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SHORT COMMUNICATION

Does Hypoxia Prompt Fetal Brain-Sparing in the Absence of Fetal Growth Restriction?

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Summary

The fetus develops normally in a hypoxic environment but exaggerated hypoxia late in pregnancy is a worrisome sign often observed in hypertensive disorders of pregnancy, placental insufficiency, or fetal growth restriction (FGR). Serial fetal biometry and the cerebroplacental ratio (CPR, calculated as the middle cerebral artery [MCA] / the umbilical artery [UmbA] pulsatility indices [PI]), are commonly used to indicate fetal "brain sparing" resulting from exaggerated fetal hypoxia. But unclear is the extent to which a low CPR indicates pathology or is a physiological response for maintaining cerebral blood flow. We studied 31 appropriate for gestational age (AGA) pregnancies at low (LA, 1670 m) or high (HA, 2879 m) altitude, given the chronic hypoxia imposed by HA residence, and 54 LA women with a clinical diagnosis of FGR. At week 34, the MCA PI was lower in the LA-FGR than the LA-AGA group but lower still in the HA-AGA compared to either LA groups due to a trend toward higher end-diastolic velocity (EDV). We concluded that the lower MCA PI was likely due to greater cerebral vasodilation in the HA-AGA group and an indication of physiological versus pathological fetal hypoxia. Future reporting of serial MCA and UmbA values and their determinants along with the CPR could improve our ability to distinguish between physiological and pathological fetal brain sparing.

Keywords

Birth weight • Cerebroplacental ratio • Fetal physiology • HDP • High altitude

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Hypoxia plays a central role during prenatal life. During 1st-trimester embryogenesis and placental development, fetal epithelial-derived trophoblast cells invade maternal uterine tissue and plug the maternal spiral end-arterioles, making the amniotic cavity extremely hypoxic [1]. The very low resultant tissue pO_2 (<20 mmHg) is thought favorable for preventing reactive oxygen species production and damage to developing tissues [2]. Trophoblast plugs are removed after the completion of placentation late in the 1st trimester, enabling a pronounced rise in uterine artery (UtA) blood flow and oxygen, as well as other nutrient, delivery to the developing fetus.

Chronic hypoxia later in pregnancy is a worrisome sign commonly observed in hypertensive disorders of pregnancy, placental abruption or other signs of placental insufficiency, or fetal growth restriction (FGR). These conditions are not only associated with increased perinatal morbidity and mortality but also greater susceptibility to cardiovascular and other diseases later in life for both mother and child. Therefore, indices of fetal hypoxia are an important means for identifying pregnancies at increased risk. Such indices include elevated resistance indices obtained by Doppler ultrasound for the UtA, umbilical (UmbA), middle cerebral arteries (MCA), and the ductus venosus; serial fetal biometry measures indicative of slowed or restricted growth; and reduced birth weight after adjusting for gestational age and sex [3]. Of these, birth weight is the least sensitive since it alone cannot discriminate between

babies who are constitutionally small *versus* those who are growth restricted, nor can it identify those who are constitutionally small but have been subject to fetal hypoxia. While birth weight percentiles continue to be used, especially since they are only such measure available in many parts of the world, the use of serial fetal-biometry and vascular resistance measures are preferable as they can be monitored over time and therefore provide a timelier means for clinical management.

The commonly used vascular resistance indices are the systolic to diastolic ratio (S/D, calculated as the peak systolic [PSV] to end-diastolic velocity [EDV]), the pulsatility index (PI, calculated as the [PSV-EDV] divided by the mean flow velocity throughout the cardiac cycle or TAM), and the resistive index (RI, calculated as PSV-EDV divided by the PSV). These indices describe the velocities or mean velocities observed, using Doppler ultrasound, of the middle cerebral artery which serves as a major source of blood flow to the brain and of the umbilical artery which describes the velocity profile of blood returning to the placenta when propelled by the fetal heart. These indices play key roles in the surveillance, diagnosis, and clinical management of suspected FGR and are particularly useful for distinguishing early (< 32 weeks) *versus* late (≥ 32 weeks) suspected FGR [3]. Early FGR cases generally show increased UtA and UmbA PI due to placental insufficiency, whereas late-gestation FGR are more often marked by redistribution of cerebral blood flow to favor the cerebral circulation or "brain sparing" and calculated as the MCA PI/UmbA PI [3]. Given that the estimated fetal weight (EFW) may be insufficient for diagnosing FGR, a low cerebroplacental ratio (CPR) is commonly used as an index of brain sparing due to exaggerated fetal hypoxia.

The multiple physiological factors contributing to brain sparing have been extensively reviewed elsewhere [4]. The question being addressed in this short communication is whether a low CPR necessarily indicates pathology or whether it may also be a physiological response by which the fetus maintains cerebral blood flow under conditions of chronic maternal hypoxia. Studies at high altitude (HA, conventionally defined as > 2500 m or 8250 ft as that is where maternal arterial oxygen saturation [SaO_2] measurably declines), provide a means to answer this question since pregnant women at such altitudes necessarily experience chronic hypoxia. However, even though average birth weight falls ~100 gm/1000 m elevation gain and FGR is approximately 3-fold more common at HA [5], some HA babies are appropriate for gestational age and sex (AGA). Therefore, we address the question of whether hypoxia prompts fetal brain-sparing in the absence of FGR by comparing CPR values in clinically diagnosed FGR pregnancies at low altitude (LA, <1670 m) to those observed in healthy, LA- and HA-AGA pregnancies. Additionally, since the CPR is a ratio of two ratios and therefore affected by several factors, chiefly the MCA and the UmbA PSV and EDV, we ask which of these CPR determinants differed in the three groups.

Our study measured CPR and its key determinants in 31 healthy women experiencing uncomplicated AGA pregnancies at LA (Denver, Colorado [1670 m]), 27 AGA pregnancies at HA (Summit and adjacent Colorado counties [2879 m]), and 54 LA (Denver) women with a clinical diagnosis of FGR based on repeated EFW values below the 10^{th} percentile for gestational age and sex. All studies were performed in accordance with the 2000 Declaration of Helsinki, with approval from the Colorado Multiple Institutional Human Subjects Review Committee, and all Doppler ultrasound exams were conducted by the same ultrasonographers. The LA- and HA-AGA pregnancies were studied at pregnancy weeks 20 and 34 (20.2 ± 0.8 and 20.8 ± 1.0, 34.7 ± 1.4 and 34.3 ± 1.2 at LA and HA, respectively), whereas data from LA-FGR women were only available at week 34 (34.0 ± 2.0). Information collected in all three groups included maternal demographics (age, pre-pregnancy body mass index [BMI]), obstetric history (gravidity, parity), fetal biometry, CPR (averaged from both UmbA and MCA), and delivery characteristics (vaginal or Cesarean section delivery, gestational age at birth, birth weight, infant sex and ponderal index). Additionally, maternal hemoglobin (Hb), SaO_2, average right and left UtA diameter, time-averaged mean blood flow velocity (TAM) for calculating total UtA blood, and the average PI were measured at pregnancy weeks 20 and 34 in LA- and HA-AGA groups as previously described [6]. The same variables except for UtA blood flow, UmbA PSV and EDV were recorded in LA-FGR women at week 34. Further details concerning these LA- or HA-AGA and LA-FGR groups are available elsewhere [7,8]. Comparisons between two groups were conducted using student's t-tests and among the three groups by one-way analysis of variance with post-hoc comparisons to identify the specific groups whose values differed. Statistical significance was assessed as a p value < 0.05 and trends noted when the $0.05 < p < 0.10$. All comparisons were conducted using Graph Pad Prism version 10.2.3.

Table 1. Subject characteristics

Variable	LA-AGA	HA-AGA	LA-FGR	P value
n	31	27	54	
Maternal characteristics				
Age, yr	32.0 ± 4.7[a]	32.0 ± 4.3[a]	28.1 ± 4.9[b]	<0.0001
European ancestry, %	74 [56, 86]	100 [88, 100]	80 [68, 89] [b]	<0.01
Parity, no.	1.6 ± 0.6	1.5 ± 0.7	1.8 ± 1.0	NS
Pre-pregnant BMI, kg/m^2	23.2 ± 2.8	23.5 ± 3.2	24.4 ± 4.6	NS
SaO_2, wk 34, %	97.4 ± 1.3	94.7 ± 1.3	--	<0.0001
Hb, wk 34, gm/dL	13.0 ± 2.6	13.5 ± 1.5	--	NS
Wk 20 UtA diam, cm	0.31 ± 0.08	0.29 ± 0.07	--	NS (0.08)
TAM, cm/s	35 ± 12	34 ± 13	--	NS
blood flow, ml/min	356 ± 166	264± 102	--	<0.05
PI	0.82± 0.17	0.84 ± 0.29		NS
Wk 34 UtA diam, cm	0.34 ± 0.08	0.32 ± 0.08	--	NS
TAM, cm/s	42 ± 11	47 ± 15	--	NS
blood flow, ml/min	429 ± 175	469± 243	--	NS
PI	0.66± 0.18	0.65 ± 0.24	0.72 ± 0.21	NS
C-section, %	16 [7, 33]	36 [21, 54]	35 [22, 50]	NS
Fetal characteristics, wk 20				
MCA PSV, cm/s	26.5 ± 4.0	25.4 ± 4.4	--	NS
EDV, cm/s	5.8 ± 0.7	6.4 ± 1.6	--	NS
PI	1.60 ± 0.37	1.38 ± 0.12	--	<0.01
UmbA PSV, cm/s	35.1 ± 5.9	33.2 ± 4.9	--	NS
EDV, cm/s	9.1 ± 3.6	9.6 ± 2.8	--	NS
PI	1.36 ± 0.18	1.25 ± 0.16	--	<0.05
CPR	1.18 ± 0.25	1.12 ± 0.17	--	NS
EFW, gm	351 ± 58	356 ± 56	--	NS
Fetal characteristics, wk 34				
CPR	2.08 ± 0.47	1.80 ± 0.53	1.94 ± 0.53	NS
CPR < 1.08 (no.)	0 [0, 12]	6 [1, 27]	6 [2, 15]	NS
EFW, gm	2444 ± 301[a]	2412 ± 2653[a]	1878 ± 222[b]	<0.0001
Infant characteristics				
Birth weight, g	3460 ± 436[a]	3141 ± 328[b]	2442 ± 410[c]	<0.0001
Male sex, %	55 [38, 70]	54 [36, 70]	33 [22, 46]	NS (0.07)
Ponderal index, kg/cm^3	2.68 + 0.27[a]	2.54 + 0.26[a]	2.40 + 0.25[b]	<0.001
Gest. age at birth, wk	39.7 ± 1.1[a]	39.1 ± 1.5[a]	37.6 ± 1.4[b]	<0.0001
Preterm, %	3 [0, 16]	14 [6, 31]	15 [7, 28]	NS
<10th percentile, %	0 [0.9, 1.0]	11 [4, 27]	52 [38, 67]	<0.0001
<5th percentile, %	--	3 [0.2, 18]	22 [12, 38]	<0.01

Abbreviations: AGA, appropriate-for-gestational-age and sex; BMI body mass index; CPR, cerebral placental ratio; C-section, Cesarean section; EDV, end-diastolic velocity; EFW, estimated fetal weight; Hb, hemoglobin; HA, high altitude; LA, low altitude; MCA, middle cerebral artery; no, number; PSV, peak systolic velocity; PI, pulsatility index; SaO_2, arterial oxygen saturation; TAM, time-averaged mean; UtA, uterine artery; Wk, week. Mean ± standard deviation or 95% confidence intervals in brackets. Different superscripts indicates the specific groups whose values differed using post-hoc tests for results obtained using one-way analyses of variance.

The LA-FGR women were younger and more often self-identified as being of non-European ancestry than LA- or HA-AGA women but similar in parity, gravidity (data not shown), and pre-pregnant BMI (Table 1). Compared to LA-AGA pregnancies, the HA-AGA had lower SaO_2, higher Hb, and lower UtA blood flow at week 20 due to a trend toward smaller vessel diameter, but UtA blood flow parameters were similar at week 34. UtA PI was similar in LA-AGA and HA-AGA women at week 20 and in all three groups at week 34. The frequency of Cesarean-section delivery was also similar in all three groups.

With respect to fetal characteristics, those in the HA-compared to the LA-AGA group had lower week 20 MCA and UmbA PI values, but changes were proportionate such that the CPR values did not differ (Table 1). At week 34, the UmbA PSV, EDV, and PI values were similar among all three groups but there were considerable differences in the MCA PSV, EDV, and PI values (Fig. 1). Specifically, the LA-FGR group tended to have lower MCA PSV and EDV than the LA-AGA, a trend toward lower values than the HA-AGA, and higher MCA PI than the HA-AGA but no differences in the CPR or the percent with CPR values below the cutoff value of 1.08 (Table 1) [9]. Of note, the MCA PI values in the HA-AGA fetuses were lower than those seen in either the LA-AGA or LA-FGR groups (Fig. 1 and Table 1).

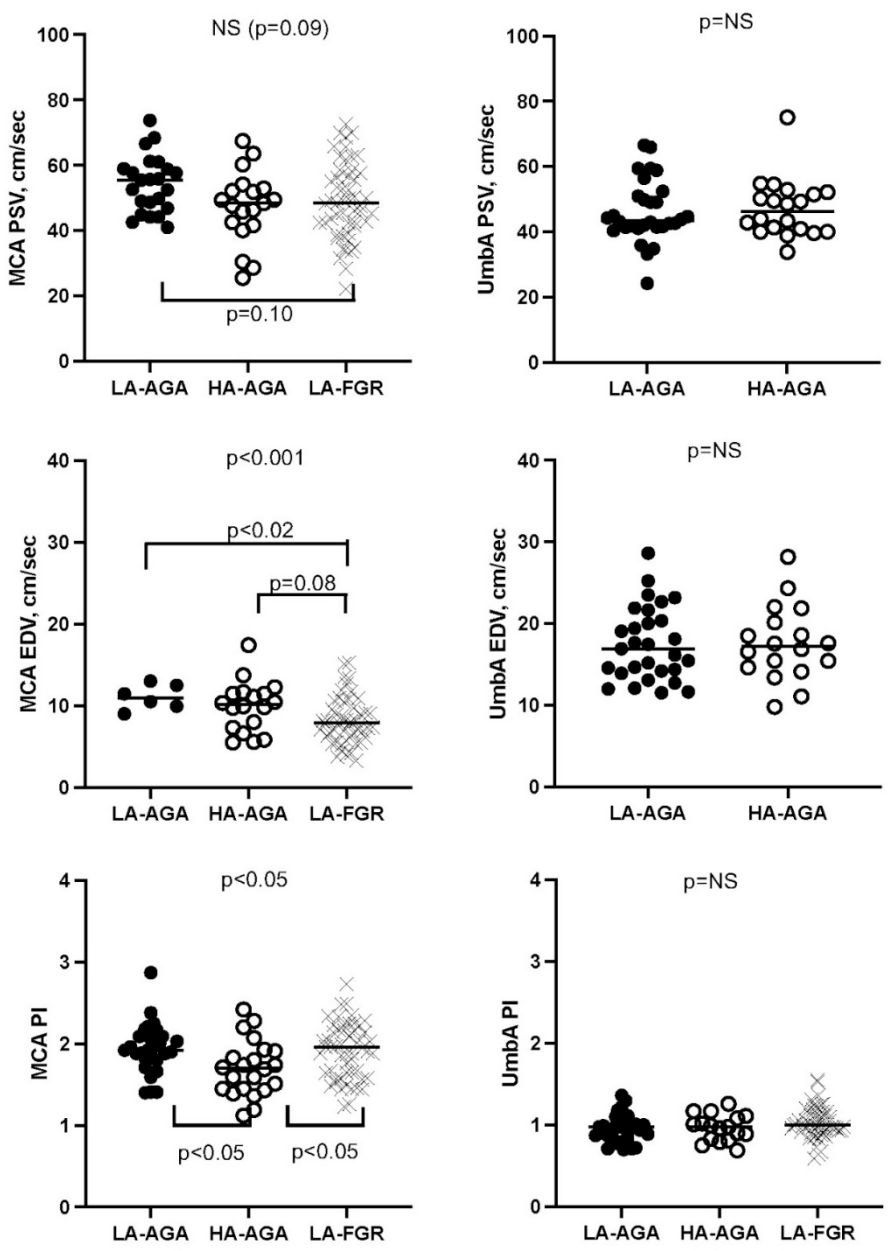

Fig. 1. Lefthand panels: Pregnant women were studied at week 34 who resided either at low (LA, <1670 m, n=31), high altitude (HA, 2879m, n=27) with fetal weights that were appropriate for gesta-tional age and sex (AGA) and in 55 LA women with a clinical diagnosis of fetal growth restriction (FGR). Fetuses in the LA-FGR tended to have lower middle cerebral artery (MCA) peak systolic velocity (PSV) and lower end-diastolic velocity (EDV) than the LA-AGA group, as well as a trend toward lower EDV compared to HA-AGA babies. The MCA pulsa-tility index (PI) was lower in the HA-AGA fetuses than in either the LA-AGA or -FGR groups. Righthand panels: The umbilical artery (UmbA) PSV and EDV values were similar in the LA- or HA-AGA groups at week 34, as were the PI values in all three groups. Filled circles designate LA-AGA, open circles HA-AGA, and x's LA-FGR groups.

EFW was similar in the LA- and HA-AGA groups at pregnancy weeks 20 and 34 but, as expected, both groups had higher values at week 34 than those observed in the LA-FGR cases (Table 1). Birth weights and ponderal indices were highest in the LA-AGA, moderately reduced in HA-AGA, and lowest in LA-FGR groups, with corresponding differences seen in the frequencies of birth weights below the 10^{th} or 5^{th} percentiles. There was a trend toward fewer male LA-FGR babies but no differences in gestational age at delivery or the percentage of preterm births (Table 1).

We interpreted these study findings as showing that differences in fetal growth evident at week 34 or at birth were not accompanied by alterations in the UmbA's PI or its PSV or EDV components, but were paralleled by changes in the MCA PSV, EDV and PI. Moreover, these MCA parameters appeared to differ in physiological *versus* pathological reductions in fetal growth; specifically, whereas the MCA PI was the same in the LA-FGR and LA-AGA pregnancies, the HA-AGA had a lower MCA PI due to a trend toward higher EDV. While it must be acknowledged that neither PSV, EDV nor PI truly measure vascular resistance given that by definition vascular resistance is blood pressure divided by blood flow, the lower PI and trend toward higher EDV in HA-AGA group suggested that the lower MCA PI resulted from greater cerebral vasodilation.

Our understanding of how a fetus can maintain normal growth under conditions of chronic hypoxia is limited by the technical difficulties encountered for directly measuring fetal cardiovascular function *in vivo* as well as to the fact that chronic hypoxia is usually accompanied by some other pregnancy complication such as preeclampsia or placental insufficiency [4]. Given such limitations, we considered that a comparison of the non-invasive fetal vascular resistance parameters obtained by Doppler ultrasound in clinically-diagnosed FGR *versus* AGA yet chronically hypoxic babies would be useful for differentiating between fetal brain-sparing indicative of adaptive or physiological responses to hypoxia *versus* that seen in pathological conditions associated with stillbirth and perinatal loss [10]. HA studies have the unique advantage of being able to examine the mechanisms by which the fetus responds to chronic hypoxia in the absence of overt pathology. Studies at HA provide several lenses through which physiological *versus* pathological fetal responses to chronic hypoxia can be distinguished since HA birth weights vary due to 1) the increased frequency of FGR but also the existence of AGA fetuses and also to 2) the operation of natural selection that has resulted in genetic protection from altitude-associated FGR in multigenerational HA populations (Tibetans and Andeans) *versus* HA newcomers [11-14]. The present study conducted in Colorado LA and HA residents suggested that a strategy distinguishing physiological from pathological fetal hypoxia is a reduction in the MCA PI due, in part, to higher EDV relative to the PSV that, in turn, helps defend cerebral blood flow. Speculatively, this preference on the part of the fetus for sending more blood to the brain as opposed to the placenta suggests a possible role for hypoxic vasoconstriction. Future studies are required to determine, however, such a mechanism as well as investigations in multigenerational HA populations to determine if lower MCA PI values and other indices of physiological brain sparing are present and, if so, whether genetic factors are involved.

The strengths of our study stemmed from the availability of subjects residing at either LA or HA within sufficient proximity that Doppler ultrasound studies could be performed by the same ultrasonographers at each location. While our study was not designed to evaluate the mechanisms by which the HA fetuses sustained a lower MCA PI and possibly greater cerebral blood flow, our observation of lower PI in the MCA and UmbA at week 20 indicated that altitudinal differences were already present by mid-gestation. Since cord blood Hb values were similar in the LA- and HA-AGA groups (15.3 ± 1.8 *versus* 15.5 ± 2.3 g/dL, respectively; p=NS) and there were no relationships between Hb and the MCA or UmbA vascular resistance parameters, the lower PIs at HA did not appear to be due to altitudinal differences in blood viscosity. But our study also had several limitations. One was that 3^{rd} trimester measurements were only available at week 34 for the LA-FGR group, so early FGR or that present by week 32 could not be studied. Another was that not all the babies with a clinical diagnosis of FGR met Delphi criteria [15] since only 52 % weighed less than the 10^{th} percentile at birth.

We concluded that the brain sparing seen in the high-altitude AGA fetuses indicated that indeed, fetal brain-sparing can occur in the absence of FGR. Therefore, while convenient, reliance on a low CPR for diagnosing FGR could be misleading insofar as it might not detect more subtle changes in the MCA PSV or EDV flow velocity parameters. Given the difficulties inherent

in making direct measurements of fetal MCA or UmbA vascular resistance, we suggest that reporting serial MCA and UmbA PSV, EDV, and PI along with the CPR measurements in future studies could improve our ability to distinguish between physiological and pathological fetal brain sparing.

Conflict of Interest

There is no conflict of interest.

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