

ASSESSMENT OF LATE-ONSET IUGR IN THE FETAL BRAIN USING ¹H-MRS

Rui Vasco Simões¹, Magdalena Sanz-Cortes¹, Nuria Bargallo², Francesc Figueras¹, and Eduard Gratacos¹

¹Dept of Maternal-Fetal Medicine, Hospital Clinic, Barcelona, Barcelona, Spain, ²Dept of Radiology, Hospital Clinic, Barcelona, Barcelona, Spain

INTRODUCTION: Intrauterine growth restriction (IUGR) is clinically defined as an ultrasound estimated fetal weight less than the 10th percentile for gestational age (GA) (1) and is due to placental insufficiency (2). This disease occurs in ten percent of gestations and is associated with suboptimal neurodevelopment during infancy and adulthood (3-5). Little is known about the metabolic changes underlying these effects, which could be useful for early therapeutic intervention. Of particular interest in the clinical setting are late-onset IUGR cases, which, unlike early-onset IUGR, present normal umbilical artery Doppler. Proton (¹H) MRS studies have been carried out in the fetal brain (6,7) but not focusing of late-IUGR fetuses or taking into account the clinical risk factors in this population.

PURPOSE: To identify pre-natal brain MRS signatures of late-onset IUGR while accounting for clinical risk factors.

METHODS: In a prospective cohort of 136 consecutive singleton pregnancies, 71 were diagnosed as late-onset IUGR and 65 as adequate for GA (control). Prenatal Doppler ultrasound examinations were performed within one week from the MRI scan. Late-onset IUGR was defined by an estimated and confirmed birth weight <10th centile and normal umbilical artery pulsatility index (PI) (<95th centile). Cases with congenital mal-formations, chromosomal abnormalities, perinatal infections, chronic maternal pathology and non-cephalic presentations were discarded. Predictors of poorer perinatal outcome (risk factors) were: abnormal Middle cerebral artery PI (<5th centile: indicative of cerebral blood flow redistribution) and/or abnormal Uterine artery PI (>95th centile) and/or a birth weight below the 3rd centile. Our sample was divided into three groups: controls, IUGR- (cases without the presence of risk factors) and IUGR+ (cases with the presence of risk factors). All cases were scanned at 37 weeks GA in a Siemens TIM TRIO 3T scanner, without sedation. A receiver RF coil with 8 elements was wrapped around the mother's abdomen, as near as possible to the fetus. Single-shot T2-w HASTE images were acquired. Single voxel, water suppressed ¹H-MRS data were acquired with PRESS localization (frontal lobe): 2000 ms TR, 145 ms TE, 40x20x20 mm³ voxel size, 98 scans, and 3.5 min/scan. Each MR exam did not exceed 45 minutes. MR spectra were processed using two different approaches: (i) frequency domain-fitting of the raw data using LCModel and statistical analysis of metabolite ratios (8); (ii) normalization of each spectrum (Unit Length 2), used as ASCII vector for classification based on pattern recognition analysis (SpectraClassifier 3.1) (9).

RESULTS: Based on the quality criteria defined for each approach, 54% and 49% of the total MRS data obtained were used for fitting (Fig. 1 A-C: 30 controls; 32 IUGR+; 11 IUGR-) and pattern recognition analysis (Fig. 1 D-F: 32 controls; 28 IUGR+; 6 IUGR-), respectively. Metabolite ratios obtained from spectral fittings (Fig. 1-A and 1-B) showed that late IUGR fetuses had significantly reduced total NAA/Cho levels, independent of risk factors (Fig. 1-C), as reported previously in mixed population of early-late IUGR fetuses (7). This decrease followed a linear trend when the three clinical severity groups were considered. Pattern recognition analysis of the spectral vectors automated selected six features for classification in the three clinical groups (Fig. 1-D): 2.34 ppm (glutamate region), 2.56 ppm (glutathione and NAA region), 1.53 ppm (nearby alanine, 1.47ppm), 3.13 ppm (phenylalanine and ethanolamine regions), 1.36, and 4.1 ppm (lactate region). LDA/fisher correctly classified 68% of the MRS vectors (Fig. 1-E and 1-F). Another classifier trained specifically for IUGR+ and IUGR- subgroups achieved 85% predictive accuracy, based on two features only: 2.54 and 2.56 ppm (results not shown).

CONCLUSION: Our preliminary results indicate that late-onset IUGR fetuses have specific metabolic disturbances (NAA/Cho ratio) that are independent of risk factors. MRS pattern classification also suggests the existence of metabolic signatures for each subgroup. These signatures may reflect slight changes in glycolysis, the TCA cycle and oxidative stress between controls, IUGRs at risk, and IUGRs without the presence of risk factors. Further work will validate these results in a larger population, including a neurobehavioral follow-up study and improving both the acquisition and quantification/classification of the MRS data (10).

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