

ORIGINAL PAPER

ARTÍCULO ORIGINAL

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Prognostic utility of cervical length and uterine artery pulsatility index for imminent preterm delivery in symptomatic patients

Utilidad pronóstica de la longitud cervical e índice de pulsatilidad de la arteria uterina en el parto pretérmino inminente en pacientes sintomáticas

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ABSTRACT

Objective: To establish the prognostic usefulness of cervical length and uterine artery pulsatility index for imminent preterm delivery in symptomatic patients. **Design:** Case-control study. **Setting:** Central Hospital "Dr. Urquinaona", Maracaibo, Venezuela. **Participants:** Patients with preterm delivery within 7 days (group A) and pregnant women with preterm delivery within more than 7 days (group B). **Methods:** Cervical length and uterine artery pulsatility index were determined at hospital admission and all were followed until delivery. **Main outcome measures:** General characteristics, cervical length, uterine artery pulsatility index, imminent preterm delivery, and prognostic efficacy. **Results:** 119 participants were assigned to group A and 362 patients to group B. Cervical length was lower in group A, and the uterine artery pulsatility index was higher compared with group B ($p < 0.0001$). Cervical length showed an area under the curve of 0.972, while the uterine artery pulsatility index presented an area under the curve of 0.843. The difference between the two measurements was significantly different between groups A and B ($p < 0.001$). Combination of both measurements showed a significantly lower value in prediction capacity (0.987) compared with both measurements individually ($p < 0.0001$). **Conclusion:** The combined use of cervical length and pulsatility index of the uterine artery was useful in the prediction of imminent preterm delivery in symptomatic patients. **Key words:** Cervical length, Pulsatility index, Uterine artery, Preterm delivery, Prediction.

RESUMEN

Objetivo. Establecer la utilidad pronóstica de la longitud cervical e índice de pulsatilidad de la arteria uterina en el parto pretérmino inminente en pacientes sintomáticas. **Diseño.** Estudio de casos-contróles. **Institución.** Hospital Central "Dr. Urquinaona", Maracaibo, Venezuela. **Participantes.** Pacientes con parto pretérmino en los siguientes 7 días (grupo A) y embarazadas con parto pretérmino más allá de los 7 días (grupo B). **Métodos.** Las mediciones de la longitud cervical e índice de pulsatilidad de la arteria uterina se realizaron al ingreso de las gestantes al hospital y todas fueron seguidas hasta el parto. **Principales medidas de resultado.** Características generales, longitud cervical, índice de pulsatilidad de la arteria uterina, parto pretérmino inminente y eficacia pronóstica. **Resultados.** 119 participantes fueron asignadas al grupo A y 362 pacientes al grupo B. La longitud cervical fue menor en el grupo A, mientras que el índice de pulsatilidad de la arteria uterina fue mayor comparado con el grupo B ($p < 0,0001$). La medición de la longitud cervical presentó un valor de área bajo la curva de 0,972, mientras que el índice de pulsatilidad de la arteria uterina mostró un área bajo la curva de 0,843. La diferencia de la diferencia entre ambas mediciones se consideró estadísticamente significativa ($p < 0,001$). La combinación de ambas mediciones tuvo un valor bajo la curva significativamente superior en capacidad de predicción (0,987) comparada con ambas mediciones en forma individual ($p < 0,0001$). **Conclusión.** El uso combinado de las mediciones de la longitud cervical y el índice de pulsatilidad de la arteria uterina resultó útil en la predicción de parto pretérmino inminente en pacientes sintomáticas. **Palabras clave.** Longitud cervical, Índice de pulsatilidad, Arteria uterina, Parto pretérmino, predicción.



INTRODUCTION

Preterm delivery (PD) is an obstetric problem and an important cause of perinatal morbimortality⁽¹⁾. Threatened preterm delivery is often treated with tocolytics to delay delivery and to improve perinatal outcomes⁽²⁾. Various studies have shown that this treatment is associated with pregnancy prolongation, but not with reducing perinatal complications^(3,4).

A meta-analysis showed that the incidence of imminent preterm delivery (during the following seven days) varies from 2% to 29%⁽⁵⁾ and that the ability to forecast it is limited. One of the challenges in the management of threatened preterm delivery is identifying the at-risk group of pregnant women. If we could recognize this group in a precise manner, interventions like hospitalization, tocolysis and corticosteroid administration could be used more efficiently.

There are prediction models that consider demographic and clinical factors at the time of evaluation⁽⁶⁻⁸⁾. The combination of cervical length (CL), maternal characteristics and obstetric history has proven to be useful for predicting⁽⁹⁾. However, these models lack enough sensitivity to be implemented. Furthermore, access to biochemical markers is not always possible⁽¹⁰⁾. Therefore, there is a need for strategies to identify the group at high risk of imminent preterm delivery.

A uterine artery Doppler study is efficient to detect conditions related to placental insufficiency. There is evidence that the altered remodeling of uteroplacental arteries might be associated to preterm delivery^(11,12). An increase in the uterine artery pulsatility index (IP-AUt) during the second pregnancy trimester has been associated with a higher risk for preterm delivery^(13,14). Similarly, there is an increase in the intraplacental vascular impedance associated to PD in *in vitro* pregnancies⁽¹⁵⁾. However, two studies did not confirm this association^(16,17). Consequently, it is unknown if measuring the IP-AUt could contribute to predicting imminent PD.

The objective of this study was to establish the prognostic utility of cervical length and the uterine artery pulsatility index for imminent preterm delivery in symptomatic patients.

METHODS

This was a case-control study performed at the Central Hospital "Dr. Urquinaona", Maracaibo, Venezuela, from June 2014 to March 2018. We evaluated women with single pregnancies with a gestational age between 24 and 35 weeks who had been diagnosed with threatened preterm delivery, presenting up to three uterine contractions in 30 minutes, a cervical dilatation of up to 3 cm and a cervix effaced to 80% or less, with intact membranes. The study was approved by the ethical review boards of the Medical Faculty of the University of Zulia and of the hospital. Written informed consent was obtained from each participant upon selection.

We excluded patients with the following conditions: multiple pregnancies, history of use of progesterone or any other tocolytic during the present pregnancy, cervical insufficiency diagnosis or history of cervical cerclage, premature membrane rupture or amniotic fluid alterations, uterine anomalies, abnormal placentation, history of maternal cardiac pathologies, active inflammatory or infectious disease, hypertension and pre-gestational or gestational diabetes, intrauterine growth restriction, congenital fetal anomalies, acute chorioamnionitis and unknown gestational age. We also excluded from the study the patients who declined to participate.

In the hour following admission, and before starting any treatment, the participants underwent speculoscopy, and the fern and Nitrazine tests to rule out membrane rupture. Immediately after this, we performed a digital exam to evaluate cervical dilatation, consistency and position, followed by a fetal ultrasound evaluation to determine the placental insertion site, fetal head and abdominal circumferences, femur length and amniotic fluid index. Fetal cardiac frequency and uterine contractions were monitored by external tocodynamometry.

The evaluation of cervical length by transvaginal ultrasound was performed with the Voluson® V730 Expert (GE Healthcare, USA). Patients were placed in dorsal lithotomy position with an empty bladder, and the 7,5 MHz transducer was positioned in the anterior vaginal fornix. Measure-



ments were made orienting the transducer to show the external and internal cervical os in the same sagittal plane, with both labia, posterior and anterior, of equal width. After the image was amplified, cervical length was measured as a straight line between the electronic markers, identified by the cervical canal's sonolucency. If the endocervical canal was too curved, we measured two portions and added them up. We obtained three images and used the one that showed the shortest length.

We obtained the transabdominal measurement of the IP-AUt with a 7,5 MHz transducer, at the optimal setting for Doppler gain. Iliac and uterine arteries were identified by visualizing the color Doppler flow, establishing the flow waveforms and velocimetry of both uterine arteries with an insonation angle below 25° ⁽¹⁶⁾. After identification, we used pulsed wave Doppler with a sampling window of 2 mm to show the vessel, with an insonation angle below 30° , one centimeter distal to the crossing point and a maximum systolic velocity of 30 to 50 cm/second for selective identification. When we obtained three similar consecutive waveforms with a diastolic notch, we measured the IP-AUt, calculating the average of both uterine arteries. For the cases with lateral placenta, we chose the ipsilateral IP-AUt value to represent the uteroplacental circulation better. In cases with central placenta, we picked the lowest index for representation⁽¹⁸⁾.

Participants were indicated rest in left lateral decubitus position and hydration with 500 mL of Ringer solution. If we observed cervical changes or if contractions persisted two hours after treatment, the patients were hospitalized and started tocolytic therapy with nifedipine. During hospitalization, we administered intramuscular betamethasone to induce fetal lung maturity. Tocolytics were suspended 48 hours after the first corticosteroids dose. We did not use tocolytics nor corticosteroids in pregnancies past week 34.

The main study variable was the frequency of imminent delivery (within seven days after evaluation). All data were stored for subsequent analysis and were not available during hospitalization.

Data are presented as absolute and relative values. Qualitative variables were analyzed using the chi-square test. Quantitative variables with a normal distribution were compared with Student's t-test.

Variables with a non-normal distribution were compared with the Wilcoxon-Rank test. We used a Receiver Operating Characteristic curve to determine the best cut-off point and evaluate the diagnostic precision of cervical length, IP-AUt and the combination of both for predicting imminent preterm delivery. We used Hanley and McNeil's methodology to compare the difference in the tests' areas under the curve. We also calculated the prognostic parameters with a 95% confidence interval. The statistical significance level was $p < 0,05$. All analyses were performed with the statistical package SPSS® version 22.0 (SPSS Inc, USA).

RESULTS

For the study, we selected 518 patients, of which we excluded 21 because they had premature membrane rupture, five because of preeclampsia and one because of uterine anomalies diagnosed during follow-up. Ten patients were excluded due to incomplete data. For the final analysis, we selected 481 pregnant women, of which 119 (24.8%) delivered prematurely in the seven days following the evaluation (group A) and 362 patients (75.2%) who gave birth after seven days (group B).

The groups' characteristics are shown in table 1. The frequency of history of preterm delivery and genital bleeding were significantly higher in the patients in group A compared to the patients in group B ($p < 0.05$). The interval between evaluation and delivery was 4.3 ± 1.6 days in group A and 56.3 ± 27.2 days in group B ($p < 0.0001$). We did not find significant differences in the rest of general characteristics ($p = ns$).

The average value of cervical length in group A was 18.4 ± 5.9 mm, and it was 34.3 ± 5.6 mm in group B (figure 1). Meanwhile, the IP-AUt values were 2.24 ± 0.51 and 1.57 ± 0.36 for the patients in groups A and B, respectively (figure 2). These differences were significant ($p < 0.0001$).

In figure 3, we show the receiver operating characteristic curve for cervical length, IP-AUt and the combination of both measurements. Cervical length (CL) presented an area under the curve of 0.972 (95% confidence interval (CI) 0.772 to 1.000), while the area under the curve of IP-AUt was 0.843 (95% CI 0.801 to 0.885). The difference between both was considered significant ($p < 0.001$). Nevertheless, the combination



TABLE 1. GENERAL CHARACTERISTICS OF PATIENTS STUDIED.

n (%)	Group A. Delivery within 7 days (n = 113)	Group B. Delivery after 7 days (n = 362)	p
Maternal age, in years	28.5 +/- 5.7	29.4 +/- 7.1	0.2196
Nulliparity, n (%)	62 (54.8)	213 (58.8)	0.8274
History of preterm delivery, n (%)	27 (23.9)	50 (13.8)	0.0186
History of smoking before delivery, n (%)	19 (16.8)	54 (14.9)	0.6545
Body mass index, kg/m ²	27.4 +/- 6.4	28.4 +/- 5.0	0.0843
Gestational age at admission, in weeks	29.1 +/- 2.7	29.5 +/- 3.1	0.2181
Interval between admission and delivery, in days	4.3 +/- 1.6	56.3 +/- 27.7	0.0001
Genital bleeding, n (%)	65 (57.5)	146 (40.3)	0.0016
Use of corticosteroids, n (%)	67 (59.3)	195 (53.1)	0.3309
Birth weight, in grams	1 900 +/- 844	2 627 +/- 773	0.0001

FIGURE 1. CERVICAL LENGTH VALUES OBTAINED BY ULTRASOUND IN EACH OF THE GROUPS (X AXIS: GROUP A, GROUP B; Y AXIS: CERVICAL LENGTH, IN MILLIMETERS).

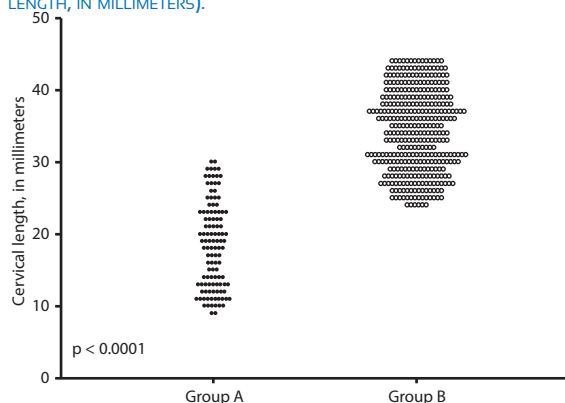
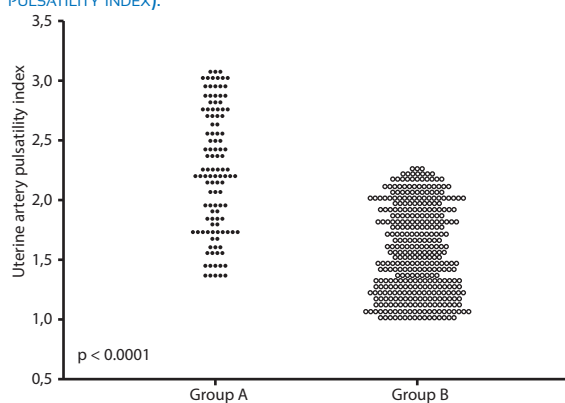
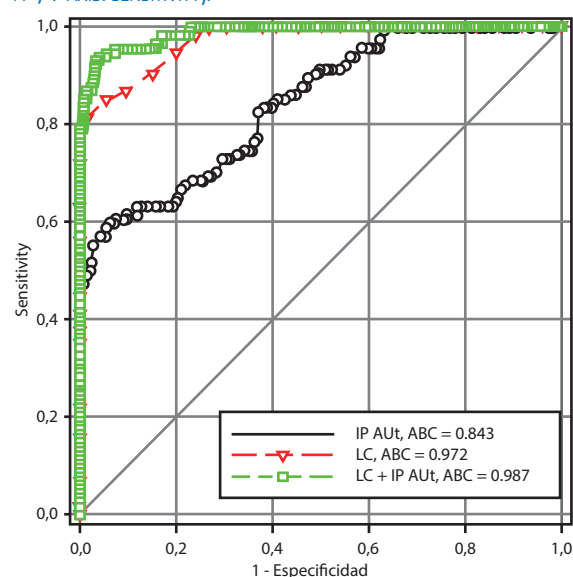


FIGURE 2. VALUES OF THE UTERINE ARTERY PULSATILITY INDEX IN EACH OF THE GROUPS (X AXIS: GROUP A, GROUP B; Y AXIS: UTERINE ARTERY PULSATILITY INDEX).



of measurements with the formula $X = (9.982671 + ((3.464345 * IP-AUt) - (0.661065 * CL)))$ had a significantly superior value (0.987; 95% CI 0.979 a 0.995) compared with IP-AUt and cervical length ($p < 0,0001$) individually. The rest of predictive values for imminent preterm delivery are shown in table 2.

FIGURE 3. RECEIVER OPERATING CHARACTERISTIC CURVE FOR CERVICAL LENGTH, UTERINE ARTERY PULSATILITY INDEX AND THEIR COMBINATION, FOR PREDICTING IMMINENT PRETERM DELIVERY (X AXIS: "1 – SPECIFICITY"; Y AXIS: SENSITIVITY).



DISCUSSION

Our results show that cervical length is superior to IP-AUt for predicting imminent preterm delivery. Nevertheless, the combination of both measurements presents significant differences and a superior discriminating capacity, compared with the individual measurements. This suggests that they can be useful for predicting imminent preterm delivery, contributing to a timely treatment for this high-risk group.

Preterm delivery is a global health problem. Research in useful prediction models may reduce health care costs and perinatal complications. Cervical length is a sensitive and simple method to predict the risk for PD⁽¹⁹⁾. While a short CL is



TABLE 2. PREDICTIVE VALUES OF CERVICAL LENGTH AND UTERINE ARTERY PULSATILITY INDEX FOR IMMINENT PRETERM DELIVERY .

Variable	Área under the curve	Cut-off value	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Prognostic precision	Likelihood ratio for a positive result	Likelihood ratio for a negative result
Cervical length	0.972 (0.772 - 1.000)	24	81.6 (73.5 - 87.6)	98.3 (96.4 - 99.2)	93.9 (87.4 - 97.2)	94.4 (91.6 - 96.3)	94.3 (91.9 - 96.1)	49.08 (22.09 - 109.05)	0.19 (0.13 - 0.18)
Uterine artery pulsatility index	0.843 (0.801 - 0.885)	2.1	59.6 (50.5 - 68.2)	94.2 (91.3 - 96.2)	76.4 (66.6 - 84.0)	88.1 (84.5 - 90.9)	85.9 (82.5 - 88.7)	10.25 (6.59 - 15.95)	0.43 (0.34 - 0.54)
Cervical length + uterine artery pulsatility index	0.987 (0.979 - 0.995)	--	93.9 (87.9 - 97.0)	95.8 (93.3 - 97.5)	87.7 (80.7 - 92.4)	98.0 (96.0 - 99.0)	95.4 (93.1 - 96.9)	22.59 (13.73 - 37.16)	0.06 (0.03 - 0.13)

associated with a higher risk for PD, its application potential to identify which pregnant women with uterine contractions will present imminent preterm delivery is limited⁽²⁰⁾.

The cut-off value for CL that predicts imminent PD in our study was 24 mm. Previous studies have evaluated its utility in patients with threatened PD. The first showed that patients with PD had on average a shorter CL compared with those who delivered at term⁽²¹⁾. Another study in symptomatic patients receiving tocolytic treatment found that this was successful in patients with an average CL of 27 mm⁽²²⁾. It has also been observed that over half of patients with deliveries in the following 28 days have a CL below 20 mm, while only 7% of those who give birth after 28 days present such values⁽²³⁾. Finally, another study showed that a CL under 20 mm presented in over two thirds of the cases with preterm delivery, but only in 21% of the patients who delivered at term⁽²⁴⁾. Nevertheless, CL is not always associated to PD, and it is not useful for distinguishing between high and low-risk groups. This is supported by the lack of correlation between CL and time of delivery, even after adjusting for confounding factors⁽²⁵⁾.

The possible relationship between placental insufficiency and PD is endorsed by studies that show less remodeling of uteroplacental arteries in samples obtained from women who delivered prematurely⁽¹²⁾. It has been also described that IP-AUt is highest in patients who deliver before week 33⁽¹⁴⁾. These findings support our present results, where patients with imminent PD presented higher IP-AUt values. However, a previous study did not find differences between patients who delivered prematurely and at term⁽¹⁶⁾.

Our study's findings suggest that IP-AUt increases the predictive performance of CL, so it can be used alone or combined with CL to aid in the prediction of imminent PD in symptomatic patients

with intact membranes. These measurements detect different components of PD, so the IP-AUt would allow to identify high-risk groups that present minimal changes in CL^(18,23).

Olgan et al.⁽¹⁸⁾ performed the only previous study that evaluated the combination of CL and IP-AUt for predicting PD. Their research showed that both individual measurements were useful for predicting imminent PD (area under the curve of 0.83 for CL and 0.72 for IP-AUt). Findings suggest that both measurements combined help to identify the group of patients at a higher risk for PD, regardless of whether they have received tocolytics or not. In this study, the area under the curve of CL increased when combined with IP-AUt, improving its prediction capacity for imminent PD. This improvement in its discriminating capacity might be because women with PD conform a heterogeneous group regarding underlying pathogenic mechanisms and the combination may facilitate their identification.

The advantage of this evaluation is that it obtains non-invasive measurements with fast, objective and quantitative results that are easy to interpret. However, in cases of placental insufficiency, the IP-AUt might be elevated since the increase in intrauterine pressure may affect the uterine blood flow^(13,18).

This study has several strengths. Participants were followed until delivery. The treating physicians did not know the results of the ultrasound and Doppler evaluations, which limited possible biases.

On the other hand, some selected patients had an imminent PD, which could have also decreased the possibility of errors in the analysis. The study also has weaknesses, such as a lack of inter-observer variability analysis in the measurements. This research took place in a single center with a homogeneous population, which may hinder the generalization of our results.



In conclusion, the combined use of CL and IP-AUT is useful for predicting imminent preterm delivery in symptomatic patients. The combination of both tests increases the discriminating capacity, compared with both measurements individually.

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