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Prognostic value of the aortic isthmus Doppler assessment on late onset fetal growth restriction

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Abstract

Background: As conflicting results have been reported about the association of reversed flow on the aortic isthmus (AoI) and adverse perinatal results in fetal growth restriction (FGR), we aim to compare perinatal outcomes (including tolerance to labor induction) of late-onset FGR between those with antegrade and reversed AoI flow.

Methods: This was an observational retrospective cohort study on 148 singleton gestations diagnosed with late-onset FGR (diagnosis $\geq 32+0$ weeks), with an estimated fetal weight (EFW) $< 10^{\text{th}}$ centile and mild fetal Doppler alteration: umbilical artery (UA) pulsatility index (PI) $> 95^{\text{th}}$ centile, middle cerebral artery (MCA)-PI $< 5^{\text{th}}$ centile or cerebral-placental ratio $< 5^{\text{th}}$ centile. Antegrade AoI flow was present in $n = 79$ and reversed AoI flow in $n = 69$. Delivery was recommended from 37 weeks in both groups. Perinatal results were compared between the groups.

Results: The global percentage of vaginal delivery of fetuses with antegrade and reversed blood flow was 55.7% vs. 66.7% ($P = 0.18$) and the percentage of cesarean section (C-section) for non-reassuring fetal status was 12.7% vs. 15.9% ($P = 0.29$), respectively. When evaluating those that underwent labor induction, the vaginal delivery rate was 67.9% vs. 77.2% ($P = 0.17$), respectively. There were no significant differences regarding any other perinatal variables and there were no cases of severe morbidity or mortality.

Conclusion: We observed that the presence of reversed AoI flow does not worsen perinatal outcomes on fetuses with late-onset growth restriction with mild Doppler

alterations. Attempt of labor induction is feasible in these fetuses regardless of the direction of AoI flow.

Keywords: aortic isthmus; Doppler; fetal growth restriction; labor induction; perinatal outcome.

Introduction

Fetal growth restriction (FGR) of placental origin refers to a condition in which a fetus is not able to fully reach its genetic growth potential due to a mismatch between placental supply and fetal demands and is associated with an increase of both neonatal morbidity and mortality [1]. Prenatal identification of FGR and assessment of its severity is crucial for optimizing the mode and timing of delivery [2].

Both experimental and clinical investigations have demonstrated that placental insufficiency causes fetal hypoxemia by reducing umbilical blood flow. In this setting, the fetal circulatory response implies the well-known brain-sparing effect in order to maintain adequate oxygenation to both the brain and the heart [3]. Identifying this blood flow redistribution which precedes fetal hypoxia is essential when evaluating FGR, especially in the late-onset forms (those diagnosed at or after 32 weeks) as, contrary to what happens in early-onset FGR, placental underperfusion is rarely reflected in the umbilical artery (UA) Doppler. Of the multiple prognostic tools that have been described for FGR assessment [4], the Doppler study of the middle cerebral artery (MCA) [5] and of the aortic isthmus (AoI) [6] have shown the best performance to demonstrate this fetal adaptation to hypoxemia.

The flow in the AoI is a reflection of both the cerebral and systemic resistances, and under normal circumstances the direction of blood flow in the AoI is antegrade, towards the descending aorta. However, the increase in placental resistances and the decrease in cerebral resistances can reverse the flow direction preceding hemodynamic decompensation [7]. Although some groups have observed poorer perinatal and postnatal outcomes in fetuses with reversed AoI flow [8], there are still discrepancies regarding the value of the study of the AoI flow in clinical practice [9, 10]. The aim of this study is to

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evaluate if perinatal results of late-onset growth-restricted fetuses with mild Doppler alterations vary depending on blood flow at the AoI (antegrade vs. reversed).

Materials and methods

This was an observational retrospective study of 164 consecutive singleton fetuses diagnosed of late-onset growth restriction (diagnosis $\geq 32+0$ weeks) with mild Doppler abnormalities between January 2014 and July 2017. The studied fetuses fulfilled the following criteria: the estimated fetal weight (EFW) was below the 10th customized centile and they had either UA pulsatility index (PI) $>95^{\text{th}}$ centile [11], MCA-PI $<5^{\text{th}}$ centile [12] or cerebral-placental ratio (CPR) $<5^{\text{th}}$ centile, they were delivered at our center and their follow-up was complete. In 16 cases (9.8%) the AoI flow was not recorded either for technical reasons ($n=5$) or missed measurements ($n=11$), leaving a study population of 148 cases. Multiple pregnancies, fetuses with chromosomal anomalies, major malformations or congenital infections were also excluded.

According to the organization of the prenatal care of our sanitary area, all fetuses suspected of being small for gestational age by uterine fundal height or by third trimester ultrasound scan, that in our country is included routinely in the prenatal care and is usually done at 33–35 weeks, are referred to our Fetal Medicine Unit where a complete fetal survey including biometry and Doppler study of UA, MCA, AoI and uterine arteries is performed. All examinations are performed by fetal medicine specialists with a high-quality equipment (Aplio 500, Canon Medical Systems Corporation; Tokyo, Japan). EFW is calculated using Hadlock's formula [13], and for this study the EFW used for analysis was the last obtained, that in all cases was within the prior week to delivery. All centiles were customized according to age, parity, ethnicity and pregestational body mass index, using the same software program (GROW – Gestation Related Optimal Weight), available at <http://www.gestation.net/cc/6/884259.htm>. Gestational age was calculated following the guidelines of the American College of Obstetricians and Gynecologists [14].

Color and pulsed Doppler were used to identify and explore the AoI in a longitudinal aortic arch view or in the three vessels and trachea view of the fetal upper mediastinum, as previously described [15]. Three consecutive flow velocity waveforms were obtained with an ultrasound angulation of 30° or less. The AoI was classified as antegrade or reversed depending on the diastolic blood flow direction, without taking into account the brief reversed flow at the end-systole that is usually seen in the third trimester (Figure 1). Whenever reversed flow at the AoI was observed, a confirmation scan was performed ≥ 24 h. If the finding was not confirmed, the flow was finally classified as antegrade. All data related to the ultrasound used for analysis were obtained from the last scan prior to delivery. Doppler results including AoI were not blinded to the obstetric care providers, but none of the managing decisions were based on the AoI status.

We recommended in all cases finishing the pregnancy from 37 weeks. In the absence of a contraindication for vaginal delivery, the method for labor induction was chosen depending on the Bishop's index at admission: this was initiated using oxytocin if the index was >7 , and with vaginal prostaglandins or cervical Foley catheter placement if cervical ripening was required. This policy was not influenced by the AoI status.

We studied the following perinatal variables: mode of delivery, indications for cesarean section (C-section), Apgar score at 5 min, UA pH, admission to the neonatal intensive care unit (NICU) and composite neonatal morbidity (necrotizing enterocolitis, bronchopulmonary dysplasia, grade III or IV intraventricular hemorrhage, hypoxic-ischemic encephalopathy or periventricular leukomalacia). The study was approved by the Institutional Review Board of our hospital. The retrospective nature of the study and the anonymization of patients' data made it unnecessary to have a signed consent form.

A descriptive analysis of the study variables on the two study groups (antegrade vs. reversed AoI flow) was performed. Categorical variables were expressed as percentage and continuous variables as mean [standard deviation (SD)] or mean [interquartile range (IQR)]. Univariate analysis for comparisons was made using Student's *t*-test (when data were normally distributed) or the Mann-Whitney *U*-test (for skewed data) for continuous variables and the χ^2 -test or Fisher's exact test (when the expected cell count was less than 5) for

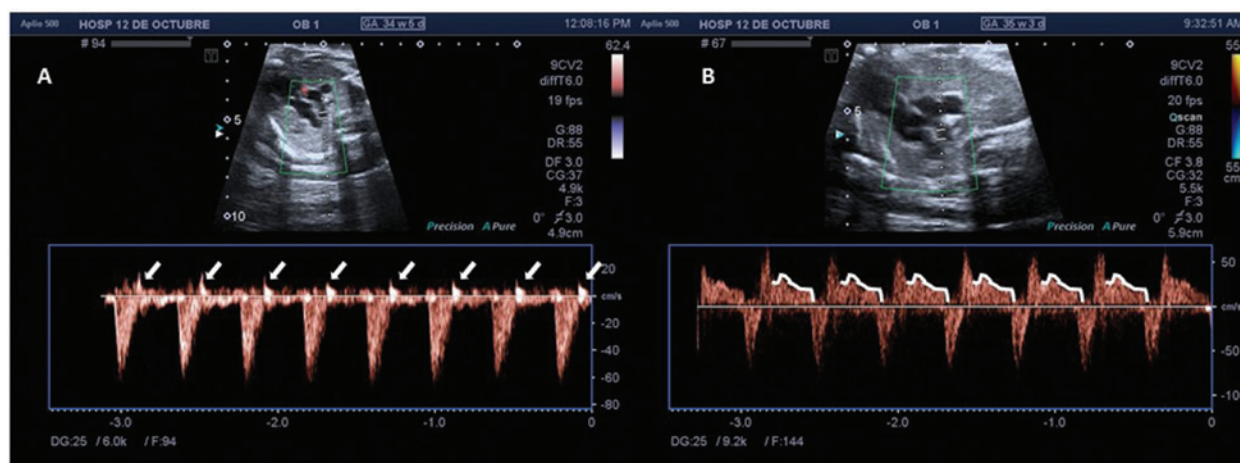


Figure 1: Examples of (A) normal and (B) pathological aortic isthmus (AoI) Doppler waveforms obtained in a three vessels and trachea view. Arrows show the brief reversed flow at end-systole that is commonly seen in an otherwise antegrade diastolic flow of the AoI. Solid lines show the true reversed diastolic flow component of the AoI.

categorical variables. Two sided P-values less than 0.05 were considered significant. Analysis was conducted with STATA, version 14.1 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX, USA: StataCorp LP.)

Results

Out of the 148 cases, 79 were classified as having antegrade flow at the AoI, and 69 as reversed.

For four cases (5.5%), the reversed AoI was not confirmed on the follow-up scan performed after 24 h. The AoI was obtained from the three vessels and the trachea view in 98% of the cases. Prenatal characteristics of both groups are summarized in Table 1. Regarding maternal parameters, no significant differences were found for most variables, with the exception of the smoking status that was more common among the cases with antegrade flow at the AoI. According to the characteristics of the study population, the overall prevalence of preeclampsia was high (12.2%).

Regarding fetal characteristics, while only 15% of the fetuses of the study population showed to have an abnormal UA-PI ($n = 22$), many had an abnormal MCA-PI ($n = 73$, 49.3%) and most had an abnormal CPR ($n = 117$, 79%). The results of both groups are summarized in Table 2, and significant differences were found on both MCA-PI and CPR, these signs being more altered in fetuses with reversed flow at the AoI compared to those with antegrade flow (1.12 vs. 1.30, $P < 0.01$, and 0.99 vs. 1.19, $P < 0.01$, respectively).

Perinatal outcomes are shown in Table 3. The overall rate of vaginal delivery was 60.8%. No significant

differences were found on any of the variables being studied, including the C-section rate for non-reassuring status in cases where vaginal delivery was attempted, that was similar in cases with an antegrade or reversed flow at the AoI (12.7% vs. 15.9%, $P = 0.29$, respectively).

Discussion

The main observation of our study was that tolerance to labor and vaginal delivery among fetuses classified as late-onset FGR with mild Doppler alterations did not differ between those with reversed flow in the AoI and those with an antegrade flow. The study of the MCA-PI and the CPR were demonstrated to be superior to the UA alone for anticipating the tolerance to labor [16] and perinatal outcome [17] in late-onset FGR. Although in our study the presence of reversed AoI flow was associated with slightly lower MCA-PI and CPR values, we did not find that the Doppler study of the AoI provided clinically relevant information of the late-onset growth-restricted fetuses that could be helpful neither for establishing the route for delivery nor to predict perinatal outcomes.

The study of the AoI started off as a promising tool to evaluate fetal redistribution in growth-restricted fetuses given its critical location between two different fetal circulations. The presence of reversed diastolic blood flow in the AoI implies the presence of redistribution of fetal circulation as it is a consequence of the decrease of the vascular resistances in the brain together with their increase in the lower body and placenta. Therefore, theoretically it

Table 1: Maternal characteristics of the study population, composed by 148 cases of stage I late-onset FGR, divided into groups based on the direction of the aortic isthmus flow.

Maternal characteristic	Aortic isthmus flow		P-value
	Antegrade ($n = 79$)	Reversed ($n = 69$)	
Maternal age in years, mean (SD)	32.3 (5.5)	32.3 (6.2)	0.88
Prepregnancy BMI in kg/m^2 , mean (SD)	23.9 (4.5)	23.7 (5.1)	0.85
Smoker, n (%)	18 (22.8)	7 (10.1)	0.04
Spontaneous conception, n (%)	74 (93.6)	62 (89.9)	0.40
Nulliparous, n (%)	61 (77.2)	50 (72.5)	0.51
Ethnicity/race, n (%)			
Caucasian	57 (72.2)	46 (66.8)	0.23
Asian	1 (1.3)	2 (2.9)	
North African	4 (5.0)	5 (7.2)	
South American	15 (19.0)	13 (18.8)	
Black	2 (2.5)	3 (4.3)	
Previous C-section, n (%)	4 (5.1)	3 (4.4)	0.84
Preeclampsia, n (%)	10 (12.7)	8 (11.8)	0.62
Bishop score at admission, median (IQR)	4 (1)	4 (2)	0.62

BMI, body mass index; GA, gestational age; IQR, interquartile range; SD, standard deviation.

Table 2: Fetal characteristics on the study population, composed by 148 cases of stage I late-onset FGR, divided into groups based on the direction of the aortic isthmus flow.

Fetal characteristics	Aortic isthmus flow		P-value
	Antegrade (n = 79)	Reversed (n = 69)	
GA at diagnosis in weeks (mean, SD)	35.6 (2.2)	35.6 (2.5)	0.97
GA at delivery in weeks (mean, SD)	37.9 (5.8)	37.1 (1.9)	0.34
Estimated fetal weight			
Mean (SD) in g	2142 (400)	2152 (412)	0.84
Centile (median, IQR)	4 (5)	4 (5)	0.89
<3 rd centile (n, %)	36 (45.6)	31 (44.9)	0.73
Uterine artery mean PI			
Mean (SD)	0.91 (0.5)	0.89 (0.4)	0.80
Centile (median, IQR)	83 (69)	81 (62)	0.85
>95 th centile (n, %)	32 (40.5)	27 (39.1)	0.84
Umbilical artery PI			
Mean (SD)	1.13 (0.2)	1.16 (0.4)	0.76
Centile (median, IQR)	74 (27)	69 (40)	0.85
>95 th centile (n, %)	8 (10.1)	14 (20.3)	0.08
Middle cerebral artery PI			
Mean (SD)	1.30 (0.3)	1.12 (0.3)	<0.01
Centile (median, IQR)	8 (17)	4 (7)	0.07
<5 th centile (n, %)	34 (43.0)	39 (56.5)	0.10
Cerebro-placental ratio			
Mean (SD)	1.19 (0.4)	0.99 (0.4)	<0.01
Centile (median, IQR)	8 (17)	4 (8)	0.07
<5 th centile (n, %)	63 (79.5)	52 (75.4)	0.97

BMI, body mass index; EFW, estimated fetal weight; FGR, fetal growth restriction; GA, gestational age; IQR, interquartile range; PI, pulsatility index; SD, standard deviation.

Table 3: Perinatal results on the study population, composed by 148 cases of stage I late-onset FGR, divided into groups based on the direction of the aortic isthmus flow.

Perinatal results	Aortic isthmus flow		P-value
	Antegrade (n = 79)	Reversed (n = 69)	
Vaginal delivery (n, %)	44 (55.7)	46 (66.7)	0.18
Onset of labor			
Spontaneous (n, %)	8 (10.1)	2 (2.9)	0.08
Labor induction (n, %)	53 (67.1)	57 (82.6)	
Programmed C-section (n, %)	18 (22.8)	10 (14.5)	
Vaginal delivery			
Globally (n, %)	44 (55.7)	46 (66.7)	0.18
On labor induction (n, %)	36 (67.9)	44 (77.2)	0.17
Cesarean, for NR-CTG (n, %)	10 (12.7)	11 (15.9)	0.29
Reason for cesarean section if AOVD			
FLI/LA	6 (35.3)	3 (21.4)	0.30
NR-CTG	10 (58.8)	11 (78.6)	
Others	1 (5.9)	0 (0)	
Neonatal weight in g (mean, SD)	2243 (337)	2222 (455)	0.95
Arterial pH (mean, SD)	7.24 (0.1)	7.13 (0.9)	0.15
Arterial pH <7 (n, %)	1 (1.3)	0 (0)	0.19
Apgar score at 5 min (median, IQR)	10 (0)	10 (1)	0.36
Apgar score at 5 min <7 (n, %)	0 (0)	0 (0)	–
Severe morbidity (n, %)	0 (0)	0 (0)	–
NICU admission (n, %)	1 (2.6)	5 (8.7)	0.39
Composite poor outcome ^a	1 (1.3)	0 (0)	0.19

AOVD, attempt of vaginal delivery; EFW, estimated fetal weight; IQR, interquartile range; FLI, failure of labor induction; LA, labor arrest; CPD, cephalopelvic disproportion (CPD); NRFS, non-reassuring fetal status; NICU, neonatal Intensive Care Unit. ^aComposite poor outcome comprised perinatal death, severe morbidity, Apgar score at 5 min <7 or arterial pH <7.0.

can be used as an indicator of “brain sparing” when monitoring FGR. However, its clinical use remains unproven, and large studies like the PORTO study have shown that monitoring AoI on small for gestational age fetuses was of no benefit [18].

Among the explanations that can justify why the utility of the AoI remains controversial is that the isthmus is the smallest part of the aortic arch, is relatively short and there are also small vessels in close vicinity, which complicates the recording of pure and good-quality Doppler signals [19]. These technical difficulties explain why the qualitative approach, simply observing the antegrade or reversed flow, is the most commonly used method in the clinical setting [9], even though they can be largely overcome by using high-quality equipment in expert hands as was the case in our study. Thus, in an attempt to obtain a more objective measurement of the AoI flow, quantitative (PI, systolic volume) and semi-qualitative isthmic flow index (IFI) methods have been described, but a consensus has not yet been reached. Some authors advocate calculating whether the net blood flow during the cardiac cycle is antegrade or reversed by using the velocity-time integral of the antegrade flow/velocity-time integral of the reversed flow, being reversed when the ratio is <1 [20]. However, IFI relies on manual calculations, its measurement is angle-dependent and its potential to classify the AoI flow into more types does not seem to provide clinical benefits [21, 22].

Another important limitation added to the measurement of the AoI is that it changes physiologically throughout pregnancy, becoming more common to find reversed flow the further along it goes [23, 24]. In our experience, the presence of a reversed AoI flow was statistically associated with slightly lower resistances on the MCA territory, but this finding resulted in limited clinical relevance as the percentage of MCA-PI or CPR $<5^{\text{th}}$ centile was not different between groups. It is worth noting that about one in four fetuses in the reverse AoI group still maintained a CPR $\geq 5^{\text{th}}$ percentile, reinforcing the idea that there are more factors, beyond the “brain sparing effect”, playing a role in this parameter that may blur its meaning, especially in the third trimester of pregnancy. Therefore, the relationship of reverse AoI with a high degree of brain sparing should be taken with caution.

Some groups have proposed finishing the pregnancy in the late preterm period when a reversed flow is detected on the AoI and through C-section due to a possible lower tolerance to labor [25] and even because its presence has been associated with a poorer neurodevelopmental status [26, 27]. These findings have been consistently demonstrated for early-onset FGR but, after analyzing our data,

we believe that these results are not transposable to late-onset FGR, in which the direction of flow at the AoI may not be a reliable indicator of the fetal well-being. In our hospital, we maintained the indication of finishing the pregnancies diagnosed of late onset FGR with mild Doppler alterations through labor induction from 37 weeks, regardless of the AoI status. Given our results, where perinatal outcomes do not differ depending the flow on the AoI, we ratify our attitude, at least until further evidence from randomized studies proves otherwise.

We also acknowledge some limitations. Firstly, this was not designed as a management study and, therefore, conclusions on when to deliver a late-onset growth restricted fetus cannot be drawn from our findings. Secondly, we included in our reversed AoI group both fetuses with a reversed and a net reversed blood flow, thereby mixing fetuses that may have different prognoses. Thirdly, we have found that the observation of a reverse AoI flow at a specific moment may not be consistent over time (in 5.5% of cases when it is reevaluated after 24 h). However, further studies are needed to confirm if this percentage can be higher when the reassessment is conducted blindly and to assess if duration of reversed AoI flow may be relevant in terms of perinatal results. Finally, it was underpowered to evaluate rare events such as severe neonatal morbidity or mortality.

In conclusion, the Doppler study of the flow at the AoI does not provide any clinically useful information for predicting the tolerance to labor nor the perinatal outcome in late-onset growth restricted fetuses with mild Doppler alterations. Labor induction is feasible and should be considered when indicating when to finish these pregnancies.

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