for childbirth after multiple prior cesarean deliveries.

There are a few large-scale studies addressing safety and efficacy after trial of labor after multiple prior cesarean deliveries.[4–6] Previous studies have been primarily retrospective, and most are within single institutions encompassing long study periods.[4,6–8] Our study is unique in its large-scale, multicenter, prospective design with trained obstetric research staff using standardized definitions.[3] In designing this study, we specifically planned for a sufficient sample size to address the question of whether multiple prior cesarean deliveries are associated with an increased rate of uterine rupture in women undergoing trial of labor.

In the largest series to date, Miller and colleagues[4] reported their 10-year experience with 1,827 women with multiple prior cesarean deliveries undergoing trial of labor. Uterine rupture occurred in 1.7% of women with more than one prior cesarean compared with 0.6% in women with single prior operation (OR 3.06, 95% CI 1.95–4.79). This analysis, however, did not control for potential confounding variables, including labor induction and prior obstetric history. Caughey and colleagues[5] conducted a single-center retrospective review from a 12-year period in which the rate of uterine rupture was 3.7% (5/134) in women with 2 prior cesareans compared with 0.8% (31/3,757) in women with one previous uterine scar. These authors controlled for labor characteristics and obstetric history and reported that women with two scars were 4.8 times more likely to experience uterine rupture during trial of labor than women with one scar (OR 4.8, 95% CI 1.8–13.2). Most recently, in a large scale multicenter retrospective study, Macones et al[6] reported a smaller, but increased rate of uterine rupture of 1.8% (20/1,082) in women with 2 prior cesareans versus 0.9% (113/12,535) in women with one previous cesarean delivery (adjusted OR 2.30, 95% CI 1.37–3.85). Interestingly, in a subsequent case-controlled analysis from the same cohort, these authors did not confirm multiple prior cesareans as an independent historical risk factor for uterine rupture with trial of labor (adjusted OR 1.45, 95% CI 0.64–3.27).[9] Thus, our findings contrast with most prior reports and Macones' observation of a small, but statistically significant increased risk of uterine rupture for women with multiple prior cesarean deliveries.[6] We powered our study to detect a RR of 2.5–3.0, so that it remains possible that the increasing risk for uterine rupture, if present, may be closer to a two-fold difference as reported by Macones. Alternatively, differences in population characteristics and obstetric practice may account for the discordant findings among studies. In our study, the trial-of-labor rate for women with multiple prior operations was 9.2%, compared with 27.2% in Macones' report and 49.0% in Miller's study. Caughey and colleagues did not report their trial-of-labor rate for women in their 12-year data analysis. A potentially more selective approach for choosing candidates for trial of labor over the last few years might be associated with a reduced risk for uterine rupture present in our study population.

Our report provides a large-scale, prospective comparison of maternal outcomes in women with multiple prior operations undergoing trial of labor versus those having elective repeat cesarean. This comparison addresses the clinically relevant question as to the preferred mode of delivery for this population of women. Our study and the work of Macones and colleagues demonstrate that uterine rupture is the complication with the greatest risk attributable to trial of labor. Our finding of an increased risk for an adjusted composite of maternal morbidity with trial of labor (OR 1.41) confirms Macones' observation (OR 2.26).[6] Both studies thus reveal a relatively low level of increased risk that will likely be acceptable to many women considering VBAC. Although our study also provides perinatal outcome data demonstrating no apparent increased risk with trial of labor compared with elective repeat cesarean delivery after multiple prior cesareans, we recognize that the population size is insufficient to address differences in these outcomes. It is, however, likely that a larger study population would demonstrate a small but increased risk for adverse perinatal outcomes in women undergoing trial of labor as we have demonstrated in the combined cohort of women with single and multiple prior operations.[3]

We have confirmed that the majority of women with multiple prior cesarean deliveries undergoing trial of labor can expect to achieve a successful vaginal birth. Our reported success rate of 66% is, however, significantly lower than for women with one prior cesarean delivery (73%). This difference has been consistently reported in other studies.[4,5] This finding does contrast with Macones' observation of similar success rates (75.5% versus 74.6%) between study groups. Both our study and Macones' analysis reveal high rates of prior vaginal delivery in women with multiple prior cesarean delivery attempting trial of labor, yet these rates were not higher than in women with single prior operation. It is possible that our finding, and that of others, of lower VBAC

success with multiple prior cesarean deliveries may be explained by differences in study population characteristics that affect labor success.[10]

Our study does have several limitations. Women with multiple prior cesarean deliveries who undergo counseling and then elect a trial of labor have characteristics that are different from both women with a single prior operation and those who elect a repeat operation. We attempted to control for these differences in our analysis, but different approaches to labor management in particular are likely to be present among comparison groups. Our study does not provide long-term outcome data, which is particularly relevant for women undergoing multiple repeat operations who have the associated risk for hemorrhage from accreta and hysterectomy. We also recognize that our data collection process did not provide information regarding certain potential risk factors associated with uterine rupture, such as prior uterine closure technique. Nonetheless, we did attempt to control for most recognized factors and, in doing so, confirmed an association between oxytocin augmentation and induction with uterine rupture as well as the protective effect of prior vaginal delivery.[3,11]

In summary, it appears that any increased risk for uterine rupture in women with multiple prior cesarean deliveries attempting VBAC must be statistically small. As with women who have a single prior cesarean, this risk may be modified by clinical factors such as the need for induction and history of vaginal delivery. However, a requirement that a history of vaginal delivery be present in women with multiple prior cesarean deliveries to be considered candidates for trial of labor seems unwarranted given the apparent level of risk for uterine rupture and adverse outcomes in this population. Moreover, a comparison of outcomes after trial of labor in women with multiple prior cesarean versus those undergoing elective repeat operation indicates that both options should remain available for eligible women.

REFERENCES

1. Hamilton BE, Martin JA, Ventra S, Sutton PD, Menacher F. Births: preliminary data for 2004. Natl Vital Stat Rep 2005;54: 1–17.
2. Vaginal birth after previous cesarean delivery: clinical management guidelines for obstetrician-gynecologists. ACOG Practice Bulletin No. 54. American College of Obstetricians and Gynecologists. Obstet Gynecol 2004;104:203–12.
3. Landon MB, Hauth JC, Leveno KJ, Spong CY, Leindecker S, Varner MW, et al. Maternal and perinatal outcome associated with a trial of labor after prior cesarean delivery. N Engl J Med 2004;351:2581–89.
4. Miller DA, Diaz FG, Paul RH. Vaginal birth after cesarean: a 10-year experience. Obstet Gynecol 1994;84:255–8.
5. Caughey AB, Shipp TD, Repke JT, Zelop CM, Cohen A, Lieberman E. Rate of uterine rupture during trial of labor in women with one or two prior cesarean deliveries. Am J Obstet Gynecol 1999;181:872–6.
6. Macones GA, Cahill A, Pare E, Stamilio DM, Ratcliffe S, Stevens E, et al. Obstetric outcomes in women with two prior cesarean deliveries: Is vaginal birth after cesarean delivery a viable option? Am J Obstet Gynecol 2005;192:1223–9.
7. Askura H, Myers SA. More than one previous cesarean delivery: a 5-year experience with 435 patients. Obstet Gynecol 1995;85:924–9.
8. Novas J, Myers SA, Gleicher N. Obstetric outcome of patients with more than one previous cesarean section. Am J Obstet Gynecol 1989;160:364–7.
9. Macones GA, Peipert J, Nelson DB, Odibo A, Stevens EJ, Stamilio DM, et al. Maternal complications with vaginal birth after cesarean delivery: a multicenter study. Am J Obstet Gynecol 2005;193:1656–62.
10. Landon MB, Leindecker S, Spong CY, Hauth J, Bloom S, Varner MW, et al. The MFMU Cesarean Registry: factors affecting the success of trial of labor after previous cesarean delivery. Am J Obstet Gynecol 2005;193:1016–23.
11. Zelop CM, Shipp TD, Repke JT, Cohen A, Caughey AB, Lieberman E. Uterine rupture during induced or augmented labor in gravid women with one prior cesarean delivery. Am J Obstet Gynecol 1999;181:882–6.

APPENDIX

In addition to the authors, other members of the National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network are as follows:

The Ohio State University, Columbus, OH: J. Iams, F. Johnson, S. Meadows, H. Walker

University of Alabama at Birmingham, Birmingham, AL: D. Rouse, A. Northen, S. Tate *University of Texas Southwestern Medical Center, Dallas, TX:* K. Leveno, J. Mc Campbell, D. Bradford

University of Utah, Salt Lake City, UT: M. Belfort, F. Porter, B. Oshiro, K. Anderson, A. Guzman

University of Chicago, Chicago, IL: J. Hibbard, P. Jones, M. Ramos-Brinson, M. Moran, D. Scott

University of Pittsburgh, Pittsburgh, PA: K. Lain, M. Cotroneo, D. Fischer, M. Luce

Wake Forest University, Winston-Salem, NC: P. Meis, M. Swain, C. Moorefield, K. Lanier, L. Steele

Thomas Jefferson University, Philadelphia, PA: A. Sciscione, M. DiVito, M. Talucci, M. Pollock *Wayne State University, Detroit, MI:* M. Dombrowski, G. Norman, A. Millinder, C. Sudz, B. Steffy

University of Cincinnati, Cincinnati, OH: T. Siddiqi, H. How, N. Elder

Columbia University, New York, NY: F. Malone, M. D'Alton, V. Pemberton, V. Carmona, H. Husami

Brown University, Providence, RI: H. Silver, J. Tillinghast, D. Catlow, D. Allard

Northwestern University, Chicago, IL: M. Socol, D. Gradishar, G. Mallett

University of Miami, Miami, FL: G. Burkett, J. Gilles, J. Potter, F. Doyle, S. Chandler

University of Tennessee, Memphis, TN: W. Mabie, R. Ramsey

University of Texas Health Science Center at San Antonio, San Antonio, TX: D. Conway, S. Barker, M. Rodriguez

University of North Carolina at Chapel Hill, Chapel Hill, NC: K. Moise, K. Dorman, S. Brody, J. Mitchell

University of Texas Health Science Center at Houston, Houston, TX: L. Gilstrap, M. Day, M. Kerr, E. Gildersleeve

Case Western Reserve University, Cleveland, OH: P. Catalano, C. Milluzzi, B. Silvers, C. Santori

The George Washington University Biostatistics Center, Washington, DC: S. Gilbert, H. Juliussen-Stevenson, M. Fischer

National Institute of Child Health and Human Development, Bethesda, MD: D. McNellis, K. Howell, S. Pagliaro