Cervical vascularization indices in the prediction of imminent preterm labor
Índices de vascularización cervical en la predicción de parto pretérmino inminente

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ABSTRACT
Objective: To establish the usefulness of cervical vascularization indices in the prediction of impending preterm labor. Design: Case-control study. Institution: “Dr. Urquinaona” Central Hospital, Maracaibo, Venezuela. Participants: Patients with preterm delivery within 7 days (group A) and pregnant women with preterm delivery beyond 7 days (group B). Methods: Pregnant women were evaluated using transvaginal ultrasound and followed until delivery. Main outcome measures: General characteristics, cervical vascularity indices (vascularity index, flow index and vascularity / flow index), impending preterm delivery, and prognostic efficacy. Results: A total of 350 patients were included, 75 women presented imminent preterm labor (group A) and 251 patients were considered as controls (group B). Patients in group A had significantly lower values of vascularization index and flow index compared to group B (p = 0.0122 and p < 0.0001, respectively). Patients in group B had significantly higher values of vascularization / flow index compared to patients in group A (p = 0.0103). The three indices and the combination of these did not show the ability to discriminate imminent preterm labor. Conclusions: Patients with imminent preterm labor showed significant differences in the vascularization indices compared to patients presenting preterm labor beyond 7 days of ultrasound evaluation. However, they are not useful in predicting impending preterm labor.

Key words: Cervix uteri, blood flow, Cervical vascularization indexes; Obstetric labor, prematurity, prediction

INTRODUCTION

Preterm delivery is the leading cause of perinatal morbidity, affecting between 7% and 11% of all pregnancies. It is also responsible for more than half of the incidence of neonatal mortality. Identification of risk factors and prevention of prematurity are important areas of research in obstetrics. However, despite improvements in diagnosis and treatment, the prevalence has not decreased in the last two decades.
Both uterine contractions and cervical changes precede the development of preterm labor. Different studies have attempted to identify early the different cervical changes as predictors\(^{(6-7)}\). Cervical ultrasonography is a reliable and objective way of cervical evaluation and ultrasonographic measurement of cervical length has proven to be a useful screening test and is becoming a routine evaluation in the care of pregnant women at high risk for obstetric complications\(^{(6-9)}\). However, despite its high clinical predictive value, it has low sensitivity\(^{(7,10)}\). Therefore, it is necessary to investigate other cervical parameters with better predictive capabilities.

Three-dimensional ultrasound has the potential to provide more accurate measurements than conventional two-dimensional ultrasound and combined with power Doppler can provide angiography-like information on cervical vascular architecture\(^{(11)}\). This imaging technique allows evaluation of both blood flow and vascularization by calculating vascular indices using the program VOCAL (Virtual Organ Computer-Aided Analysis), which has been used in different studies in obstetrics\(^{(12-14)}\). However, there is limited research evaluating the cervix during pregnancy with this type of technique\(^{(15,16)}\). Although a previous study showed that cervical vascular indices remained stable throughout normal pregnancy\(^{(16)}\), there is little information on the potential changes of these parameters in determining the risk of imminent preterm delivery in high-risk patients.

The aim of this study was to establish the usefulness of cervical vascularization indices in the prediction of impending preterm delivery.

**Methods**

This was a prospective study conducted at the Hospital Central "Dr. Urquinaona", Maracaibo, Venezuela, from June 2014 to October 2021. For this purpose, women with singleton pregnancies between 24 and 35 weeks determined by ultrasound at the beginning of the second trimester, with clinical diagnosis of threatened preterm labor, with up to 3 uterine contractions in 30 minutes, cervical dilatation less than 3 centimeters by physical examination, effacement less than 80% and intact membranes were consecutively selected and evaluated. The study was approved by the institutional review board of La Universidad del Zulia and the Ethics Committee of the hospital. Written informed consent was obtained at the time of selection of each participant for the study.

Exclusion criteria were: multiple pregnancies, history of progesterone or any other tocolytic use in the current pregnancy, known cervical insufficiency or history of cerclage, premature rupture of membranes, uterine anomalies, abnormal placentation, maternal cardiac alterations, active inflammatory or infectious disease, hypertension and pregestational or gestational diabetes, intrauterine growth restriction of the fetus, congenital fetal anomalies, alterations in amniotic fluid volume, acute chorioamnionitis and unknown gestational age. Patients who refused to participate were also excluded from the study.

Within one hour of hospital admission and prior to the start of any treatment, participants underwent examination of the cervix with a sterile speculum, performing the fern and nitrazine paper tests to rule out rupture of membranes. Immediately afterwards, a digital examination was performed by the on-call staff and confirmed by one of three investigators after this evaluation, to define dilatation, maturation, consistency and position of the cervix, in addition to fetal wedging for calculating Bishop’s score. They then underwent transabdominal fetal ultrasound evaluation to determine fetal presentation, placental insertion site, measurement of fetal head and abdominal circumference, femur length and amniotic fluid index. Subsequently, continuous fetal heart rate monitoring and observation of the characteristics of uterine contractions by external tocodynamometry were initiated.

Cervical three-dimensional scanning was performed with the Voluson 730 Expert ultrasound machine (Diamond II, GE Medical Systems, Milwaukee, WI, USA) equipped with 5 to 9 MHz three-dimensional transvaginal transducer. A pillow was placed under the pregnant woman’s buttocks to prevent rectal gas from obscuring the outer cervix. For the evaluation of cervical vascularity, the power Doppler settings in the evaluations were: frequency 3 to 9 MHz, gain -5.0, pulse repetition frequency 0.6 KHz and motion filter ‘below 1’. After drawing the cervical
contours while the view was rotated by 30° automatically to minimize post-processing time, 6 cervical contours were obtained (Figure 1). The cervical image was magnified to occupy more than 70% of the screen size. The VOCAL program calculated the vascularization index (VI), flow index (FI) and vascularization/flow index (VFI). The IV reflects the density of the blood vessels, the IF the energy reflected by the blood corpuscles within the vessels, and the IVF, the density of the blood vessels and the number of blood corpuscles flowing in the vessels.

All ultrasound measurements were performed by a single specialist in maternal-fetal medicine who was part of the research team and who was not involved in the clinical care of the participants. The duration of the evaluation was less than 10 minutes in all cases and the members of the hospital team performing the care were unaware of the results. Therefore, the ultrasound measurements did not influence the management of the participants.

Initially, all selected pregnant women were admitted for treatment with bed rest in left lateral decubitus and hydrated with 500 mL of lactated Ringer's solution. If progressive cervical changes were documented or contractions persisted for at least 2 hours after treatment, they were hospitalized and tocolytic treatment was initiated, with calcium channel blockers as first-line therapy. During hospitalization, two 12-mg doses of intramuscular betamethasone were administered at 24-hour intervals to induce fetal lung maturation. Tocolytics were discontinued 48 hours after the first steroid dose. Neither tocolytics nor steroids were used in pregnancies older than 35 weeks.

A form was prepared that included the following data: identification number, maternal age, gestational age at the time of examination, parity, presence of bleeding, history of preterm delivery, digital cervical examination with determination of dilation and effacement, station and consistency and cervical position and cervical vascularization values. The main study variable was the frequency of imminent delivery (that occurred within 7 days of the evaluation). Data on birth weight and time interval between the evaluation and delivery were also included. All data were recorded and stored for subsequent analysis.

Data distribution was evaluated according to the Shapiro-Wilk normality test. Categorical variables were analyzed using the chi-square test or Mann-Whitney U test. Continuous variables with normal distribution were compared with Student's t test. Those variables with non-normal distribution were compared with the Wilcoxon rank sum test. Operator-receptor curves were used to determine the best cutoff point and to evaluate the diagnostic accuracy of vascularization indices in predicting preterm delivery within 7 days of evaluation. Sensitivity, specificity, negative predictive value, positive predictive value, and positive and negative likelihood ratios with their 95% confidence intervals in the prediction of impending preterm delivery were calculated for the optimal cutoff based on the response operator curve (ROC). The optimal cutoff was that corresponding to the point on the curve furthest from the reference line. The alpha level of statistical significance was \( p < 0.05 \). All analyses were performed with the SPSS® version 22.0 statistical package (SPSS Inc., USA).

**Results**

A total of 350 patients with symptomatic preterm labor were consecutively selected, of which 26 were excluded from the investigation (10 patients were diagnosed with hemorrhage in the second half of pregnancy, 7 women had premature rupture of membranes, 5 cases were diagnosed with preeclampsia and 4 patients had incomplete data during the evaluation). Therefore, for the final analysis, data from 326 patients were analyzed, of which 75 cases (23.0%) had imminent preterm labor (group A) and 251 patients (77.0%) delivered after 7 days (group B).
Table 1 shows the general characteristics of the patients in each study group. Patients in both groups had no significant differences in maternal age, nulliparity, history of smoking before pregnancy, body mass index, gestational age at evaluation, frequency of genital bleeding, and corticosteroid use ($p = ns$). Patients in group A had a shorter interval between ultrasound evaluation and delivery compared to patients in group B (4.1 +/- 1.5 days compared to 63.1 +/- 27.7 days, $p < 0.0001$). Significant differences were also found in newborn birth weight ($p < 0.0001$).

Regarding vascularization indices (Table 2), patients in group A showed significantly lower values of VI and FI compared to group B ($p = 0.0122$ and $p < 0.0001$, respectively). Patients in group B had significantly higher values of VFI compared to patients in group A ($p = 0.0103$). Differences in assessed values between groups showed no differences after adjusting for maternal age, body mass index and gestational age at the time of evaluation ($p = ns$).

Table 3 and Figure 2 show the prognostic ability measurements of the different cervical vascularization indices in the prediction of impending labor in symptomatic patients. The VI (area under the curve 0.595, 95% confidence interval, 0.510 to 0.679), FI (area under the curve 0.652, confidence interval 0.551 to 0.753), VFI (area under the curve 0.401 (0.329 to 0.474) and the combination of the three indices (area under the curve 0.621, 95% confidence interval 0.527 to 0.716) did not show discriminatory capacity for imminent preterm delivery by presenting a value below the cutoff value of 0.750 ($p = ns$).

**Table 1. General characteristics of the study groups.**

<table>
<thead>
<tr>
<th></th>
<th>Group A Delivery before 7 days (n = 75)</th>
<th>Group B Delivery after 7 days (n = 251)</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age, years</td>
<td>28.2 +/- 6.6</td>
<td>30.0 +/- 7.3</td>
<td>0.0565</td>
</tr>
<tr>
<td>Nulliparity, n (%)</td>
<td>51 (68.0)</td>
<td>177 (70.5)</td>
<td>0.0753</td>
</tr>
<tr>
<td>History of preterm</td>
<td>7 (9.3)</td>
<td>27 (10.7)</td>
<td>0.8318</td>
</tr>
<tr>
<td>preterm birth, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking before pregnancy, n (%)</td>
<td>13 (17.3)</td>
<td>47 (18.7)</td>
<td>0.0752</td>
</tr>
<tr>
<td>Body mass index, kg/m2</td>
<td>23.6 +/- 5.0</td>
<td>24.1 +/- 4.4</td>
<td>0.4037</td>
</tr>
<tr>
<td>Gestational age at the time of evaluation, weeks</td>
<td>30.5 +/- 2.7</td>
<td>30.0 +/- 2.9</td>
<td>0.1843</td>
</tr>
<tr>
<td>Interval between the evaluation and delivery, days</td>
<td>4.1 +/- 1.5</td>
<td>63.1 +/- 27.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Genital bleeding, n (%)</td>
<td>42 (56.0)</td>
<td>138 (54.9)</td>
<td>0.8955</td>
</tr>
<tr>
<td>Corticosteroid use, n (%)</td>
<td>47 (62.6)</td>
<td>163 (64.9)</td>
<td>0.7863</td>
</tr>
<tr>
<td>Newborn birth weight at birth, grams</td>
<td>1,853 +/- 815</td>
<td>2,654 +/- 759</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Table 2. Average values of vascularization indexes and cervical volume in each group.**

<table>
<thead>
<tr>
<th></th>
<th>Group A Delivery before 7 days (n = 75)</th>
<th>Group B Delivery after 7 days (n = 251)</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascularity index</td>
<td>14.1 +/- 2.7</td>
<td>15.1 +/- 3.1</td>
<td>0.0122</td>
</tr>
<tr>
<td>Flow index</td>
<td>30.4 +/- 1.5</td>
<td>31.5 +/- 2.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Vascularization / flow index rate</td>
<td>4.8 +/- 1.1</td>
<td>4.4 +/- 1.2</td>
<td>0.0103</td>
</tr>
</tbody>
</table>

Table 3 and Figure 2 show the prognostic ability measurements of the different cervical vascularization indices in the prediction of impending labor in symptomatic patients. The VI (area under the curve 0.595, 95% confidence interval, 0.510 to 0.679), FI (area under the curve 0.652, confidence interval 0.551 to 0.753), VFI (area under the curve 0.401 (0.329 to 0.474) and the combination of the three indices (area under the curve 0.621, 95% confidence interval 0.527 to 0.716) did not show discriminatory capacity for imminent preterm delivery by presenting a value below the cutoff value of 0.750 ($p = ns$).

**Discussion**

Several ultrasound techniques are currently available for evaluation of the characteristics of the pregnant cervix, including two-dimensional and three-dimensional ultrasound. However, ultrasound measurement of cervical length can predict the development of preterm labor, depending on the selected cutoff point, with sensitivity values between 68% and 100% and specificity values of 44% to 79%[18]. But, this technique has some limitations when used as the only screening test, due to its low sensitivity and low positive predictive value[19]. Therefore, it is very useful to have new cervical characteris-
butions throughout normal pregnancy and their values do not show changes related to gestational age\textsuperscript{(16)}. In contrast to the results of this investigation, a previous study evaluated the vascularization values in patients with preterm delivery and found that the values were similar to those of patients who delivered at term\textsuperscript{(22)}. The authors proposed that this could be due to methodological deficiencies of the study or perhaps that the method only could detect significant changes in vascularization\textsuperscript{(20)}. However, another study showed increased vascularization and blood flow intensity in asymptomatic women with short neck in response to increased vessel number, flow volume and/or erythrocyte density. In addition, the FI was higher in asymptomatic women\textsuperscript{(23)}. These results indicate that cervical vascularization and blood flow change in preparation for delivery.

The possible explanation for the findings of this research is that cervical changes produce alterations in the density of small cervical vessels, characterized by changes in their quantity accompanied by a decrease in red blood cells and backscatter energy. On the other hand, FI is not an perfusion indicator and does not provide information on the volume of blood passing through the vessel in a given period, making it less reliable than VI and VFI\textsuperscript{(24)}. Although the results of this research suggest that cervical vascularity is somewhat related to cervical ripening in preterm pregnancies, this is a complex method that does not provide substantial benefits to simpler evaluations such as Bishop’s score or cervical length alone.

Since the process of cervical modification leading to delivery may be affected by different factors related to cervical morphology, additional measurements may be useful to improve the accuracy of screening for preterm delivery\textsuperscript{(25,26)}. However, multiparity, previous cervical surgical procedures, or infection may result in alterations of cervical morphologic characteristics\textsuperscript{(27)}. Similarly, factors that are likely to affect the results of three-dimensional power Doppler indices are: pressure exerted by the transducer on the cervical tissue during evaluation, uterine contractions that have effects on blood flow velocity, and physiological changes in cervical blood circulation during scanning\textsuperscript{(28,29)}. In addition, there are other important technical factors, such as the angle of insonation of the ultrasound waves. Although power Doppler ultrasound is independent of the insonation angle,
this is not entirely true. The ultrasound beam incident on the bloodstream at a 90° angle will not generate any evidence of a Doppler wave\(^\text{10}\). Therefore, small changes in transducer position may produce differences in cervical flow power signals. In addition, there may be difficulties in defining the boundaries of the cervix, the lower uterine segment and the vagina. These difficulties have been described by other investigators who evaluated the cervix by three-dimensional ultrasound\(^\text{11}\).

This study has several strengths. It is the investigation with the largest number of patients with a diagnosis of preterm labor known to date using this imaging technology and included symptomatic pregnant women at high risk of imminent labor.

Limitations include that the VOCAL evaluation technique used in this study can be difficult to apply due to technical requirements, which can lead to inaccurate calculations, thus requiring staff training and high-resolution equipment. Another drawback of the use of this ultrasound technique is its high cost and limited availability in non-specialized care centers. Finally, the lack of standardization may hinder the correct extrapolation of the results to other at-risk populations.

In conclusion, patients with imminent preterm labor present significant differences in vascularization indices compared to patients with preterm labor beyond 7 days of ultrasound evaluation. However, they are not useful in predicting imminent preterm labor.

REFERENCES


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