Effect of second-trimester sonographic cervical length on the risk of spontaneous preterm delivery in different risk groups: a prospective observational multicenter study

Tove Wikström¹ ², Henrik Hagberg¹ ², Bo Jacobsson¹ ², Pihla Kuusela³, Jan Wesström⁴, Peter Lindgren⁵ ⁶, Helena Fadl⁷, Ulla-Britt Wennerholm¹ ²*, Lil Valentin⁸ ⁹*

*Contributed equally

¹Centre of Perinatal Medicine and Health, Department of Obstetrics and Gynecology, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

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2 Department of Obstetrics, Sahlgrenska University Hospital, Gothenburg, Sweden
3 Södra Älvsborg Hospital, Borås, Sweden
4 Center for Clinical Research Dalarna, Falu Hospital, Falun, Sweden
5 Department of Clinical Science, Intervention and Technology, Karolinska Institute, Stockholm, Sweden
6 Center for Fetal Medicine, Karolinska University Hospital, Stockholm, Sweden
7 Department of Obstetrics and Gynecology, Faculty of Medicine and Health, Örebro University, Örebro, Sweden
8 Department of Obstetrics and Gynecology, Skåne University Hospital, Malmö, Sweden
9 Department of Clinical Sciences Malmö, Lund University, Lund, Sweden

Corresponding author
Lil Valentin
Department of Obstetrics and Gynecology, Skåne University Hospital, 205 02 Malmö, Sweden
E-mail: lil.valentin@med.lu.se
Lil Valentin ORCID ID: 0000-0002-3830-6414

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ABSTRACT

Introduction: The aim of the study is to compare the effect of cervical length measured with transvaginal ultrasound in the second trimester on the risk of spontaneous preterm delivery between different risk groups of asymptomatic women with a singleton pregnancy.

Material and methods: This is a pre-planned exploratory analysis of the CERVIX study, a prospective blinded multicenter diagnostic accuracy study. Asymptomatic women with a singleton pregnancy were consecutively recruited at their second-trimester routine ultrasound examination at seven Swedish ultrasound centers. Cervical length was measured with transvaginal ultrasound at 18-20 weeks (Cx1; n=11 072) and 21-23 weeks (Cx2, optional; n=6288). The effect of cervical length on the risk of spontaneous preterm delivery and its discriminative ability was compared between women with: i. previous spontaneous preterm delivery, late miscarriage or cervical conization (high-risk group; n=1045); ii. nulliparae without risk factors (n=5173); iii. parae without risk factors (n=4740). Women with previous indicated preterm delivery were excluded (n=114). Main outcome measures were: effect of cervical length on the risk of spontaneous preterm delivery expressed as odds ratio per 5 mm decrease in cervical length with interaction analysis using logistic regression to test if the effect differed between groups, area under the receiver operating characteristic curve (AUC), sensitivity, specificity, number needed to screen to detect one spontaneous preterm delivery.

Results The effect of cervical length at Cx2 on the risk of spontaneous preterm delivery <33 weeks was similar in all groups (odds ratios 2.26 to 2.58, interaction P-value 0.91). The discriminative ability at Cx2 was superior to that at Cx1 and was similar in all groups (AUC 0.69 to 0.76). Cervical length ≤25 mm at Cx2 identified 57% of spontaneous preterm deliveries <33 weeks in the high-risk group with number needed to screen 161. The number needed to screen for groups ii and iii were 1018 and 843.

Conclusions The effect of cervical length at 21-23 weeks on the risk of spontaneous preterm delivery <33 weeks is similar in high- and low-risk pregnancies. The differences in number needed to screen should be considered before implementing a screening program.
Keywords
Preterm delivery; cervical length measurement; second trimester; pregnancy, high-risk; diagnostic screening program; preterm birth; ultrasonography

Abbreviations
AUC; area under the receiver operating characteristic curve
PTD, preterm delivery

Key message
The effect of cervical length at 21-23 weeks on the risk of spontaneous preterm delivery <33 weeks is similar in high- and low-risk pregnancies. The diagnostic performance of cervical length at 21-23 weeks is superior to that at 18-20 weeks.
INTRODUCTION

Globally 14.8 million babies are estimated to be born preterm (<37 gestational weeks) each year, the occurrence ranging from 5% of all births in northern Europe to 18% in some African countries.\(^1,2\) Preterm delivery (PTD) is a major cause of perinatal mortality and neonatal morbidity.\(^3,4\) The risks of death and long-term impairments are inversely proportional to gestational age at birth.\(^5,6\)

Vaginal progesterone may reduce the number of spontaneous PTDs <33 weeks by 30% in asymptomatic women with a singleton pregnancy and with a short cervix as measured with transvaginal ultrasound in the second trimester.\(^7\) Therefore, universal screening of singleton pregnancies with ultrasound measurement of cervical length has been proposed.\(^8\) However, the ability of cervical length to predict spontaneous PTD and the optimal cervical length cut-off may depend on the characteristics of the screened population, eg ethnicity, or on the proportion of women at high risk of spontaneous PTD.\(^9\) To estimate the clinical consequences of screening one needs to know the performance of cervical length screening in different risk groups.

Our study aim is to compare the effect of sonographic cervical length on the risk of spontaneous PTD between different risk groups.

MATERIAL AND METHODS

Study design and participants

The study is a planned exploratory analysis of the CERVIX-study, a prospective blinded multicenter diagnostic accuracy study conducted at seven hospitals in Sweden (https://doi.org/10.1186/ISRCTN18093885). The CERVIX-study has been described in detail elsewhere\(^10\) and is briefly outlined below.

We recruited women at their routine second-trimester fetal ultrasound examination between May 2014 and June 2017. Women ≥18 years old with a live singleton pregnancy between 18 weeks+0 days (18+0 weeks) and 20+6 weeks were invited to participate. We estimated gestational age...
based on ultrasound measurement of the fetal biparietal diameter, or on the day of embryo transfer in case of in vitro fertilization (see Swedish guidelines at https://www.sfog.se/media/336451/fetometri.pdf). Exclusion criteria at the scan were fetal malformations, ruptured membranes, ongoing miscarriage, current use of progesterone, cerclage in situ, difficulties with understanding the study information. We also excluded women with medical termination of the pregnancy after inclusion and those with missing information about pregnancy outcome.

The study protocol included two cervical length measurements: one between 18+0 and 20+6 weeks performed on the day of the routine scan (Cx1) and another between 21+0 and 23+6 weeks with at least 14 days between the two measurements (Cx2; optional).

Procedures

The cervical length measurements were performed by 25 midwife sonographers who had been certified to perform cervical length measurements after theoretical and practical training. Cervical length was measured with the study participants in the lithotomy position with empty urinary bladder. A 5-9 MHz transvaginal probe connected to a GE Healthcare Voluson E8 Expert or E6 ultrasound system (GE Corporate, Fairfield, CT, USA) was used. The ultrasound images needed to fulfill five quality criteria (Figure 1). We present results for the shortest of three measurements of endocervical length taken during at least 3 min. The measurement results and standardized anamnestic information obtained from the women were recorded in a web-based electronic case record form (MedSciNet AB, Stockholm, Sweden, www.medscinet.se). The results were disclosed to staff and participants only if ultrasound showed the amniotic sac to bulge into the vagina. Participants were followed up until delivery. A woman could participate in the study with only one pregnancy.

Data collection

We obtained information on the participants’ self-reported ethnicity from the electronic case record forms. Information on other participant characteristics and pregnancy outcomes was obtained from the Swedish Pregnancy Register (www.graviditetsregistret.se). If delivery data
was missing in the Swedish Pregnancy Register, we searched the medical records for information. If no information was found, the participant was contacted by mail or telephone.

We received information on redeemed prescription of vaginal progesterone after registration in the study from the Swedish Prescribed Drug Register. To obtain information on cerclage insertion after registration and on history of cervical conization before registration we used the Swedish National Patient Register (Table 1). Information on previous spontaneous PTD and previous indicated PTD was obtained from the Swedish Medical Birth Register (Table 1). In case of contradictory information regarding the type of previous PTD, we searched the medical records. The Swedish Prescribed Drug Register, the Swedish National Patient Register, and the Swedish Medical Birth Register are hosted by the Swedish National Board of Health and Welfare (www.socialstyrelsen.se).

To obtain reliable information on previous late miscarriages, we scrutinized the medical records of participants with self-reported previous late miscarriage. We define late miscarriage as: 1) spontaneous miscarriage at 16+0 to 21+6 weeks according to last menstrual period, 2) missed abortion if fetal size measured with ultrasound corresponded to 16+0 to 21+6 weeks, 3) self-reported miscarriage between 16 and 22 weeks, if no information was found in the medical records.

Reference standard

Our reference standard is gestational age at delivery based on fetal biometry (see above). The primary outcome is spontaneous PTD between 22+0 and 32+6-weeks (<33 weeks) including stillbirths and late miscarriages. The secondary outcome is spontaneous PTD between 22+0 and 36+6 weeks (<37 weeks) including stillbirths and late miscarriages.

We define spontaneous PTD as delivery <259 days of gestation (<37 weeks) either after spontaneous onset of labor or after preterm prelabor rupture of membranes, the latter regardless of whether labor was induced (Table 1). We validated the diagnosis spontaneous PTD in the index pregnancy by scrutinizing the medical records, the assessor being blinded to the results of the cervical length measurements.
Statistical analyses

Sample size calculation was not done for this planned exploratory analysis but was done for the CERVIX-study.10

We divided our study population into three main risk groups: women at high risk of spontaneous PTD, nulliparous women without risk factors for spontaneous PTD, and parous women with only term deliveries and no risk factors for spontaneous PTD. Our high-risk group includes women with previous spontaneous PTD <37+0 weeks (singleton or multiple)15,16,17, previous late miscarriage15,18 or cervical conization before inclusion19,20. Women with previous indicated PTD were excluded, because the association between previous indicated PTD and the risk of subsequent spontaneous PTD is insufficiently known17.

To test if the effect of cervical length on the risk of spontaneous PTD (odds ratio per 5 mm decrease in cervical length with 95% confidence interval) was similar in different risk groups, we performed interaction analysis using logistic regression with spontaneous PTD as dependent variable and cervical length, risk-group, and risk-group*cervical length as independent variables. A P-value <0.05 indicated a statistically significant interaction.

We describe the ability of cervical length, or a change in cervical length, to discriminate between women who deliver before or after a defined gestational week (discriminative ability) as area under the receiver operating characteristic curve (AUC), sensitivity, specificity, positive and negative predictive value, positive and negative likelihood ratio, number of false positive test results per one true positive test result, and number needed to screen to identify one spontaneous PTD. We use Youden’s index to determine which cervical length cut-off yields the highest proportion of correctly classified cases (“best cut-off”).21 We also estimate the discriminative ability of cervical length cut-offs suggested by others: <20 mm, <25 mm, <29 mm (“best cut-off” at Cx1 in the CERVIX-study) and <27 mm (“best cut-off” at Cx2 in the CERVIX-study).7,8,10,22-25 Changes in cervical length between Cx1 and Cx2 in women with at least 14 days between the two measurements (Cx1Cx2 population) are expressed in mm and in percent of the Cx1 measurement.
We present results as mean, standard deviation, or as median, interquartile range, minimum and maximum for continuous variables. For categorical variables, we present results as numbers and percentages. We used the Statistical software SAS System Version 9.4 (SAS-Institute, Cary, NC, USA).

**Ethical approval**

The study was approved by the Regional Ethical Review Board in Gothenburg (Dnr: 825-13, 13 November 2013; T053-14, 17 January 2014; T691-14, 25 September 2014; T972-15, 7 December 2015; T122-16, 25 February 2016; T896-17, 17 October 2017; T645-18, 13 July 2018, T878-18, 11 October 2018; T970-18, 6 November 2018). All participants gave written informed consent before taking part in the study.

**RESULTS**

A flow chart showing patient recruitment is presented in Figure S1. Loss to follow-up was minimal (missing delivery data in 34 participants). The study population includes 11,072 women with delivery data and results of Cx1 (Cx1 population), 6,288 women with delivery data and results of Cx2 (Cx2 population) and 6,179 women with delivery data and results of both Cx1 and Cx2 with at least 14 days between the two measurements (Cx1Cx2 population). Spontaneous PTD <33 weeks (including late miscarriages) occurred in 0.6% (63/11,072) of the Cx1 population and in 0.4% (26/6,288) of the Cx2 population. Spontaneous PTD <37 weeks occurred in 3.8% (417/11,072) and 3.6% (225/6,288), respectively.

The study population with its risk groups is described in Figures 2a and 2b. The Cx1 population (n= 11,072) includes 1,045 (9.4%) women classified as high risk, 5,173 (46.7%) nulliparae with no risk factors, and 4,740 (42.8%) parous women with no risk factors. The Cx2 population (n= 6,288) includes 643 women (10.2%) classified as high risk, 3,053 (48.6%) nulliparae with no risk factors, and 2,529 (40.2%) parous women with no risk factors. Most high-risk women (>90%) had only one risk factor. Previous spontaneous PTD was the only risk factor in 33%, and previous conization was the only risk factor in 60% of the women. (Table S1).
Maternal characteristics in each risk group are shown in Tables S2a and S2b. They were similar in the three main risk groups (Table S2a): about 90% of the women were of white ethnicity and had at least 12 years of education. In the high-risk group, the proportion of women with low socioeconomic status (education ≤9 years, unemployment, or sick leave) was less than 10%. Non-white ethnicity and low socioeconomic status were more common in women with prior spontaneous PTD or late miscarriage than in women with cervical conization as the only risk factor (Table S2b).

Figures 2a and 2b show pregnancy outcome in terms of spontaneous PTD <33 weeks and <37 weeks (details in Tables S3a and S3b). Spontaneous PTD <33 weeks and <37 weeks occurred most frequently in women with previous spontaneous PTD or late miscarriage (1.5% and 12.9% in the Cx1 population, 1.2% and 12.0% in the Cx2 population) and least frequently in parous women with no risk factors (0.3% and 2.3% in the Cx1 population, 0.2% and 2.3% in the Cx2 population). In all, 18/11 072 (0.2%) women redeemed prescribed progesterone after inclusion in the study. Redeemed prescription was most common among women with a previous spontaneous PTD or late miscarriage (1.7% in the Cx1 population, 1.2% in the Cx2 population). No woman with conization as the only risk factor redeemed prescription of progesterone. One woman got a cerclage after inclusion in the study.

Cervical length at Cx1 and Cx2 is shown in Table S4. The cervix was shortest in high-risk women (median cervical length 33 mm both at Cx1 and Cx2), and longest in parous women with no risk factors (median cervical length at Cx1 36 mm and at Cx2 37 mm). The cervix was shorter in women with cervical conization as the only risk factor than in women with previous spontaneous PTD or late miscarriage as risk factors (median cervical length at Cx1 32 mm vs 35.5 mm, at Cx2 32 mm vs 35 mm).

The effect of cervical length on the risk of spontaneous PTD <33 and <37 weeks was similar in the three main risk groups with one exception: the effect of cervical length at Cx2 on the risk of spontaneous PTD <37 weeks was smallest in parous women with no risk factors and greatest in nulliparae with no risk factors with a statistically significant interaction effect (Figure 3). There was no difference in the effect of cervical length at Cx2 on the risk of spontaneous PTD between women with previous spontaneous PTD or late miscarriage and those with conization as the only risk factor (Figure 4). There was also no difference in effect between women with and without a
history of cervical conization, and no difference between those with and without a previous spontaneous PTD or late miscarriage (Figure S2).

The ability of cervical length at Cx1 and Cx2 to correctly predict spontaneous PTD <33 weeks and <37 weeks (discriminative ability) in different risk groups is presented as AUC values in Figures 3, 4 and Figure S2 and illustrated as receiver operating characteristic curves in Figure 5 and Figures S3-S6. The discriminative ability of the Cx1 measurements was poor in the three main risk groups (AUC 0.56 to 0.73) and so was the ability of cervical length at Cx2 to correctly predict spontaneous PTD <37 weeks (AUC 0.53 to 0.66; poorest ability in parous women with no risk factors, best in nulliparae with no risk factors). The ability of cervical length at Cx2 to correctly predict spontaneous PTD <33 weeks was better than its ability to predict spontaneous PTD <37 weeks, and the ability was similar in the three main risk groups (AUC 0.69 to 0.76) (Figures 3 and 5). In none of the three main risk groups was a change in cervical length between Cx1 and Cx2 superior to one measurement at Cx2 for correct prediction of spontaneous PTD (Table S5).

Table 2 shows the sensitivity, specificity, and clinical consequences (the number of false positive test results per one true positive test result, the number needed to screen to detect one spontaneous PTD <33 weeks) of cervical length screening in the three main risk groups when using different cut-offs for the Cx2 measurement. The corresponding positive predictive values, negative predictive values, and positive and negative likelihood ratios are shown in Table 3. At Cx2 the 25 mm cervical length cut-off identified 57% (4/7) of the spontaneous PTDs <33 weeks in the high-risk group, with 18 false positive test results per one true positive test result and a number needed to screen of 161. The corresponding numbers for nulliparae with no risk factors were 25% (3/12), 36 and 1018, and for parous women with no risk factors 50% (3/6), 27 and 843.

**DISCUSSION**

We have shown that the effect of second-trimester sonographic cervical length on the risk of spontaneous PTD <33 weeks is similar in asymptomatic women with a singleton pregnancy at high risk of spontaneous PTD, in nulliparae with no risk factors for spontaneous PTD, and in parous women with no risk factors for spontaneous PTD. In all risk groups, the ability of cervical
length to predict spontaneous PTD <33 weeks was superior to predicting spontaneous PTD <37 weeks, and cervical length measurements taken at 21-23 weeks performed better than measurements taken at 18-20 weeks. In no group did a change in cervical length between the two measurements perform better than one measurement at 21-23 weeks. The effect of cervical length at 21-23 weeks on the risk of spontaneous PTD <33 weeks was similar in women with previous conization as only risk factor and in women with previous spontaneous PTD or late miscarriage.

To our knowledge, this study is the first to compare the effect of cervical length on the risk of spontaneous PTD between different risk groups. Another strength is blinding and negligible intervention (progesterone treatment or cerclage) between inclusion and outcome. Blinding is essential for estimating the true association between test results and outcomes and so is a low intervention rate. The multicenter design is another strength because it increases the likelihood that the results are generalizable. Minimal loss to follow-up (0.3%), detailed description and quality control of the cervical length measurements, and strict validation of risk factors for spontaneous PTD are additional strengths.

An important limitation is that the number of women with spontaneous PTD in each risk group is low (particularly in women with previous spontaneous PTD or late miscarriage as risk factors, or previous conization as only risk factor). This makes the estimates of effects and test performance in the risk groups imprecise. Because this is an exploratory study, we think this is acceptable. Another limitation is that the Swedish National Patient Register, from which we obtained information on previous conization, does not have full coverage, especially not before 2001. Therefore, some participants with a previous conization might not have been included in the risk groups. Even though our study is blinded, clinical management may have differed between the risk groups. This may have introduced performance bias. However, any performance bias should be small, since interventions that may prevent PTD, ie progesterone and cervical cerclage, were used in only 0.2% of our study population. Another possible limitation is that women with previous indicated PTD but no other risk factors, were not placed in any risk group. However, including the women with previous indicated PTD in our high-risk group changed our results minimally (Figure S7, Table S6). It may be seen both as a strength and limitation that our study population is homogenous (mainly white ethnicity and high socioeconomic status): the strength is that one knows to which type of population our results are generalizable, the limitation is that our
results might not be generalizable to women with other demographic characteristics or to populations with higher prevalence of spontaneous PTD.

Review articles (including also unblinded studies) conclude that sonographic cervical length is related to the risk of spontaneous PTD in different groups of women (asymptomatic singleton pregnancies including both high- and low-risk pregnancies, twin pregnancies, symptomatic singleton or twin pregnancies, different types of high-risk singleton pregnancies). Based on these reviews, a direct comparison of the effects of cervical length on the risk of spontaneous PTD between different risk groups is not possible. Three blinded studies examined the ability of second-trimester sonographic cervical length to predict spontaneous PTD in women at high risk of spontaneous PTD. They report only the ability of the 25 mm cervical length cut-off to discriminate between women who do and do not give birth spontaneously preterm. Contrary to our results, Carvalho et al showed that cervical length had better discriminative performance in women with than without previous PTD (Table S7).

In our study, women with conization as the only risk factor for spontaneous PTD were as likely to give birth spontaneously <33 weeks as women with a previous spontaneous PTD or late miscarriage. However, the number of spontaneous PTDs <33 weeks is too low to reliably estimate the ability of cervical length at 21-23 weeks to correctly predict spontaneous PTD <33 weeks in women with conization as the only risk factor. To our knowledge no other blinded study has estimated this ability, and no randomized controlled trial has tested or compared prophylactic treatments to prevent spontaneous PTD in women treated for cervical dysplasia. There is no consensus if and how spontaneous PTD can be prevented in this group. A randomized controlled trial is needed.

Even though the ability of sonographic cervical length at 21-23 weeks to predict spontaneous PTD <33 weeks was similar in our three main risk groups, the clinical consequences of screening differed between them. Differences in the prevalence of spontaneous PTD mainly explain this. Using the 25 mm cervical length cut-off, the number needed to screen to detect one spontaneous PTD <33 weeks was at least five times higher in women with no risk factors than in the high-risk group (1018 and 843 vs 161). The number of false positive test results per one true positive test result was also substantially higher in the former (36 and 27 vs 18). Screening requires resources, and because positive test results must be dealt with and false positive test results cause harm (unnecessary anxiety, follow-up examinations, sick leave, and prophylactic treatment), one might
want to consider using different cervical length cut-offs in different risk groups to obtain better balance between positive and negative effects of screening. If to screen parous women with no risk factors, it might be reasonable to use the 20 mm cervical length cut-off instead of the 25 mm cut-off. This would decrease the number of women identified as high risk of spontaneous PTD and lower the number of false positive test results per one true positive test result in this group (Tables 2 and 3). On the other hand, a slightly higher cut-off (27 mm), might be preferable in nulliparae with no risk factors. This would increase the detection rate and lower the number needed to screen to detect one spontaneous PTD <33 weeks in this group. However, it would also increase the proportion of nulliparae with no risk factors classified as high risk of spontaneous PTD (Tables 2 and 3). The 20 mm cervical length cut-off dramatically increased the likelihood of spontaneous PTD <33 weeks and was associated with similar positive predictive value (12-14%) and number of false positive test results per one true positive test result (6 to 8) in all three risk groups (Tables 2 and 3). This could be an argument for using the 20 mm cut-off in all women. On the other hand, the 20 mm cut-off detected only a small proportion of all spontaneous PTDs <33 weeks (9/26, 35%). This means that selecting women with cervix <20 mm for progesterone prophylaxis would have minimal effect on the total number of babies born preterm.10

CONCLUSION

The effect of sonographic cervical length at 21-23 weeks on the risk of spontaneous PTD <33 weeks is similar in asymptomatic women with a singleton pregnancy at high risk of spontaneous PTD, in nulliparae with no risk factors for spontaneous PTD, and in parous women with no risk factors for spontaneous PTD. The diagnostic performance of second-trimester sonographic cervical length is at best moderate in all groups. A health economic analysis comparing different strategies of cervical length screening for spontaneous PTD is justified.

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Author contributions

LV, BJ, HH and UBW conceived and designed the CERVIX-study. PK, BJ, PL, HF, JW, UBW and LV oversaw recruitment and the examination of study participants and collection of data at the local centres. LV, UBW, TW, BJ, and HH wrote the statistical analysis plan for the subgroup analysis together with statistician Mattias Molin at the Statistical Consulting Group in Gothenburg. TW, UBW and LV performed the data cleaning together with statistician Mattias Molin. TW, LV, UBW, BJ, HH and PK interpreted the data. TW, LV and UBW wrote the first draft of the article, which was then critically reviewed and revised by the other co-authors. All authors approved the final version of the article for submission. All authors had full access to all the data in the study. LV and UBW are the guarantors. They take responsibility for the integrity of the data and the accuracy of the data analysis. The corresponding author (LV) had final responsibility for the decision to submit for publication and attests that all authors meet the criteria for authorship and that no others meeting the criteria have been omitted. UBW and LV contributed equally (last authors).

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| Variable                              | Definition                                                                                                           | ICD 10 code                                                                 |
|---------------------------------------|---------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------|
| **Previous spontaneous preterm delivery** | Delivery <259 gestational days (<37 weeks) + checkbox “yes” for spontaneous onset of delivery in medical record and/or ICD 10 code 060.1 and/or 042.0, 042.1 or 042.9. In case of checkbox “yes” for spontaneous onset of delivery and coexisting ICD 10 code 060.3 without O60.1 or O42.0, O42.1 or 042.9, we scrutinized medical records. | O60.1- preterm spontaneous labor with preterm delivery  
O42.0- preterm pre-labor rupture of membranes, onset of labor within 24 hours  
O42.1- preterm pre-labor rupture of membranes, onset of labor after 24 hours |
|                                      |                                                                                                                     | Data obtained from the Swedish Medical Birth Register                       |
| **Spontaneous preterm delivery in index pregnancy** | Delivery <259 gestational days (<37 weeks) + checkbox “yes” for spontaneous onset of labor in medical record and/or ICD 10 code 060.1 and/or 042.0, 042.1 or 042.9.  
Delivery <259 gestational days (<37 weeks) and a PROM-diagnosis (ICD 10 code: O75.6A, O75.6B, O75.6X)  
The diagnosis was validated by scrutiny of medical records. | O60.3- preterm delivery without spontaneous labor  
O75.6A- delayed delivery after spontaneous rupture of membranes; spontaneous onset of labor  
O75.6B- delayed delivery after spontaneous rupture of membranes; induction of labor  
O75.6X- delayed delivery after spontaneous rupture of membranes; unspecified |
|                                      |                                                                                                                     | Data obtained from the Swedish Pregnancy Register                           |
**History of cervical conization**

One of the following NCSP surgical procedure codes before registration in the study:

- LDC00- conization of cervix uteri using cold knife
- LDC03 - conization of cervix uteri using diathermy or laser
- LDC10 - partial excision of cervix uteri
- LDC96 - other excision of cervix uteri

Data obtained from the Swedish National Patient Register (in-patient register from 1987 and out-patient register from 2001)

**Cerclage insertion after registration in the study**

NCSP surgical procedure code after registration in the study:

- MAB00 - cerclage of cervix uteri of pregnant uterus

PROM, prelabor rupture of membranes; ICD 10, International Classification of Diseases 10; NCSP, Nordic Medico Statistical Committee (NOMESCO) Classification of Surgical Procedure Codes
Table 2. The ability of sonographic cervical length 21+0 to 23+6 weeks (Cx2, n=6288) to discriminate between women who do an do not deliver spontaneously <33 weeks

| Risk group | No. (n%) | <20 mm | Sensitivity [95% CI] | Specificity [95% CI] | FP/TP NNS | Best cut-off<sup>2</sup> | Sensitivity [95% CI] | Specificity [95% CI] | FP/TP NNS | Sensitivity [95% CI] | Specificity [95% CI] | FP/TP NNS |
|------------|----------|--------|----------------------|----------------------|-----------|------------------------|----------------------|----------------------|-----------|----------------------|----------------------|-----------|
| High-risk group<sup>1</sup> n=643 | 7 (1.1%) | 0.76 | 24/37 (64.9%) | [9.9%; 81.6%] | 615/636 (96.7%) | 0.75 (11.7%) | 4/7 (57.1%) | [18.4%; 90.1%] | 565/636 (88.8%) | 18/161 (11.8%) | 214/216 (99.3%) | 0.75 (11.7%) | 4/7 (57.1%) | [18.4%; 90.1%] | 565/636 (88.8%) | 18/161 (11.8%) | 214/216 (99.3%) |
| Nulliparae with no risk factors<sup>2</sup> n=3053 | 12 (0.4%) | 0.74 | 23/32 (71.9%) | [5.5%; 87.7%] | 3021/3041 (99.3%) | 0.75 (11.7%) | 3/12 (25.0%) | [11.8%; 88.2%] | 2933/3041 (96.4%) | 36/1018 (3.5%) | 111/112 (99.1%) | 0.75 (11.7%) | 3/12 (25.0%) | [11.8%; 88.2%] | 2933/3041 (96.4%) | 36/1018 (3.5%) | 111/112 (99.1%) |
| Para with no risk factors<sup>2</sup> n=2529 | 6 (0.2%) | 0.69 | 22/33 (66.7%) | [11.8%; 88.2%] | 2504/2523 (99.2%) | 0.84 (3.3%) | 3/6 (50.0%) | [11.8%; 88.2%] | 2442/2523 (96.8%) | 27/843 (3.2%) | 843/849 (99.4%) | 0.84 (3.3%) | 3/6 (50.0%) | [11.8%; 88.2%] | 2442/2523 (96.8%) | 27/843 (3.2%) | 843/849 (99.4%) |

<sup>1</sup> High-risk group: women with a history of previous preterm birth or delivery, or with a family history of preterm birth or delivery.

<sup>2</sup> Nulliparae with no risk factors: nulliparous women without a history of preterm birth or delivery, or a family history of preterm birth.

<sup>3</sup> Para with no risk factors: parous women without a history of preterm birth or delivery, or a family history of preterm birth.

<sup>4</sup> Best cut-off: the cervical length that best discriminates between women who do or do not deliver spontaneously <33 weeks.
| Risk group | No. sPTD (%) | AUC | Cervical length* |
|------------|--------------|-----|-----------------|
|            |              |     | 0-20 mm         | 0-25 mm         | 0-27 mm         | Best cut-off* |
|            | n^a | Sensitivity [95% CI] | Specificity [95% CI] | FP/TP NNS | n^b | Sensitivity [95% CI] | Specificity [95% CI] | FP/TP NNS | n^c | Sensitivity [95% CI] | Specificity [95% CI] | FP/TP NNS | mm^d |
| sPTD, spontaneous preterm delivery, No., number of; AUC, area under the receiver operating characteristic curve; CI, confidence interval; FP, false positive; TP, true positive; NNS, number of women needed to screen to detect one sPTD <33 weeks |
| Cervical length is the shortest of three measurements of the closed endocervical canal, see Figure 1 |
| Number of women with cervical length ≤20, ≤25, ≤27 mm and ≤ best cut-off, respectively |
| Best cut-off value according to Youden's index^2 |
| Women with previous sPTD (singleton or multiple), late miscarriage or cervical conization |
| Nulliparous women with no cervical conization and no late miscarriage |
| Parous women with only previous term deliveries, no cervical conization and no late miscarriage |
Table 3. The ability of sonographic cervical length at 21+0 to 23+6 weeks (Cx2, n=6288) to discriminate between women who do an do not deliver spontaneously <33 weeks expressed as positive and negative predictive value, positive and negative likelihood ratio

| Risk group | No. sPTD | Cervical length<sup>a</sup> | 0-20 mm | 0-25 mm | 0-27 mm | Best cut-off<sup>b</sup> | mm<sup>c</sup> |
|------------|----------|-----------------------------|---------|---------|---------|--------------------------|----------|
|            | (%)      | PPV [95% CI]                | NPV [95% CI] | LR+ [95% CI] | LR- [95% CI] | PPV [95% CI] | NPV [95% CI] | LR+ [95% CI] | LR- [95% CI] | PPV [95% CI] | NPV [95% CI] | LR+ [95% CI] | LR- [95% CI] |
| High-risk group<sup>d</sup> | 7 (1.1%) | 3/24 (12.5%) | 0-20 mm | 4/75 (5.3%) | 0.59 | 5/121 (4.1%) | 4/75 (5.3%) | 0.59 | 5/121 (4.1%) | 4/75 (5.3%) | 0.59 | 5/121 (4.1%) | 4/75 (5.3%) | 0.59 |
|           |          | 615/619 (99.4%) | [5.00; 33.67] | [98.4; 99.8] | [1.5; 13.1] | 5/121 (4.1%) | 4/75 (5.3%) | 0.59 | 5/121 (4.1%) | 4/75 (5.3%) | 0.59 | 5/121 (4.1%) | 4/75 (5.3%) | 0.59 |
| Nulliparous with no risk factors<sup>e</sup> | 12 (0.4%) | 3/23 (13.0%) | 0-20 mm | 3/111 (2.7%) | 0.75 | 6/228 (2.6%) | 6/228 (2.6%) | 0.75 | 6/228 (2.6%) | 6/228 (2.6%) | 0.75 | 6/228 (2.6%) | 6/228 (2.6%) | 0.75 |
|           |          | 3021/3030 (99.7%) | [13.00; 111.15] | [99.4; 99.9] | [0.54; 1.05] | 6/228 (2.6%) | 6/228 (2.6%) | 0.75 | 6/228 (2.6%) | 6/228 (2.6%) | 0.75 | 6/228 (2.6%) | 6/228 (2.6%) | 0.75 |
| Parous with no risk factors<sup>f</sup> | 6 (0.2%) | 3/22 (13.6%) | 0-20 mm | 3/84 (3.6%) | 0.50 | 3/154 (1.9%) | 3/154 (1.9%) | 0.50 | 3/154 (1.9%) | 3/154 (1.9%) | 0.50 | 3/154 (1.9%) | 3/154 (1.9%) | 0.50 |
|           |          | 2504/2507 (99.9%) | [6.80; 35.66] | [99.4; 99.9] | [0.23; 1.15] | 3/154 (1.9%) | 3/154 (1.9%) | 0.50 | 3/154 (1.9%) | 3/154 (1.9%) | 0.50 | 3/154 (1.9%) | 3/154 (1.9%) | 0.50 |

sPTD, spontaneous preterm delivery; No., number of; PPV, positive predictive value; CI, confidence interval; NPV, negative predictive value; LR+, positive likelihood ratio; LR-, negative likelihood ratio

<sup>a</sup>Cervical length is the shortest of three measurements of the closed endocervical canal, see Figure 1

<sup>b</sup>Best cut off value according to Youden’s index<sup>c</sup>

<sup>d</sup>Women with previous sPTD (singleton or multiple) or late miscarriage or cervical conization

<sup>e</sup>Nulliparous women with no cervical conization and no late miscarriage

<sup>f</sup>Parous women with only previous term deliveries, no cervical conization and no late miscarriage
Legends of tables

**Table 1.** Definitions of spontaneous preterm delivery, history of cervical conization and cerclage insertion

**Table 2.** The ability of sonographic cervical length at 21+0 to 23+6 weeks (Cx2, n=6288) to discriminate between women who do and do not deliver spontaneously <33 weeks

**Table 3.** The ability of sonographic cervical length at 21+0 to 23+6 weeks (Cx2, n=6288) to discriminate between women who do and do not deliver spontaneously <33 weeks expressed as positive and negative predictive value, positive and negative likelihood ratio

Figure legends

**Figure 1.** Measurement of cervical length when isthmus is absent (a) or present (b). Isthmus is the lowest part of the uterine corpus that develops into the lower uterine segment as pregnancy progresses. A denotes the external os, B denotes the internal os. C is the innermost end of the juxtaposed anterior and posterior isthmus. Measurements were taken as a straight line from A to B (endocervical length), B to C (isthmus length), and A to C. Three measurements of each distance were taken during at least 3 min, each measurement being taken on a new image. We present results for the shortest of the three measurements of endocervical length (A-B).

**Figure 2a and 2b.** Overview of the study population with its risk groups. Figure 2a describes the study population with cervical length measurement at 18+0 to 20+6 weeks (Cx1), Figure 2b describes the study population with cervical length measurement at 21+0 to 23+6 weeks (Cx2). The high-risk group includes women with previous spontaneous preterm delivery or previous late miscarriage, or cervical conization. Nulliparae with no risk factors include nulliparous women with no cervical conization and no late miscarriages. Parae with no risk factors include parous women with only previous term deliveries, no cervical conization and no late miscarriages. Indicated preterm deliveries were excluded, because the association between indicated preterm...
delivery on the risk of subsequent spontaneous preterm delivery is insufficiently known.\textsuperscript{17} sPTD, spontaneous preterm delivery; iPTD, indicated preterm delivery.

**Figure 3.** The effect of cervical length (odds ratio per 5 mm decrease) on the risk of spontaneous preterm delivery and ability of cervical length to correctly predict spontaneous preterm delivery (area under the receiver operating characteristic curve) in different risk groups. The high-risk group includes women with previous spontaneous preterm delivery, late miscarriage or cervical conization. Nulliparae with no risk factors include nulliparous women with no cervical conization and no late miscarriage. Parae with no risk factors include parous women with only previous term deliveries, no cervical conization and no late miscarriage. \(P\)-values for interaction analysis are shown. sPTD, spontaneous preterm delivery; OR, odds ratio; AUC, area under the receiver operating characteristic curve; CI, confidence interval, \(^a\)Nulliparae with no risk factors; \(^b\)Pare with no risk factors.

**Figure 4.** The effect of cervical length (odds ratio per 5 mm decrease) on the risk of spontaneous preterm delivery and the ability of cervical length to correctly predict spontaneous preterm delivery (area under the receiver operating characteristic curve) in the two sub-groups constituting the high-risk group: women with previous spontaneous preterm delivery or late miscarriage as risk factors and women with cervical conization as only risk factor. \(P\)-values for interaction analysis are shown. sPTD, spontaneous preterm delivery; OR, odds ratio; AUC, area under the receiver operating characteristic curve; CI, confidence interval.

**Figure 5.** Receiver operating characteristic curves illustrating the ability of cervical length at 21+0 to 23+6 weeks (Cx2) to correctly discriminate between women who do and do not deliver spontaneously <33 or <37 weeks in different risk groups. The digits on the receiver operating characteristic curves denote cervical length cut-offs. Red bullets show the results for "best cut-off", ie the cut-off yielding the highest proportion of correctly classified cases (Youden’s index).\textsuperscript{21} The high-risk group includes women with previous spontaneous preterm delivery, late miscarriage or cervical conization. Nulliparae with no risk factors include nulliparous women

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with no cervical conization and no late miscarriages. Parae with no risk factors include parous women with only previous term deliveries, no cervical conization and no late miscarriages.

n/N, number of sPTDs/number in group; AUC, area under the receiver operating characteristic curve; sPTD, spontaneous preterm delivery; CI, confidence interval.
Supporting information legends

**Table S1.** Distribution of risk factors in the high-risk group.

**Table S2a.** Baseline maternal characteristics by risk group.

**Table S2b.** Baseline maternal characteristics for high-risk women with cervical conization as only risk factor and for high-risk women with previous spontaneous preterm delivery or late miscarriage as risk factors.

**Table S3a.** Pregnancy, delivery, and neonatal outcome by risk group.

**Table S3b.** Pregnancy, delivery, and neonatal outcome in high-risk women with cervical conization as only risk factor and in high-risk women with previous spontaneous preterm delivery or late miscarriage as risk factors.

**Table S4.** Cervical length at 18+0 to 20+6 weeks (Cx1) and at 21+0 to 23+6 weeks (Cx2) by risk group.

**Table S5.** Area under the receiver operating characteristic curve for sonographic cervical length with regard to spontaneous preterm delivery <33 weeks or <37 weeks for the study population with two cervical length measurements: at 18+0 to 20+6 weeks (Cx1) and at 21+0 to 23+6 weeks (Cx2) with at least 14 days between the two measurements (Cx1Cx2, n=6179).

**Table S6.** The ability of sonographic cervical length at 21+0 to 23+6 weeks (Cx2, n=6288) to discriminate between women who do and do not deliver spontaneously <33 weeks in a high-risk group that includes women with previous spontaneous or indicated preterm delivery, late miscarriage or cervical conization (n=706).
Table S7. Diagnostic performance of cervical length <25 mm or <25 mm when measured with ultrasound in the second trimester for prediction of spontaneous preterm delivery in women at high risk of spontaneous preterm delivery: summary of the literature.

Figure S1. Flow chart showing patient recruitment. aused as controls in the CERVIX-study (Kuusela P, Jacobsson B, Hagberg H, et al. Second trimester transvaginal ultrasound measurement of cervical length for prediction of preterm birth: a blinded prospective multicenter diagnostic accuracy study. BJOG. 2020;128(2):195-206). bIn some women, their discomfort made it impossible to measure the cervix. cOne woman got a cerclage and gave birth at 33 gestational weeks, one woman miscarried after 2 days of bed rest.

Figure S2. The effect of cervical length (odds ratio per 5 mm decrease) on the risk of spontaneous preterm delivery and ability of cervical length to correctly predict spontaneous preterm delivery (area under the receiver operating characteristic curve) in women with and without a history of cervical conization and in women with and without previous spontaneous preterm delivery or late miscarriage (16+0 to 21+6 weeks). P-values for interaction analysis are shown. sPTD, spontaneous preterm delivery; OR, odds ratio; AUC, area under the receiver operating characteristic curve; CI, confidence interval.

Figure S3. Receiver operating characteristic curves illustrating the ability of cervical length at 18+0 to 20+6 weeks (Cx1) to correctly discriminate between women who do and do not deliver spontaneously <33 or <37 weeks in different risk groups. The digits on the receiver operating characteristic curve denote cervical length cut-offs. Red bullets show the results for "best cut-off", ie the cut-off yielding the highest proportion of correctly classified cases (Youden's index (Habibzadeh F, Habibzadeh P, Yadollahie M. On determining the most appropriate test cut-off value: the case of tests with continuous results. Biochem Med (Zagreb). 2016;26(3):297-307)). The high-risk group includes women with previous spontaneous preterm delivery, late miscarriage
or cervical conization. Nulliparae with no risk factors include nulliparous women with no cervical conization and no late miscarriages. Paraes with no risk factors include parous women with only previous term deliveries, no cervical conization and no late miscarriages. n/N, number of sPTDs/number in group; AUC, area under the receiver operating characteristic curve; CI, confidence interval.

**Figure S4.** Receiver operating characteristic curves showing the ability of cervical length at 18+0 to 20+6 weeks (Cx1) and 21+0 to 23+6 (Cx2) to correctly discriminate between women who do and do not deliver spontaneously <33 or <37 weeks in the two subgroups constituting the high-risk group: women with cervical conization as only risk factor and women with previous spontaneous preterm delivery or late miscarriage as risk factors. The digits on the receiver operating characteristic curves denote different cervical length cut-offs. Red bullets show the results for "best cut-off", ie the cut-off yielding the highest proportion of correctly classified cases (Youden’s index (Habibzadeh F, Habibzadeh P, Yadollahie M. On determining the most appropriate test cut-off value: the case of tests with continuous results. Biochem Med (Zagreb). 2016;26(3):297-307)). n/N, number of sPTDs/number in group; AUC, area under the receiver operating characteristic curve; sPTD, spontaneous preterm delivery; CI, confidence interval.

**Figure S5.** Receiver operating characteristic curves showing the ability of cervical length at 18+0 to 20+6 weeks (Cx1) and at 21+0 to 23+6 weeks (Cx2) to correctly discriminate between women who do and do not deliver spontaneously <33 or <37 weeks in women with and without a history of cervical conization. The digits on the receiver operating characteristic curve denote cervical length cut-offs. Red bullets show the results for "best cut-off", ie the cut-off yielding the highest proportion of correctly classified cases (Youden’s index (Habibzadeh F, Habibzadeh P, Yadollahie M. On determining the most appropriate test cut-off value: the case of tests with continuous results. Biochem Med (Zagreb). 2016;26(3):297-307)). n/N, number of sPTDs/number in group; AUC, area under the receiver operating characteristic curve; sPTD, spontaneous preterm delivery; CI, confidence interval.
**Figure S6.** Receiver operating characteristic curves showing the ability of cervical length at 18+0 to 20+6 weeks (Cx1) and at 21+0 to 23+6 weeks (Cx2) to correctly discriminate between women who do and do not deliver spontaneously <33 or <37 weeks in women with and without previous spontaneous preterm delivery or late miscarriage. The digits on the receiver operating characteristic curve denote cervical length cut-offs. Red bullets show the results for "best cut-off", i.e., the cut-off yielding the highest proportion of correctly classified cases (Youden’s index (Habibzadeh F, Habibzadeh P, Yadollahie M. On determining the most appropriate test cut-off value: the case of tests with continuous results. Biochem Med (Zagreb). 2016;26(3):297-307)). n/N, number of sPTDs/number in group; AUC, area under the receiver operating characteristic curve; sPTD, spontaneous preterm delivery; CI, confidence interval.

**Figure S7.** The effect of cervical length (odds ratio per 5 mm decrease) on the risk of spontaneous preterm delivery and ability of cervical length to correctly predict spontaneous preterm delivery (area under the receiver operating characteristic curve) in different risk groups. The high-risk group includes women with previous spontaneous or indicated preterm delivery, late miscarriage or cervical conization. Nulliparae with no risk factors include nulliparous women with no cervical conization and no late miscarriages. Parae with no risk factors include parous women with only previous term deliveries, no cervical conization and no late miscarriages. P-values for interaction analysis are shown. sPTD, spontaneous preterm delivery; OR, odds ratio; AUC, area under the receiver operating characteristic curve; CI, confidence interval. aNulliparae with no risk factors; bParae with no risk factor.
Figure 1. Measurement of cervical length when isthmus is absent (a) or present (b).
Isthmus is the lowest part of the uterine corpus that develops into the lower uterine segment as pregnancy progresses. A denotes the external os, B denotes the internal os. C is the innermost end of the juxtaposed anterior and posterior isthmus. Measurements were taken as a straight line from A to B (endocervical length), B to C (isthmus length), and A to C. Three measurements of each distance were taken during at least 3 min, each measurement being taken on a new image. We present results for the shortest of the three measurements of endocervical length (A-B).
Figure 2a

11 072 women with cervical length measurement at 18+0 to 20+6 weeks (Cx1) and delivery data

Excluded: Parae with previous iPTD  
n = 114/11 072 (1.0%)  
Outcome:  
sPTD <33 weeks: 1/114 (0.9%)  
sPTD <37 weeks: 9/114 (7.9%)

High-risk group  
n = 1045/11 072 (9.4%)  
Outcome:  
sPTD <33 weeks: 15/1045 (1.4%)  
sPTD <37 weeks: 90/1045 (8.6%)

Nulliparae no risk factors  
n = 5173/11 072 (46.7%)  
Outcome:  
sPTD <33 weeks: 32/5173 (0.6%)  
sPTD <37 weeks: 210/5173 (4.1%)

Parae no risk factors  
n = 4740/11 072 (42.8%)  
Outcome:  
sPTD <33 weeks: 15/4740 (0.3%)  
sPTD <37 weeks: 108/4740 (2.3%)

Excluded: Parae with cervical conization + previous iPTD  
n = 10/1045 (1.0%)  
Outcome:  
sPTD <33 weeks: 1/10 (10%)  
sPTD <37 weeks: 1/10 (10%)

Conization as only risk factor  
n = 631/1045 (60.4%)  
Outcome:  
sPTD <33 weeks: 8/631 (1.3%)  
sPTD <37 weeks: 37/631 (5.9%)

Previous sPTD or late miscarriage  
n = 404/1045 (38.7%)  
Outcome:  
sPTD <33 weeks: 6/404 (1.5%)  
sPTD <37 weeks: 52/404 (12.9%)
Figure 2b. Overview of the study population with its risk groups. Figure 2a describes the study population with cervical length measurement at 18+0 to 20+6 weeks (Cx1), Figure 2b describes the study population with cervical length measurement at 21+0 to 23+6 weeks (Cx2). The high-risk group includes women with previous spontaneous preterm delivery or previous late miscarriage, or cervical conization. Nulliparae with no risk factors include nulliparous women with no cervical conization and no late miscarriages. Parae with no risk factors include parous women with only previous term deliveries, no cervical conization and no late miscarriages. Indicated preterm deliveries were excluded, because the association between indicated preterm delivery on the risk of subsequent spontaneous preterm delivery is insufficiently known. sPTD, spontaneous preterm delivery; iPTD, indicated preterm delivery.

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Figure 3. The effect of cervical length (odds ratio per 5 mm decrease) on the risk of spontaneous preterm delivery and ability of cervical length to correctly predict spontaneous preterm delivery (area under the receiver operating characteristic curve) in different risk groups. The high-risk group includes women with previous spontaneous preterm delivery, late miscarriage or cervical conization. Nulliparous with no risk factors include nulliparous women with no cervical conization and no late miscarriage. Parae with no risk factors include parous women with only previous term deliveries, no cervical conization and no late miscarriage. $P$-values for interaction analysis are shown. sPTD, spontaneous preterm delivery; OR, odds ratio; AUC, area under the receiver operating characteristic curve; CI, confidence interval, $^a$Nulliparae with no risk factors; $^b$Parae with no risk factors.
Figure 4. The effect of cervical length (odds ratio per 5 mm decrease) on the risk of spontaneous preterm delivery and the ability of cervical length to correctly predict spontaneous preterm delivery (area under the receiver operating characteristic curve) in the two sub-groups constituting the high-risk group: women with previous spontaneous preterm delivery or late miscarriage as risk factors and women with cervical conization as only risk factor. P-values for interaction analysis are shown. sPTD, spontaneous preterm delivery; OR, odds ratio; AUC, area under the receiver operating characteristic curve; CI, confidence interval.
Outcome, sPTD <33 weeks

- High-risk group, n/N 7/843
  - Sensitivity: 0.76 (95% CI 0.54; 0.97)

- Nulliparae with no risk factors, n/N 12/3053
  - Sensitivity: 0.74 (95% CI 0.59; 0.89)

- Paraie with no risk factors, n/N 6/2529
  - Sensitivity: 0.89 (95% CI 0.38; 0.99)

Outcome, sPTD <37 weeks

- High-risk group, n/N 50/843
  - Sensitivity: 0.59 (95% CI 0.51; 0.68)

- Nulliparae with no risk factors, n/N 110/3053
  - Sensitivity: 0.66 (95% CI 0.60; 0.71)

- Paraie with no risk factors, n/N 59/2529
  - Sensitivity: 0.53 (95% CI 0.46; 0.61)
Figure 5. Receiver operating characteristic curves illustrating the ability of cervical length at 21+0 to 23+6 weeks (Cx2) to correctly discriminate between women who do and do not deliver spontaneously <33 or <37 weeks in different risk groups. The digits on the receiver operating characteristic curves denote cervical length cut-offs. Red bullets show the results for "best cut-off", ie the cut-off yielding the highest proportion of correctly classified cases (Youden’s index). The high-risk group includes women with previous spontaneous preterm delivery, late miscarriage or cervical conization. Nulliparae with no risk factors include nulliparous women with no cervical conization and no late miscarriages. Parae with no risk factors include parous women with only previous term deliveries, no cervical conization and no late miscarriages. n/N, number of sPTDs/number in group; AUC, area under the receiver operating characteristic curve; sPTD, spontaneous preterm delivery; CI, confidence interval.