Doppler Study of the Fetal Vertebral Artery in Small for Gestational Age Fetuses With Intrauterine Growth Restriction

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Objectives—The purposes of this study were to evaluate the Doppler resistive index of the fetal vertebral artery in small for gestational age (SGA) fetuses and to examine the ability of the vertebral artery resistive index in the diagnosis of intrauterine growth restriction (IUGR).

Methods—A total of 437 Doppler examinations of the vertebral and umbilical artery resistive indices were performed in 437 fetuses between 26 and 41 weeks’ gestation. According to birth weight, fetuses were classified into 5 groups: 1, above the 10th percentile; 2, between the 10th and 5th percentiles; 3, between the 5th and 3rd percentiles; 4, below the 3rd percentile; and 5, below the 3rd percentile with an umbilical artery resistive index above the 95th percentile. Subsequently, vertebral artery resistive index values were converted into multiples of the median, and box and whisker charts were generated to evaluate differences. Finally, receiver operating characteristic curves were calculated to assess the accuracy of the vertebral artery resistive index for predicting IUGR and a low Apgar score.

Results—Compared to normally grown fetuses, vertebral artery resistive index values were lower in fetuses with birth weight below the 3rd percentile, and this difference was greater in fetuses with birth weight below the 3rd percentile and Doppler anomalies of the umbilical artery. The receiver operating characteristic analysis showed that the vertebral artery resistive index diagnosed SGA fetuses and low Apgar scores poorly. However, it performed better in cases of severe IUGR with high umbilical artery resistive index values.

Conclusions—Preliminary data show that the vertebral artery resistive index diminishes in growth-restricted SGA fetuses. Doppler examination of the vertebral artery seems to identify a group of fetuses with brain sparing and severe IUGR.

Key Words—brain sparing; fetal Doppler sonography; fetal growth restriction; fetal vertebral artery
from chronic hypoxia, is also found before the onset of labor, during labor contractions, when fetal anemia is present, and in cases of congenital heart disease decreasing brain oxygenation.8–12

The vertebral artery is one of the two vascular gates supplying the brain and nourishes mainly the cerebellum and the brain stem, which are areas especially resistant to hypoxia, hypercapnia, and hypotension.13–25 However, despite these evolutionary advantages, no research has been published describing the existence of brain sparing in the vertebral artery system. In a previous work,16 we described vertebral artery resistive index nomograms, which, to our knowledge, had not been reported previously. The aim of this study was to investigate whether a reduction in impedance (brain sparing) occurs in the vertebral artery system in small for gestational age (SGA) fetuses (estimated fetal weight <10th percentile) affected with growth restriction to determine the possibility of applying the vertebral artery resistive index measurement as a diagnostic test for IUGR at different restriction levels.

Materials and Methods

We retrospectively studied 437 Doppler examinations of the vertebral and umbilical artery resistive indices performed between 26 and 41 weeks' gestation in 437 fetuses with reliable gestational ages according to the first-trimester crown-rump length. In fetuses with serial recordings, to avoid selection biases, only one examination was chosen at random. In addition, fetuses with morphologic anomalies were excluded. Depending on birth weight nomograms,17 examinations were classified into 5 groups: group 1 (control group) included normally grown fetuses with birth weight above the 10th percentile; group 2 included fetuses with birth weight between the 10th and 5th percentiles; group 3 included fetuses with birth weight between the 5th and 3rd percentiles; group 4 included fetuses with birth weight between the 3rd and 1st percentiles; and group 5 included fetuses with birth weight below the 1st percentile and an umbilical artery resistive index above the 95th percentile in published nomograms.18

Sonographic examinations were performed with a Voluson E6 ultrasound machine and a 2- to 8-MHz convex volume probe (GE Healthcare, Milwaukee, WI), a Voluson 730 ProV machine with a 2- to 8-MHz convex probe (GE Healthcare), and a SonoAce 8000 machine with a 3- to 7-MHz convex probe (Samsung Medison Co, Ltd, Seoul, Korea). To obtain Doppler signals of the vertebral artery, it was essential to understand the vertebral artery anatomy. In summary, the vertebral artery, a branch of the subclavian artery, ascends through the transverse foramen of the 6 first cervical vertebrae. At the level of the atlas, it surrounds its lateral masses and enters the brain through the foramen magnum, extending small branches into the brain stem and cerebellum. The vertebral arteries of both sides finally join in a common basilar artery, which anastomoses with the internal carotid artery system at the circle of Willis. According to these references, vertebral artery measurements were obtained during fetal apnea on the basis of our previous work.16 Initially, the color Doppler window was positioned on the nuchal area with the fetal spine in an anterior position. Afterward, the Doppler cursor with an amplitude of 2 to 3 mm was accurately placed in the space between the first cervical vertebra and the occipital bone, at the anatomic point where the artery passes the lateral masses of the atlas. To obtain high-quality images, the cervical area was amplified so that only halves of the thoracic spine and head were included within the screen. At the point of measurement, the vertebral artery ran perpendicular to its previous direction through the transverse foramen. There, a tiny colored curved shape corresponding to either the right or left vertebral artery was depicted (Figure 1). We did not distinguish between the right and left arteries because we thought that the resistive index differences would be insubstantial at this anatomic position. Vertebral artery Doppler waveforms were obtained with the pulse repetition frequency set low, at 1.3 to 4.4 KHz, and their resistive index values were obtained after freezing the image, averaging a minimum of 3 consecutive high-quality stable cycles (Figure 2). Umbilical artery measurements were done on free-floating loops of cord according to previously published descriptions.19

Figure 1. Vertebral artery in a 32-week fetus surrounding the lateral masses of the atlas at the measurement point (arrow).
To assess intraobserver and interobserver agreement, two Bland-Altman plots were generated by the following methods: for intraobserver agreement, 17 examinations were performed with an interval of greater than 1 minute (the examiner performed an examination once and then it after >1 minute); and for interobserver agreement, 12 examinations were consecutively performed without interruption by two different examiners. The Bland-Altman chart has several advantages over other methods: it conforms to the definition of repeatability established by the British Standards Institute, and it is useful for revealing a relationship between the differences and the magnitude of measurements to determine any systematic bias and identify any possible outliers. By this procedure, the differences between the two examinations were plotted against the averages of the two examinations, and horizontal lines were drawn at the mean difference and at the 95% confidence intervals (CIs) of the limits of agreement. The CIs were defined as the mean differences ± 1.96 times the standard deviations of the differences, and the bias was computed as the value determined by one method minus the value determined by the other method. If differences were by chance, the average of the differences would be close to 0. If not, the value indicated that the two methods produced different results. We therefore considered the vertebral artery resistive index examination a reproducible parameter when the 95% CI of agreement included differences that were not clinically significant or when the average of the differences was close to 0.

According to the classification into groups described earlier, the vertebral artery resistive index values were plotted on a scattergram along with the 10th, 50th, and 90th percentiles obtained previously. However, to avoid the influence of gestational age and make comparisons feasible, all of the vertebral artery resistive index values were converted into multiples of the median, a method that has been widely applied to adjust for gestational age in fetal Doppler research.20-26 Because the median coincides with the 50th percentile, the multiples of the median were calculated by dividing by the 50th percentile value at each gestational age.

Although we now examine most of the vertebral artery Doppler parameters (resistive index, pulsatility index, end-diastolic velocity, and peak systolic velocity), initially we started measuring only the vertebral artery resistive index; therefore, before the study, most of our database consisted of resistive index values, and thus we chose that parameter for the study. However, we considered it equivalent to the pulsatility index and assumed that conclusions would not differ using one or the other.

After this procedure, descriptive statistics (mean, standard deviation, standard error, lower and upper 95% CIs of the mean, and 10th, 25th, 50th, 75th, and 90th percentiles) for the values belonging to groups 1 to 5 (earlier converted into multiples of the median) were calculated and compared graphically in a box and whisker chart, and receiver operating characteristic (ROC) curves were generated to assess the performance of the vertebral artery resistive index as a diagnostic test for IUGR at different restriction levels and for a low Apgar score (≤7) 1 minute after delivery. To evaluate the accuracy of the test, ROC curves were obtained with the corresponding areas under the curves (AUCs), P values, and 95% CIs.

The study was approved by the Institutional Review Board, and informed verbal consent was obtained from the patients. Statistical analysis was performed and the charts were generated with Prism 5a software for Apple Macintosh (GraphPad Software, Inc, San Diego, CA). Significance was determined by t tests (Mann-Whitney U) at P < .05.

Results

The 437 patients studied represented a standard pregnancy population with a mean maternal age of 30.9 years (SD, 5.1 years; range, 16-44 years), a mean gestational age at delivery of 39.6 weeks (SD, 1.69 weeks; range, 27-42 weeks), and a mean birth weight of 3230 g (SD, 526 g; range, 650-4630 g). The incidence of abnormal umbilical artery Doppler findings was low in fetuses with birth weight above the 10th percentile (5.8%), increasing in fetuses with birth weight below the 10th, 5th, and 3rd percentiles (24%, 23%, and 35%, respectively). Indeed, most of the fetuses with high umbilical artery resistive index values in group 1...
had borderline values without clinical importance at the
time of examination. Interestingly, the only fetus in group
1 with absent umbilical artery diastolic flow was affected
by abruptio placentae. As a general rule, the time to deliv-
ery depended on the gestational age at examination and
the presence of reversed umbilical artery diastolic flow or
a nonreassuring fetal tracing in any examination performed
afterward.

The vertebral artery was easily detected in all patients
studied. Compared to the middle cerebral artery, the ver-
tebral artery seems more difficult to visualize. However, a
vertebral artery Doppler examination is also an easy pro-
cedure, which can be performed by an inexperienced
examiner with very basic training.

The Bland-Altman analysis (Figure 3) showed biases
of 0.003 (SD, 0.063) and 0.037 (SD, 0.057) with 95% lim-
its of agreement of –0.120 to 0.126 and –0.149 to 0.074 for
the intraobserver and interobserver agreement, respec-
tively. Because the levels of disagreement did not include
clinically important discrepancies, and the averages of the
differences were close to 0, we concluded that the method
was reproducible.

Figure 4 depicts the vertebral artery resistive index val-
ues along with the 10th, 50th, and 90th percentiles. Values
for groups 1 (triangles) and 2 (inverted triangles) spanned
the percentiles without any tendencies. Conversely, values
for groups 3 to 5, in which the examinations were per-
formed on fetuses with birth weight below the 5th per-
centile (gray, dotted, and black circles) showed a tendency
to be situated at the lower areas of the percentiles, and this
finding was more pronounced for fetuses with birth weight
below the 3rd percentile and an umbilical artery resistive
index above the 95th percentile.

Figure 5 and Table 1 represent the means and per-
centiles (10th, 25th, 50th, 75th, and 90th) of the vertebral
artery resistive index values converted into multiples of the
median. No statistically significant differences were pres-
ent between fetuses with birth weight above the 10th per-
centile and fetuses with birth weight between the 10th and
3rd percentiles. Conversely, these differences were clear
for fetuses with birth weight below the 3rd percentile (P <
.01), especially when an abnormal umbilical artery resist-
itive index was present (P < .01).
According to the ROC analysis, the vertebral artery resistive index did not predict a low Apgar score 1 minute after delivery (AUC, 0.54; \( P = .57 \)). In addition, ROC curves generated to assess the ability of the vertebral artery resistive index as a test for IUGR varied depending on the ponderal restriction threshold applied (Figure 6). First, when we used the 10th percentile for birth weight (defining SGA fetuses), the vertebral artery resistive index performance was poor (AUC, 0.56; \( P = .13 \); SE, 0.043; 95% CI, 0.476–0.645). Second, when we used the 3rd percentile for birth weight, the vertebral artery resistive index performed better (AUC, 0.66; \( P = .01 \); SE, 0.058; 95% CI, 0.544–0.772). With this threshold, the optimal vertebral artery resistive index value was 0.98 multiple of the median (sensitivity, 65%; specificity, 61%). Finally, when we used a stricter definition of IUGR (fetuses with birth weight <3rd percentile and an umbilical Doppler resistive index >95th percentile), the vertebral artery resistive index performed as a good diagnostic test (AUC, 0.74; \( P = .02 \); SE, 0.076; 95% CI, 0.593–0.891). With this threshold, the optimal vertebral artery resistive index value was 0.96 multiple of the median (sensitivity, 87%; specificity, 69%). The outcomes of SGA fetuses with significant vertebral artery resistive index differences were poor: in group 4 (birth weight <3rd percentile), 10 fetuses (43%) finished pregnancy with a cesarean delivery; 2 (9%) had absent or reversed end-diastolic flow; 1 pregnancy (4%) had preeclampsia; and 1 pregnancy (4%) had rupture of membranes at 32 weeks.

**Discussion**

Accurately detecting fetuses with true growth restriction while excluding those growing adequately is one of the principal objectives of current perinatology. With the aim of discriminating between true- and false-positive findings, Doppler examinations have been applied in fetuses with a suspicion of IUGR, and diverse fetal arteries have been studied. Growth anomalies actually start with increases in the umbilical artery resistive index and progress when cerebral impedances decrease. Subsequently, if growth restriction gets worse,27,28 the venous Doppler anomalies reflect progressive cardiac failure, ending with deterioration of the biophysical profile.29,30 Interestingly, postnatal studies have shown that brain sparing in the internal carotid artery/middle cerebral artery system does not entirely protect the brain because children with circulatory redistribution during gestation are more likely to have behavioral problems later.31,32 Therefore, the brain-sparing effect in the internal

![Figure 5. Vertebral artery (VA) resistive index (RI) values converted into multiples of the median (MoM). Center line indicates 50th percentile (median); box limits, 25th and 75th percentiles; and whiskers, 10th and 90th percentiles. Gray boxes represent groups in which Doppler impedance was significant (\( P < .01 \)). P indicates percentile; and UA, umbilical artery.

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<th>Table 1. Descriptive Statistics for Groups 1 to 5</th>
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Vertebral artery resistive index values are expressed as multiples of the median. CI indicates confidence interval.
carotid artery/middle cerebral artery system probably reflects a more advanced stage in IUGR than was earlier assumed and should be considered a sign of probable brain damage.

The vertebral artery is one of the two vascular entries to the fetal brain and supplies blood to the cerebellum and brain stem. Because these areas are more resistant to hypoxia and hypotension,13–15 we assumed that the brain-sparing effect might also occur in the vertebral artery system. However, to our knowledge, no research had previously been done to examine the fetal vertebral artery, and only one study describing normal vertebral artery resistive index reference values had been published.16 Consequently, the objectives of our study were 2-fold: (1) to evaluate the existence of brain sparing in the vertebral artery system; and (2) to assess the performance of the vertebral artery resistive index measurement as a diagnostic test for IUGR according to different birth weight thresholds.

Small for gestational age fetuses with birth weight between the 10th and 3rd percentiles showed vertebral artery resistive index values similar to those of normally grown fetuses. However, when growth decreased to below the 3rd percentile, the vertebral artery resistive index became significantly lower, showing a clear brain-sparing effect (P<.01). Interestingly, this decrease in the vertebral artery resistive index was higher when umbilical artery resistive index abnormalities were present, indicating that these fetuses represented a group with severe growth restriction.

In SGA fetuses (birth weight <10th percentile), the ability of the vertebral artery resistive index as a diagnostic test was poor (AUC, 0.56; P = .13), especially when compared to the estimated fetal weight (AUC, >0.8) and the umbilical artery Doppler examination (AUC, 0.74).32 However, it was better than the middle cerebral artery resistive index (AUC, 0.52)33,34 and the splenic artery resistive index (AUC, 0.54).20 The low accuracy of the vertebral artery resistive index for detecting SGA fetuses was not surprising because similarly to the middle cerebral artery or splenic artery, Doppler changes in the vertebral artery system were late and therefore absent in most of the fetuses with initial IUGR.

In fetuses with severe growth restriction (birth weight <3rd percentile), the diagnostic ability of the vertebral artery resistive index became slightly better (AUC, 0.66; P = .01). Although this value was still far from the estimated fetal weight (AUC, 0.87), it compared favorably to the umbilical artery resistive index (AUC, 0.63).35 However, in fetuses with birth weight below the 3rd percentile and abnormal umbilical artery Doppler findings, the AUC increased to 0.74, close to the diagnostic level for the estimated fetal weight. Therefore, as occurs with the middle cerebral artery,36,37 the increase in the vertebral artery resistive index seemed to identify a group of fetuses with severe IUGR.

Finally, the vertebral artery resistive index was a poor predictor of a low Apgar score 1 minute after delivery. Again, this finding means that Doppler changes in the vertebral artery occur only with long-term chronic hypoxia and are not predictive of acute hypoxia.38

Similarly to the internal carotid artery/middle cerebral artery system, our preliminary results have shown that the reduction of impedance in the vertebral artery system is a late phenomenon happening only in fetuses with advanced IUGR. Therefore, statistically significant differences and high AUC values appear in a standard population of fetuses only when restriction is chronic and severe. Both the vertebral artery and the internal carotid artery/middle cerebral artery system show brain sparing, which means that cerebral arteries work in unison with changes appearing at both sites initiated by the same hypoxia signals. However, because the vertebral artery system supplies the most primitive areas of the brain, a more advanced brain-sparing mechanism that is probably triggered at earlier stages of growth restriction might occur in the vertebral artery. To this end, future studies will be needed to compare the accuracy of vertebral and middle cerebral artery examinations in the diagnosis of severe IUGR.
References


