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**Correlation between umbilical arterial pH values and fetal vertebral artery Doppler waveforms at the beginning of the second stage of labor: a pilot prospective study**

Danila Morano<sup>1</sup>, Gennaro Scutiero<sup>1</sup>, Piergiorgio Iannone<sup>1</sup>, Giulia Nencini<sup>1</sup>, Elena Mantovani<sup>1</sup>, Antonio Farina<sup>2</sup>, Pantaleo Greco<sup>1</sup>

*1 Department of Morphology, Surgery and Experimental Medicine, Section of Obstetrics and Gynecology, University of Ferrara, S. Anna University Hospital, Cona, Ferrara, Italy*

*2 Division of Obstetrics and Gynecology, Sant'Orsola-Malpighi Polyclinic, Department of Medical and Surgical Sciences (DIMEC), University of Bologna, Via Massarenti 9, 40138 Bologna, Italy*

Corresponding Author: Danila Morano, MD Department of Morphology, Surgery and Experimental Medicine, Section of Obstetrics and Gynecology, University of Ferrara, S. Anna University Hospital, via Aldo Moro, 8, Cona, Ferrara, Email: moranodanila@gmail.com. Telephone: 0532/236297.

# **Correlation between umbilical arterial pH values and fetal vertebral artery Doppler waveforms at the beginning of the second stage of labor: a pilot prospective study**

**Objective:** The aim of this study was to evaluate the association between umbilical arterial pH and fetal vertebral artery Doppler velocimetry waveforms measured at the beginning of the second stage of labor in physiological term pregnancies.

**Methods:** This was a prospective cohort study of 250 pregnancies. The resistance index, pulsatility index and peak systolic velocity were measured. The relationship between the fetal Doppler and the umbilical arterial pH was evaluated. A simple linear regression and a general linear model were used to explore possible correlations of Doppler parameters with fetal and neonatal outcome adjusted for confounders.

**Results:** Umbilical arterial pH values were directly associated with Vertebral artery pulsatility index . Fetuses with lower pulsatility index values were at increased risk of a subsequent diagnosis of pathological fetal heart rate tracing patterns (presence of decelerations or reduced variability according to FIGO criteria). during the second stage of labor). We estimated a decrease in pulsatility index of 10% in those fetuses destined to show a pathological fetal heart rate tracing.

**Conclusion:** Vertebral artery Doppler waveforms correlates with umbilical pH in normal pregnancies and is also a function of fetal heart rate patterns. If this proportional association would be demonstrated also for abnormal pH values, vertebral artery pulsatility index might be useful to evaluate fetal wellbeing in those cases of suspected hypoxia/acidemia.

Doppler, intrapartum care, fetal vertebral artery, labor ultrasound, fetal hypoxia

## **Introduction**

Labor is a physiological event for the fetus, but it may become stressful and a potential risk for his life (1).

Intrapartum fetal heart rate (FHR) monitoring is still the only method to evaluate fetal wellbeing and indirectly antepartum acidemia and to prevent dramatic complications during labor (2), (3)(4). However, FHR tracings interpretation is burdened with a higher rate of false positive leading to unnecessary operative deliveries without neonatal benefits (5). Therefore, an efficient non-invasive technique integrating FHR would be useful for detecting antenatal fetal acidemia, especially in case of suspicious FHR. Doppler represents a valid method to fulfill these requirements. Many papers in fact have widely shown the predictive values for the intrapartum fetal compromise of the cerebroplacental ratio (CPR) which incorporates the umbilical and middle cerebral arteries (6) (7)(8) and umbilical venous Doppler parameters (9).

Recently Morales-Rosellò has shown significant Doppler index modifications in late onset fetal growth restriction (FGR), by studying vertebral artery (VA) modifications, hypothesizing that VA might early detect fetal cerebral hypoxia (10). VA represents 30% of fetal cerebral flow. It nourishes mainly the cerebellum and the brain stem, which are interestingly resistant to hypoxia, hypercapnia, and hypotension (11). It is known that VA pulsatility index (PI) diminishes in case of FGR as middle cerebral artery (MCA) and it could be a valid alternative to it in evaluating fetal wellbeing and the “brain sparing” (cerebral vasodilatation) (10), (12).

Recent studies have shown that vertebro-placental ratio (VPR) is associated to neonatal pH values as cerebro-placental ratio (CPR), representing a good alternative to it. VPR shows also a better association to venous pH values than CPR identifying small for gestational age (SGA) fetus (<10<sup>th</sup> centile) with lower pH values (13). This technique might represent a valid instrument to evaluate fetal wellbeing in cases of suspected acidemia, especially with suspicious FHR patterns.

Only Morales-Rosellò evaluated the association between VA Doppler and umbilical artery pH (UA pH) values at birth, but no study has ever evaluated VA Doppler parameter during labor.

The primary outcome of this study is to evaluate the association between fetal acidemia and fetal VA Doppler during the beginning of the second stage of labor in physiological term pregnancies.

## Methods

In order to improve the results of our observational research, the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist was utilized. This was a monocentric, prospective, pilot study based on term patients between 37 and 41 weeks of gestation in labor at the University Clinic of Ferrara, Italy.

## ***Study design***

A prospective cohort study was conducted between March 2016 and July 2017 and involved 250 non consecutive pregnant women at term out of 2258 deliveries that occurred in our hospital in the time-window considered. To reduce the risk of bias, just one physician (DM) and three midwives attended all the labors and deliveries included in the study. The study was carried out following the ethical rules of Sant'Anna Hospital Ferrara, Italy.

## ***Setting***

Women being seen for care in the Department of Morphology, Surgery and Experimental Medicine, Division of Obstetrics and Gynecology at the University of Ferrara, Italy, a tertiary referral hospital, were recruited to have an ultrasound measurement of VA PI, either left and right. The ultrasound evaluation was performed at the beginning of the second stage of labor of each patient by the same sonographer (DM). All the women had a normal FHR pattern at the time of Doppler measurement and a normal labor length. The first stage of labor was defined as the time from 4 cm dilation to complete dilation. The fetal station was assessed at full dilation before pushing in all cases; the transabdominal sonogram was carried out at the same time as the vaginal examination, which established the end of the first stage of labor. The second stage of labor was defined as the time from complete cervical dilation to fetal delivery.

According to international protocols (3), normal second stage duration was defined as follows: up to 60 min for multiparous women without an epidural, 120 min for multiparous women with an epidural and nulliparous woman without an epidural, and 180 min for nulliparous women with an epidural. All the enrolled women had a normal labor length.

Informed consent was given by the patients before data were entered in a dedicated database. Patients were recruited during the first clinical visit at the Term Pregnancy Clinics at the University of Ferrara (37 weeks' gestation).

Eligibility criteria were normal single pregnancy at term without any known fetal or maternal clinical complication, a satisfactory measurement of VA PI (in the 9% of the cases was not possible to obtain a correct measurement), and ability to understand and sign the informed consent. Participants were selected if a complete follow-up of the pregnancy was available and for those patients Hospitalized in the obstetrical ward of the Division for delivery. Medical and obstetrical history was collected by specialist doctors and Obstetrics and Gynecology residents at the University of Ferrara. The recruitment of patients has not modified the usual, scheduled health pathway of pregnant women.

Criteria of exclusion were: lack of follow-up recorded in a dedicated electronic data base, neonatal macrosomia (>4000 g), retained placenta/membranes, morbidly adherent placenta, pharmacological induction of labor by prostaglandin gel, presence of uterine myomas, any surgical interventions on the uterus, diabetes in pregnancy, hypertensive disorders, mild or severe intrauterine growth restriction (IUGR). Mild IUGR was defined when the abdominal circumference (AC) was between the 5<sup>th</sup> and 10<sup>th</sup> centile, with a normal AC at the routine scan at 20-22 weeks of gestation, or decreased more than 40 percentiles from the routine mid-trimester scan. Severe IUGR was defined when the abdominal circumference (AC) was <5<sup>th</sup> centile at recruitment, with a normal AC at the routine scan at 20-22 weeks of gestation. The total number of cases was decided on the basis of the sample size calculation (see below). The main outcome of interest of the study was the relationship between UA pH values and VA Doppler waveform. Secondary outcomes were the association between suspicious and pathological FHR patterns and VA Doppler. Potential confounders and effect modifiers on UA pH values could be abnormal length of first/second stage of labor and failure to progress of fetal head (even if all the enrolled women had a normal labor as reported in the inclusion criteria), Uterine tachysystole, hypertonus or hyperstimulation and pathologic FHR patterns.

*Sample size:* Power analysis for a linear regression was performed using Power Analysis Sample Size (PASS) software (Kaysville, UT, USA). Power analysis was conducted before the enrollment started. We estimated that given an estimated standard deviation of 0.05 for UA pH (range 7.18-7.38 (14)) and a standard deviation of VA Doppler parameters of 0.20 for PI to 8 for VPS (11), a total of 237 cases would be necessary to reach a power of 80% at a 5% Type I error for a R<sup>2</sup> of correlation of 0.18 and a slope of 0.05

### ***Ultrasound examination***

The ultrasound was performed with SAMSUNG device, 2-8 MHz convex probe. Indeed, in order to obtain Doppler waves, it is mandatory to know the VA anatomy.

The VA, subclavian artery branch, enters the transversal foramen of the first six cervical vertebrae. At Atlantis level, it enters the brain through foramen magnum and extends small branches in the cerebellum and cerebral trunk. The vertebral arteries of both sides form the common basilica artery, which anastomoses the carotid artery system within the Willis circle.

The acoustic window is put above the nuchal area with the fetal vertebral column in the anterior position. Then, Doppler is set with 2-3 mm width in the area between the first cervical vertebra and the occipital bone, at the anatomic level where the VA passes by at Atlantis level. **(Figure 1 near here)**

To gain high quality images, the cervical area is amplified in order that only half thoracic vertebral column and the head are included in the screen.

At the measurement level, the VA runs perpendicularly to its previous direction through the foramen magnum. At that point it forms a small coloured curve corresponding to either the left or the right VA. We have made no distinction between left and right VAs because we hypothesized that the possible PI differences are irrelevant in this anatomical position. The VA wave forms have to be obtained with a low frequency repetition rate, 1.3 and 4.4 KHz. The values of PI were obtained on a frozen image with at least 3 high quality consecutive cycles, using the default automatic analysis.

### ***Umbilical cord gas analysis***

We used the umbilical artery blood instead of umbilical vein blood as the arterial pH and base deficit provide the most accurate information on fetal acid-base status and correlate best with newborn morbidity. To obtain fetal blood for acid-base analysis, the cord was double clamped immediately after delivery at a minimum length of 10 cm with the placenta in situ and both the artery and vein were sampled in pre-heparinized labelled 1 mL syringes and analyzed within 10 minutes.

### ***Statistical Analysis***

A descriptive analysis of the available data was performed. Parametric analysis was used after testing for normality by Shapiro Wilk test. Mean  $\pm$  SD (standard deviation) or percentages were calculated for each available variable. Generated subgroups of patients were compared by a Student t test. The correlation of VA vs. fetal/neonatal quantitative parameters was evaluated by a simple linear regression and, in order to explore possible confounding factors, also a general linear regression model (GLM) was used. The intraobserver repeatability of the measurements were examined using intraclass correlation coefficients (ICC) and its 95% confidence intervals (CIs). Data were analyzed using IBM SPSS Statistics for Windows, (Version 23.0. Armonk, NY: IBM Corp). A p-value < 0.05 was considered statistically significant.

### **Results**

Table 1 shows the demographic characteristics of the patients who joined the study. It can be observed that pH and base deficit values of the recruited patients are all within the normality range. Simple regression analysis showed that PI (either left and right VA), was associated with neonatal pH (p-value < 0.001,  $R^2=0.183$ ).

**Table 1 near here**

The intraobserver repeatability ICC was found to be 0.93 (0.86–0.96 CIs), *p*-value < 0.001, No interobserver analysis was performed since all the measurement were taken by one operator (DM). The analysis was conducted on 80% of the population enrolled.

PI was associated with abnormal FHR patterns (suspect and pathological) appeared subsequently in labor. As shown in Figure 2 a decrease in PI values of 10 % about is estimated in pathological FHR patterns but with healthy neonatal outcome.

Figure 2 also shows the output of the GLM coefficients. As shown both VA PI and CTG (abnormal and pathological) are independent predictors of arterial pH.

Moreover, Figure 2 shows the correlation between PI and pH stratified according to abnormal FHR patterns. UA pH is a function of both VA PI and FHR being lower in pathological FHR patterns.

**Figure 2 near here**

Other covariates such as second stage labor length, stained amniotic fluid, analgesia, labor induction did not influence the neonatal outcomes and did not correlate with VA Doppler waveforms.

## Discussion

The majority of intrapartum fetal hypoxia occurs in uncomplicated pregnancies. Current intrapartum monitoring techniques have not resulted in a reduction in the incidence of cerebral palsy in term neonates. This pilot study has observed for the first time the association between fetal VA Doppler PI velocimetry evaluated at the beginning of the second stage of labor and fetal acidemia (detected with pH and base deficit) in physiologic term pregnancies. Results have shown that PI is a function of both UA pH and suspected and/or abnormal FHR pattern. Even if the study was not designed to evaluate a possible predictive value of VA PI we noted that a lower VA PI of about 10% was associated with an abnormal FHR pattern observed later in labor after the Doppler assessment.

In order to prevent neurological disorders, the researchers aim is to identify arteries leading to pathology and “brain sparing” effect earlier than neurological insult. VA, as the middle-cerebral artery, has been largely studied in the current literature. The two arteries both play a role in “brain sparing” phenomenon: cerebral vasodilatation due to hypoxic insult. VA and middle-cerebral artery PIs decrease in FGR cases as MCA; thus, it might represent a good alternative to evaluate pathological fetuses (10). Morales-Rosellò et al. have demonstrated significant modifications of Doppler indexes in mild and severe late onset FGR fetuses, exclusively with VA evaluation, concluding that, in these fetuses, VA Doppler measurement might represent the best option to early detect the state of fetal cerebral hypoxia (15).



Recent studies have shown that vertebral-placental ratio (VPR, ratio between VA and umbilical artery) is associated to neonatal pH values like cerebro- placental ratio (CPR), representing a good alternative to CPR. In addition, VPR shows a better association with umbilical venous pH values than CPR: it has been shown that VPR and not CPR, is able to detect small for gestational age (SGA) fetuses, whose arterial and venous pH values are lower than physiological values (12) (13).

According to our results, we have shown that VA PI values are correlative to low pH values at birth, even if within physiological ranges.

### ***Limit of the study***

We acknowledge that the VPR analysis would be an important extra parameter to consider even if all the infants had a normal outcome. The association between PI and pH was not influenced by other variables of the study, probably due to the absence of pathological cases. Given the lack of confounding effect, our results could overestimate the real association between VA PI and pH and could not be fully confirmed in situations of abnormal labor duration and fetal dystocia.

However, is it possible that VA indexes measurement technique might represent a valid and effective instrument to evaluate fetal wellbeing in cases of suspected hypoxia/acidemia, above all in those cases with suspicious CTG, but also in those cases at high risk of perinatal morbidity or stillbirth (16).

### **Conflict of interest**

The authors report no conflicts of interest.

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Table 1. Characteristics of the patients (n=250). Data are expressed as mean  $\pm$  Standard deviation or percentage

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<b>Variable</b>	<b>Value</b>
Age	29 ±5.6
Gestational age (days)	277± 9.6
Pulsatility Index (PI)	1.37± 0.11
Umbilical arterial pH	7.23± 0.02
Base Deficit mmol/L	6.4±3.13
<b>Second stage of labor length (min)</b>	
Multiparous women without an epidural	50±22
Multiparous women with an epidural and 3 nulliparous without an epidural	102±40
Nulliparous women with an epidural	112±31
Induction (%)	18%
Meconium stained amniotic fluid (%)	12.5%
Analgesia (%)	70.8%
<b>Intrapartum Cardiography</b>	
Normal	76.3%
Pathological	10%
Suspect	16.4 %
<b>Mode of delivery</b>	
Spontaneous	86.4
Vacuum delivery	4.4
Cesarean section	9.2
Neonatal weight (gr)	3270±330

Table 1. Characteristics of the patients (n=250). Data are expressed as mean  $\pm$  Standard deviation or percentage

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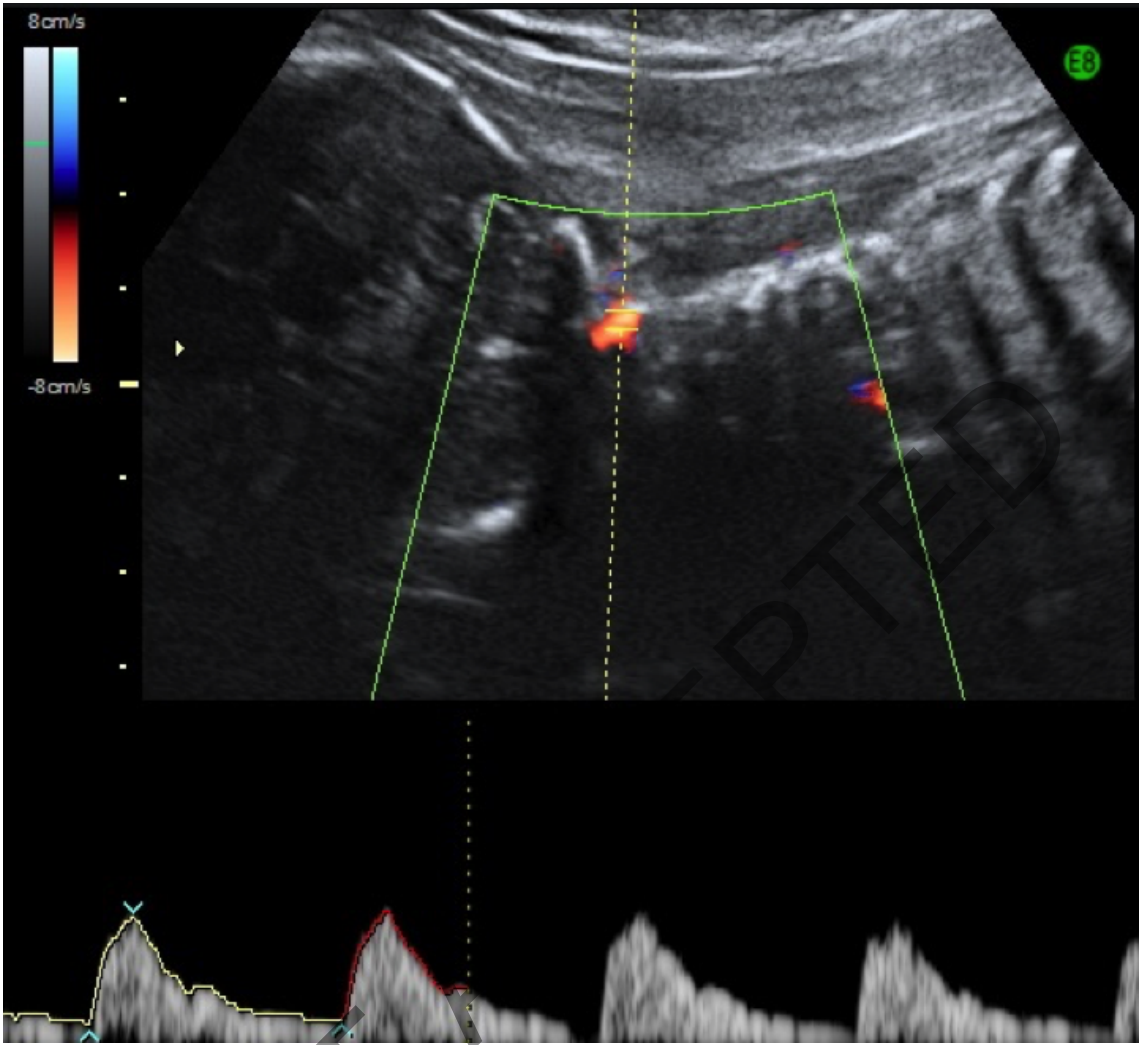
<b>Variable</b>	<b>Value</b>
Age	29 ±5.6
Gestational age (days)	277± 9.6
Pulsatility Index (PI)	1.37± 0.11
Resistance Index (RI)	0.73± 0.09
Systolic peak velocity	43 7±0.11
Umbilical arterial pH	7.23± 0.02
Base Deficit mmol/L	6.4±3.13
<b>Second stage of labor length (min)</b>	
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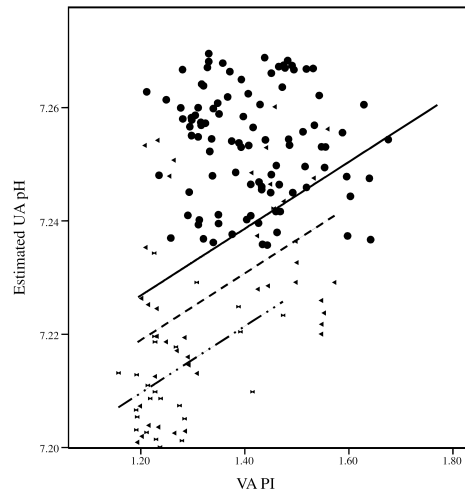


Neonatal weight (gr)

3270±330

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**Legend:**

UA Umbelical Artery  
 VA Vertebral Artery  
 PI Pulsatility Index  
 CTG Cardiotocography:  
 ● Normal — Normal  
 ▲ Suspect - - - Suspect  
 △ Pathologic - · - Pathologic

\*\*p-value 0.003 (T3  
 Dunnet post hoc test) in  
 the comparison of  
 Normal vs. suspect FHR  
 pattern

\*\*p-value <0001 (T3  
 Dunnet post hoc test) in  
 the comparison of  
 Normal vs. Pathological  
 FHR pattern

Variable	VA PI and UA pH according to FHR (Data are expressed as mean ± standard deviations)			General Liner Model (GLM) output (UA pH is the dependent variable)				
	VA PI	UA pH	N of cases	T	Standard Error	p-value	95% Confidence Interval	
							Lower	Upper
Intercept				7.139	0.013	<0.001	7.114	7.164
VA PI				0.059	0.010	<0.001	0.040	0.078
Normal CTG	1.38± 0.11	7.23± 0.02	184	0.017	0.004	0.000	0.010	0.025
Suspect CTG	1.35± 0.13	7.22± 0.02*	41	0.009	0.005	0.040	0.000	0.018
Pathological CTG	1.26± 0.08 **	7.21± 0.10**	25	Reference				

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