Chapter 4

The capacity of mid-pregnancy cervical length to predict preterm birth in low-risk women: a national cohort study

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Acta Obstetricia et Gynecologica Scandinavica. Conditionally accepted.

Abstract

Objective: To investigate the predictive capacity of mid-trimester cervical length (CL) measurement for spontaneous and iatrogenic preterm birth in low-risk women.

Design: Observational cohort study in a population of nulliparous women and low-risk multiparous women with a singleton pregnancy between 16^{+0}-21^{+6} weeks in The Netherlands.

Methods: We expressed the prognostic capacity of mid-trimester CL, transvaginally measured, for spontaneous and iatrogenic preterm birth (< 37 weeks) using likelihood ratios (LR) and receiver-operating-characteristic (ROC) analysis. Numbers needed to screen to prevent one preterm birth were calculated assuming different risk reductions of treatment and using several cut-off values of CL. Main outcome measures: preterm birth <32, <34 and <37 weeks of gestation.

Results: We studied 11 943 women, of whom 666 (5.6 %) delivered preterm, 464 (3.9%) spontaneous and 202 (1.7%) iatrogenic. Mean CL was 44.1 mm (SD 7.8 mm). In nulliparous women, the likelihood ratio's for spontaneous preterm birth varied between 27 (95% CI: 7.7-95) for a CL ≤ 20 mm, and 2.0 (95% CI: 1.6-2.5) for a CL between 30 and 35 mm. For low- risk multiparous women, these likelihood ratios were 37 (95%CI: 7.5-182) and 1.5 (95%CI: 0.97-2.2) respectively. At a CL ≤ 30 mm, only 28 (6.0%) of 464 women with spontaneous preterm birth were identified. The number needed to screen to prevent one case of preterm birth was 618 in nulliparous women and 1417 for low-risk multiparous women (40% treatment effect, cut-off 30 mm).

Conclusion: In women at low risk of preterm birth, cervical length measurement has a limited capacity to predict spontaneous preterm birth.

Introduction

Preterm birth (PTB) is associated with an increased risk of perinatal mortality and morbidity as well as with an increased risk of disability and development disorders in childhood and in later life[1–4]. PTB, defined as delivery between 22^{+0} weeks and 36^{+6} weeks of gestation occurs in 7.7% of all pregnancies in the Netherlands, which is comparable with the rest of Europe[5,6]. In the Netherlands PTB accounted for 75.3% of all perinatal mortality with a mortality risk of 82.6 per 1000 births[7].These data indicate that prevention of PTB is of imminent importance in the reduction of perinatal mortality.

A major problem in the prevention of PTB is the fact that it occurs mostly in low-risk women. While previous spontaneous PTB and twin pregnancy are well known risk factors, these factors only explain a minority of the PTBs[8]. Thus, prediction of PTB among low-risk women stays of the utmost importance.

It has been known for almost two decades that mid-trimester cervical length (CL) measurement can identify women at increased risk for preterm delivery[9]. Until recently, there was no effective treatment to prevent PTB and efforts to develop screening programs remained therefore unsuccessful. Recent data on the use of progestogens have changed this perspective. Two randomised clinical trials demonstrated a statistically significant reduction of PTB using progesterone in women with a mid-pregnancy short cervix[10, 11]. These two studies defined a short cervix as a CL below 15 mm and between 10 and 20 mm, respectively. Given this treatment effect, identification of women at risk for preterm delivery in an unselected low-risk population is crucial in the development of screening strategies.

We designed a multicentre prospective cohort study in the Netherlands to evaluate the predictive capacity of CL measurement on PTB in low-risk women, the Triple P screening study.

Methods

Between November 2009 and July 2013 we performed a national prospective cohort study that was approved by the institutional review board of the Academic Medical Centre, Amsterdam, The Netherlands (MEC AMC 08/374). The study was positioned within the infrastructure of the Dutch Obstetric Research Consortium for research in Women's health (www.studies-obsgyn.nl). In this study, 160 primary

care midwifery practices, 29 ultrasound centres, 23 general and seven university hospitals in the Netherlands participated.

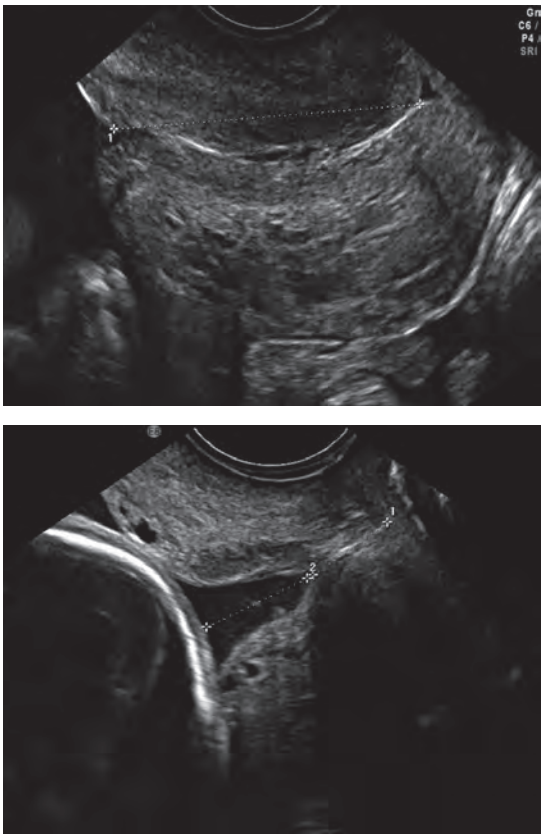
Procedure and recruitment

Nulliparous women and multiparous women without a history of spontaneous PTB <34 weeks of gestation of 18 years or older with a singleton pregnancy were eligible for the study. All women received written information -available in several languages and were informed about the possibility of having their CL measured. Women who had given informed consent had their CL measured immediately following the fetal anomaly scan between 16^{+0}-21^{+6} weeks of gestation. Women with painful regular uterine contractions, ruptured membranes, or a cervical cerclage at the time of screening were not included, as well as women in which the fetus had chromosomal or major structural anomalies. Women with a short CL (≤ 30mm) were invited to a randomized clinical trial to evaluate the effectiveness of subsequent progesterone treatment[12,13]. Women who refused to participate in the trial were not treated.

Sonographers in this study were certified to perform 20-week routine fetal anomaly scans, indicating they had attended special training and performed at least 150 anomaly scans annually. In addition, prior to the introduction of the study, all participating sonographers were trained in CL measurement. They were asked to complete an e-learning module, specifically designed to learn the CL measurement technique, and to present pictures of five measurements, which had to be approved by the project team (MH or EP)[14].

Women were asked to empty their bladder prior to the measurement, immediately after the routine fetal anomaly scan. Subsequently, CL was measured using a vaginal probe. In order to obtain a sagittal view of the cervix, the probe was placed, without exerting any pressure, in the anterior fornix of the vagina and the image had to display the full length of the endocervical mucosa with an equal thickness of anterior and posterior cervical wall. The cervical canal was visualized as a thin echogenic line between the internal os and the external os. The calipers were placed at the distance between the triangular area of echo density at the external os and the V-shaped notch at the internal os across a straight line. This is according to the guidelines of the Dutch society of Obstetrics and Gynaecology (NVOG)[15] and to the technique described by Mella *et al*[16] and by To *et al.*[17] (Figure 1). Each examination was performed during a period of about three minutes to observe any cervical changes that might arise due to contractions. At least three CL images were obtained and the shortest measurement was recorded for further use.

Figure 1: Measurement of cervical length by transvaginal sonography. On the left is a normal cervix, and on the right there is severe shortening with marked funnelling.



Data collection

The sonographer recorded the data of CL in a web based database, together with women's date of birth, the four numbers of her postal code and the expected date of delivery. This information was used to link women to the Dutch Perinatal Registry database to obtain data on course and outcome of the pregnancy and delivery. The Dutch Perinatal Registry is a population-based database containing perinatal outcome from 22 gestational weeks onwards of 96% of all pregnancies, deliveries and (re)admissions until 28 days after birth[18]. The Dutch Perinatal Registry database is obtained by a validated linkage of four different registries: the LVR1-registry (midwives), the LVRh-registry (general practitioners), the LVR2-registry (obstetricians) and the LNR-registry (paediatricians/ neonatologists)[19,20]. In order to reduce mismatching we connected the data within a range around the entered

expected date of delivery. The Dutch Perinatal Registry board approved the use of their database for the purpose of this study (approval number 13.07). Because pregnancy outcomes were available in the Dutch Perinatal Registry database for all pregnancies that ended before January 1st 2013, we used all CL measurements entered in the study database till August 2012, in order to avoid any confounding of PTB outcomes of pregnancies with an expected date of delivery after January 1st 2013.

Outcome measures and analysis

The analysis focused on the ability of CL to identify women at increased risk of PTB before 32, 34 and 37 weeks of gestation. We stratified the risks of spontaneous and iatrogenic PTB for the total cohort by parity. Iatrogenic PTB was defined as either elective caesarean section or induction of labour due to maternal or fetal reasons, usually pre-eclampsia, pregnancy related hypertension and/or fetal growth restriction. All other PTBs were classified as spontaneous, including emergency caesarean section after spontaneous onset of labour.

Baseline characteristics of nulliparous and low-risk multiparous women, obtained from the Dutch Perinatal Registry linkage data base, were compared using student's t-test, chi-square and Mann-Whitney U test statistics. Rates of spontaneous and iatrogenic PTB were registered. Subsequently, we calculated likelihood ratios (LR) per CL category (<20, 21-25, 26-30, 31-35, and >35 mm) spontaneous and iatrogenic PTB combined, as well as for spontaneous and iatrogenic PTB separately. In the latter when performing calculations for spontaneous PTB, women with iatrogenic PTB combined with term births were the comparison, while when performing calculations for iatrogenic PTB, women with spontaneous PTB combined with the term births were the comparison. LR of iatrogenic PTB were calculated since women with an iatrogenic PTB might have delivered prematurely on their own for other reasons if there had been no intervention. Furthermore, there is evidence that women with a previous iatrogenic PTB are also at increased risk of a subsequent spontaneous preterm delivery[21,22].

The predictive capacity of CL to predict spontaneous PTB was constructed with ROC curves for nulliparous and low-risk multiparous women separately. Areas under the ROC-curves were compared between the two groups using a method proposed by Hanley *et al.* based on the z statistic[23].

We then calculated numbers needed to screen to prevent one spontaneous PTB before 37 weeks assuming different risk reductions of treatment (20, 40 and 60% risk reduction) and using CL cut-off values varying from ≤ 35mm, ≤ 30 mm, ≤ 25mm

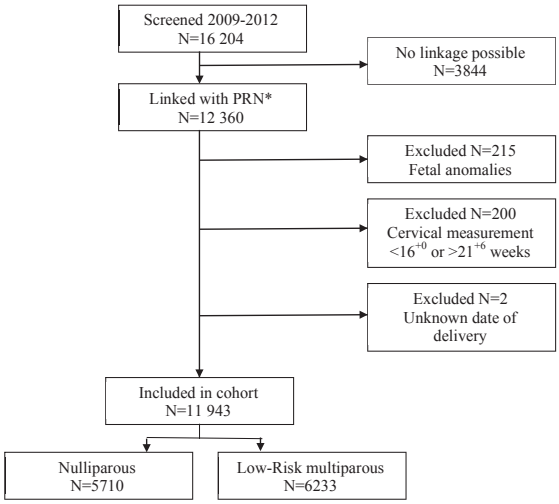
and ≤ 20mm respectively. Analyses were performed using IBM SPSS Statistics (version 20.0, IBM Corp).

Results

Study population

Between October 2009 and August 2012, a total of 16 222 women had a CL measurement performed. Before linkage 18 double entries were removed from women with the same date of birth, postal code and expected date of delivery, leaving 16 204 women. We were able to link data for 12 360 of the 16 204 women (74.4%) using the Dutch Perinatal Registry. The most common reasons inhibiting matching our data were incorrect digit entry in the study database and change of residence between ultrasound and birth. As a consequence, pregnancy outcome was not available for these women. After application of our exclusion criteria data 5710 nulliparous women and 6233 low-risk multiparous women remained for analysis (figure 2).

Figure 2: Flow diagram of screened population



* Dutch Perinatal Registry

We compared clinical characteristics between linked women (N=12 360) and those lost to follow-up (N=3844) showing no difference in incidence of CL ≤30 mm (1.8% versus 2.1%, *p= 0.21*), see supplemental table 1.

Supplemental Table 1: Characteristics compared of linked cases and lost to follow-up of our study group after exclusions

	Linked cases	Lost to Follow-up	p-value
	N= 12 360	N=3844	
Maternal age at screening	30.9	30.7	0.06
Gestational age at screening median (IQR)	142 (140-144)	142 (140-145)	<0.0001
Cervical length median/ IQR	43 (38-49)	43 (39-49)	0.06
Cervical length ≤ 30 mm	212 (1.8%)	89 (2.1%)	0.21

Table 1 shows the clinical characteristics of the study group. Nulliparous women were younger than low-risk multiparous women (29.7 vs 32.0 years, *p<0.0001*) and more often conceived through in vitro fertilization (2.3% vs 0.9%, *p<0.0001*) or with help of other fertility treatments (5.7% vs 1.9% *p<0.0001*). Gestational age at CL measurement did not differ between nulliparous and low-risk multiparous women. Mean CL was shorter in nulliparous women than in low-risk multiparous women (43.1mm vs 45.1mm, *p<0.0001*). In addition, more nulliparous women had a short CL (≤ 30mm 2.2% vs 1.4%, *p=0.001*, and ≤ 35mm 14.0% vs 9.8%, *p<0.0001*).

Table 1: Clinical characteristics of the total cohort

Characteristic		**Nulliparous**	**Low-risk multiparous**	**p value**
		N=5710 N(%)*	N=6233 N(%)*	
Maternal age at screening, mean (SD)		29.7 (4.7)	32.0 (4.4)	<0.0001
Non-Caucasian		671 (11.8)	820 (13.2)	0.02
Low socio-economic status		1413 (24.9)	1701 (27.6)	0.001
Conception:	Spontaneous	5248 (91.9)	6059 (97.2)	<0.0001
	IVF**	134 (2.3)	55 (0.9)	
	Other fertility treatment	328 (5.7)	119 (1.9)	
Pre-existing hypertension		70 (1.2)	54 (0.9)	0.06
Pre-existing diabetes mellitus		28 (0.5)	27 (0.4)	0.69
Gestational age at CL screening, median (IQR)		20^{+2} (20^{+0}-20^{+4})	20^{+2} (20^{+0}-20+4)	0.52
Cervical length mm, median (IQR)		42 (38-48)	44 (40-50)	<0.0001

* unless reported otherwise
** IVF = in vitro fertilisation

Preterm birth risk

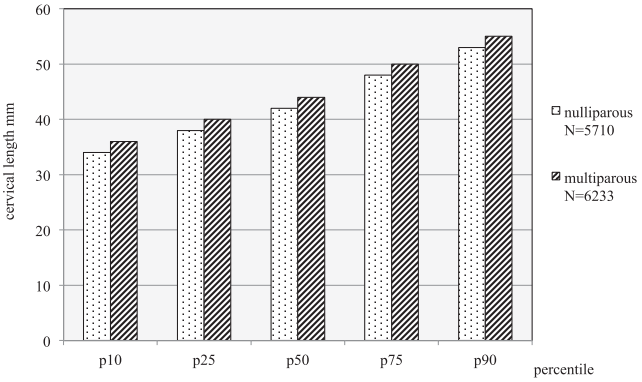
Table 2A (nulliparous women) and 2B (low-risk multiparous women) show the likelihood of a spontaneous and iatrogenic PTB before 32 weeks, 34 weeks, and 37weeks, and term births specific for certain CLs. Nulliparous women more often had a spontaneous PTB at all gestational age categories compared to low-risk

multiparous women (5.3% (N=300) vs 2.6% (N=164) overall *p<0.0001*). The rates of iatrogenic PTBs at separate gestational age categories did not significantly differ between nulliparous and low-risk multiparous women, although the overall rate was higher in nulliparous women (1.9% vs 1.5%, *p=0.046*).

The risk of spontaneous PTB was higher for all CL categories ≤ 35 mm in both nulliparous and low-risk multiparous women compared to women with a CL > 35 mm. The risk of spontaneous PTB in nulliparous women with a CL between 31 and 35 mm was more than twofold higher compared to women with a CL over 35 mm (10.1% vs 4.3%, *p<0.0001*). In low-risk multiparous women this difference was also present, although it was less pronounced and did not reach statistical significance (3.8% vs 2.4%, *p=0.06*).

Figure 3 shows CL percentiles for nulliparous and low risk multiparous women.
The CL distribution in the total study group is shown in the supplemental figure 1.

Figure 3: Cervical length percentiles of nulliparous and low-risk multiparous women



Supplemental figure 1: Cervical length distribution of the study group.
Number of cervical lengths ≤30 mm: N=212 (1.8%).

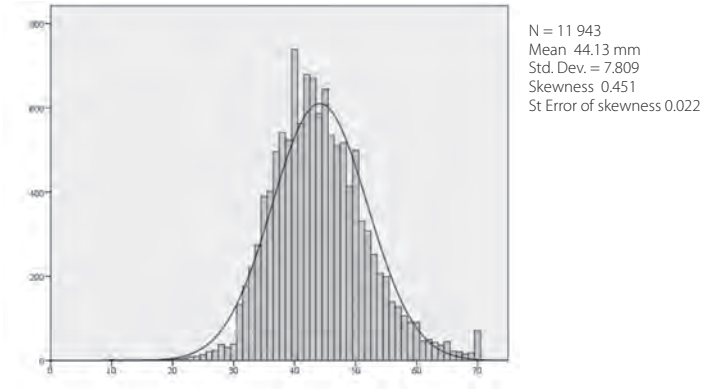


Table 2A Nulliparous women. Rates and Likelihood ratios (LR) of spontaneous preterm births, iatrogenic preterm births, term births

Nulliparous	PTB* <37 weeks									Term births		
	Spontaneous			Iatrogenic			Total					
Cervical length	N	%	LR (95%CI)	N	%	LR (95%CI)	N	%	LR (95%CI)	N	%	LR (95%CI)
>35 mm	213	4.3	0.81 (0.75-0.87)	82	1.7	0.86 (0.77-0.96)	295	6.0	0.85 (0.80-0.90)	4618	94	1.2 (1.1-1.3)
31-35 mm	68	10	2.0 (1.6-2.5)	25	3.7	2.0 (1.4-2.8)	93	13.8	2.1 (1.7-2.5)	579	86.2	0.48 (0.40-0.59)
26-30 mm	8	8.9	1.8 (0.86-3.6)	3	3.3	1.7 (0.56-5.4)	11	12.2	1.8 (0.96-3.4)	79	87.8	0.56 (0.30-1.0)
21-25 mm	5	20	4.5 (1.7-12)	1	4.0	2.1 (0.29-15.4)	6	24	4.1 (1.6-10)	19	76	0.25 (0.10-0.61)
<20 mm	6	60	27 (7.7-95)	0	0		6	60	19 (5.5-68)	4	40	0.05 (0.01-0.18)
Total	300	5.3		111	1.9		411	7.2		5299	92.8	

	PTB <34 weeks								
	Spontaneous			Iatrogenic			Total		
Cervical length	N	%	LR (95%CI)	N	%	LR (95%CI)	N	%	LR (95%CI)
>35 mm	47	1.0	0.71 (0.59-0.84)	30	0.6	0.87 (0.73-1.0)	77	1.6	0.76 (0.67-0.87)
31-35 mm	21	3.1	2.4 (1.6-3.4)	6	0.9	1.3(0.61-2.7)	27	4.0	2.0 (1.4-2.8)
26-30 mm	3	3.3	2.5 (0.82-7.8)	3	3.3	4.9(1.6-15)	6	6.6	3.4 (1.5-7.7)
21-25 mm	2	8.0	6.4 (1.5-26)	1	4.0	5.9 (0.62-42)	3	12	6.5 (2.0-21)
<20 mm	4	40	49 (14.0-139)	0	0		4	40	31 (9.1-111.44)
Total	77	1.3		40	0.7		117	2	

	PTB <32 weeks								
	Spontaneous			Iatrogenic			Total		
Cervical length	**N**	**%**	**LR (95%CI)**	**N**	**%**	**LR (95%CI)**	**N**	**%**	**LR (95%CI)**
>35 mm	23	0.5	0.67 (0.51-0.87)	17	0.3	0.86 (0.67-1.1)	40	0.8	0.74 (0.61-0.89)
31-35 mm	12	1.8	2.6 (1.6-4.2)	3	0.5	1.1 (0.39-3.2)	15	2.2	2.1 (1.3-3.2)
26-30 mm	1	1.1	1.6(0.23-11)	2	2.2	5.6(1.5-21)	3	3.3	3.1 (1.0-9.5)
21-25 mm	1	4.0	5.9 (0.82-43)	1	4.0	10.3 (1.5-73)	2	8.0	7.8 (1.9-32)
<20 mm	3	30	61 (16-227	0	0		3	30	38(10-145)
Total	40	0.7		23	0.4		63	1.1	

* PTB = preterm birth

Table 2B Low-risk multiparous women. Rates and Likelihood ratios (LR) of spontaneous preterm births, iatrogenic preterm births, term births.

Low-risk	PTB <37 weeks									Term births		
Multiparous	Spontaneous			Iatrogenic			Total					
Cervical length	N	%	LR (95%CI)	N	%	LR (95%CI)	N	%	LR (95%CI)	N	%	LR (95%CI)
>35 mm	135	2.4	11 (9-12)	78	1.4	9.9 (8.8-11.1)	213	3.8	13(11-14)	5410	96.2	1.1(1.0-1.1)
31-35 mm	20	3.8	1.5 (0.97-2.4)	11	2.1	1.5 (0.83-2.5)	31	5.9	1.5 (1.1-2.1)	492	94.1	0.68 (0.48-0.95)
26-30 mm	6	9.5	3.9 (1.7-8.9)	1	1.6	1.1 (0.16-8.0)	7	11	3.0 (1.4-6.4)	56	88.9	0.34 (0.16-0.74)
21-25 mm	0	0	0.0	1	5.6	3.2 (0.44-24)	1	5.6	1.4 (0.18-10)	17	94.4	0.73 (0.10-5.4)
<20 mm	3	50	37 (7.5-182)	0	0		3	50	23 (4.8-116)	3	50	0.04(0.01-0.21)
Total	164	2.6		91	1.5		255	4.1		5978	95.9	

	PTB<34 weeks								
	Spontaneous			Iatrogenic			Total		
Cervical length	N	%	LR (95%CI)	N	%	LR (95%CI)	N	%	LR (95%CI)
>35 mm	18	0.3	7.6 (5.8-9.8)	18	0.3	8.2 (6.5-10)	36	0.6	8.1 (6.7-9.7)
31-35 mm	4	0.8	1.9 (0.78-4.7)	4	0.8	2.1 (0.85-5.1)	8	1.5	2.0 (1.1-3.8)
26-30 mm	1	1.6	4.0 (0.58-27)	0	0		1	1.6	2.1 (0.49-15)
21-25 mm	0	0		1	5.6	0.96 (0.88-1.1)	1	5.6	7.6 (1.0-51)
<20 mm	2	33	124 (24-647)	0	0		2	33	64 (12-343)
Total	25	0.4		23	0.4		48	0.8	

	PTB*<32 weeks								
	Spontaneous			Iatrogenic			Total		
Cervical length	**N**	**%**	**LR (95%CI)**	**N**	**%**	**LR (95%CI)**	**N**	**%**	**LR (95%CI)**
>35 mm	11	0.2	4.4 (2.8-6.9)	13	0.2	8.0 (6.1-10)	24	0.4	7.9 (6.4-9.8)
31-35 mm	2	0.4	1.6 (0.44-5.8)	3	0.6	2.1 (0.75-5.9)	5	1.0	1.9 (0.83-4.2)
26-30 mm	0	0		0	0		0	0	
21-25 mm	0	0		1	5.6	22 (3.0-153)	1	5.6	0.94 (0.84-1.1)
<20 mm	2	33	207 (41-1047)	0	0		2	33	97 (18-510)
Total	15	0.2		17	0.3		32	0.5	

* PTB = preterm birth

In nulliparous women, 125 had a CL ≤ 30mm (2.2%) and 300 (5.3%) pregnancies ended in a spontaneous PTB < 37 weeks. In the nulliparous group with CL ≤ 30 mm 15.2% ended in a spontaneous PTB < 37 weeks versus 5.0 % in the group with CL > 30mm. In the group low-risk multiparous women 87 (1.4%) had a CL ≤ 30mm (nulliparous vs low-risk multiparous p=0.001) and 164 (2.6%) ended in a spontaneous PTB < 37 weeks (nulliparous vs low-risk multiparous, p< 0.0001). In the low-risk multiparous group with CL ≤ 30 mm 10.3% ended in a spontaneous PTB versus 4.0% in the group with CL > 30mm. Although the number of women with a mid-trimester CL ≤ 20 mm are small, over 50% suffered a spontaneous PTB < 37 weeks (nulliparous 60%, low-risk multiparous women 50%)

In nulliparous women, the LRs for spontaneous PTB were 27 (95%CI: 7.7-95) for a CL ≤ 20 mm, to 2.0 (96% CI 1.6-2.5) for a CL between 30 and 35 mm, and 0.82 (95%CI: 0.76-0.88) for a CL > 35 mm (table 2A). For low-risk multiparous women, these LRs were 37 (95% CI:7.5-1.82) for a CL ≤ 20 mm, to 1.5 (95% CI: 0.97-2.2) for a CL between 30 and 35 mm, and 0.92 (95% CI: 0.86-0.99) for a CL > 35 mm (table 2B).

For iatrogenic PTB, the LRs in women with a CL between 30 and 35 mm were 1.9 (95% CI: 1.4-2.8) for nulliparous women and 1.5 (95% CI: 0.83-2.5) for low-risk multiparous women, which is almost identical to the LRs for spontaneous PTB. For lower cervical lengths, LRs were higher and also comparable to those for spontaneous PTB, although absolute numbers were low.

Of all 464 women who suffered a spontaneous PTB, only 28 (6%) had a mid-trimester CL ≤ 30 mm. Nineteen nulliparous women (6.3%) of the 300 with spontaneous PTB had a mid-trimester CL ≤ 30 mm, versus nine (5.5%) of the 164 low-risk multiparous women.

The ability of CL to predict spontaneous PTB was poor and did not significantly differ between nulliparous and low-risk multiparous women, with AUC of 0.61 (95% CI: 0.57-0.64) and 0.58 (95%CI: 0.54-0.63) respectively (*p=0.79*) (figure 4).

Figure 4: ROC curves of continuous cervical length in the prediction of spontaneous preterm birth < 37 weeks separate for nulliparous and low-risk multiparous women.

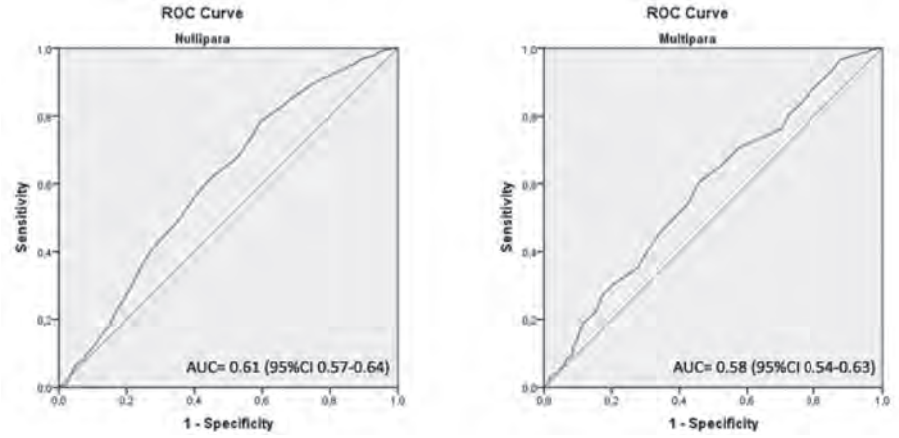


Table 3 shows the numbers needed to screen to prevent one PTB, for different assumed effectiveness of treatment in the prevention of PTB (20, 40 and 60%). With an effective assumption of 40% (motivated by Fonseca *et al.*[10] and Hassan *et al.*[11]) the number of nulliparous women needed to screen to prevent one PTB varied from 122 (with a CL cut-off of ≤ 35mm) to 2083 women (with a 20 mm cut-off). Under the same effectiveness assumption, the number of low-risk multiparous women needed to screen to prevent one PTB varied from 370 women (with a CL cut-off of ≤ 35 mm) to 5000 women (with a 20 mm cut-off).

Table 3: Number needed to screen and number needed to treat to prevent one preterm birth (PTB) before 37 weeks of gestation with different effectiveness assumptions of progesterone.

	Assumed reduction of PTB with progesterone	Number needed to treat to prevent one PTB	Number needed to screen to prevent one PTB			
			CL ≤35 mm	CL ≤30 mm	CL ≤25 mm	CL ≤20 mm
Nulliparous PTB	20%	5	244	1235	2430	4167
	40%	2.5	122	618	1214	2083
	60%	1.7	82	412	810	1389
Low-risk multiparous FTB	20%	5	739	2835	7485	10 000
	40%	2.5	370	1417	3742	5000
	60%	1.7	246	945	2495	3333

Discussion

In this study, among nulliparous and low-risk multiparous women, the preterm delivery rate was 5.6 % (3.9% (464) spontaneous and 1.7% (202) iatrogenic). In nulliparous women, the LRs for spontaneous PTB varied between 27 (95%CI: 7.7-95) for a CL ≤ 20 mm, and 2.0 (96% CI 1.6-2.5) for a CL between 30 and 35 mm. For low-risk multiparous women, these LRs were 37 (95% CI: 7.5-182), and 1.5 (95% CI: 0.97-2.2) respectively. For iatrogenic PTB these indices were comparable. At a CL ≤ 30 mm, only 28 (6.0%) of 464 women with spontaneous PTB were identified. The number needed to screen to prevent one case of PTB was 618 in nulliparous women and 1417 for low-risk multiparous women (40% treatment effect, cut-off 30 mm).

Inter- and intra-observer variation

Transvaginal cervical imaging is highly reproducible with low inter- and intra-observer variability[16,24,25] Burger *et al.*[25] described the widest variation in measurements occurring in women with the longest CL. After implementation of a standard procedure for measuring CL 87% of all measurements had a difference of 2 mm or less. We developed, specifically for our study, a CL measurement e-learning module to guarantee the quality of the CL measurements in our study[14]. The participation of many midwifery practices, ultrasound centres and hospitals indicate that the study provides a representative sample of all pregnant women in the Netherlands. The proportion of nulliparous women in our study group was slightly higher than estimates for the Dutch population (47.8% versus 45.8%), which can partly be explained by the exclusion of multiparous women with a history of spontaneous PTB before 34 weeks of gestation[26]. We found that 88% of our participants was of Caucasian origin versus 81% off all women giving birth in the general Dutch population[26]. We tried to involve as much as possible non-Caucasian women, as patient information was, apart from Dutch, also available in English, French, Polish, Turkish and Arabic. Previous studies have reported a shorter mean CL in women of non-Caucasian origin[27], this could have resulted in somewhat a higher mean CL in our study as compared to Palma-Dias *et al.* (37 mm with 79% women of Caucasian origin)[28]. Although the Dutch Perinatal Registry database contains information on pregnancy outcome of 96% of all pregnancies that ended after 22 weeks of gestation, about a quarter of all cases could not be linked to pregnancy outcomes. As for these women only the information entered in the study database

was available, we were uninformed on ethnicity, socio-economic status, PTB rates and other pregnancy complications in this group. We found no difference between mean CL (*p=0.17*) nor in the percentage of CL ≤ 30 mm (*p=0.21*) between linked women and those lost to follow-up. The prevalence of spontaneous PTB among nulliparous women in our study group is comparable to that of a previous Dutch study, thus making it unlikely that the outcome of the missing women would have influenced our results[5]. The power of the study was based on the embedded randomized trial in women with a short cervix. We aimed to screen 40 000 women in order to recruit 1920 women for the randomized trial[12].

As the number of women with a short cervix was much lower than expected, we stopped the randomized controlled trial after recruitment of 80 women with a short cervix, while 375 had potentially been eligible for the study[13]. At that time, 20,234 women had their CL measured.

Our study confirms that women with a short CL are at increased risk for PTB. In our study group over 50% of all women with CL < 20 mm delivered before 37 weeks. Noteworthy is the mean CL of 44.3 mm in our study group, with the 10th percentile being 35 mm. Other studies reported lower mean CL and also lower 10th percentiles[9,29,30]. The prevalence of CL < 15 mm and CL between 15-25 cm is fairly consistent in those studies, 0.9–1.9% and 7.9–8.7%, respectively. In our study the prevalence of CL < 15 mm is 0.08% and of CL 15-25 mm 0.42%; which is remarkably lower than reported before. In our study group only 1.8% had CL ≤30 mm. Orzechowski *et al.*[31] compared CL (measured between 18^{+0} and 23^{+6} weeks of gestation) of nulliparous women to women with a prior term birth and found 1.3% CL ≤ 25 mm, compared to 0.5 % in our study.

There are three explanations for our higher mean CL and lower rate of short CLs as compared to other studies. First, our method of CL measurement might be different. In most previous studies[9,16,27,32–34] the calipers are placed at the notches made by the internal os and external os, using the sonolucent endocervical mucosa as a guide to the true position of the internal os. To *et al.*[1]a search of our database was made to identify all women who had undergone cervical assessment as part of a policy of routine screening. In those with cervical length of less than 26 mm the thermal images of the cervix were used to obtain straight and curved measurements. The frequency of curved cervix was calculated and the relationship between the ratio of straight to curved measurement to the curved one was determined.\n\nRESULTS: In the prospective study curvature of the cervix was observed in 143 (48%[7] mention the influence of cervical curvature on CL measurements. However, this should not

have any clinical implications because at short CL (less than 16 mm) the cervix appears to be always straight. Stone *et al.*[35] measured CL from the internal os to the external os incorporating only the length that was bordered by endocervical mucosa. Positioning the caliper at the internal os or at the mucosa may have an effect on the mean CL[36]. Since shortening of the cervix starts at the internal os, it is unlikely that positioning of the calipers will have an effect on short CL rate. Second, the timing of our measurements might be different. We measured between 16+0 and 21+6 weeks of gestation, about two to four weeks earlier than most previous studies. It is known that CL gradually decreases with advancing gestational age[33–37]. Both Silva *et al.*[37] and Salomon *et al.*[34] measured a difference of 2 mm between mean CL at 20 weeks versus at 22 weeks of gestation.

Thirdly, we measured CL in a low-risk population, which is probably the main explanation for both the higher mean CL as well as the lower rate of short CL in our study group.

A surprising finding was that cervical length also predicts for iatrogenic PTB. Apparently, mechanisms underlying spontaneous PTB and causes of iatrogenic PTB might have similar pathways, both leading to a shortening of the cervix. A detailed analysis of the causes of iatrogenic PTB was beyond the scope of our paper.

We analysed the number needed to screen and the number needed to treat (table 3) assuming the effectiveness of treatment is equal in all CL categories. However it is unknown if the treatment effect of for instance progesterone is the same in women with a CL of 10 mm compared to women with a CL of 25 mm. Research on the effectiveness of progesterone in subgroups defined by CL is important to calculate the number needed to screen. This can be used in a cost-effectiveness analysis before CL measurement and treatment in the prevention of PTB are introduced in a National Health Program. In addition, we recommend research into the use of progesterone in comparison with other treatment interventions, such as a pessary, in low-risk women with short CL.

Conclusion

We found the risk of PTB to be inversely related to mid-trimester CL both in nulliparous as in low-risk multiparous women for a CL ≤ 35 mm. However, as the prevalence of PTB was low and prognostic capacity was limited, the value of CL measurement as a screening tool for PTB seems limited.

Statement of contribution

AV, BK and EP wrote the first draft of the paper. BK and CK analyzed the data. BM, EP, MH, AW, EM and CV conceived the study and obtained funding. AV, MO, CK, CV, PK, MP, CW, MW, JS, FR, MH and EP collected data. MO, BK, AW, FR, PB, CG, EP and BM critically revised the manuscript for important intellectual content. All authors approved of the final version of the manuscript to be submitted.

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