

Epidural analgesia at Trial of Labor after Cesarean (TOLAC): a significant adjunct to successful vaginal birth after cesarean (VBAC)

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Abstract

Introduction: Epidural analgesia has been considered a risk factor for labor dystocia at Trial of Labor after Cesarean (TOLAC) and uterine rupture. We evaluated the association between exposure to epidural during TOLAC and mode of delivery and maternal - neonatal outcomes.

Materials and methods: A single center retrospective study of women that consented to TOLAC within a strict protocol between 2006 -2013. Epidural "users" were compared to "non-users". Primary outcome was the mode of delivery: repeat in-labor cesarean or vaginal birth after cesarean (VBAC). Secondary outcomes were maternal/neonatal morbidities. Univariate/multivariate analyses for associations between epidural and mode of delivery were adjusted for significant covariates/mediators.

Results: 105,471 births were registered, 9464 (9.0%) were eligible for TOLAC; 7149 (75.5%) women consented to TOLAC, among which 4081 (57.1%) had epidural analgesia. The in labor cesarean rate was significantly lower for the epidural "users" 8.7% versus "non-users" 11.8%, $p < 0.0001$, with a parallel increased rate of instrumental delivery. Uterine rupture rates were comparable: 0.4% and 0.29% respectively ($p = 0.31$). The adjusted multivariate model showed that epidural "users" were more likely to experience a VBAC, OR 4.58 [3.67; 5.70]; $p < 0.0001$ with a similar rate of adverse maternal- neonatal outcomes

Conclusion: Epidural analgesia at TOLAC may emerge as a safe and significant adjunct for VBAC

Key words: cesarean section; epidural analgesia; TOLAC; uterine rupture; vaginal delivery; VBAC

Abbreviations:

OR, Odds Ratio

TOLAC, Trial of Labor after Cesarean

VBAC, Vaginal Birth after Cesarean

Key message: Epidural analgesia during TOLAC is associated with a high VBAC rate and is safe for mother and neonate.

Introduction

Cesarean section rates have reached an all-time high around the world. (1, 2) Many factors account for the trend; however, the low vaginal birth after cesarean (VBAC) rate and increased repeat Cesarean section rate (3, 4) have important consequences for women in future pregnancies and to family size. (5) Attempts to increase the trial of labor after cesarean (TOLAC) rate and decrease the repeat cesarean section rate were hampered by the morbidity associated with TOLAC labor dystocia, i.e., uterine rupture, (6) which especially engendered difficulties for the obstetrician to use adequate augmentation of labor to treat hypotonic labor dysfunction. Epidural analgesia is for many women a pre-requisite in their commitment to TOLAC while for the obstetrician is a mean to allow adequate and long-lasting pain relief by while managing normal and dysfunctional labor. (7) Even without the presence of a previous cesarean section, epidural analgesia placement during labor was held accountable for dysfunctional labor, prolongation of labor throughout all stages, relaxed pelvic floor muscles, delayed rectal pressure and pushing efforts during the second stage and an increased risk of operative deliveries. (8, 9) Some studies have implied, that the epidural analgesia concealed one of the first clinical warning sign of uterine rupture, i.e. excessive pain thus increased the risk of complete uterine rupture (10) therefore escalating the risk for the mother and neonate at TOLAC. Reversely, denial of adequate pain relief during labor may augment maternal exhaustion, prolong emotional disturbances and "tocophobia" (the fear of pregnancy and childbirth), and is one of the causes for TOLAC refusal. (11) The different policies for labor dystocia management and epidural placement permissiveness at TOLAC challenge the interpretation of previous studies. Thus, we aimed to evaluate the association between epidural analgesia and TOLAC outcome, in a single center with a strict and uniform protocol for TOLAC eligibility, management and epidural.

Material and methods

A retrospective cohort study was conducted using the computerized medical records database of single obstetric center with a mean of 13,206 deliveries per year, between 2006 -2013. Data on demographic and obstetric characteristics as well as data on the

course of delivery and delivery complications were derived from the electronic database management software, which is updated during labor. The database is periodically audited by technical personnel to ensure the validation of the information. Since the data was retrieved from a clinical dataset which is updated during labor, all women had complete data regarding the targeted outcomes that were reviewed. The data file was anonymized and constructed for analysis.

For the study purpose all women with a single live fetus in cephalic presentation at 24-42 weeks and eligible for TOLAC under the department admission and management protocol were included. The eligibility criteria for TOLAC are: confirmation of a single previous low-transverse segment cesarean section either by a written operative report or/and telephone confirmation performed and documented in the admission notes by the obstetrician in authority of the admission; fetal weight is estimated at <4200 grams (either by clinical assessment or ultrasound exam within a week from admission); and TOLAC is offered irrespective of the number of layers of the uterine closure at the Cesarean Section. A diagnosis of dystocia of labor for the previous cesarean is not considered a contraindication for TOLAC. Women are informed by a brief discussion with the admitting obstetrician of TOLAC protocol and consequences and verbal consent is documented.

Induction of labor is performed either by mechanical means by ATAD Balloon, artificial rupture of membranes, or oxytocin ripening of the cervix. Any prostaglandin preparation is contraindicated by department protocol. Oxytocin augmentation is provided according to obstetrical indications during all stages of labor and according to the traditional definitions of stages of labor and prolongation or arrest disorders. (12) Women admitted for TOLAC are managed by certified midwives and decisions for eligibility for TOLAC, induction of labor or oxytocin augmentation, and mode of delivery are taken by board certified obstetricians.

For the purpose of the study women who delivered by planned cesarean section or at the time of admission were referred for cesarean section without a TOLAC were excluded. Small for gestational age (SGA) was defined as a birth weight <10th percentile and large for gestational age (LGA) was defined as > 90th percentile relative to healthy populations. (13)

Epidural analgesia

Epidural analgesia is offered upon request. Women that have antenatal preparatory course are given ample explanation on analgesia during labor; all women sign an epidural analgesia informed consent form after receiving explanatory details from the anesthesia staff in service.

The epidural protocol has been established in 2005 and implemented since.

Epidural analgesia is performed in L3-L5 lumbar area with a loss of resistance technique. Loading dose includes 10 ml Bupivacaine 0.1% solution with 2µgm/ml Fentanyl and continued with patient controlled analgesia.

patient controlled analgesia protocol includes 10 ml/h continuous infusion rate of Bupivacaine/Fentanyl solution (in a concentration similar to the loading dose), lock-out interval was 15 minutes with patient- controlled bolus injection of 5ml as a rescue dose. Blood pressure is measured every 5 minutes during the first 20 minutes and hourly during the continuous of patient controlled analgesia usage. This protocol of monitoring is well accepted and safe for mother and neonate as reported in the literature (14).

According to the indication specified by local protocol no epidural is offered/administered after full dilation.

All women are covered by the National Health and Drug Insurance plan for antenatal and peripartum care.

Definition of measures and outcomes

The primary outcome was the mode of delivery: vaginal birth or repeat cesarean section during TOLAC. Secondary outcomes were maternal and neonatal adverse events. Maternal adverse events were defined for the study purpose: complete uterine rupture defined if the rupture included the myometrium, peritoneum and fetal membranes, while incomplete uterine rupture (dehiscence) was defined as rupture of the myometrium at the previous scar with intact peritoneum and/or fetal membranes.

Uterine rupture was defined at failed TOLAC and cesarean or exploratory laparotomy after birth in cases of suspected intra-abdominal hemorrhage since revision of previous scar after birth is not part of the routine departmental protocol at VBAC. All reports of

uterine rupture underwent secondary chart review to ensure accuracy of the coded diagnosis. Post-partum hemorrhage was defined as loss of >1000 ml blood within 24 hours of birth and/or transfusion of blood products within 72 hours of birth and/or a drop-in hemoglobin concentration of >3 gram/dl.

Neonatal adverse events defined: 5' Apgar score <7, neonatal intensive care unit (NICU) admission for >72 hours, and neonatal death (defined as any death from the moment of delivery until hospital discharge).

The main exposure variable was epidural analgesia during delivery, thereby subdividing the group into "users" and "non-users". Additional study variables included maternal age (reported as absolute years and by aggregate categories), parity (as medians, interquartile range [IQR] or categorical: 2-4, and ≥ 5 births), induction of labor, oxytocin augmentation in labor, instrumental delivery (vacuum or forceps *versus* spontaneous delivery), modified Cervical score at admission (calculated as cervical dilation, effacement, position and head position)(15) and used in the model both as a continuous variable or dichotomous variable [<6 and ≥ 6]), prolonged second stage of labor (>3 hours in first birth with epidural; >2 hours in first birth without epidural or subsequent births without epidural; >1 hour in subsequent births without epidural) (16) Information about smoking and Body Mass Index (BMI) was not routinely registered during the study period.

Statistical analysis

Women who received epidural "users" were compared to those who did not "non-users". Univariate comparisons used the Wilcoxon-Mann Whitney Test or the χ^2 test, as appropriate. Multivariable logistic regression models were fitted to examine the association between the use of epidural analgesia during TOLAC and in labor cesarean section, controlling for known confounders : maternal age >35 years, ethnicity, maternal education >12 years, gestational age at birth <37 weeks (preterm), hypertensive disorder of pregnancy, gestational diabetes mellitus, previous vaginal birth, previous miscarriages, artificial reproductive techniques, induction of labor, and oxytocin augmentation during labor. (17-19) Additional multivariate logistic regression was fitted with further adjustment for cervical score at admission.

A level of 5% was considered statistically significant. Analyses were carried out using SPSS software (version 20.0 statistical package; IBM, Armonk, NY).

The study protocol was submitted to the institutional Helsinki Committee (12 November 2013) and was exempted (IRB number 89/13) on the basis of an analysis of anonymized data.

Results

During the study period 105,471 births were recorded. At admission for delivery we identified 9,464 (9.0%) women who had had a single previous low transverse segment cesarean section. We excluded 206 (2.17%) multi-fetal gestations, 55 (0.6%) home/ambulance births, 126 (1.33%) non-vertex presentation, 95 (1.00%) women who declined TOLAC and 1833 (9.9%) who were either not eligible for TOLAC as delineated in the department protocol or because of maternal and/or fetal complications at admission indicating the necessity of an emergent cesarean section without TOLAC (for example, severe preeclampsia, placental abruption or suspected fetal distress at admission). After these exclusions, the study population consisted of 7,149 (75.5%) women engaged in TOLAC among which 4081 (57.1%) were epidural "users".

The rate of cesarean section in labor was lower in epidural "users" as compared with "non-users" ($p<0.0001$) with a parallel increased rate of instrumental delivery ($p<0.0001$). The rate of uterine rupture was comparable between groups ($p=0.314$). The epidural "users" were less likely to have had a favorable cervical score, a higher rate of oxytocin use either as induction or augmentation of labor and a longer labor time ($p<0.0001$). The baseline characteristics of the study population by epidural usage are described in Table 1. The indication for induction of labor and labor management characteristics are described in Table 2.

The specific diagnoses registered for indications for induction of labor for both study groups are comparable and presented in Table 3. All diagnosis registered as indications for repeat cesarean section during labor differed significantly for both groups and are presented in detail in Table 4.

The neonatal outcomes were comparable between the groups with the exception of an increased rate of small for gestational age newborn ($p=0.006$) in the "non-users" group. (Table 5)

A multivariate analysis that included the background characteristics and variables considered to be significant clinical/ obstetrical mediators for the mode of delivery showed a significant increased rate of VBAC for the epidural "users" OR

4.57[3.67;5.70], $p < 0.0001$ (Table 6). The cervical score at admission is an important confounder for TOLAC success; we were able to retrieve complete information in order to calculate the cervical score for 3475 women (48.6%) included in the study. The women in the group for which the information was incomplete differed significantly by a lower rate of advanced maternal age (35 years) 23.1% versus 20.8%, $p = 0.020$, and were comparable for maternal education > 12 years, (98.1% versus 98.2%, $p = 0.753$). The model fitted to examine the association between epidural usage and cesarean section during TOLAC for the sub-group of women that we had full information to compute the modified Cervical score at admission showed that epidural use was significantly associated with a higher rate of vaginal delivery at TOLAC. Similar to the analyses performed for the entire study group, a cervical score ≥ 6 at admission as a variable, underscored the significantly increased rate of VBAC in the epidural "users" OR=3.34 (95%CI 2.44- 4.59, $p = 0.0001$) (Table 7).

According to our coding, among the "non-users" there was a high percentage who had undergone repeat cesarean sections because of maternal request for cesarean in labor 24.1% versus 5.5% ($p < 0.0001$), (i.e. decided to stop TOLAC after an initial decision to have one) which might implicate incomplete pain relief and/or an additional tocophobia. Thus, we performed an additional sub analysis after excluding the maternal request for cesarean after consenting for TOLAC and while in labor and the results remain similarly significant; i.e. "non-users" had a significant higher risk for a cesarean section at TOLAC OR=3.69 (95%CI 2.93-4.66, $p < 0.001$).

Discussion

Labor is a painful experience with as many as 30% of mothers finding it more painful than expected. (20) A previous delivery by a cesarean section is a significant addition to the emotional stress which may influence the women's initial consent to TOLAC and the pursue of vaginal delivery itself; reversely a TOLAC followed by VBAC increases maternal satisfaction and motivation for future vaginal births. (21)

The main aim of the study was to assess the association between epidural and VBAC. Our primary hypothesis is that epidural is beneficial for successful VBAC. Indeed, we showed that the use of epidural analgesia at TOLAC is associated with a significant higher TOLAC/VBAC rate, independent of background pregnancy complications,

maternal age, the mode of initiation of labor, the cervical score at admission, time in labor, and use of oxytocin (22).

Although we included women with more than one VBAC and this may cause overrepresentation of this subgroup of women, the group with no epidural included significantly more of these women (85% vs 65% $p<0.0001$) thus if there is any bias with overrepresentation removing this subgroup will only strengthen our results. The uterine rupture rates were comparable and even lower than the literature in both groups (6), as also supported by the similar neonatal outcome of the study groups.

We found that epidural "users" had higher rates of instrumental deliveries 11.7% versus 2.8%, concurrent with the literature.(23, 24) The reported rates vary appreciably between 10-56%, most probably due to different local anesthetic concentration, combined regimens with opioids, different degrees of motor blockade. However, the rates are within the range of our center: instrumental delivery at the first delivery rate is 14% and at repeated delivery is 2%, with an overall rate of 5%. The elevated rate of instrumental delivery in the epidural "users" was not related to an increased rate of adverse maternal and neonatal outcomes.

Approximately half of the women (48.6%) included in the present study had complete information on the cervical data that allowed a calculation of the cervical score. The group of women that had incomplete information on the cervical score differed for a higher rate of advanced maternal age. However, when separate multivariate analyses were fitted to evaluate the association between epidural usage and TOLAC/VBAC for the group with complete information on the cervical score, the pattern was similar in significance and magnitude with the multivariate analyses for the entire study population; i.e. epidural users had a higher rate of vaginal delivery at TOLAC: OR=4.57 (95% CI 3.67-5.70, $p=0.0001$) for the entire study group and OR=3.34 (95%CI 2.43-4.58, $p=0.0001$) for those with complete information on the cervical score. We do not have valid information regarding the point in time of labor when the epidural was administered; by protocol there were no second stage epidurals. However, there is predominantly high-quality evidence including a Cochrane study in which it is demonstrated that early or late initiation of epidural analgesia for labor have similar effects on all measured outcomes. (25-27) The motivation/indication behind epidural anesthesia is not

documented thus may have biased the association with the repeat cesarean section decision.

The limitations of the study include: [1] it is a retrospective study that does not afford us insight into decision-making of the individual woman regarding TOLAC and/or the use epidural analgesia; (28) we can only speculate about patient decision-making, which is highly influenced by personal experience and physician counseling (17). [2] the database lacks information about smoking history although the study population consists primarily of Jewish orthodox women with a documented low rate of smoking habits;(29) [3] Body mass index (BMI) could not be recorded because heights were not taken in most cases; [4] the cervical score information was complete for half of the population, however those without complete information had a similar background. A separate multivariate analyses which included this group with complete cervical data showed a similar “protective” effect of epidural usage at TOLAC [5] there were no records of the community consultations regarding TOLAC, but because of the national health care and a low private care rate (<5% of all births in our center) together with a low refusal rate of TOLAC, we assume that this is due to high motivation to achieve large size families; [6] the data base does not include a scale for assessment of the degree of pain relief achieved with analgesia by epidural, albeit the strict protocol imposed on all women equally presupposes similar rates of epidural failure among all women; [7] although the cause for the previous cesarean section prior to TOLAC is not coded in the database, and while labor arrest as a cause for previous cesarean is considered a risk factor for failure of TOLAC, the rate of successful TOLAC in the presence of this cause is still 51-83%.(30) and the overall TOLAC success was actually higher than in the literature and which in the presence of a predictive model including causes of previous cesarean sections and number of vaginal deliveries (31) reached about 50% VBAC (i.e., 20% less than in the predicted model); and [8] the center population characteristics particularly with regard to motivation for a large family size is probably atypical compared to other populations with similar economic status, which may preclude generalization to other populations, however this does not alter the high VBAC rates and the possibility to achieve them[8] the retrospective data studies are characterized by misclassification that we cannot define as random or systemic,

however partially alleviated in the present study by the uniformity of the criteria for inclusion and management.

The strengths of the study include: [1] the large study population comprising more than a third of the deliveries in the Jerusalem area and 10% of all national deliveries; [2] the use of a strict and documented department protocol for TOLAC eligibility, management and epidural; [3] uniform level of care and decision-making in the process of labor and delivery due to a consistent obstetrical protocols such as the constrained indications for use of induction and oxytocin for hypotonic labor; (32)

Several investigators have attempted to create formulae to calculate individual specific results of the TOLAC. Costantine et al. (31) described a cohort of term women with a history of a single previous cesarean section to create a predictive model. Variables analyzed included age, body mass index, ethnicity, prior vaginal delivery, prior VBAC, and indication for prior cesarean section. This model showed that women's likelihood of successful VBAC did not significantly differ from the predicted rate when it was <50%, but VBAC success rates were 10%-20% lower for women who had a predicted VBAC success rates of >50%. (32)

Grobman et al. (33) also created a nomogram using factors available at the first prenatal visit, and concluded that it was a potentially useful tool for patient-specific rates of VBAC success. Other useful equations are accessible via Internet portals: physicians input patient demographic information to obtain a "VBAC success rate" for that specific patient. Patients whose likelihood of a successful VBAC is >50% are assumed to be appropriate candidates.

While this information is useful, it has yet to be clinically validated. If a woman presents with a 60%-80% likelihood of TOLAC/VBAC success, the clinician should be able to identify factors that place the patient at either end of this range of predicted VBAC success. (6, 31, 34, 35)

Moreover, none of this prediction models have mentioned mode of analgesia and/or satisfaction with pain relief at TOLAC as a factor in the success of TOLAC. Nor has any model considered the possibility to use labor augmentation until satisfactory uterine contractions are obtained, thereby reducing rates of the failed induction/augmentation and dystocia in labor that are causes for repeat cesareans. The importance of epidural at TOLAC is underscored by the significantly higher rate of women which requested

repeat cesarean section in active labor and had no benefit of an epidural analgesia. There are reports on the association between the intensity of labor pain and dystocia(36, 37); the greater labor pain the higher the rate of obstructed labor, while the relief of pain leads to progression of labor (38). A correlation was shown between endogenous plasma epinephrine and cortisol levels with labor progression (39). Remarkably, women in labor that require to have epidural analgesia have significantly higher cortisol levels than of women who do not. The maternal level decreases after relief of pain, along with the level of epinephrine (40, 41). This decrease in alpha- and beta-adrenergic stimulus, which sensitivity is characteristic of the uteroplacental vascular bed, rather than the systemic vasculature, may enhance uterine perfusion leading to an effective uterine contraction pattern (23, 42). Thus, we may further postulate that epidural analgesia reduces maternal epinephrine levels by eliminating psychological and physical stress associated with painful uterine contractions and thus promoting labor and delivery

We may postulate that these women were easily exhausted by the pain and could not cope with the continuation of the TOLAC although they consented at its initiation.

This potentially beneficial adjunct to greater TOLAC opportunities is emphasized by the low rate of side effects for the various modes of epidural anesthesia for both mother and fetus.(43)

In summary, epidural analgesia at TOLAC is safe for mother and neonate, and possibly emerging as a significant adjunct to successful VBAC after a single previous cesarean.

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Declaration of interest

None of the authors has any conflicts of interest to declare.

Ethics Approval

The study protocol was submitted to the institutional Helsinki Committee (12 November 2013) and was exempted (IRB number 89/13) on the basis of the protocol being an analysis of anonymized data.

References

1. Zeitlin J, Mohangoo A, Delnord M. European Perinatal Health Report. Health and Care of Pregnant Women and Babies in Europe in 2010 [Available from: <http://www.europeristat.com/reports/european-perinatal-health-report-2010.html>.
 2. Quinlan JD, Murphy NJ. Cesarean delivery: counseling issues and complication management. *American Family Physician*. 2015;91(3):178-84.
 3. Spong CY, Berghella V, Wenstrom KD, Mercer BM, Saade G. R. . Preventing the first cesarean delivery: summary of a joint Eunice Kennedy Shriver National Institute of Child Health and Human Development, Society for Maternal-Fetal Medicine, and American College of Obstetricians and Gynecologists Workshop. *Obstetrics and Gynecology*. 2012;120(5 SRC - GoogleScholar):1181-93.
 4. Landon MB, Hauth JC, Leveno KJ, Spong CY, Leindecker S, Varner MW. Maternal and perinatal outcomes associated with a trial of labor after prior cesarean delivery. *New England Journal of Medicine*. 2004;351(25 SRC - GoogleScholar):2581-9.
 5. Cook JR, Jarvis S, Knight M, Dhanjal MK. Multiple repeat caesarean section in the UK: incidence and consequences to mother and child. A national prospective cohort study *British Journal of Obstetrics and Gynecology*. 2013;120(9 SRC - GoogleScholar):1154-5.
 6. Lydon-Rochelle M, Holt VL, Easterling TR, Martin DP. Risk of uterine rupture during labor among women with a prior cesarean delivery. *New England Journal of Medicine*. 2001;345(1 SRC - GoogleScholar):3-8.
 7. Sakala EP, Kaye S, Murray RD, Munson LJ. Epidural analgesia. Effect on the likelihood of a successful trial of labor after cesarean section *Journal of Reproductive Medicine*. 1990;35(9 SRC - GoogleScholar):886-90.
 8. Anwar S, Anwar MW, Ahmad S, J. Effect of epidural analgesia on labor and its outcomes. *Medical College Abbottabad*. 2015;27(1 SRC - GoogleScholar):146-50.
 9. Yvonne W, Brian L, James M, Aaron B, Second C, A. Cheng, Shaffer, Nicholson, ,and of Labor and Epidural Use Effect Than Previously Suggested *Obstet Gynecol*. 2014;123 SRC - GoogleScholar:527-35.
 10. Barger MK, Weiss J, Nannini A, Werler M, Heeren T, Stubblefield PG. Risk factors for uterine rupture among women who attempt a vaginal birth after a previous cesarean: a case-control study. *Journal of Reproductive Medicine* 56 313320. 2011:7-8
- SRC - GoogleScholar.
11. Di Renzo GC. Tocophobia: a new indication for cesarean delivery? *J Matern Fetal Neonatal Med*. 2003 Apr;13(4):217. PubMed PMID: 12854919.
 12. Wing DA, Farinelli CK. Abnormal labor and induction of labor. In: Gabbe SG NJ, Galan HL, Jauniaux ERM, Landon MB, Simpson JL, Driscoll DA, editor. *Obstetrics: Normal and problem pregnancies 6th Edition*: Philadelphia: Elsevier/Saunders; 2012. p. 287-311.
 13. Dollberg S, Haklai Z, Mimouni FB, Gorfein I, Gordon ES. Birth weight standards in the live-born population in Israel. *Israeli Medical Association Journal*. 2005;7 SRC - GoogleScholar:311-4.
 14. Konefal H, Jaskot B, Czeszynska MB, Pastuszka J. Remifentanyl patient-controlled analgesia for labor - monitoring of newborn heart rate, blood pressure and oxygen saturation during the first 24 hours after delivery. *Arch Med Sci*. 2013 Aug 30;9(4):697-702. PubMed PMID: 24049531. PMCID: PMC3776166.

15. Bujold E, Gauthier RJ. Should we allow a trial of labor after a previous cesarean for dystocia in the second stage of labor? *Obstetrics and Gynecology*. 2001;98(4 SRC - GoogleScholar):652-5.
16. E KSaG. Chapter 13- Normal Labor and Delivery. In: Gabbe SG NJ, Galan HL, Jauniaux ERM, Landon MB, Simpson JL, Driscoll DA, editor. *Normal and Problem Pregnancies* 6th Edition. Philadelphia: Elsevier; 2012. p. 267-86.
17. Rietveld AL, Kok N, Kazemier BM, de Groot CJ, Teunissen PW. Trial of labor after cesarean: attempted operative vaginal delivery versus emergency repeat cesarean, a prospective national cohort study. *Journal of Perinatology*. 2015;35(4 SRC - GoogleScholar):258-62.
18. Dharan VB, Srinivas SK, Parry S, Ratcliffe SJ, Macones G. Pregestational diabetes: a risk factor for vaginal birth after cesarean section failure? *American Journal of Perinatology*. 2010;27 SRC - GoogleScholar:265-70.
19. Waldenstrom U, Irestedt L. Obstetric pain relief and its association with remembrance of labor pain at two months and one year after birth. *J Psychosom Obstet Gynaecol*. 2006 Sep;27(3):147-56. PubMed PMID: 17214449.
20. Witt WP, Wisk LE, Cheng ER, Mandell K, Chatterjee D, Wakeel F. Determinants of cesarean delivery in the US: a lifecourse approach. *Maternal and Child Health Journal*. 2015;19(1):84-93.
21. Dunn EA, Herlihy C. O'Comparison of maternal satisfaction following vaginal delivery after caesarean section and caesarean section after previous vaginal delivery *European Journal of Obstetrics, Gynecology, and Reproductive Biology*. 2005;121(1 SRC - GoogleScholar):56-60.
22. Hung TH, Hsieh TT, Liu HP, A., S. Differential Effects of Epidural Analgesia on Modes of Delivery and Perinatal Outcomes between Nulliparous and Multiparous Women: Cohort Study. *PLoS ONE*. 2017;10(3 SRC - GoogleScholar).
23. Anim-Somuah M, Smyth RM, Jones L. Epidural versus non-epidural or no analgesia in labour. *Cochrane Database Systematic Reviews* CD000331. 2011;12 SRC - GoogleScholar.
24. Sentilhes L, Beucher G, Deneux-Tharaux C, Deruelle P, Diemunsch P, Vayssi re, C., . Delivery for women with a previous cesarean: guidelines for clinical practice from the French College of Gynecologists and Obstetricians (CNGOF). *European Journal of Obstetrics, Gynecology, and Reproductive Biology*. 2013;170(1 SRC - GoogleScholar):25-32.
25. Wassen MM, Zuijlen J, Roumen FJ, Smits LJ, Marcus MA, Nijhuis JG. Early versus late epidural analgesia and risk of instrumental delivery in nulliparous women: a systematic review. *British Journal of Obstetrics and Gynecology*. 2011;118(6 SRC - GoogleScholar):655-61.
26. Wang F, Shen X, Guo X, Peng Y, Gu X. Labor Analgesia Examining Group. Epidural analgesia in the latent phase of labor and the risk of cesarean delivery a fiveyear randomized controlled trial *Anesthesiology*. 2009;111(4 SRC - GoogleScholar):871-80.
27. Sng BL, Leong WL, Zeng Y, Siddiqui FJ, Assam PN, Lim Y, et al. Early versus late initiation of epidural analgesia for labour. *Cochrane Database Syst Rev*. 2014 Oct 09(10):CD007238. PubMed PMID: 25300169.
28. Bernstein SN, Matalon-Grazi S, Rosenn BM. Trial of labor versus repeat cesarean: are patients making an informed decision? *American Journal of Obstetrics and Gynecology*, , 204. 2012;207(3 SRC - GoogleScholar):e1-6.
29. Shmueli A, Tamir D. Health Behavior and Religiosity among Israeli Jews. *Israeli Medical Association Journal*. 2007;9 SRC - GoogleScholar:703-7.
30. Fagerberg MC, Mar  al, K., K  ll  n, K., . Predicting the chance of vaginal delivery after one cesarean section: validation and elaboration of a published prediction model 2015. 88-94 p.

31. Costantine MM, Fox K, Byers BD, Mateus J, Ghulmiyyah LM, Blackwell S. Validation of the prediction model for success of vaginal birth after cesarean delivery. *Obstetrics and Gynecology*. 2009;114(5 SRC - GoogleScholar):1029-33.
32. Gilbert SA, Grobman WA, Landon MB, Varner MW, Wapner RJ, Sorokin Y. Lifetime cost-effectiveness of trial of labor after cesarean in the United States. *Value Health*. 2013;16(6):953-64.
33. Grobman WA, Lai Y, Landon MB, Spong CY, Leveno K, Rouse DJ. J. . Does information available at admission for delivery improve prediction of vaginal birth after cesarean? *American Journal of Perinatology*. 2009;26(10 SRC - GoogleScholar):693-701.
34. Cahill AG, Stamilio DM, Odibo AO, Peipert JF, Ratcliffe SJ, Stevens EJ. Is vaginal birth after cesarean (VBAC) or elective repeat cesarean safer in women with a prior vaginal delivery? *American Journal of Obstetrics and Gynecology*. 2006;195(4 SRC - GoogleScholar):1143-7.
35. Mercer BM, Gilbert S, Landon MB, Spong CY, Leveno KJ, Rouse DJ. Labor outcomes with increasing number of prior vaginal births after cesarean delivery. *Obstetrics and Gynecology*. 2008;111(2 Pt 1):285-91.
36. Alexander J, Sharma S, McIntire D, Wiley J, Leveno K. Intensity of labor pain and cesarean delivery. *Anesthesia and Analgesia PubMed* 11375838. 2001;92 SRC - GoogleScholar:1524-8.
37. Panni M, Segal S. Local anesthetic requirements are greater in dystocia than in normal labor. *Anesthesiology PubMed* 12657859. 2003;98 SRC - GoogleScholar:957-63.
38. Grant EN, Tao W, Craig M, McIntire D, Leveno K. Neuraxial analgesia effects on labour progression: facts, fallacies, uncertainties and the future. *BJOG*. 2015 Feb;122(3):288-93. *PubMed PMID*: 25088476. *PMCID*: PMC4308552.
39. Lederman RP, Lederman E, Work BA, McCann DS. The relationship of maternal anxiety, plasma catecholamines, and plasma cortisol to progress in labor. *American Journal of Obstetrics and Gynecology PubMed* 717451. 1978;132(5 SRC - GoogleScholar):495-500.
40. Thornton C, Carrie L, Sayers L, Anderson A, Turnbull A. A comparison of the effect of extradural and parental analgesia on maternal plasma cortisol concentrations during labor and the puerperium. *British Journal of Obstetrics and Gynaecology PubMed* 952794. 1976;83 SRC - GoogleScholar:631-5.
41. Shnider S, Abboud T, Artal R, Henriksen E, Stefani S, Levinson G. Maternal catecholamines decrease during labor after lumbar epidural anesthesia. *American Journal of Obstetrics and Gynecology PubMed* 6614080. 1983;147(1 SRC - GoogleScholar):13-5.
42. Jouppila R, Hollmen A. The effect of segmental epidural analgesia on maternal and foetal acid-base balance, lactate, serum potassium and creatine phosphokinase during labour. *Acta Anaesthesiol Scand*. 1976;20(3):259-68. *PubMed PMID*: 961334.
43. Jones L, Othman M, Dowswell T, Alfievic Z, Gates S, Newburn M, et al. Pain management for women in labour: an overview of systematic reviews. *Cochrane Database Systematic Reviews* CD009234. 2012;3 SRC - GoogleScholar.

Table 1: Maternal characteristics of the study population

Characteristic	TOLAC epidural "users" N= 4081	TOLAC epidural "non- users" N=3,068	p value
Maternal age (years)	30.6 ± 5.1	31.8 ± 5.5	<0.0001
Maternal Age >35 years	769 (18.8)	804 (26.2)	<0.0001
Jewish ethnicity	3837 (94)	2804 (91.4)	<0.0001
Education ≥12 years	4028 (98.7)	2988 (97.4)	<0.0001
Artificial reproductive techniques	122 (3.0)	68 (2.2)	0.033
Median parity	2 [2-5]	4 [3-6]	<0.0001
Gestational diabetes mellitus	171 (4.2)	98 (3.2)	0.023
Hypertensive disorders of pregnancy	53 (1.3)	59 (1.9)	0.069
Previous vaginal delivery	2652 (65)	2542 (82.9)	0.0001

Data are mean± standard deviation; median [interquartile range]; number (%);

Table 2: Labor characteristics of the study population

Characteristic	TOLAC epidural "users" N= 4081	TOLAC epidural "non- users" N=3,068	p value
Gestational age at delivery (weeks)	39.5 ± 1.5	39.4 ± 1.9	0.006
Cervical score ≥6 at admission*	1484 (67.2)	893 (76.5)	<0.0001
length of labor (hours)	4.82 [2.95-7.72]	1.27 [0.53-2.70]	0.0001
Preterm birth (<37 weeks gestation)	122 (3)	129 (4.2)	0.008
Labor Induction	272 (6)	99 (3.2)	<0.0001
Oxytocin use during labor	1018 (24.9)	268 (8.7)	<0.0001
Spontaneous vaginal delivery	3246 (79.5)	2622 (85.5)	<0.0001
Instrumental delivery	479 (11.7)	85(2.8)	<0.0001
Cesarean section delivery	356 (8.7)	361 (11.8)	<0.0001
Early Postpartum hemorrhage	98 (2.4)	77 (2.5)	0.593
Uterine rupture (all)	18 (0.4)	9 (0.29)	0.314
Incomplete	6 (0.1)	3 (0.1)	0.602
Complete	12 (0.3)	6 (0.2)	0.602
Prolonged maternal hospitalization**	616 (15.1)	448(14.6)	0.62

Data are mean± standard deviation; median [interquartile range]; number (%);

*Full data on cervical score components were registered for 3475 mothers in the study group (48.6%)

**Length of hospitalization > 3days for vaginal and > 4 days for cesarean section

Table 3: Indications for labor induction

	TOLAC epidural "users"	TOLAC epidural "non- users"	p value
	N= 4081	N=3,068	
Induction of labor (n=371)	272 (6.7)	99 (3.2)	<0.0001
Term PROM	92 (33.8)	25 (25.3)	
Post-term (completed 42 weeks)	31 (11.4)	17 (17.2)	
Maternal complications (hypertension, diabetes)	52 (19.1)	17 (17.2)	0.379
Suspected intrauterine fetal compromise	86 (31.6)	36 (36.4)	
Other	11 (4.0)	4 (4.0)	

Data are number (%);

Table 4: Indications for cesarean section of the study population

Indications for Cesarean section at TOLAC	TOLAC epidural "users" N= 4081	TOLAC epidural "non- users" N=3,068	p value
Non-progression of labor	153 (43)	87 (24.1)	<0.0001
Failed induction of labor	14 (3.9)	28 (7.8)	
Suspected fetal distress in labor	169 (47.5)	152 (42.1)	
Patient's request during active labor	20 (5.6)	87 (24.1)	
Other	0 (0)	7 (1.9)	
Overall Cesarean section at TOLAC	356 (8.7)	361 (11.8)	<0.0001

Data are number (%);

Table 5: Neonatal characteristics and outcomes

Characteristic	TOLAC epidural "users" N=4081	TOLAC epidural "non-users" N=3068	P value
birth weight (grams)	3346 ± 461	3315 ± 521	0.008
Small for Gestational Age (SGA)	241 (5.9)	233 (7.6)	0.006
Large for Gestational Age (LGA)	461 (11.3)	380 (12.4)	0.191
Male gender	2064 (50.6)	1559 (50.8)	0.84
Neonatal Intensive care unit (NICU) admission >72 hours	68 (1.6)	68 (2.2)	0.309
5'Apgar <7	45 (1.1)	40 (1.3)	0.44

Data are mean± standard deviation; number (%);

Table 6: Significant factors associated with TOLAC-VBAC mode of delivery in the presence of epidural: multivariate analysis

Covariate	OR	95%CI	P value
Epidural analgesia	4.57	3.67-5.70	0.0001
Maternal Age>35 years old	0.54	0.43-0.69	0.0001
Hypertensive disorder in pregnancy	0.46	0.27-0.81	0.007
Gestational diabetes mellitus	0.59	0.40-0.85	0.007
Preterm delivery (<37 weeks)	0.65	0.43-0.97	0.38
Labor induction	0.658	0.49-0.87	0.005
Previous vaginal delivery	3.11	2.53-3.82	0.0001
Oxytocin during labor	0.06	0.04-0.07	0.0001

*Adjusted for the following confounders: maternal age >35 years, ethnicity, maternal education >12 years, gestational age at birth <37 weeks (preterm), hypertensive disorder in pregnancy, gestational diabetes mellitus, previous vaginal birth, previous miscarriages, artificial reproductive techniques, induction of labor, oxytocin augmentation during labor.

Table 7: Significant factors associated with TOLAC-VBAC mode of delivery in the presence of epidural: multivariate analysis a model adjusted for the modified cervical score at admission

Covariate	OR	95%CI	P value
Epidural	3.34	2.43-4.58	0.0001
Modified Cervical score ≥ 6	1.97	1.49-2.60	0.0001
Maternal age >35 years old	0.45	0.31-0.54	<0.0001
Hypertensive disorder in pregnancy	0.82	0.31-2.17	0.82
Gestational diabetes mellitus	0.47	0.30-0.99	0.047
Preterm delivery (<37 weeks)	1.45	0.60-3.49	0.39
Labor induction	0.66	0.42-10.3	0.71
Previous vaginal delivery	3.98	2.92-5.43	0.0001
Oxytocin during labor	0.085	0.062-0.11	0.0001

*Adjusted for the following confounders: maternal age >35 years, ethnicity, maternal education >12 years, gestational age at birth <37 weeks (preterm), hypertensive disorder in pregnancy, gestational diabetes mellitus, previous vaginal birth, previous miscarriages, artificial reproductive techniques, induction of labor, oxytocin augmentation during labor.