Uterocervical angle as a predictor of preterm birth on a high-risk collective between 20 and 31 weeks of gestation: A cohort analysis

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Introduction: The cervical length (CL) measurement is a widely used method to estimate the risk of preterm birth. Due in particular to the high false-positive rate, the establishment of markers with improved test characteristics is a great challenge. A potential predictor of preterm birth is the uterocervical angle (UCA) and this additional measurement may improve the risk assessment. It was the aim of this study to compare the test properties of CL and UCA on patients at risk for preterm birth.

Material and methods: 109 patients with at least one of the following signs of threatening preterm birth between 20+0/7 and 31+6/7 weeks were included in a prospective cohort analysis: regular (>3/30 min) or painful uterine contractions, CL below 25 mm or a history of preterm birth. Exclusion criteria were premature rupture of membranes, hypertensive disorders, vaginal bleeding, surgical cerclage, Arabin pes sary or cervical dilation of more than 30 mm. The determination of the UCA was carried out in a standardized manner using the image documents captured by vaginal sonographic CL measurement. The primary endpoint was preterm birth <34 weeks, secondary endpoints were delivery <37 weeks and within 7 days.

Results: The UCA was on average 103° and the mean UCA in preterm and term groups did not differ significantly (P = .924). The UCA was not predictive for threatened preterm birth, even if only singletons were considered. For CL the best predictive accuracy for preterm birth <34 weeks was observed at a cut-off value of 14 mm with sensitivity 0.50, specificity 0.80, positive predictive value 0.30, negative predictive value 0.90, positive likelihood ratio 2.4, negative likelihood ratio 0.6 and an odds ratio of 3.9 (95% confidence interval 1.3-11.7, P = .016).

Conclusions: The assessment of UCA in patients at risk for preterm birth was not suitable to predict the probability of a threatened preterm birth. Measurement of UCA cannot be recommended in this situation.

Abbreviations: AUC, area under the curve; BMI, body mass index; CI, confidence interval; CL, cervical length; IQR, interquartile range; MRI, magnetic resonance imaging; OR, odds ratio; PAMG-1, placental alpha-microglobulin-1; phIGFBP-1, phosphorylated insulin-like growth factor binding-protein-1; PTB, preterm birth; ROC, receiver operator characteristic; UCA, uterocervical angle.
1 | INTRODUCTION

One of the greatest challenges in obstetrics is to lower the prevalence of preterm birth (PTB), which was 10.6% worldwide in 2014. The diagnosis of threatened PTB is based on clinical parameters such as premature labor and pressure in the vagina or technical parameters such as cervical length (CL) reduction or a positive tocogram. All of these parameters revealed a high false-positive rate, which results in a substantial overtreatment of symptomatic patients. A single screening tool that had both a high detection rate and a low false-positive rate, is currently not available. Biochemical point of care tests with measurement of fetal fibronectin (fFN), placentalt alpha-microglobulin-1 (PAMG-1) or phosphorylated insulin-like growth factor binding-protein-1 (phIGFBP-1) in cervicovaginal fluid have been added in recent years to improve the prediction of PTB. However, it is yet not clear what the optimal algorithm for the application of these new biochemical parameters will be – instead or in addition to the CL measurement. Furthermore, a routine application of the commercial available kits will increase the financial burden with costs up to 50€ per test. In Germany and many other countries, the most commonly used surrogate parameter in everyday clinical practice for definition of patients at risk for PTB is a shortened CL measured by transvaginal ultrasound. An improvement of the test accuracy by the addition of a complementary sonographic parameter would be highly attractive. A potential predictor, therefore, is the measurement of uterocervical angle (UCA). The reasoning behind UCA being used as a diagnostic tool for PTB goes back to publications about the Arabin pessary. Cannie et al showed in a magnetic resonance imaging (MRI) study that inserting the pessary leads to a reduction of the UCA. According to the authors, the mechanism is responsible for the observed reduction of PTB is by decreasing the pressure on the internal cervical os. Consecutively, the hypothesis was made that an enlarged UCA can be regarded as a risk factor for PTB. Historical cohort studies suggested that an increased UCA during the early second trimester has a higher predictive power in the prediction of PTB than a shortened CL has in singletons as well as twin gestations. The aim of our study was to determine and compare the test properties of CL and UCA for the prediction of PTB on patients at increased risk for PTB between 20 and 31 weeks of gestation within a prospective cohort analysis.

2 | MATERIAL AND METHODS

2.1 | Patient selection and inclusion criteria

We included pregnant women with at least one of the following criteria: regular labor (>3/30 min), severe uterine contractions, CL <25 mm or a personal history of PTB or abortion >16 weeks of gestation. We

**FIGURE 1** Measurement of the uterocervical angle by transvaginal ultrasound. (A) Schematic representation of the topographic anatomy and the measurement of the uterocervical angle (UCA). UCA represents the angle of the connecting black dotted lines between the outer and inner cervix and the tangent along the anterior wall of the uterus. (B) Representative photograph of a transvaginal ultrasound picture with drawn UCA (white dotted lines) [Color figure can be viewed at wileyonlinelibrary.com]
included women with singletons as well as multiple gestations between 20\textsuperscript{+0/7} and 31\textsuperscript{-6/7} weeks of gestation from January 2017 until April 2019 who contacted our university hospital (Rostock, Germany) because of the abovementioned symptoms with threatened PTB. Premature rupture of membranes, hypertensive gestational diseases, vaginal bleeding, existing cerclage or Arbin pessary or cervical dilation >30 mm, tocolysis in the previous 7 days, hypertensive disorders and iatrogenic indication for termination of pregnancy within 7 days after study inclusion were the exclusion criteria.

A measurement of the CL at admission is a standard of care in our institution. On the basis of printed documentation of the shortest CL measurement, the UCA was determined by one person (K.G.) using a protractor. The UCA is defined as the angle of the connecting line between the outer and inner cervix and the tangent along the anterior wall of the lower uterine segment (Figure 1). The measurement of the UCA in special situations such as a large funnel or a curved cervix was carried out as described in the study of Dziadosz et al.\textsuperscript{8}

The clinician on duty was responsible for the further treatment decisions of patients including the indication for tocolysis and corticosteroid prophylaxis. It was unlikely that UCA influenced the clinical decision, as the results were not communicated to the treating physicians. Commercially available biomarkers such as fFN, PAMG-1 and phiGFBP-1 were not tested.

The primary outcome was the evaluation of CL and UCA or a combination of both sonographic parameters as a potential marker for a risk of PTB at <34 weeks. Secondary endpoints were PTB <37 weeks and within 7 days. Gestational age was calculated from the first day of the last menstrual period and was corrected by ultrasound if measurements of the crown-rump length during the first trimester were different for more than 7 days.

2.2 | Statistical analyses

All data were stored and analyzed using the IBM SPSS statistical package 21.0 (SPSS Inc., Chicago, IL, USA) and Microsoft EXCEL 2003 (Microsoft Corp., Redmond, WA, USA). Descriptive statistics included mean and standard deviation for parametric variables. Otherwise, median, minimum, maximum or interquartile range (IQR) were presented. For categorical variables, frequencies and relative frequencies are shown. Testing for differences of parametric variables between the groups was accomplished using Student’s t test and for non-parametric variables by the U test of Mann-Whitney. Test selection was based on evaluation of the variables for standard distribution using the Kolmogorov-Smirnov test. Comparison between the groups for categorical variables was performed using the Chi-square test. All P values resulted from two-sided statistical tests and values of P < .05 were considered statistically significant.

For correlation analysis, Pearson’s correlation coefficient (r) was calculated if normally distributed variables were given. Otherwise, Spearman’s correlation coefficient was assessed. For CL and UCA, receiver operating characteristic (ROC) curves were computed and the areas under the curve (AUC) were reported. Optimal cut-off value (minimal distance to sensitivity and specificity of 1) was calculated using the following equation: (1 – sensitivity)\textsuperscript{2} + (1 – specificity)\textsuperscript{2}. Criteria of diagnostic validity for CL were computed and presented as sensitivity, specificity, positive predictive value, negative predictive value, positive and negative likelihood ratios.

Diagnostic odds ratios (OR) with 95% confidence interval (CI) for various predictive variables were calculated. Adjusted OR for CL was computed in a sequential logistic regression model with addition of the following confounding variables: multiple gestations, body mass index (BMI). For computation, only risk factors that fit the model were included. Assisted reproductive technique and gestational diabetes were removed because collinearity with multiple gestation with respect to BMI was present.

2.3 | Ethical approval

This study was conducted as a part of the “Analysis of diagnostic accuracy of predictive biomarkers in risk assessment of threatening preterm birth” (ADAPROB) study. The protocol was approved by the local ethics committee of the University of Rostock (IRB-No. A2016-0162, 26 August 2016) and the study was registered with the German Clinical Trials Register (DRKS-ID: DRKS00010763). Written informed consent was obtained from all participants.

3 | RESULTS

3.1 | Maternal and neonatal characterization

During the 27-month recruitment period, 109 women (95 singletons and 14 multiple gestations) were included. PTB below 37 weeks occurred in a third of the study participants (33.0%, n=36) and in 16 women below 34 weeks (14.7%), six of whom delivered within 7 days (5.5%). Risk of PTB was higher in multiple gestations than in singletons (<34 weeks: 57.1% vs 8.4%, \(P\ < .001\), OR 14.5, 95% confidence interval [95% CI] 4.0-52.3; <37 weeks: 85.7% vs 25.3%, \(P\ < .001\), OR 17.8, 95% CI 3.7-85.1). Further risk factors for PTB were obesity (defined as BMI ≥30 kg/m\textsuperscript{2}) and gestational diabetes (Table 1).

Clinical signs of threatened PTB such as subjective uterine contractions or pressure in the vagina or back pain (n = 78, 71.6%) were not predictive for PTB at either <34 weeks (OR 1.2, 95% CI 0.3-4.6) or <37 weeks (OR 0.9, 95% CI 0.3-2.4). Likewise, no differences for PTB were found for a positive tocogram on admission (<34 weeks: OR 1.3, 95% CI 0.4-4.0; <37 weeks: OR 0.7, 95% CI 0.3-1.5) or a positive history of PTB among the multigravida (<34 weeks: OR 2.3, 95% CI 0.7-7.7; <37 weeks: OR 1.4, 95% CI 0.5-3.9).

3.2 | Ultrasound parameter cervical length

The median length of the cervix at admission was positively correlated with gestational age at delivery − 15 mm (IQR 6-21) <34 weeks,
18 mm (IQR 13-23) between 34 and 36 weeks and 22 mm (IQR 16-35) ≥37 weeks (P = .008) – and the CL was correlated significantly with the gestational week at delivery (r = 0.3, P = .002) (Figure 2A,B). ROC analysis for the prediction of PTB <34 weeks by CL revealed an 

UCA could be determined in 84% of all patients (92/109) and in 83% of singleton pregnancies (79/95). Reasons for failure were elapsed cervix and non-representation of the anterior uterine segment.

The mean UCA (± standard deviation) in the total cohort was 103.24 ± 19.7°. We did not observe a difference in mean UCA between singletons and multiple gestations (103.5 ± 20.1° vs 101.6 ± 17.7°, P = .751). UCA did neither correlate to gestational age at admission (r = −0.01, P = .924) or at delivery (r = −0.07, P = .984). In contrast, there was a slightly positive correlation of UCA with the pregravid BMI (r = 0.23, P = .03). The UCA was not predictive for PTB in the ROC analysis (Figure 3C,D). Subgroup analysis of singletons resulted in an AUC of 0.53 (95% CI 0.26-0.81, P = .803) for prediction of PTB <34 weeks and an AUC of 0.54 (95% CI 0.40-0.69, P = .586) for PTB <37 weeks.

### 3.3 Ultrasound parameter uterocervical angle

UCA could be determined in 84% of all patients (92/109) and in 83% of singleton pregnancies (79/95). Reasons for failure were elapsed cervix and non-representation of the anterior uterine segment.
Several retrospective case-control and cohort studies demonstrated that a wide UCA was associated with an increased risk of PTB. Measurement of UCA in all of these studies was performed during the first and second trimester, mostly between 14 and 24 weeks on asymptomatic women. Even if a more obtuse UCA in cases of PTB vs term delivery was observed, the mean UCA between the preterm groups of various studies differed widely, with a range between 93° and 127°. Moreover, studies revealed substantial inner group variances of UCA with a large overlap of term and PTB, which limits its application as a clinical predictive test parameter. Several studies assumed an increase of the UCA at higher gestational age. However, a cross-sectional study from Thailand that investigated the normal UCA between 16 and 24 weeks of gestation on 249 healthy pregnancies with term delivery by repeated transvaginal measurements, did not find an increase.
with progression of pregnancy.\textsuperscript{15} The mean UCA was 102.3 \(\pm\) 21.7°, and therefore significantly higher compared with the previously reported values in women with term delivery. Our study confirmed the independence of UCA from gestational age at measurement, even if only women with term delivery were considered. Two studies investigated the UCA in women at risk for PTB: a cohort study (\(n = 211\)) included only women with symptoms of threatened PTB between 16 and 29 weeks.\textsuperscript{16} Furthermore, a matched pairs analysis (\(n = 405\)) investigated UCA dependent on CL (\(<25\ vs \geq 25\ mm\) between 18 and 23 weeks.\textsuperscript{17} The studies demonstrated that the UCA was not an independent predictive marker of PTB in symptomatic women and did not improve the predictive capability of CL. An interim analysis of an ongoing prospective Spanish study with in vivo measurement of UCA between 18 and 23 weeks of gestation, confirmed the doubtful predictive potential of the parameter. In 499 already-delivered women, mean UCA in the second trimester was 101.7° in the group with spontaneous PTB (\(n = 18\)) and 103.6° (\(n = 465\)) in those with delivery at term.\textsuperscript{18} Of course, for a definitive evaluation, the final results have to be awaited. These multiple “negative” results have not been fully published so far, suggesting that at present some publication bias on this topic exists. Nevertheless, there is increasing evidence that the predictive performance of the UCA was overestimated by previous study results. Our negative results further increase doubt about whether UCA allows a sufficient distinction of women with spontaneous PTB and term delivery. However, for interpretation, the different study characteristics need to be considered. We included only women at increased risk for PTB including symptomatic patients with shortened cervix (64.2% with CL \(<25\ mm\) or premature contractions. Moreover, measurements were carried out at later gestational ages (mean 26.1 weeks, range 21-31 weeks), prohibiting a direct comparison with previous studies. A strength of our study is the prospective study design and that the included study population reflected the normal clinical situation. The study may be limited by the small number of patients but, as there was not even a trend to a more obtuse UCA observed in the group of PTB, it seems unlikely that a bigger cohort would discover a clinically significant difference. A further possible limitation may be the heterogeneous study cohort with inclusion of multiple gestations. Singleton cases were therefore analyzed separately, but this did not change the results. Two previous retrospective studies analyzed UCA in twin pregnancies and both showed predictive capability for multiple gestations.\textsuperscript{9,19} In their historical cohort analysis on twin pregnancies, Knight et al calculated \((n = 259)\) an optimal cut-off value for prediction of PTB \(<32\ weeks\) of 110° and \(<28\ weeks\) of 114°.\textsuperscript{9} The measurements were carried out between 18 and 23 weeks. A second, as yet unpublished study measured a mean UCA of 124° on 137 women between 14 and 24 weeks. The risk of a spontaneous PTB \(<37\ weeks\) was significantly associated with the UCA using the singleton cut-off values of 95°/105° from the study of Dziadosz et al.\textsuperscript{8,19} We did not find any difference between mean UCA in relation to multiple gestation and singletons, and therefore also analyzed both groups together.

### 5 | CONCLUSION

In our study, the UCA was not predictive for PTB in women at risk between 20 and 31 weeks of gestation and therefore was not able to ameliorate the test characteristics of the CL. In contrast, the CL revealed a significant, albeit only moderate accuracy for prediction of PTB. However, most women with a CL \(>14\ mm\) will not develop PTB \(<34\ weeks\), which could help reassure this subgroup of patients.

### ACKNOWLEDGMENT

Open access funding enabled and organized by Projekt DEAL

### CONFLICT OF INTEREST

None.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Gründler K, Gerber B, Stubert J. Uterocervical angle as a predictor of preterm birth on a high-risk collective between 20 and 31 weeks of gestation: A cohort analysis. *Acta Obstet Gynecol Scand*. 2020;99:1527–1533. https://doi.org/10.1111/aogs.13955