ORIGINAL RESEARCH

Yue-Zhou Yang, MD^{*1}
Xu-Ping Ye, BSc^{*2}
Xiao-Xi Sun, PhD¹

^{*}These authors contributed equally to this paper

¹Shanghai Jiaí Genetics and IVF Institute and

²Department of Obstetrics and
Gynecology, Obstetrics and Gynecology
Hospital of Fudan University, Shanghai
200011, China

Maternal and neonatal morbidity: repeat Cesarean versus a trial of labour after previous Cesarean delivery

Abstract

Purpose: The purpose of this study was to perform a meta-analysis comparing the rates of uterine rupture, and other maternal and neonatal complications, between women who undergo a trial of labour (TOL) after a prior Cesarean delivery and those to undergo elective repeat Cesarean delivery (ERCD).

Source: Medline, Cochrane, EMBASE and Google Scholar were searched until May 6, 2015 using the keywords/phrases: trial of labour, Cesarean section, elective, repeat, pregnancy and vaginal birth. Randomized controlled trials (RCTs), two-arm prospective studies, one-arm studies and retrospective studies were included. The primary outcome was uterine rupture.

Principal findings: Sixteen studies were included in the meta-analysis. TOL after prior Cesarean delivery was associated with higher odds of uterine rupture as compared with ERCD (Peto odds ratio [OR] = 4.685, 95% confidence interval [CI]: 3.077 to 7.133, $p < 0.001$). TOL was associated with a higher rate of endometritis, a lower rate of hysterectomy, and a lower rate of respiratory problems in newborns. There were no differences between the groups with respect to neonatal intensive care unit admissions, postpartum hemorrhage, thromboembolic disease, sepsis and neonatal mortality.

Conclusions: TOL may be associated with a higher risk of uterine rupture and endometritis, but lower risk of hysterectomy and neonatal respiratory problems than ERCD.

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Correspondence to:

Xiao-Xi Sun

Shanghai Jiaí genetic & IVF institute, Obstetrics and Gynecology Hospital of Fudan University, 588 Fangxie Road, Huangpu District, Shanghai 200011, China

Email: JIAI_IVF@163.com

Cesarean delivery is one of the most commonly performed surgical procedures, and elective repeat Cesarean delivery (ERCD) accounts for a large proportion of Cesarean deliveries [1,2]. While ERCD is considered relatively low risk, it is associated with maternal and neonatal complications. The primary neonatal complication is respiratory morbidity [3], whereas maternal complications include placenta accreta, visceral injury, intensive care unit admission, hysterectomy, blood transfusion and a longer hospital stay [4].

A trial of labour (TOL) and subsequent vaginal birth after Cesarean delivery (VBAC) has been advocated as a method to reduce the rate of Cesarean deliveries and subsequent maternal and neonatal morbidity [5]; however, TOL after Cesarean delivery is not without risk; including endometritis, blood transfusion [6] and, the most catastrophic, uterine rupture [7]. Prior Cesarean delivery is the most common cause of uterine rupture, though the frequency during TOL labour is <1% [8]. While uterine rupture is associated with severe maternal and perinatal morbidity, overall outcomes are generally favorable [9,10].

An early metaanalysis of articles published from 1982-1989 did not identify advantages of ERCD as compared with TOL with respect to uterine rupture and perinatal death [11]. A subsequent meta-analysis of articles published from 1989 to 1999 reported a higher rate of uterine rupture and perinatal death following TOL than with ERCD [12]. More recently, an apparent increase in the frequency of uterine rupture and concern about maternal and perinatal morbidity has called into question the safety and appropriateness of TOL and VBAC [6], and a 2015 meta-analysis indicated that induction of labour in patients with a prior Cesarean delivery increases the risk of uterine rupture and repeat Cesarean delivery [13].

The purpose of this study was to perform a systematic review of the literature and meta-analysis comparing the rates of uterine rupture and other maternal and neonatal complications between women who underwent TOL after a prior Cesarean delivery and those who underwent ERCD.

Materials and Methods

Literature search strategy and study selection

This systematic review and meta-analysis was conducted in accordance with PRISMA guidelines [14]. Medline, Cochrane, EMBASE and Google Scholar were searched from inception until May 6, 2015, using combinations of the keywords/phrases: trial of labour, Cesarean section, elective, repeat, pregnancy and vaginal birth. Reference lists of relevant

studies were hand-searched. Inclusion criteria were as follows: 1) randomized controlled trials (RCTs), two-arm prospective, one-arm and retrospective studies; 2) maternal and perinatal outcomes were compared between women who had TOL and those who underwent ERCD without labour or other indications for Cesarean delivery; and, 3) quantitative outcome data were reported. Cohort studies, letters, comments, editorials, case reports, proceedings, and personal communications were excluded, as were studies in which no quantitative primary outcome data were reported.

Studies were identified by the search strategy by two independent reviewers. Where there was uncertainty regarding eligibility, a third reviewer was consulted. The following information/data were extracted from studies that met the inclusion criteria: the name of the first author, year of publication, study design, number of participants in each group, participants' age, body mass index (BMI) at the first prenatal visit, previous vaginal delivery and Cesarean delivery history and quantitative outcome data.

Quality assessment

The quality of the included studies was examined using the tool developed by Hayden *et al.* [15]. Briefly, six sources of bias related to study participation, study attrition, measurement of prognostic factors, measurement of and controlling for confounding variables, measurement of outcomes and analysis approaches were examined.

Outcome measures and data analysis

The primary outcome measure was the rate of uterine rupture. Secondary outcomes were the rates of postpartum hemorrhage, endometritis, hysterectomy, thromboembolic disease, neonatal intensive care unit (NICU) admissions, neonatal respiratory problems, neonatal sepsis and neonatal mortality. Neonatal respiratory problems included respiratory distress, transient tachypnea of the newborn, pneumonia and meconium aspiration. The Peto odds ratio (OR) with 95% confidence interval (CI) was used as the measure of effect size in order to avoid problems with computation of estimates and standard errors when the events are very rare [16,17]. An OR > 1 indicated a higher likelihood of a maternal or neonatal complication in the TOL group compared with the ERCD group.

Heterogeneity among the studies was assessed by the Cochran Q and the I² statistics. A Q statistic with a $p < 0.10$ was considered to indicate statistically significant heterogeneity. The I² statistic indicates the percentage of the

FIGURE 1. PRISMA Flow Diagram

observed between-study variability due to heterogeneity, and a value $> 50\%$ was considered to indicate significant heterogeneity. If heterogeneity existed between studies (Q statistic $p < 0.1$ or an I^2 statistic $> 50\%$), a random-effects model (DerSimonian-Laird method) of analysis was used. Otherwise, a fixed-effects model was used (Mantel-Haenszel method). Pooled estimates across studies for each outcome were generated. A two-sided p -value < 0.05 was considered statistically significant.

To account for the inclusion of women with both successful and failed TOL in the same study, we specifically compared the effect of successful TOL with ERCD on all outcomes. Sensitivity analysis was performed based on the leave-one-out approach in which each study was removed in turn. We further performed subgroup analyses to examine whether the pooled results regarding uterine rupture might be influenced by study quality. Furthermore, funnel plots were created and a one-sided Egger's test was performed to evaluate publication bias for the primary outcome. All statistical analyses were performed using the statistical software

Comprehensive Meta-Analysis, version 2.0 (Biostat, Englewood, NJ, USA).

Results

Literature search

A flow diagram of study selection is shown in Figure 1. A total of 328 records were identified in the database searches. After screening by titles and abstracts, 308 non-relevant studies were excluded and the full texts of 20 articles were assessed. Of these, four were excluded, the reasons for which are shown in Figure 1; thus, 16 studies were included in the meta-analysis [6,18-32].

Study characteristics are summarized in Table 1. Of the 16 studies, six were prospective and 10 were retrospective. The number of patients ranged from 121 to 39,117, with a mean patient age of 27.8 to 33.9 years. Less than half of the patients had a previous vaginal delivery, with incidence ranging from 11.1 to 49.8%.

TABLE 1. Characteristics of the studies included in the meta-analysis

First author (publication year)	Study design	Gestation age inclusion criteria	Comparison	Number of patients	Age (y)	BMI at first prenatal visit (kg/m ²)	Previous vaginal delivery (%)	Multiple previous Cesarean sections (%)
Mone (2014)	Retrospective	NR	TOL	385	31.5 (4.8)	26.3 (5.2)	35.7	NR
			ERCD	493	31.0 (4.7)	27.6 (5.8)	11.8	
Studsgaard (2013)	Prospective	NR	TOL	1161	< 30 y: 24.5%	< 25: 62.4%	11.1	NR
					30-34 y: 51.9%	25-29: 18.8%		
					≥ 35 y: 23.5%	> 30: 8.0%		
			ERCD	622	< 30 y: 22.3%	< 25: 64.0%	17.2	
					30-34 y: 46.3%	25-29: 20.4%		
					≥ 35 y: 31.4%	> 30: 15.6%		
Gilbert (2012)	Retrospective	Term singleton	TOL	8297	NR	NR	NR	NR
			ERCD	6207				
Al-Zirqi (2010)	Retrospective	≥ 28 weeks	TOL	11954	NR	NR	NR	NR
			ERCD	6840				
Spong (2007)	Retrospective	Term singleton	TOL	15323	28.7 (5.7)	32.1 (6.6)	49	4
			ERCD	23794	29.6 (5.7)	33.4 (7.0)	17.9	34
Tan (2007)	Retrospective	36-42 weeks, singleton	TOL	768	31.4 (4.3)	NR	44.5	NR
			ERCD	232	31.9 (4.8)		22.4	
Kwee (2006)	Prospective	≥ 16 weeks.	TOL	3274	NR	NR	NR	NR
			ERCD	1295				
Landon (2004)	Prospective	≥ 20 weeks, singleton	TOL	17898	28.7 (5.8)	31.9 (6.7)	49.8	5.5
			ERCD	15801	29.9 (5.6)	33.5 (7.0)	15.8	38.2
Loebel (2004)	Retrospective	37-42 weeks, singleton.	TOL	927	30.7	NR	33	NR
			ERCD	481	32.2		11	
Fisler (2003)	Retrospective	Term singleton	TOL	313	31.9 (5.3)	NR	NR	NR
			ERCD	136	33.9 (4.6)			
Delaney (2003)	Retrospective	≥ 20 weeks	TOL	38	30.8 (4.9)	NR	NR	NR
			ERCD	83	30.6 (4.0)			
Blanchette (2001)	Prospective	NR	TOL	754	31.8	NR	NR	NR
			ERCD	727	32.1			
Bais (2001)	Retrospective	≥ 20 weeks, singleton	TOL	184	NR	NR	NR	14.3
			ERCD	68				
Hook (1997)	Prospective	Term singleton	TOL	492	NR	NR	NR	NR
			ERCD	497				
Flamm (1994)	Prospective	NR	TOL	5022	29.4 (5.1)	NR	NR	1.13 (0.37) ^a
			ERCD	2207	30.5 (5.2)			1.60 (0.76) ^a
Eriksen (1989)	Retrospective	38 weeks, singleton	TOL	71	27.8 (4.6)	NR	NR	NR
			ERCD	68	27.9 (4.8)			

^aPresented as mean and standard deviation. BMI, body mass index; ERCD, elective repeat Cesarean delivery; NR, not reported; TOL, trial of labour after Cesarean delivery.

FIGURE 2. Forest plots for the meta-analysis of uterine rupture after a prior Cesarean delivery. TOL, trial of labour after Cesarean delivery; ERCD, elective repeat Cesarean delivery.

FIGURE 3. Forest plot for comparison of uterine rupture between successful TOL and ERCD after a prior Cesarean delivery.

FIGURE 4. Sensitivity-analysis for uterine rupture after a prior Cesarean delivery. TOL, trial of labour after Cesarean delivery; ERCD, elective repeat Cesarean delivery.

FIGURE 5. Funnel plot for evaluation of publication bias for the primary outcome, uterine rupture.

TABLE 2. Pooled results for maternal and neonatal complications after elective repeat Cesarean delivery *vs.* a trial of labour after previous Cesarean delivery

Outcomes	Number of studies	Heterogeneity			Pooled results				
		Q	<i>p</i> -value	I ²	Peto OR	Lower limit	Upper limit	Z-value	<i>p</i> -value
NICU admission	9	11.88	0.157	32.7%	0.999	0.773	1.291	-0.009	0.993
Postpartum hemorrhage	10	135.73	< 0.001	93.4%	1.163	0.790	1.714	0.765	0.444
Endometritis	5	8.18	0.085	51.1%	1.355	1.149	1.597	3.612	0.000
Hysterectomy	6	7.33	0.197	31.8%	0.505	0.358	0.712	-3.893	0.000
Thromboembolic disease	2	0.10	0.747	0.0%	0.551	0.291	1.041	-1.835	0.067
Respiratory problems	7	5.76	0.450	0.0%	0.785	0.658	0.936	-2.701	0.007
Sepsis	5	9.28	0.054	56.9%	1.500	0.744	3.023	1.133	0.257
Neonatal mortality	11	9.59	0.477	0.0%	1.276	0.796	2.045	1.011	0.312

NICU, neonatal intensive care unit.

Primary outcome

Nine studies [6,20,22,25,27-30,32] provided data with respect to uterine rupture during TOL (Figure 2). There was evidence of large heterogeneity among the studies ($Q = 26.68$, $p = 0.001$, $I^2 = 70.0\%$), and a random-effects model of analysis was used. The pooled results showed that TOL after a prior Cesarean delivery was associated with higher odds of uterine rupture as compared with ERCD (Peto OR = 4.685, 95% CI: 3.077 to 7.133, $p < 0.001$).

Secondary outcomes

The pooled results for secondary outcomes are summarized in Table 2. There were no differences between the TOL and ERCD groups with respect to NICU admissions (Peto OR = 0.999, 95% CI: 0.773 to 1.291, $p = 0.993$), postpartum hemorrhage (Peto OR = 1.163, 95% CI: 0.790 to 1.714, $p = 0.444$), thromboembolic disease (Peto OR = 0.551, 95% CI: 0.291 to 1.041, $p = 0.067$), sepsis (Peto OR = 1.500, 95% CI: 0.744 to 3.023, $p = 0.257$) and neonatal mortality (Peto OR = 1.276, 95% CI: 0.796 to 2.045, $p = 0.312$). Women in the

FIGURE 6. Quality assessment. A) Risk of bias summary. B) Overall assessment of risk of bias.

TOL group had a significantly higher likelihood of endometritis (Peto OR = 1.355, 95% CI: 1.149 to 1.597, $p < 0.001$), but a lower likelihood of hysterectomy (Peto OR = 0.505, 95% CI: 0.358 to 0.712, $p < 0.001$) as compared with those in the ERCD group. Newborns in the TOL group had a significantly lower likelihood of respiratory problems (Peto OR = 0.785, 95% CI: 0.658 to 0.936, $p = 0.007$) as compared with those in the ERCD group.

Comparison between successful TOL and ERCD

Four studies [6,25,27,30] provided data to examine the risk of uterine rupture between women with a successful TOL and ERCD. The risk of uterine rupture with a successful TOL was not significantly higher than with ERCD (Peto OR = 1.945, 95% CI: 0.337 to 11.216, $p = 0.457$) (Figure 3).

Secondary outcomes with at least two studies reporting results were included in the analysis, and results are summarized in Table 3. There was no significant difference in the risk of endometritis between successful TOL and ERCD (Peto OR = 0.769, 95% CI: 0.433 to 1.367, $p = 0.371$). Newborns in the successful TOL group had a lower likelihood of respiratory problems than those in the ERCD group (Peto OR = 0.561, 95% CI: 0.323 to 0.973, $p = 0.040$).

Sensitivity analysis

Sensitivity analysis using the leave-one-out approach indicated that the magnitude and direction of the associations between TOL after prior Cesarean delivery and uterine rupture did not change significantly when studies were removed in turn, indicating the result of the meta-analysis was reliable (Figure 4).

Subgroup analysis by study quality

Subgroup analyses for the effect of TOL *vs.* ERCS on uterine rupture according to study quality (study attrition and accounting for confounders) was performed, and there was no difference in the risk of uterine rupture between TOL and ERCD regardless of the influence of study attrition and accounting for confounders (Supplemental Table 1).

Publication bias

A funnel plot for the evaluation of publication bias with respect to the primary outcome is shown in Figure 5. No significant asymmetry, indicating no evidence of publication bias (Egger's test: one-tailed $p = 0.293$).

TABLE 3. Subgroup analyses for effect of successful TOL vs. ERCS on secondary outcomes

	Heterogeneity				Pooled results				
	Number of studies	Q	<i>p</i> -value	I ²	Peto OR	Lower limit	Upper limit	Z-value	<i>p</i> -value
NICU admission	5	15.3	0.004	73.8	1.029	0.531	1.995	0.085	0.932
Postpartum hemorrhage	5	15.8	0.003	74.7	0.698	0.285	1.711	-0.786	0.432
Endometritis	2	1.9	0.169	47.3	0.769	0.433	1.367	-0.894	0.371
Respiratory problems	3	3.7	0.158	45.8	0.561	0.323	0.973	-2.058	0.040
Sepsis	3	4.4	0.111	54.6	1.333	0.321	5.532	0.396	0.692
Neonatal mortality	2	0.0	0.978	0.0	4.377	0.529	36.242	1.369	0.171

NICU, neonatal intensive care unit.

Quality assessment

Quality assessment results are summarized in Figure 6. Overall, there was low risk of bias in study participation, prognostic factor measurement, and analysis, but relative high risk in confounding measurement and accounting for confounders.

Discussion

The main finding of the current analysis was that TOL after previous Cesarean delivery was associated with a higher risk of uterine rupture than ERCD. Women in the TOL group had a higher rate of endometritis, but a lower rate of hysterectomy. Newborns in the TOL group had lower possibility of respiratory problems, and there were no differences between the TOL and ERCD groups with respect to NICU admissions, postpartum hemorrhage, thromboembolic disease, sepsis and neonatal mortality. The results need to be interpreted with caution, however, due to the large degree of heterogeneity between studies.

Though the overall risk of uterine rupture is low for both TOL after prior Cesarean delivery (<1%) and ERCD (0.03%) [8,33], the relative risk for women undergoing TOL is 20.47 (95% CI: 9.77 to 44.02, $p < 0.001$) as compared with ERCD [33]. Factors increasing the risk of uterine rupture after a prior Cesarean delivery include multiple gestation, BMI >30 kg/m², a pregnancy interval shorter than 24 months, gestational age >40 weeks, estimated fetal weight >4,000 grams, and prostaglandin administration [33,34]. Although low, the absolute risk of maternal death is greater for women to undergo ERCD *vs.* TOL (0.013% *vs.* 0.004%) [33].

A 2008 systematic review and meta-analysis examined maternal morbidity associated with TOL after prior Cesarean

delivery and ERCD [35]. The results showed that VBAC was successful in 17,905 of 24,349 patients (73%). Maternal morbidity, blood transfusion and hysterectomy were similar in women planning VBAC or ERCD, whereas the rate of uterine rupture was greater with TOL (1.3% *vs.* 0.4%). Maternal morbidity, uterine rupture, blood transfusion and hysterectomy were more common after failed TOL (17%, 4.4%, 3% and 0.5%, respectively) than after successful VBAC (3.1%, 0.2%, 1.1% and 0.1%, respectively) or ERCD (4.3%, 0.4%, 1% and 0.3%, respectively). A more recent meta-analysis indicated that induction of labour increases the risk of uterine rupture in women with a prior Cesarean delivery [13].

Factors associated with an increased likelihood of successful VBAC include history of prior vaginal delivery or VBAC, non-recurring indication for prior Cesarean delivery (e.g., malpresentation), and spontaneous rupture of the membranes or favorable cervix at the time of presentation [33,36]. Factors associated with a decreased likelihood of successful VBAC include obesity (BMI > 30 kg/m²), gestational age >40 weeks, estimated fetal weight >4,000 grams and induction of labour [33,34,36,37].

Study has shown that perinatal mortality (stillbirth or death within 28 days after birth) and neonatal mortality (death within the first 28 days after birth) are increased in TOL as compared to ERCD (0.13% *vs.* 0.5%, and 0.11% *vs.* 0.06%, respectively) [33]. The impact of TOL *vs.* ERCD on neonatal respiratory complications is less clear. The incidence of bag mask ventilation/transient tachypnea of the newborn appears similar between infants born after TOL and ERCD (5.4% *vs.* 2.5%, respectively) [33]. While a review indicated that the incidence of hypoxic-ischemic encephalopathy or asphyxia was not different between infants born after TOL *vs.* ERCD [33],

a prospective 4-year observational study that included over 33,000 women with a prior Cesarean delivery reported that hypoxic-ischemic encephalopathy occurred in no infants in the ERCD group while 12 cases were noted in the TOL group ($p < 0.001$); seven of the cases followed uterine rupture and there were two neonatal deaths [6].

Our study did not examine induction of labour *vs.* expectant management after a prior cesarean delivery. A recent report by Lappen *et al.* [38], which included 6,033 women attempting TOL after a prior Cesarean delivery, found that induction of labour in women with one prior Cesarean delivery was associated with an increased risk of failed VBAC as compared with expectant management. Another study indicated that induction after a single Cesarean delivery with oxytocin and amniotomy where the cervix is favorable is not associated with added maternal or fetal morbidity [39].

There are limitations to this analysis that need to be considered. There was moderate to extreme heterogeneity among studies with respect to uterine rupture, postpartum hemorrhage, endometritis, sepsis and NICU admission. On the other hand, the sensitivity analysis indicated that the pooled estimates regarding uterine rupture were reliable. The publication time of the studies in the current analysis varied greatly, from 1989 to 2014, and methods and standards of care have changed over this period of time. The overall results may be different if older studies had been excluded from the analysis. The gestational age inclusion criteria varied between the studies, and this may have influenced the results. Lastly, no RCTs were identified in the literature search. The lack of RCTs on this topic is likely due to the difficulty in recruiting patients willing to be randomized with respect to TOL.

In conclusion, the results of this meta-analysis suggest that TOL after previous Cesarean delivery is associated with a greater risk of uterine rupture and endometritis, but lower risk of hysterectomy and neonatal respiratory problems than ERCD.

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Supplemental Table

SUPPLEMENTAL TABLE 1. Subgroup analyses for the effect of TOL vs. ERCD on uterine rupture according to study quality (study attrition and accounting for confounders)

	Heterogeneity					Pooled results				
	Number of studies	Q	<i>p</i> -value	I ²		Peto OR	Lower limit	Upper limit	Z-value	<i>p</i> -value
Study attrition										
Low risk	4	22.9	0.000	86.9		4.051	1.712	9.588	3.183	0.001
High risk/unclear	5	2.8	0.588	0.0		5.752	4.315	7.668	11.927	0.000
Account for confounders										
Low risk	4	13.4	0.004	77.6		3.793	2.083	6.909	4.359	0.000
High risk/unclear	5	6.0	0.200	33.3		6.292	3.865	10.242	7.399	0.000

ERCD, elective repeat cesarean delivery; OR, odds ratio; TOL, trial of labor.