Original Paper

Prediction of Preterm Birth with Serial Measurements of Ultrasound Markers

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ABSTRACT: To compare the ability of cervical length (CL), anterior cervical angle (ACA), and cervical consistency index (CCI) to predict premature birth. Methods. This prospective study involved 85 pregnant women who gave birth prematurely and a control group of 31 pregnant women who gave birth at term. The study was performed in the Obstetrics and Gynecology Clinic of the Municipal Clinical Hospital Filanthropia Craiova between January 1, 2019, and January 1, 2022. Cases were examined using transvaginal ultrasonography (TVU) in the second and third trimesters of pregnancy, and cervical length (CL), Anterior Cervical Angle (ACA), and Cervical Consistency Index (CCI) were measured. Results. The mean value from the three measurements at all three parameters was statistically significant with preterm birth ($p<0.05$). Cervical length <25mm, was highly significant in the prediction of preterm labor with a sensitivity of 99%, specificity of 61%, positive predictive value (PPV) of 78%, negative predictive value (NPV) of 97 %, and a positive likelihood ratio (LR+) of 2.54 and negative likelihood ratio (LR-) of 0.02. CCI also remains, despite low specificity and PPV values, a potential predictive parameter in the prediction of preterm birth, with a sensitivity of 73%, NPV of 92% and a LR+of 1.32 and LR- of 0.6 also correlated with CL, CCI being more difficult to interpret as an independent predictive parameter. Conclusions. CL remains the standard parameter for predicting the preterm birth, but in combination with other parameters, the prediction rate can increase significantly.

KEYWORDS: *cervical length, anterior cervical angle, cervical consistency index, preterm birth.*

Introduction

It is estimated worldwide that 1 in 10 children are born prematurely, and approximately 1 million children are born prematurely each year [1].

Therefore, the prediction of premature birth is extremely important both for the impact that premature birth has on a personal level and in terms of economic and health impact.

There is currently no single safe test to predict premature birth, but it has been found that a combination of tests can do this, or at least include the pregnant woman in a risk group, benefiting from a series of prophylactic interventions and of optimal decision management [2].

It seems that a "short cervix" measured in the second trimester of pregnancy by vaginal ultrasound, may represent an increase in the probability of premature birth if we refer to singleton pregnancies.

But the detection and monitoring of this marker in the second trimester may allow the administration of a specific treatment, thus reducing this increased likelihood [3].

There are also situations in which in the second trimester the cervix may have a normal length or maybe at the lower limit, which has been recommended at 25mm [4,5].

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Cervical length measurement by transvaginal ultrasound has been extensively studied for the past 30 years, becoming the subject of over 600 publications [6].

Along with this ultrasound marker, others have been used to improve the prediction of premature birth.

The measurement of the angle between the uterine wall and the cervical canal was initially used to successfully induce labor, but later it was found that an obtuse angle (≥95° and ≥105°) may be associated with an increased risk of premature birth [7,8].

Thus, this ACA parameter may be an additional ultrasound marker for predicting preterm birth.

Its detection rate can be improved if combined with other parameters, especially the length of the cervix and the presence of risk factors, considering that this can predict about 40% of premature births, which is a significant percentage [9].

Given that in recent years it has been found that measuring the length of the cervix for low-risk populations has a low detection rate [10,11], other ultrasound parameters have been found to show cervical changes that occur before labor.

Thus, another ultrasound parameter studied was the cervical consistency index, which was defined and standardized by Parra-Saavedra et al. in 2011 [6].

A better detection rate of CCI than CL for low-risk populations was found in some studies [12].

As noted, there is currently no single or combined test with high sensitivity that can certainly identify women who will give birth prematurely, so we could eliminate a several unnecessary interventions and expensive treatment.

But in the end, the most widely used ultrasound marker, CL, is a standard if not a reliable predictor of preterm birth, at least in selecting a risk group.

Materials and Methods

This prospective study included a group of 85 pregnant women who had risk factors for premature birth and who gave birth prematurely and 31 pregnant women who gave birth at term, which constituted the control group.

The study was performed in the Obstetrics and Gynecology Clinic of the Municipal Clinical Hospital "Filantropia" Craiova, between January 1, 2019, and January 1, 2022, under the auspices of the University of Medicine and Pharmacy of Craiova.

Eligibility criteria included singleton pregnancies, ages over 18, and pregnancies with accurate gestational age.

The exclusion criteria from the study were multiple pregnancies, major fetal structural abnormalities, any vaginal bleeding, labor, or any medical or psychiatric condition that compromises a woman's ability to participate.

A detailed interview was conducted at the first monitoring visit to obtain demographic, clinical, and medical history data.

Three ultrasound markers were serially monitored to predict premature birth: CL, ACA, and CCI, in 3 periods of pregnancy: 18.0-22.6 weeks, 28.0-31.6 weeks, and 32.0-35.6 weeks.

This monitoring was performed outside of standard obstetric care visits.

Cervical length was estimated as the distance between internal os and external os, measured by TVU.

The anterior cervical angle was measured by the angle created by two imaginary lines, one passing through the internal and external cervical os and another following the anterior wall of the uterus.

CCI is the ratio between the thickness of the cervix after compression by the transvaginal transducer (AP') and the thickness before compression (AP), expressed as a percentage, measuring the degree of deformity of the cervix during a standard vaginal ultrasound examination.

Statistical Analysis

For each group, we calculated the median ACA, CL, and CCI. The differences between the groups were tested with an ANOVA-test and a Student-test for normal distribution and homogeneity of variances.

A p-value of 0.05 was used as a significance level.

Sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios were calculated with their 95% Confidence Intervals.

Ethical Consideration

Patients were informed of the study design and signed informed consent.

Based on the Declaration of Helsinki, the study received the approval of the Ethics Committee of the University of Medicine and Pharmacy of Craiova.

Results

The average age of the group with premature birth was 28.5 years±4.6 SD, the control group had an average age of 29.8 years±4.7 SD; 37 (31.89%) patients who gave birth prematurely were nulliparous, compared to 23 (19.82%) patients in the control group.

History of premature births was present in 21 (18.10%) patients who gave birth prematurely and only 2 (1.72%) patients in the control group; 80 (68.96%) patients in the premature birth group had first or second-trimester miscarriage, compared to only 11 (9.48%) cases in the control group.

As noted in Table 1, there are no statistically significant differences in maternal age and BMI between groups.

But because we could not differentiate between nulliparity and miscarriage as the only risk factor in preterm birth, no other study has done this, we believe that nulliparity cannot be an independent risk factor.

This is because from the beginning, or during pregnancy, other factors are added: obesity, shortening of the cervix, pathology associated with pregnancy, etc.

Table 1. Demographic maternal characteristics of study groups in correlation with premature birth.

Parameter	Premature birth group	Control group	p-value
BMI (Median±SD)	24.2±3.34	24.5±3.03	0.955408
Maternal age in years (Median±SD)	28.5±4.62	29.8 ±4.71	0.17564
Nulliparous (n)	37	23	
History of premature births (n)	21	2	
First-trimester miscarriage (n)	57	8	
Second-trimester miscarriage (n)	23	3	

Note: BMI: body mass index

For preterm birth prediction we used CL, ACA, and CCI, evaluated in Table 2.

Cervical shortening, assessed by measuring the length of the cervix, a parameter detected a few weeks before preterm birth, is one of the most commonly used elements in predicting preterm birth.

The mean value from the three measurements showed that there was a significant difference between CL and preterm birth, with the p-value of the Student's test <0.05.

In our study, the mean value of ACA showed the same significant difference, the p-value of the Student's test <0.05.

Also, the average CCI is significantly lower in the study group, compared to the control group (<0.05).

If we establish a cut-off of 65%, as established in the specialized research for the prediction of premature birth, the correlation with CL <25mm, shows that 11 cases had CCI <65%, compared to only 4 cases with CL>25mm (Figure 1).

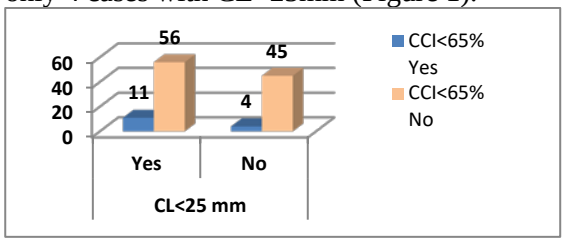

Figure 1. Distribution of cases according to CCI, and CL.

The relationship between CL, ACA, CCI, and preterm delivery are shown in Table 2.

Table 2. Correlation between CL, ACA, CCI, and preterm birth.

Parameter	Premature birth group	Term birth group	p-value
Cervical length in mm (Media±SD)	21.10±3.60	31.96±2.90	0.00
Anterior uterocervical angle (Media±SD) in degree	101.43±3.95	92.73±2.48	0.00
Cervical consistency index in % (Media±SD)	77±8.31	79.23±6.72	0.00

Note: CL: cervical length; ACA: anterior cervical angle; CCI: cervical consistency index.

Making a correlation between the three visits at different gestational ages, we wanted to see which is the most correct gestational age for predicting premature birth.

In the case of CL and ACA we noticed a statistically significant difference in the risk of premature birth at all three gestational ages studied.

In the case of CCI, only the measurement performed at visit 3 (32.0-35.6 gestational week) did not show a statistically significant difference in the risk of premature birth (Table 3).

Prevalence of CL <25mm at the first visit was 72.94% and was higher among women who gave birth preterm compared to term pregnancies (3.22%).

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During visits 2 and 3, the prevalence of CL <25mm was higher than in pregnancies that gave birth at term (75.29% vs. 0% and 12.9%, respectively).

ACA>100° had increasing values, starting from 8.23% at the first visit, at 67.05%, and 87.05% at visits 2 and 3, compared to 0% cases in pregnancies that gave birth at term.

Also, the percentage of cases that had a CCI <65%, increased from the first visit, 8.23%, to 67.05%, and 28.23% at visits 2 and 3, compared to 0% cases in pregnancies that gave birth in term (Table 3).

Table 3. Correlation between serial transvaginal CL, ACA, CCI measurements, and preterm birth.

Parameter	Premature birth 32.0-33.6 gestational week (Mean±SD)	Premature birth 34.0-35.6 gestational week (Mean±SD)	Term birth >37.0 gestational week (Mean±SD)	Prevalence of parameter in premature birth (%)	Prevalence of parameter in term birth (%)	ANOVA p-value
Cervical length (mm)				**<25mm**		
Visit 1 (18.0-22.6 gestational week)	20.85±5.04	22±4.16	34±3.47	72.94	3.22	0.00
Visit 2 (28.0-31.6 gestational week)	21±3.40	21.1±4.67	32.4±2.71	75.29	0	0.00
Visit 3 (32.0-35.6 gestational week)	21.45±3.78	20.7±3.76	29.2±5.28	75.29	12.90	0.00
Anterior cervical angle (degrees)				**>100°**		0.00
Visit 1 (18.0-22.6 gestational week)	94±3.42	95.6±4.14	90.3±2.62	8.23	0	0.00
Visit 2 (28.0-31.6 gestational week)	101.3±3.56	101.5±4.84	92.4±2.64	67.05	0	0.00
Visit 3 (32.0-35.6 gestational week)	105.5±3.97	106.28±4.63	95.2±2.52	87.05	0	0.00
Cervical consistency index (%)				**<65%**		0.00
Visit 1 (18.0-22.6 gestational week)	74.6±7.9	80.2±7.14	82.5±4.43	10.58	0	0.00
Visit 2 (28.0-31.6 gestational week)	72.7±8.58	79.5±7.34	81.2±9.05	16.47	0	0.00
Visit 3 (32.0-35.6 gestational week)	70.9±9.92	76.5±8.6	74.3±9.87	28.23	0	0.173

Sensitivity, specificity, predictive positive and negative value, as well as positive and negative likelihood ratios for the prediction of preterm birth before 37 gestational weeks, are given in Table 4.

Table 4. Predictive accuracy for preterm birth based on serial CL, ACA, and CCI measurements.

Parameter	Sn (IC 95%)	Sp (IC 95%)	PPV (IC 95%)	NPV (IC 95%)	LR+ (IC 95%)	LR- (IC 95%)
Cervical length	99%	61%	78%	97%	2.54	0.02
Anterior cervical angle	100%	29%	11%	100%	1.41	0.00
Cervical consistency index	73%	45%	16%	92%	1.32	0.6

Note: Sn: Sensitivity; Sp: Specificity; VPP: positive predictive value;
NPV: negative predictive value; LR+: positive likelihood ratio; LR-: negative likelihood ratio.

Cervical length <25mm, which is the cutoff commonly used in clinical practice, is highly significant in the prediction of preterm labor with a sensitivity of 99%, specificity of 61%, PPV 78%, NPV 97% and an LR+2.54, and LR-of 0.02.

Anterior cervical angle, despite low specificity and positive predictive value, may be significant in predicting the preterm birth with a sensitivity of 100%, NPV of 100%, an LR+of 1.41, and LR-of 0.00, especially in correlation with cervical length.

Cervical consistency index also remains, despite low specificity and positive predictive values, a potential predictive parameter in the prediction of preterm birth, with a sensitivity of 73%, NPV of 92% and an LR+1.32 and LR-of 0.6 also correlated with CL, CCI being more difficult to interpret as an independent predictive parameter.

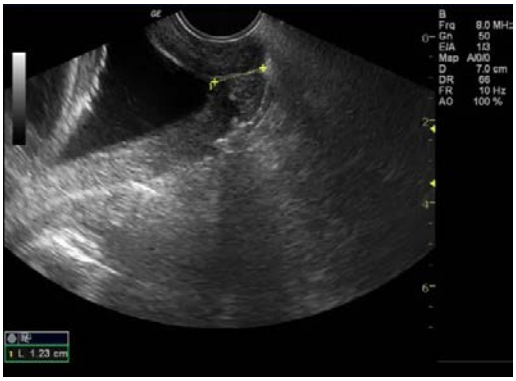

Figure 2. Pregnancy at 29.1 gestational weeks. CL=12.3mm, funneling.

Figure 3. Pregnancy at 30.6 gestational weeks. CL=16.3mm, funneling.

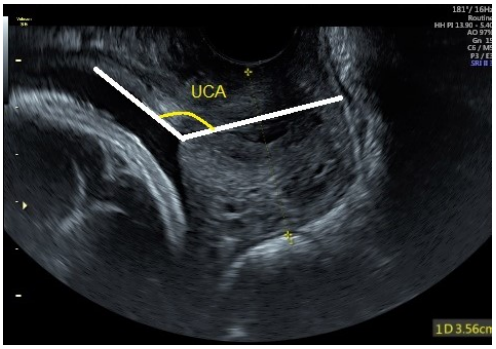

Figure 4. The anterior uterocervical angle at 27.6 gestational weeks.

Figure 5. Pregnancy at 28.3 gestational weeks. AP' 19.6mm; CCI=57.8%.

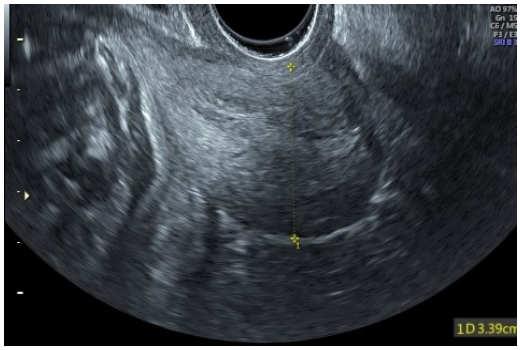

Figure 6. Pregnancy at 28.3 gestational weeks. AP 33.9mm.

Discussion

Premature birth is an important problem for modern obstetrics because it is a major cause of increased neonatal mortality and morbidity, and the installation of long-term neurological and systemic problems.

The etiology of preterm birth is not yet fully clarified, so the identification of risk factors as well as the establishment of the risk of premature birth has great importance for establishing correct obstetrical management [13].

The evaluation of the measurement of the length of the cervix is used to identify pregnant women at risk of premature birth, this measurement being a tool for predicting it.

In clinical practice, a cervical length of 25mm has been chosen as a "cut-off" for establishing a normal cervix or a shortened cervix when the value falls below 25mm [14,15].

A large study conducted by Thain et al. in 2020 showed that in the 2nd and 3rd trimesters of pregnancy there is a shortening of the length of the cervix in patients who gave birth prematurely [16].

In our study, in agreement with other studies [17-19], the average value resulting from the three measurements showed that there is a significant difference between CL and premature birth, the p-value of the Student test <0.05.

Also, cervical length <25mm (Figure 2, 3), is highly significant in prediction of preterm labor with sensitivity 99%, specificity 61%, PPV 78%, NPV 97% and a LR+of 2.54 and LR-of 0.02.

Along with cervical length, which is the standard for women with threatened preterm birth, anterior cervical angle measurement can be considered as an additional predictor of premature birth risk, as shown by Daskalakis et al. in their study [20].

But there is a weak database on the use of this parameter in the management of threatened preterm labor [21,22].

In the study performed, the mean anterior cervical angle (Figure 4) between the group with premature birth and the one with term birth showed the same significant difference, the p-value of the Student test <0.05 (preterm lot 101.43°±3.95 vs. term lot 92.73°±2.48), mean ACA at the three visits showing a significant difference (p-Anova <0.05).

Anterior cervical angle, despite low specificity and positive predictive value, may be significant in predicting preterm birth with a sensitivity of 100%, NPV of 100%, a LR+of 1.41, and LR-of 0.00, especially in correlation with cervical length.

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These results are consistent with other studies [20-22] which demonstrated the efficacy of ACA in predicting preterm birth.

Another additional ultrasound marker, the cervical consistency index (Figure 5,6), described by Parra-Saavedra et al. in 2011 [6], would allow early identification of women at high risk of premature birth [12,23,24].

The problem of the force with which cervical compression is performed was raised, but an experimental study showed that a variation of the compression force does not cause a significant variation in the results in a real clinical setting [25].

Parra-Saavedra et al. [6] found an optimal cut-off for predicting premature birth <37 weeks at 10 percentiles, which corresponds to a CCI of 46-54% at 19-24 weeks.

In the performed study we used the value of 65% as the limit with the normal value, as used by other authors, in the case of CCI, only the measurement performed at visit 3 (32.0-35.6 gestational week) did not show a statistically significant difference with the risk of premature birth.

Cervical consistency index also remains, despite low specificity and positive predictive values, a potential predictive parameter in prediction of preterm birth, with a sensitivity of 73%, NPV of 92%, an LR+of 1.32, and LR-of 0.6 also correlated with CL.

These results could be in contradiction with other studies [24,26] which show that the CCI index could be superior to cervical length measurements but in agreement with other studies [12,27], which show that it still, CL remains the standard ultrasound marker for detecting the risk of premature birth.

Conclusions

All three ultrasound markers can be used to predict premature birth, but the recommendation would be to combine ACA and CCI with CL measurement, thus significantly increasing the prediction rate.

Conflict of interests

None to declare.

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