

# Second-trimester cervical length as risk indicator for Cesarean delivery in women with twin pregnancy

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KEYWORDS: cervical-length measurement; Cesarean delivery; twin pregnancy

## **ABSTRACT**

Objective To determine whether second-trimester cervical length (CL) in women with a twin pregnancy is associated with the risk of emergency Cesarean section.

Methods This was a secondary analysis of two randomized trials conducted in 57 hospitals in The Netherlands. We assessed the univariable association between risk indicators, including second-trimester CL in quartiles, and emergency Cesarean delivery using a logistic regression model. For multivariable analysis, we assessed whether adjustment for other risk indicators altered the associations found in univariable (unadjusted) analysis. Separate analyses were performed for suspected fetal distress and failure to progress in labor as indications for Cesarean section.

Results In total, 311 women with a twin pregnancy attempted vaginal delivery after 34 weeks' gestation. Emergency Cesarean delivery was performed in 111 (36%) women, of which 67 (60%) were performed owing to arrest of labor. There was no relationship between second-trimester CL and Cesarean delivery (adjusted odds ratio (aOR): 0.97 for CL  $26^{th}$ – $50^{th}$  percentiles; 0.71 for CL  $51^{st}$ – $75^{th}$  percentiles; and 0.92 for CL > $75^{th}$ 

percentile, using  $CL \le 25^{th}$  percentile as reference). In multivariable analysis, the only variables associated with emergency Cesarean delivery were maternal age (aOR, 1.07 (95% CI, 1.00–1.13)), body mass index (BMI) (aOR, 3.99 (95% CI, 1.07–14.9) for BMI 20–23 kg/m²; 5.04 (95% CI, 1.34–19.03) for BMI 24–28 kg/m²; and 3.1 (95% CI, 0.65–14.78) for BMI > 28 kg/m²) and induction of labor (aOR, 1.92 (95% CI, 1.05–3.5)).

Conclusion In nulliparous women with a twin pregnancy, second-trimester CL is not associated with risk of emergency Cesarean delivery. Copyright © 2014 ISUOG. Published by John Wiley & Sons Ltd.

## INTRODUCTION

In nulliparous women with a singleton pregnancy delivering at term, second-trimester cervical length (CL) is associated with the risk of emergency Cesarean delivery<sup>1,2</sup>. Women with a long cervix during the second trimester have a greater risk of intrapartum Cesarean delivery at term than do those with a short cervix (odds ratio (OR), 1.81 (95% CI, 1.6–1.9))<sup>1,2</sup>. In nulliparous women, short second-trimester CL is a risk factor for preterm birth. In general, the shorter the cervix the greater the likelihood

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Accepted: 2 November 2014

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of preterm birth, with a positive predictive value of 70% for preterm birth before 35 weeks in women with a CL of < 25 mm at 14-18 weeks' gestation<sup>3</sup>. The same holds true for women with a multiple pregnancy. For CL as a predictor of preterm birth, sensitivity and specificity (which depend on gestational age at measurement, CL cut-off and definition of preterm birth) have been reported as 21-81% and 58-97%, respectively<sup>4,5</sup>.

The association between second-trimester CL and the risk of emergency Cesarean delivery in women in labor with a multiple pregnancy has not been assessed before. Haest *et al.*<sup>6</sup> and Grobman *et al.*<sup>7</sup> found a rate of 19% for emergency Cesarean section in twin pregnancies that were scheduled for vaginal delivery. Arrest of labor was the most frequent indication for Cesarean delivery in both studies, followed by malpresentation, fetal distress and umbilical cord prolapse<sup>6,7</sup>. Routinely delivering women with a twin pregnancy by elective Cesarean section brings no benefit to neonatal outcome<sup>8–11</sup>.

The aim of this study was to ascertain whether second-trimester CL is a risk indicator for emergency Cesarean delivery in twin pregnancy. To do so, we used data from two large multicenter randomized clinical trials in which possible methods of preventing preterm birth in women with a multiple pregnancy were investigated 12,13.

### **METHODS**

We used data from two multicenter randomized clinical trials conducted in The Netherlands. In the AMPHIA trial, 671 women with a multiple pregnancy were randomized to receive either  $17\alpha$ -hydroxyprogesterone (17P; n=336) or placebo (n=335) to determine the effectiveness of 17P in the prevention of adverse neonatal outcome in multiple pregnancy <sup>12</sup>. The ProTWIN trial randomized 813 women with a multiple pregnancy to receive a cervical pessary (n=403) or no pessary (n=410), and evaluated the effectiveness of a cervical pessary in preventing preterm birth and adverse perinatal outcome <sup>13</sup>. Both studies were approved by the institutional review board of the Academic Medical Centre in Amsterdam (MEC 05-102 and MEC 09-107, respectively). The design and outcomes of these studies have been reported previously <sup>12,13</sup>.

Exclusion criteria of the original studies were serious congenital defects or death of at least one fetus, early signs of twin-twin transfusion syndrome (TTTS) (AMPHIA and ProTWIN), women with a previous spontaneous preterm birth before 34 weeks' gestation or primary cerclage (AMPHIA), and women with known placenta previa (ProTWIN). For the present study, we selected nulliparous women with a twin pregnancy who attempted vaginal delivery at or after 34 weeks' gestation and with the first fetus in the cephalic position. For inclusion in the study, both twins had to be alive at the start of delivery. We excluded women who had their CL measured after 24 weeks' gestation or who had one or both fetuses with a known congenital disorder, TTTS, planned Cesarean section or were parous. The latter was to enable comparison of the study with that of Smith

et al.<sup>1</sup>, which analyzed only nulliparous women, as they are at a higher risk for failure to progress during delivery than are parous women.

The primary study outcome was emergency Cesarean delivery. We distinguished between the indications 'failure to progress' and 'suspected fetal distress' and performed additional separate analyses according to the indication. We also performed subgroup analysis for women who delivered at term (>37 weeks). According to the guidelines of the Dutch Association of Obstetrics and Gynecology, failure to progress in the first stage of labor was defined as an active phase with an increasing dilatation of < 1 cm/h<sup>14</sup>. Failure to progress in the second stage of labor was defined as active pushing for  $> 1 \, h$  for nulliparous women and  $> 0.5 \, h$ for parous women. It must be noted that the definition of failure to progress varies between groups. Suspected fetal distress was defined as abnormal fetal heart rate during continuous cardiotocography, using the International Federation of Gynecology and Obstetrics criteria for interpretation. When the indication for Cesarean delivery was a combination of failure to progress and suspected fetal distress, it was considered as failure to progress when the woman had been pushing for > 60 min in the second stage of labor. The responsible obstetrician diagnosed the indication for Cesarean section.

Risk indicators of interest were CL in the second trimester, maternal age, gestational age at delivery, chorionicity (monochorionic vs dichorionic), racial origin (Caucasian vs non-Caucasian), body mass index (BMI) (kg/m<sup>2</sup>), smoking status, growth discordance between twins (> 20% difference in birth weight), combined birth weight, induced onset of labor and intervention used in the original study. CL was measured by transvaginal ultrasound in the sagittal view and with an empty maternal bladder at the time of randomization in the original study or shortly after, but prior to administration of medication or placement of the pessary. Gestational age and chorionicity were determined at the first-trimester ultrasound examination. BMI, smoking and racial origin were recorded at the first hospital visit. BMI was calculated using the prepregnancy weight or, if this was unknown, weight measured at the first antenatal visit. Birth weight was measured directly after delivery. Randomization of women in the original studies was categorized as progesterone or placebo, and pessary or none (reference).

## Statistical analysis

Baseline characteristics of the study population were analyzed using descriptive statistics and are presented as mean  $\pm$  SD or median (interquartile range) for continuous variables when appropriate. Categorical and dichotomous variables are presented as numbers and proportions (%) of the whole population. Baseline characteristics were stratified according to quartiles of CL, and differences between quartiles were assessed using an analysis of variance model or Kruskal–Wallis rank sum test for continuous

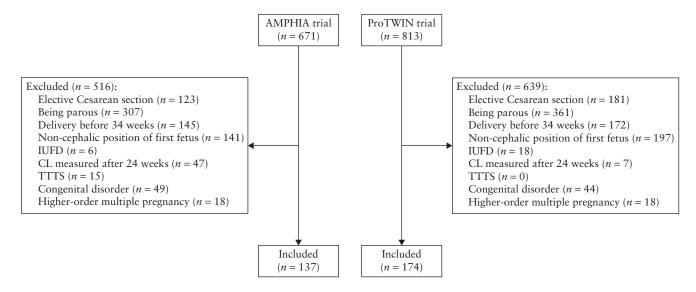


Figure 1 Flowchart of inclusion of patients from two randomized clinical trials (AMPHIA and ProTWIN) for secondary analysis of second-trimester cervical length (CL) as a predictor of emergency Cesarean delivery in twin pregnancy. Note, some women met multiple criteria for exclusion. IUFD, intrauterine fetal demise; TTTS, twin–twin transfusion syndrome.

variables, as appropriate, and the chi-square test for categorical and dichotomous variables. Several variables had missing data (ethnicity, n=1; BMI, n=33; smoking, n=8; birth weight, n=1; CL, n=22), which lowers the precision of the predictor-outcome associations and, because these are often selectively missing, i.e. related to other patient characteristics, a complete case analysis is likely to yield biased results<sup>15</sup>. To avoid generating biased results, we used observed patient characteristics to impute missing data by means of multiple imputation. Missing data were imputed (10 times) with the use of a logistic regression model that included the outcome being studied, potential predictors and other maternal outcomes.

In univariable analysis we used a logistic regression model to determine the associations between the risk indicators and emergency Cesarean delivery. Restricted cubic spline analysis was used to assess linearity of the association of continuous variables (i.e. maternal and gestational age, BMI and second-trimester CL) with the outcome. To determine adjusted associations between risk indicators and the outcome, all risk indicators were included in the multivariable analyses, i.e. no preselection was made based on univariable statistics. As imputed data sets differ from each other, predictor selection was performed separately in each of the 10 imputation sets. To determine the final multivariable associations, the regression coefficients and standard errors of the final predictors were calculated separately in each imputation set, and combined using Rubin's rules<sup>16</sup>. Statistical analysis was performed using R software, version 2.15.2 (R Foundation for Statistical Computing, Vienna, Austria), and P < 0.05was considered to be statistically significant.

## **RESULTS**

Out of 1484 patients who participated in the original studies, 311 were included in our secondary study (Figure 1).

Participants were excluded owing to higher-order multiple pregnancy (n=36), being parous (n=668), delivery before 34 weeks' gestation (n=317), CL measured after 24 weeks (n=54), elective Cesarean delivery (n=304), intrauterine fetal demise of at least one fetus (n=24), TTTS (n=15), known congenital abnormality of at least one fetus (n=93) and non-cephalic presentation of the first fetus (n=338). Some women met multiple criteria for exclusion.

Maternal age and gestational age at delivery showed a linear relationship with the outcome, while BMI and second-trimester CL did not and were therefore categorized into quartiles  $\leq 25^{\text{th}}$  percentile,  $26^{\text{th}}-50^{\text{th}}$  percentiles,  $51^{\text{st}}-75^{\text{th}}$  percentiles and  $>75^{\text{th}}$  percentile. For BMI this corresponded to <20, 20-23, 24-28 and >28 kg/m² and for second-trimester CL this corresponded to <40, 40-43, 44-48 and >48 mm.

Baseline characteristics are shown in Table 1. Only maternal age was found to be significantly related to CL in the second trimester. From restricted cubic spline analysis, the relationship between second-trimester CL and the risk of Cesarean delivery is shown in Figure 2.

Emergency Cesarean delivery was necessary in 111 (36%) women, of which 67 (60%) were performed for failure to progress. Univariable analysis showed no relationship between second-trimester CL and emergency Cesarean delivery for all CL quartiles when compared with the reference CL of < 40 mm (Table 2). There was no relationship between CL and Cesarean delivery if analysis was restricted to failure to progress as the indication for emergency delivery.

Table 2 shows the adjusted odds ratios (aOR) for predictors of Cesarean delivery. After correcting for other risk indicators, second-trimester CL was not associated with emergency Cesarean delivery. Maternal age differed significantly between women who underwent emergency Cesarean delivery and women who had a

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Table 1 Characteristics of 311 women with twin pregnancy who underwent second-trimester cervical length (CL) measurement, stratified according to CL percentile

		CL percentile				
Characteristic	<i>Total</i> (n = 311)	$ \leq 25^{th} $ $ (< 40  mm) $ $ (n = 86) $	$26^{th} - 50^{th}  (40 - 43 mm)  (n = 77)$	$51^{st} - 75^{th}$ (44-48 mm) (n = 76)	$> 75^{th}$ (> 48 mm) (n = 72)	P
Maternal age (years)	$32.1 \pm 4.5$	$31.9 \pm 4.5$	$31.1 \pm 4.7$	$32.0 \pm 4.3$	$33.6 \pm 4.0$	0.005
GA at delivery (weeks)	$36.9 \pm 1.4$	$36.9 \pm 1.4$	$36.8 \pm 1.5$	$37.1 \pm 1.4$	$36.9 \pm 1.4$	0.47
Monochorionicity	58 (19)	18 (21)	16 (21)	12 (16)	12 (17)	0.72
Caucasian	280 (90)	77 (90)	68 (88)	68 (89)	67 (93)	0.72
Smoker	18 (6)	4 (5)	6 (8)	7 (9)	1 (1)	0.06
BMI (kg/m <sup>2</sup> )	22.7 (20.9-25.0)	22.4 (21.0-25.1)	23.7 (21.5-25.1)	22.2 (21.0-24.2)	22.9 (20.7-24.8)	0.11
Intervention in original study						0.21
Progesterone	70 (23)	20 (23)	17 (22)	16 (21)	17 (24)	
Pessary	95 (31)	31 (36)	29 (38)	16 (21)	19 (26)	
Placebo	66 (21)	14 (16)	15 (19)	20 (26)	17 (24)	
None	80 (26)	21 (24)	16 (21)	24 (32)	19 (26)	
Emergency Cesarean delivery	111 (36)	33 (38)	27 (35)	25 (33)	26 (36)	0.63
Failure to progress	67/111 (60)	22/33 (67)	16/27 (59)	14/25 (56)	15/26 (58)	0.55
Induction of labor	202 (65)	52 (60)	51 (66)	55 (72)	43 (60)	0.37

Data are given as mean  $\pm$  SD, n (%), n/N (%) or median (interquartile range). BMI, body mass index; GA, gestational age.

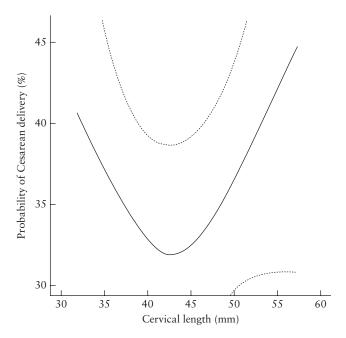


Figure 2 Restricted cubic spline analysis showing association of Cesarean delivery in women with twin pregnancy according to absolute values of cervical length in the second trimester. Dashed lines indicate 95% CI.

vaginal delivery (32.7 *vs* 31.8 years; aOR, 1.07 (95% CI, 1.00–1.13); P = 0.03). Other predictors of emergency Cesarean delivery were a BMI of 20–23 kg/m² (aOR, 3.99 (95% CI, 1.07–14.9); P = 0.02) or 24–28 kg/m² (aOR, 5.04 (95% CI, 1.34–19.03); P = 0.01) compared with a BMI of < 20 kg/m², and induction of labor (aOR, 1.92 (95% CI, 1.05–3.5); P = 0.03) compared with spontaneous labor.

Separate analysis of indications for Cesarean delivery showed that there was no relationship between CL and Cesarean delivery due to failure to progress (Table S1) or suspected fetal distress (Table S2). Among women who delivered at term (n = 172 (55%)), 66 (38%) delivered by emergency Cesarean section. In addition, no relationship was found between CL and Cesarean delivery in this subgroup of women (Table S3).

## **DISCUSSION**

Our aim was to determine if second-trimester CL is a predictor of emergency Cesarean delivery in nulliparous women with a twin pregnancy. We hypothesized that a longer CL is associated with arrest of labor. As fetal distress can be a result of labor dystocia, we analyzed this as a separate indication for Cesarean delivery. We have shown that there is no relationship between second-trimester CL and emergency Cesarean delivery in these women, but maternal age, BMI and induction of labor were independent predictors of emergency Cesarean delivery.

This study was a secondary analysis of two large multicenter randomized clinical trials on possible preventative methods for preterm birth in women with a multiple pregnancy. Combining the data of these trials resulted in a database of 1484 women with a multiple pregnancy, which allowed us to perform secondary analysis on large groups, thus improving the power of the data. Because the prevalence of Cesarean delivery was higher than the primary outcome of the original studies (adverse neonatal outcome), there was sufficient statistical power to perform the analysis in our study. However, we still had to rely on the inclusion and exclusion criteria of the original studies. The original studies found longer CL than reported in previous studies; we calculated 39 mm as the 25th centile, whereas Skentou et al. 17 reported 36 mm as the median. A possible explanation for this difference is a physiological shortening of the cervix between 16 and 20 weeks' gestation, the gestational age range of our measurement, and 23 weeks, when Skentou et al. performed their measurements.

Table 2 Odds ratios (OR) and adjusted OR for emergency Cesarean delivery in women with twin pregnancy

	Cesarean delivery				
Characteristic	Yes (n = 111)	No $(n = 200)$	OR (95% CI)*	Adjusted OR (95% CI)*	P
Cervical length					
< 40 mm (reference)	33 (30)	53 (27)	1	1	
40-43 mm	27 (24)	50 (25)	0.88(0.44-1.75)	0.97 (0.47-2.00)	0.94
44-48 mm	25 (23)	51 (26)	0.80(0.41-1.55)	0.71(0.35-1.45)	0.34
> 48 mm	26 (23)	46 (23)	0.94 (0.49-1.83)	0.92(0.45-1.89)	0.83
Maternal age (years)	$32.7 \pm 4.6$	$31.8 \pm 4.4$	1.05 (0.99-1.10)	1.07 (1.00-1.13)	0.03
GA at delivery (weeks)	$37.1 \pm 1.4$	$36.8 \pm 1.4$	1.16 (0.98-1.37)	0.96 (0.74–1.25)	0.79
Monochorionicity	25 (23)	33 (17)	1.47 (0.82-2.63)	1.64 (0.85-3.15)	0.14
Racial origin	,	, ,	,	,	
Caucasian (reference)	98 (88)	180 (90)	1	1	
Non-Caucasian	13 (12)	20 (10)	1.25 (0.59-2.63)	1.42 (0.51-3.21)	0.4
Smoker	,	, ,	,	,	
No (reference)	104 (94)	190 (95)	1	1	
Yes	7 (6)	10 (5)	1.26 (0.47-3.39)	1.97 (0.67-5.84)	0.22
Body mass index	( /	( /	,	,	
< 20 kg/m <sup>2</sup> (reference)	4 (4)	28 (14)	1	1	
$20-23 \text{ kg/m}^2$	46 (41)	79 (40)	4.04 (1.16-14.12)	3.99 (1.07-14.90)	0.02
24-28 kg/m <sup>2</sup>	51 (46)	73 (37)	4.86 (1.36–17.37)	5.04 (1.34–19.03)	0.01
$> 28 \mathrm{kg/m^2}$	10 (9)	20 (10)	3.61 (0.82–15.84)	3.10 (0.65–14.78)	0.1
Birth-weight discordance	- (- /	- ( - )	(111		
None (reference)	93 (84)	167 (84)	1	1	
> 20%	18 (16)	33 (17)	0.99 (0.53-1.85)	0.95 (0.47-1.93)	0.9
Combined birth weight (g)	$5153 \pm 741$	$4966 \pm 698$	1.04 (1.00–1.07)	1.03 (0.99–1.09)	0.11
Onset of labor			( ) ;	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	
Spontaneous (reference)	27 (24)	82 (41)	1	1	
Induced	84 (76)	118 (59)	2.16 (1.29-3.63)	1.92 (1.05-3.50)	0.03
Intervention in original study	,	,	,	,	
None (reference)	30 (27)	49 (25)	1	1	
Progesterone	24 (22)	46 (23)	0.85 (0.44–1.67)	0.98 (0.48-2.00)	0.95
Placebo	20 (18)	47 (24)	0.70 (0.35–1.39)	0.68 (0.32–1.43)	0.31
Pessary	37 (33)	58 (29)	1.04 (0.56–1.93)	1.05 (0.53–20.40)	0.9

Data are given as n (%) or mean  $\pm$  SD. \*Mean of 10 imputation sets, calculated using Rubin's rules  $^{16}$ . GA, gestational age.

We found a rate of 36% for emergency Cesarean delivery, whereas Haest *et al.*<sup>6</sup> and Grobman *et al.*<sup>7</sup> both found a rate of 19%. This difference is most probably caused by the exclusion of parous women from our study. However, in the Twin Birth Study that included parous women, 30% of women who had a planned vaginal delivery and commenced this mode of delivery underwent an emergency Cesarean section<sup>9</sup>. If we had included parous women in our cohort, the emergency Cesarean rate would have been 25% (158/634), which is comparable with data from the other studies.

The main indication for emergency Cesarean delivery in our study group was failure to progress, with a rate (67/111; 60%) that is similar to those found in some other studies, although Haest *et al.*<sup>6</sup> and Grobman *et al.*<sup>7</sup> found different rates (35% and 88%, respectively). The difference between rates in these studies is likely to result from dissimilar definitions and inclusion criteria. Other reasons for emergency Cesarean delivery are non-reassuring fetal heart rate, malpresentation of one of the fetuses, umbilical cord prolapse and maternal condition.

In contrast to findings in singleton pregnancies, we found that second-trimester CL is not a predictor for the risk of emergency Cesarean delivery in women with a twin pregnancy. In Figure 2, we can see a trend that with moderate CL, the risk of a Cesarean delivery is low. A possible

explanation for this is that women with a short CL have a higher risk of preterm delivery and therefore a Cesarean delivery due to non-reassuring fetal condition or malpresentation. The methods of our study were similar to those of Smith  $et~al.^1$ , to allow comparison. However some differences were found: Smith et~al. excluded women with a CL of < 15 mm, as these women were included in another study, but we chose to include such women in our study; Smith et~al. included only women delivering at term, but we also included women with a late preterm delivery ( $\ge 34$  weeks' gestation), as this is within the normal gestational age range for delivery of a twin pregnancy.

The process of labor is a complex business, in which preterm and post-term delivery are at the extremes, and the mechanisms associated with failure to progress in labor are similar to the findings in post-term delivery. Second-trimester CL could be an early predictor of a woman's position along this spectrum. Differences in these mechanisms in women with a singleton or multiple pregnancy are important to understand. In women with a singleton pregnancy, short CL is known to be predictive of preterm labor<sup>3</sup> and long CL of failure to progress<sup>1</sup>, while in women with a multiple pregnancy, short CL is also predictive of preterm labor<sup>4,5</sup>. In contrast to the findings in singletons, we did not find long second-trimester CL to be predictive of failure to progress in women with

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a multiple pregnancy. However, Fox et al. 18, showed that CL at 30-32 weeks in asymptomatic women with a twin pregnancy is associated with Cesarean delivery. It is notable that at 30-32 weeks overall CL is much shorter than during the second trimester, as 38 mm was used as the highest CL threshold in the study of Fox et al. 18, yet the lowest in ours. Possibly women with a physiological cervical shortening during pregnancy that does not result in preterm birth have the best chance of a successful attempt at vaginal delivery. Moreover, the decision to have a Cesarean delivery in women with a twin pregnancy is influenced by other factors, such as fetal presentation.

We were able to identify maternal age, BMI and induction of labor as independent risk factors for emergency Cesarean delivery. Grobman et al.<sup>7</sup>, also found nulliparity (OR, 4.6 (95% CI, 1.5-16.5)) and early epidural placement (OR, 4.5 (95% CI, 1.6-13)) to be associated with Cesarean delivery in term twins. Unfortunately, we were unable to assess the effect of epidural placement, as this was not recorded consistently in both our primary studies. We hypothesize that early epidural placement is not so much a causative factor, but rather is related to poor progress of labor and delivery.

Compared to singletons, women with a twin pregnancy have a higher risk of both elective and emergency Cesarean delivery<sup>19</sup>. However, the Twin Birth Study showed that there is no major benefit of delivering all twins by elective Cesarean section9. Therefore, it is important to perform a prelabor risk assessment to identify women at high risk for Cesarean delivery who will benefit from elective Cesarean delivery and, on the other hand, women at low risk for Cesarean delivery, who can safely attempt vaginal delivery.

If we can identify women with a twin pregnancy who are at high risk for Cesarean section, it may be possible to create a personalized plan for mode of delivery. Such a rule, based on easily and readily available data, could be helpful to clinicians, as it would allow for timely assessment of prognosis, which may lead to more effective decision-making during labor and could be used in the decision for primary Cesarean section. Finally, it allows for more individualized counseling of the pregnant woman. In conclusion, second-trimester CL does not contribute to assessment of risk of emergency

Cesarean delivery, but nulliparity, maternal age, BMI and induction of labor are predictors of this outcome in women with a twin pregnancy.

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## SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:



I Table S1 Association of second-trimester cervical length and Cesarean section for failure to progress

Table S2 Association of second-trimester cervical length and Cesarean section for fetal distress

Table S3 Risk factors for emergency Cesarean delivery in women with twin pregnancy who delivered at term  $(\geq 37 \text{ weeks})$