

Do women in Slovenia prefer vaginal birth after prior caesarean and what hinders its successful outcome? A single institution retrospective analysis

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Background: To analyze the mode of delivery and the outcome of a trial of labor in women with one prior caesarean birth. Methods: We extracted from the national database our hospital's information on women with a prior caesarean section from January 2014 to July 2019. They were then divided into groups that either opted for a trial of labor or repeat caesarean section. We further focused on the trial of labor group and divided them in two subgroups of either a vaginal delivery or repeat caesarean section. Results: 796 women with one prior caesarean section were identified and 201 (25.3%) opted for a trial of labor. Successful vaginal delivery was achieved in 84.1% of women that opted for a trial of labor. Women pregnant for the third time or greater delivered vaginally at a higher rate (24.3% vs 10.7%). More women who had labor induced with a Foley catheter ended in caesarean section (8.1% vs 17.9%). There was one uterine rupture without further complications. Failed trial of labor was caused by the lack of persistence (14.3%) and arrest of labor (50.0%). Conclusion: Improved counselling is needed for those women who choose a trial of labor. The rate of successful vaginal delivery following a trail of labor is high, but could be improved with more conservative management during the first stage of labor.

Keywords

Vaginal birth after a cesarean section; Trial of labor; Repeat caesarean delivery; Birth outcomes

1. Introduction

According to the World Health Organization (WHO), the optimal rate of cesarean section (CS) should not exceed 15% [1]. CS rates higher than 15% do not further reduce maternal or fetal mortality but increase the frequency of complications including higher blood loss, infection, pelvic adhesions, longer recovery period and prolonged hospitalization [2]. One CS often leads to another in subsequent pregnancies, creating an ideal milieu in the uterus for the development of placenta accrete, especially in cases with placenta previa [3]. Invasive placenta pathology is a life-threatening condition that invades not only the myometrium but also surrounding structures, such as the bladder and intestines [4].

In these cases, hysterectomy and resection of the surrounding structures are often the only effective treatment [5]. Therefore, it is of paramount importance to limit CS to those cases, where it is truly indicated. Currently, the percentage of CS is twice as high as the WHO ideal with an upward slope over the last 30 years [6].

In recent years, there has been a movement encouraging vaginal birth after CS (VBAC) that could decrease the number of repeat CS in order to reduce the overall incidence of CS [7]. This initiative has been further supported by the new operative techniques of CS associated with a lower incidence of uterine rupture during labor in a subsequent pregnancy [8]. National perinatal societies promote VBAC as a safe option, provided they are performed in a suitable hospital environment [9]. These assumptions have been repeatedly confirmed in numerous studies [10, 11].

However, despite these positive reports there is a wide range of enthusiasm for vaginal delivery after CS among women and support from medical staff varies in different countries, regions and specific hospitals [12, 13]. In Europe, Nordic countries (Finland, Sweden) and Netherland have the highest rate of VBAC (45–55%), while Ireland, Italy and Germany have the lowest (29–36%) [14].

In some regions of the world, authors emphasize that in their local settings the availability and hospital offer of VBAC is an important criterion whether a pregnant woman will select that hospital in which to deliver [15]. Others have reported that in their region the women's choice is more directed towards repeat CS in subsequent pregnancy without considering VBAC as an attractive or even a viable option [13].

Both groups of data that either advocate or ignore a trail of labor after cesarean section (TOLAC) as a feasible method for reducing the overall rate of CS, are important and should not be overlooked. The message of positive reports is that VBAC is an effective approach in order to decrease the CS rate while the message of negative reports is that data on the success-

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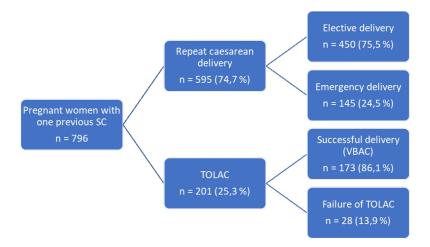


Fig. 1. Selection of the study group. TOLAC, Trial of labour after caesarean delivery; SC, Caesarean section.

ful outcome of TOLAC are insufficient for its implementation without addressing certain important obstacles specific for each environment. For example, some studies show that factors influencing TOLAC failure include the mother's obesity (BMI > 30), fetal macrosomia, chronological age, gestational diabetes, hypertension in pregnancy and also stalled labor. Successful TOLAC is associated with a previous vaginal birth, the height of the mother being greater than 170 cm and younger age [10, 16]. Therefore, it is mandatory for each hospital to reflect on its own practices and look for specific factors that could be responsible for failed TOLAC. Otherwise, the massive effort invested in the implementation and promotion of VBAC will not be successful [9]. For this reason, we conducted this retrospective outcome analysis of women with a history of one prior CS.

2. Materials and methods

In this retrospective single-institution study, we collected data on the pregnant women with a prior CS. We further focused on the group of women who underwent TOLAC at the Department of Perinatology, University Medical Centre (UMC) Maribor, Slovenia between January 2014 and July 2019 and investigated the outcome of their deliveries. This period (sample size) was chosen on the premise that practices in terms of counselling and labor management were uniform enough to produce the same effect at the beginning and at the end of the study period. Data was collected from the Slovenian National Perinatal Information System (NPIS), which according to the law registers all deliveries in Slovenia above the 22nd week of gestation with fetuses weighing more than 500 g. From the acquired series of patients, we excluded those pregnant women who had preterm labor (gestational age <37 weeks), history of two or more caesarean deliveries, multiple gestation or a previous caesarean delivery with longitudinal or inverted-T shape incision of the uterus.

According to our department's protocols, eligible pregnant women were encouraged and given extensive counseling in the hospital clinic on the benefits of TOLAC at the 36th

week of pregnancy. Counselling included a description of the general medical data about TOLAC along with our own data and experience regarding TOLAC. These pregnant women also spoke about the TOLAC option with their chosen gynecologist on the primary level during routine antenatal visits through the pregnancy.

In general, women that had a myomectomy with entrance into the uterine cavity were usually advised to have a repeat caesarean section.

We searched for the data describing the demographic characteristics of the mother (age, number of successful previous births, mode of conception, maternal diseases, use of nicotine and alcohol, physical activity, marital status and education), events during labor and delivery (labor onset, type of membrane rupture, duration of labor, appearance of amniotic fluid, use and dosages of oxytocin), complications before and after the birth of the baby and the mode of delivery. Neonatal data such as birth weight, birth length and APGAR score at 1, 5 and 10 minutes were also acquired.

In our database indications for previous caesarean section were not reliably recorded, so this was not included in our analysis.

After the initial data screening, we compared the summary statistics of outcomes and characteristics (count, averages, standard deviations) between the two subgroups (Successful TOLAC Subgroup and Failed TOLAC Subgroup). Successful TOLAC subgroup included trials of labor that ended in vaginal delivery and Failed TOLAC subgroup included trials of labor that ended in urgent caesarean section.

Statistical analysis was performed using the SPSS software version 27.0 for Mac OS (IBM Corp., Armonk, NY, USA). For comparison of categorical variables, we used the chisquare test and for continuous variables we used the Mann-Whitney U-test. The population characteristics were expressed as continuous or categorical variables and calculated as frequencies or averages (standard deviations) respectively. Statistically significant differences were identified when P < 0.05.

Table 1. Characteristics of the pregnant women in a subgroup of TOLAC with a successful vaginal delivery (successful TOLAC subgroup) and subgroup of TOLAC with repeated caesarean section (failed TOLAC).

		Successful TOLAC (n = 173)		Failed TOLAC (n = 28)			
		N	%	N	%	P value	
Age	Average (years)	31.5	-	33	-	0.81	
	SD (years)	4.3		3.7			
Education	Low	119	68.8	22	78.6	0.19	
	High	54	31.2	6	21.4		
Marritial status	Single	21	12.1	3	10.7		
	Married	57	32.9	10	35.7	0.15	
	Extramarritial community	95	54.9	15	53.6		
Smoking in pregnacy	No	166	96.0	27	96.4	0.91	
	Yes	7	4	1	3.6		
Physical activity	No	20	11.6	5	17.9	0.35	
	Yes	153	88.4	23	82.1		
Parturity	Second pregnancy	131	75.7	25	89.3	0.11	
	Third or higher pregnancy	42	24.3	3	10.7		
IVF	No	168	97.1	28	100.0	0.37	
	Yes	5	2.9	0	0	0.37	
Diseases in pregnancy	No	138	79.8	21	75	0.57	
	Mild hypertensive diseases	4	2.3	1	3.6	0.69	
	Severe preeclampsia	1	0.6	0	0	0.69	
	Gestational diabetes	23	13.3	5	17.9	0.52	
	IUGR	6	3.5	1	3.6	0.98	
	Oligohydramnios	2	1.2	0	0.0	0.57	
Medications in pregnancy	No	152	87.9	26	92.9	0.44	
	Antihypertensive drugs	2	1.2	0	0	0.57	
	Insulin	7	4	1	3.6	0.50	
	Aspirin	12	6.9	1	3.6	0.91	
Week of gestation	Before EDD	87	50.3	14	50	0.98	
	After EDD	86	49.7	14	50		

3. Results

796 women with one prior caesarean section were identified. From this group, 201 (25.3%) pregnant women opted for a trial of labor and 74.7% for a repeat caesarean delivery. 84.1% of women opting for trial of labor had a successful vaginal delivery. A detailed overview of the women's preferences and outcomes of the trial of labor are seen in Fig. 1.

The demographic characteristics of the pregnant women in the study group are presented in detail in Table 1. In general, there are no differences between women who delivered vaginally and those with a repeat caesarean section. Women pregnant for the third time or higher with one previous CS delivered more frequently via the vaginal route (24.3% vs 10.7%). One woman with severe preeclampsia opted for a trial of labor and successfully delivered vaginally.

The specifics of the labor and delivery are fully described in Table 2. A higher proportion of induced labor utilizing the Foley catheter was represented in the failed TOLAC subgroup than in the successful subgroup (8.1% vs 17.9%), but more inductions utilizing the Foley catheter ended in vaginal delivery (14 vs 5; 73.7% success rate). Higher dosages of oxytocin were more frequently used in the Successful TOLAC group (8.1% vs 3.6%).

Complications of labor are presented in detail in Table 3. Fetal intolerance to labor was more prevalent in the failed subgroup (4.0% vs 42.9%). Abnormal dilatation was present in the Failed subgroup in 7.1% while occurring 2.9% in the successful subgroup. Abnormal descent of the fetal head occurred in 10.7% in the failed subgroup and 1.2% in the successful subgroup. In the successful subgroup, there was 1 uterine rupture, one 3rd degree perineal tear, 6 manual removals of placenta with 2 uterine curettage. In this subgroup, 58.4% of women did experience some form of injury to the birth canal.

All neonates were in a good condition with an average length of 50.0 cm and weight 3387.1 g (SD 422.4 g). The Apgar scores in the 1st minute were under 7 in 4.1% of cases in the successful TOLAC arm with excellent Apgar scores at 5 and 10 minutes. A detailed description of the neonatal data can be found in Table 4.

In some cases, there were multiple reasons for a repeat CS and these are presented in Table 5. Lack of persistence to continue labor without any medical indications was the reason for failed TOLAC in 14.3%, while arrest of labor was responsible for 50% of the cases (Table 6).

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Table 2. Characteristics of the labor and delivery in the subgroup of TOLAC with a successful vaginal delivery (successful TOLAC subgroup) and a subgroup of TOLAC with a repeated caesarean section (failed TOLAC).

		Successful TOLAC ($n = 173$)		Failed TOLAC $(n = 28)$		
		N	%	N	%	P value
Position of the baby	Occipito-anterior	170	98.3	26	92.9	0.09
	Occipito-posterior	3	1.7	2	7.1	
Start of labor	Spontaneous labor	109	63.0	13	46.4	0.37
	Spontaneous rupture of membranes	47	27.2	10	35.7	
	Induction with amniotomy	3	1.7	0	0.0	
	Induction with Foley catheter	14	8.1	5	17.9	
Rupture of membranes	Spontaneous	101	58.4	15	53.6	0.002
	Amniotomy	72	41.6	10	35.7	
	During SC	0	0.0	3	10.7	
Amniotic fluid	Clear	151	87.3	25	89.3	0.77
	Meconium	22	12.7	3	10.7	
Oxytocin	No	84	48.6	10	35.7	0.21
	Yes	89	51.4	18	64.3	
Oxytocin dosages	No	84	48.6	10	35.7	0.21
	1–10 mUnits/min	75	43.4	17	60.7	
	11-22 mUnits/min	14	8.1	1	3.6	
Operative delivery	No	163	94.2	0	0.0	0.000
	Vacuum extraction	10	5.8	0	0.0	
	SC	0	0.0	28	100.0	
Duration of labor	Max (min)	660		689		-
	Min (min)	30		90		
	Average (min)	282.4		342.8		
Type of anesthesia	No	31	17.9	0	0.0	0.000
	General	6	3.5	10	35.7	
	Epidural	12	6.9	5	17.9	
	Spinal	3	1.7	13	46.4	
	Local	121	69.9	0	0.0	

4. Discussion

Our analysis showed that the great majority of pregnant women eligible for vaginal delivery after one CS chose CS as a preferred mode of a delivery for their current pregnancy (74.8%). This is surprising considering the tremendous effort of the Slovenian Association of Perinatal Medicine to promote TOLAC as the preferred method of delivery on all levels of perinatal care (primary, secondary and tertiary level) [17]. Furthermore, according to our department's protocols, eligible pregnant women are encouraged and given extensive counseling on the benefits of TOLAC at the 36th week of gestation. However, experience shows that the majority of women were completely focused on CS as the preferred option and were not willing to take into consideration the data offered at the time of the counselling. In some instances, women reported that they formed their opinion early in their current pregnancy with the help of a primary gynecologist and other members of their family. It seems that the tertiary level counselling at the 36th week of gestation is not as influential on the women's preferences as we had believed [17].

This discovery carries certain significant implications. Many authors have demonstrated that those women who had an urgent caesarean section experienced severe mental trauma. The traumatic experience of labor was not associated only with the cesarean section but was accumulated and multiplied with each step in a sequence of events [18]. From an unremarkable labor to suspicion of pathology, its confirmation and then a turbulent and by many women an uncontrolled transfer from the delivery room to the operating room were events that left an enduring trace of trauma in their subconsciousness. Even the strongest evidence of success and reasonability of TOLAC were insufficient to convince these women to have the experience of labor again [19].

The same arguments could also be valid for the medical staff confronted with data in the literature and their own emotional experience and interpretation of events in the delivery room. If our own deep subconscious beliefs concerning the safety of TOLAC are in conflict with the data in literature, it becomes difficult to hide this bias during clinical communication and is often intentionally or unintentionally projected on to the patient [20]. It could also be argued that women with an unpleasant experience with a prior CS or postoperative recovery could be a motivation for TOLAC. For all of these reasons, we conclude that women in the TOLAC group were very motivated for a vaginal delivery and according to our results, had a high likelihood of a successful vaginal de-

Table 3. Complications of the labor in a subgroup of TOLAC with a successful vaginal delivery (successful TOLAC subgroup) and a subgroup of TOLAC with a repeated caesarean section (failed TOLAC).

		Successful TOLAC (n = 173) Failed TOLAC (n = 28			28)		
		N	%	N	%	P value	
Labor abnormalities	No		92.5	13	46.4	0.000	
	Abnormal dilatation	5	2.9	2	7.1	0.26	
	Abnormal descent of the fetal head	2	1.2	3	10.7	0.003	
	Fetal distress		4.0	12	42.9	0.002	
Trauma	No	101	58.4	28	100.0	N/A	
	Trauma of vulva. vagina and superficial traum of perineum	na 69	39.9	0	0.0	N/A	
	Rupture of perineum (3rd degree)	1	0.6	0	0.0	N/A	
	Rupture of perineum (4th degree)	0	0.0	0	0.0	N/A	
	Rupture of cervix	1	0.6	0	0.0	N/A	
	Rupture of uterus	1	0.6	0	0.0	N/A	
	Manual removal of placenta or uterine curreta	ge 8	4.6	0	0.0	N/A	
Complications of third stage of labor	No	172	99.4	28	100.0		
	Postpartum hemorhage less than 500 mL	1	0.6	0	0.0	N/A	
	Postpartum hemorrhage more than 500 mL	0	0.0	0	0.0		
Wound	No	169	97.7	27	96.4		
	Episiotomy dehiscence	1	0.6	0	0.0		
	Haematoma	2	1.2	0	0.0	0.57	
	Infection	1	0.6	0	0.0	0.69	
Thromboembolic events	No	173	100.0	28	100.0	NT/A	
	Yes	0	0.0	0	0.0	N/A	
Surgery and other complications after delivery No		173	100.0	0	0.0	N/A	

Table 4. Neonatal outcomes in a subgroup of TOLAC with a successful vaginal delivery (successful TOLAC subgroup) and a subgroup of TOLAC with a repeated caesarean section (failed TOLAC).

	Successful TOLAC ($n = 173$)		Failed TO	ailed TOLAC $(n = 28)$	
	N	%	N	%	P value
Average (g)	3393.2		3350.0		0.50
SD	424.3		415.7		0.50
Average (cm)	150.1		49.6		0.15
SD (cm)	1.9		2.00		0.15
6 or less	7	4.0	6	21.4	0.001
7 or more	166	96.0	22	78.6	0.001
6 or less	0	0.0	0	0.0	N/A
7 or more	173	100.0	28	100.0	IN/ A
6 or less	0	0.0	0	0.0	NT/A
7 or more	173	100.0	28	100.0	N/A
	SD Average (cm) SD (cm) 6 or less 7 or more 6 or less 7 or more 6 or less	N Average (g) 3393.2 SD 424.3 Average (cm) 150.1 SD (cm) 1.9 6 or less 7 7 or more 166 6 or less 0 7 or more 173 6 or less 0	N % Average (g) 3393.2 SD 424.3 Average (cm) 150.1 SD (cm) 1.9 6 or less 7 4.0 7 or more 166 96.0 6 or less 0 0.0 7 or more 173 100.0 6 or less 0 0.0	N % N Average (g) 3393.2 3350.0 SD 424.3 415.7 Average (cm) 150.1 49.6 SD (cm) 1.9 2.00 6 or less 7 4.0 6 7 or more 166 96.0 22 6 or less 0 0.0 0 7 or more 173 100.0 28 6 or less 0 0.0 0	N % N % Average (g) 3393.2 3350.0 3350.0 SD 424.3 415.7 Average (cm) 150.1 49.6 SD (cm) 1.9 2.00 6 or less 7 4.0 6 21.4 7 or more 166 96.0 22 78.6 6 or less 0 0.0 0 0.0 7 or more 173 100.0 28 100.0 6 or less 0 0.0 0 0.0

livery (86.1%). These results should be emphasized during counselling, as they represent a much more reliable benchmark of success than the general reports of successful outcome from completely different environments [17].

In the TOLAC group, a successful vaginal delivery was more frequent in women with additional prior successful vaginal deliveries. Prior successful vaginal delivery could indicate that a woman was already motivated to undergo TOLAC. At that past pregnancy, her motivation for vaginal delivery could be due to her wish for larger family, which may have been prevented with second cesarean section or because she was persuaded with data of VBAC safety during counselling. A successful outcome of vaginal delivery confirmed

her positive expectations and persuaded her to opt for a vaginal delivery again in the subsequent pregnancy. In our experience these women required very little persuasion and already came to counselling with a positive attitude towards VBAC [21].

The significant role of maternal motivation for the success of TOLAC is demonstrated in cases of severe preeclampsia where a woman despite the disease state chose vaginal delivery. This choice had a positive medical effect because a caesarean section is associated with a greater blood loss than vaginal delivery and can be exacerbated in cases of disturbed coagulation as in severe preeclampsia. It should be emphasized that we did not categorize women according to the in-

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Table 5. Reasons for a failed TOLAC by individual cases.

No	Foley induction	No motivation	Uninducible cervix	No progress of labor	Non-reassuring or pathological CTG	(Pre) Acidosis
1		х				
2				x		
3					x	
4				x		
5			x			
6					x	
7				x	x	
8				x	x	
9				X	x	
10				X		
11				X	x	
12	x				x	x
13				X	x	
14	x	x				
15				X		
16				X		
17				X		
18	x				x	
19				X		
20				x		
21				x		
22					x	
23		x				
24						
25	x			x		
26	x		x			
27					x	
28					x	X

Table 6. Reasons for failed TOLAC.

No motivation	4	14.3%
Noinducible cervix	2	7.1%
No progress of labor	14	50.0%
Nonreasuring or pathological CTG	12	42.9%
(Pre) Acidosis	2	7.1%

dications for a prior CS, since this data could have influenced counselling and the women's final decision. Some studies have demonstrated that women with prior CS due to arrest of labor had a lower chance of successful TOLAC then those with other indications for CS [22]. If that was the case, the woman and even the doctor probably promoted CS instead TOLAC as a more feasible option.

With a women's motivation for vaginal delivery and unintended stratification into the TOLAC group, it could be said that the TOLAC group was self-selected and this could be a potential reason for successful vaginal birth. It is highly questionable if the same success rate would have been observed if the policy of our department was to offer TOLAC as the only option to all eligible women.

In the TOLAC group, a special challenge represents the absence of a favorable cervix in the post-term period. In our department, prostaglandins (PG) were avoided in this group

of patients because of the increased risk for a uterine rupture [23]. Some authors, however, recommend PG as a method of induction even for this group of patients and limit their use only in a group with more than two CSs [24]. However, we found a solution in the Foley catheter insertion as the method of induction for TOLAC. As a mechanical device, it proved to be a safe approach for labor induction in this group of pregnant women [25].

Complications in both TOLAC groups were rare and without major complications, such as thromboembolism, uterine atony or infections. Meanwhile, in the successful TOLAC group, we had one uterine rupture discovered immediately after the delivery owing to the mesentery fatty tissues protruding from the vagina. Fortunately, the rupture caused no major hemorrhage or pain and was immediately repaired during laparotomy. At our department, we do not routinely perform a digital examination of the lower uterine segment immediately after the extrusion of the placenta, since the evidence in literature shows that this maneuver is of little clinical benefit [26].

Even though serious complications were not frequent, minor complications were noted, such as the manual removal of the placenta (4.6%) and superficial trauma in the birth canal (39.9%) [27]. In our opinion, these complications should not discourage women from choosing TOLAC.

It is difficult to assess the casual contribution of oxytocin to the success of TOLAC, but the differences in oxytocin dosages were noted between subgroups (higher dosages in the successful TOLAC group), but were not statistically significant (43.4% vs 60.7%, P=0.21), probably because of the small numbers of patients. As a rule, much lower oxytocin dosages were used in both groups in comparison to pregnant women without prior caesarean birth (personal experience). This trend reflects the concern of medical staff not to increase the likelihood of uterine rupture with higher dosages.

It was noted that a high percentage of arrested labor was a cause for a failed trail (50.0%). A detailed analysis of the partograms in the failed TOLAC subgroup showed that arrested labor was indeed present in some cases and even in cases with maximal dilatation. The most intriguing were the cases with the diagnosis of arrested labor during the early initiation of labor when partogram recording has not even started (cervix dilated less than 3 cm). Rupture of membranes without progress with "timid" use of oxytocin were typical scenarios in these cases. We cannot determine what would have happened with a more liberal use of oxytocin and our acceptance that labor is a physiologic process. From data and our personal experience, we have an impression that fear and patience of women and the medical staff play a fundamental role in success of TOLAC.

Concerning is the discovery that in 14.3% of cases, the disappearance of women's motivation to continue with a trial of labor without any medical indications was the sole reason for TOLAC failure. We could argue that in these cases, the success of TOLAC would have been much higher with a greater persistence. Interestingly, this phenomenon of women's motivation disappearing during a trial of labor is insufficiently addressed in medical literature [28]. Therefore, we believe further research should be directed towards solving this challenge. In our opinion, simply denying women the option to change their mind mid-labor and forcing them to continue in spite of their beliefs is not the correct approach. Psychological support, preparation before labor and availability of epidural anesthesia deserve further exploration [29].

Limitations of our study are its retrospective nature and focus on single institutional data. Every department of perinatology develops its unique experience of TOLAC in which regional influences in social and professional dynamics (general beliefs of a populations including pregnant women and personal beliefs of primary gynecologist) remain hidden and inadequately explained. Smaller number of patients included in the analysis can also prevent from discovering the small differences between groups. It is with our own data that we can improve our practices over time.

5. Conclusions

Despite the great odds of success of TOLAC, a significant majority of women after one previous CS still do not choose TOLAC as the mode of delivery for their current pregnancy. For better results, our counselling process needs improve-

ment. We could increase the odds of success if we could find a suitable way to reduce both the number of women who change their minds and opt for CS in the middle of a trial of labor without any significant medical indications and the number of women who initially proclaim TOLAC as unpromising.

Author contributions

Project development: FM, VA; Data collection: VA, MS; Manuscript writing: FM, MS; Manuscript editing: VA, FM, IT; Data analysis and interpretation: FM, MS, VA, IT.

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of UMC Maribor (Reg. No. UKC-MB-KME 33/20). All patients signed a written informed consent form to allow the use of their medical records retrospectively for research purposes.

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Conflict of interest

The authors declare no conflict of interest.

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