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Perfusion and permeability assessments in mice placenta using dynamic magnetic resonance imaging (MRI) contrast media. A feasibility study

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Background: Advances in MR contrast media pharmacokinetic studies of transit through tissues and dynamic MRI allow to characterize organs physiology *in vivo*. Placental function assessment has been disappointing to date and might be achieved using analysis of dynamic contrast enhanced MRI of tracers. This aim of this study was to build up a murine model of placenta functional assessment using dynamic MRI.

Material and methods: Balb/c mice at sixteen days of gestation were injected either by a conventional contrast media (gadolinium-Dota/Dotarem® = Group A) or by an experimental macromolecular contrast agent (P792/Vistarem® = Group B) during a MR single slice, T1-weighted 2D Fast SPGR sequential acquisition. Imaging was refreshed every 1.1 second for a 15 minutes period. Signal intensities measurements in left ventricle (input function), placenta and fetus areas were performed for each time point and then converted into contrast media tissue concentrations. A compartmental model was build up to explore the kinetic parameters of placenta exchange functions using SAAM II (Software for kinetic analysis, Saam institute, University of Washington, USA).

Results: A total of 50 mice were included and used to build up the animal model. Perfusion and permeability parameters were obtained using a compartmental analysis in 20 mice with (10 mice in each group). Differences in Dotarem® and Vistarem® placental distribution and permeability were highlighted.

Conclusion: Perfusion and permeability assessment in mice placenta using dynamic MRI contrast media is feasible. Such technique allows to get near placental physiology and feto-maternal barrier. This could be of great interest to study drugs and infectious agents pathways through fetus.

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Isolated Single Umbilical Artery (SUA) and fetal growth restriction

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Objective: Single umbilical artery (SUA) is the most common malformation of the umbilical cord. Fetal growth restriction has been associated with both isolated SUA as well as SUA accompanied by chromosomal and/or structural abnormalities. The objective of this study was to determine the incidence of fetal growth restriction associated with isolated SUA and compare this with that of infants having three vessel cords.

Materials and methods: Neonates with a SUA delivered from 1980 until 2001 were identified through a provincial perinatal data base. SUA was confirmed through examination of the cord and/or infant. Infants with chromosomal or anatomic abnormalities were excluded. Birth weight percentiles were calculated for each week of gestation and infants with SUA were then compared to infants with three vessel cords.

Results: There were 188 514 deliveries with no known chromosomal or major anatomic abnormalities, of which 695 (0.37%) had an isolated SUA. Among 695 infants with SUA, 65.3% (n = 454) had birth weights below the 50th percentile compared to 48.4% (n = 90 802) of infants with a three vessel cord (p < 0.0001) while 25.2% (n = 175) had birth weights below the tenth percentile compared to 11% (n = 20 650) infants with three vessel cords (p < 0.0001). Among all infants delivered prematurely, those infants with an isolated SUA were more likely to be growth restricted both at 37 weeks (26.09% versus 16.84%, P < 0.0085) and 34 weeks

(30.23% versus 17.38%, P < 0.0279) when compared to infants with a three vessel cord.

Conclusion: Compared to fetuses with a three vessel cord, fetuses with an isolated SUA have a significantly higher incidence of fetal growth restriction. Clinical evaluation of fetal growth is often difficult, especially with a large maternal habitus. When an isolated SUA is found in a fetus, follow-up assessment of fetal growth by ultrasound should be considered.

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Isolated fetal hypoplastic left heart syndrome: sonographic evaluation of fetal growth and Doppler blood flow

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Objective: The aim of this study was to assess the influence of isolated fetal hypoplastic left heart syndrome (HLHS) on fetal growth and arterial Doppler blood flow velocity waveforms.

Methods: Sonographic and Doppler blood flow evaluations were performed in 16 fetuses with isolated HLHS between 28 and 40 wks of gestational age. Fetal biometry data included: Biparietal Diameter (BPD), frontal-occipital diameter, Head Circumference (HC), abdominal circumference, femur and humerus length. The fetal weight was calculated by Hadlock formula (1985). Doppler flow velocimetry was performed in umbilical artery (UA) and in middle cerebral artery (MCA) and the Pulsatility Index (PI) was calculated. All Doppler studies were performed in the absence of gross fetal movements or breathing. All values were plotted on normal growth curves and expressed in percentile (pc).

Results: Fetuses with HLHS showed BPD and HC values significantly lower than normal mean for gestational age (mean pc BPD 25.3° ± 17.5°; HC 30.2° ± 22.6°) compared to the other biometric parameters. No significant difference in UA PI was observed. Whereas mean pc of MCA PI was significantly lower (26.0° ± 28.8° pc) than normal mean for gestational age compared to the UA PI indicating an enhances cerebral perfusion.

Conclusions: The lower PI observed in the MCA of fetuses with HLHS may reflect a trend towards cerebral vasodilation. This phenomenon could be an indicator of hypoxemia and/or hypercapnia restricted to areas perfused by the preisthymus aorta and be related to the characteristics of the circulation in fetuses with isolated HLHS. This hypothesis could explain also the lower growth rate of the head sonographic parameters of these fetuses and may also alter the brain growth.

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Fetal growth restriction: an intrauterine self-destructive syndrome

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Objective: To assess the differences about the fetal body compartments between fetuses with normal and reduced intrauterine growth, at mid-gestation, by considering the ultrasonographically determined subcutaneous tissue thickness (SCTT).

Methods: In this case-control study 28 patients were enrolled at 30–31 weeks' gestation. We had two study groups matched for age and pre-gestational BMI: the control (n. 14) and the growth restricted (GR) group (n. 14). We measured routine ultrasonographic biometric parameters (head circumference, abdominal circumference, femur and humerus length) and then the mid-arm fat mass and

lean mass (MAFM and MALM, scm), the mid-thigh fat mass and lean mass (MTFM and MTLM, scm), the abdominal fat mass (AFM, mm) and the subscapular fat mass (SSFm, mm). The Mann-Whitney U-test and the Student t test were used to compare the two groups.

Results: The abdominal circumference and the humerus were statistically lower among the GR fetuses. Most of the SCTT values were different in the two groups; particularly the SSFM (3.6 ± 1.1 vs 2.6 ± 0.7 mm; $p = 0.011$), the AFM (5.1 ± 0.7 vs 4 ± 1 mm; $p = 0.01$), the MAFM (3.5 ± 0.9 vs 2.2 ± 0.8 scm; $p < 0.01$) and MALM (2.1 ± 0.4 vs 1.7 ± 0.5 scm; $p = 0.029$) were statistically higher in fetuses with a normal development respect to the GR fetuses.

Conclusions: We observed that, at mid-gestation, the whole set of SCTT, excluding the MTFM, is reduced among fetuses later developing an intrauterine growth restriction. Moreover we also found that the MALM was lower in GR fetuses, testifying that fat free mass and not only fat mass is involved in the incorrect fetal development. Therefore, the evaluation of SCTT allows us to understand that the whole fetal body compartments are involved in a "intrauterine dismantlement" that, if not recognized by time, might lead the fetus to death.

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Comparative evaluation of Doppler, in arteries and veins evaluated with non stress test, contraction stress test, and cord blood sampling in IUGR

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Objective: Our purpose was to identify the utility of Doppler examinations of the umbilical arteries, fetal inferior vena cava, and fetal middle cerebral arteries, contraction stress test (CST), and non-stress test (NST) compared with that of cordocentesis in growth retarded fetuses.

Methods: A total of 196 one-day examinations of 120 IUGRs including all of these tests was conducted.

Results: CST showed the highest sensitivity (92%) and specificity (94%) for fetal acidemia at the cutoff pH of 7.318. The resistance index (RI) of the umbilical artery showed the highest sensitivity (90%) and specificity (86%) at the cutoff pH of 7.318 and a SD 4.0 for RI. Continuous bradycardia occurred after cordocentesis in 10 examinations.

Conclusions: While cordocentesis is the most direct method of identification of fetal acidemia, there is risk of continuous bradycardia in approximately 5% of IUGR. CST provides an estimation of fetal acidemia with the highest accuracy. Doppler examination of the umbilical artery can also be used as an alternative to CST.

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Maternal heart structure and function in gestational and essential hypertension

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Objective: To evaluate the differences and similarities in diastolic function and left ventricular geometry in gestational and essential hypertension.

Methods: Thirty nine consecutive gestational hypertensive pregnant women in the third trimester of gestation (GH), 40 non pregnant essential hypertensive women (EH), and 38 normotensive nonpregnant women (N) matched for age underwent a maternal echocardiographic evaluation.

Results: GH and EH patients had early left ventricular diastolic filling pattern significantly different compared to N subjects: longer isovolumetric relaxation time (IVRT 86 ± 9 msec vs 97 ± 12 msec vs 97 ± 14 msec, $p < 0.01$ 1 vs 2; 1 vs 3), longer deceleration time of the E wave (DtE 179 ± 27 msec vs 203 ± 31 msec vs 201 ± 34 msec, $p < 0.001$ 1 vs 2; 1 vs 3) and lower E wave velocity in GH and EH vs N (92 ± 8 cm/sec vs 81 ± 19 cm/sec vs 86 ± 11 cm/sec, $p < 0.01$ 1 vs 2; 1 vs 3). A wave at atrial contraction in GH patients was similar to N subjects with lower A velocity (58 ± 10 cm/sec vs 62 ± 12 cm/sec vs 75 ± 10 cm/sec, $p < 0.05$ N vs EH; GH vs EH). Altered left ventricular geometry was more common in GH than in EH ($p < 0.05$), whereas normotensive subjects did not show any alteration of the geometric pattern.

Conclusions: Gestational and essential hypertension induce similarly early altered diastolic filling of the left ventricle. Essential hypertension is characterized by a compensatory late filling mechanism due to an enhancement of left atrial function. Gestational hypertension is characterized by altered left ventricular geometry far less common during essential hypertension.

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Endothelial dysfunction is correlated with preeclampsia and fetal growth

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Objective: The aim of this study was to evaluate endothelial dysfunction and oxidative stress parameters in complicated pregnancies. PAI-1/PAI-2 ratio, known to be reduced in pathological pregnancies, was taken as endothelial dysfunction index.

Methods: This study involved 53 pregnancies with preeclampsia, fetal growth restriction preterm deliveries and healthy control groups. Levels of PAI-1/PAI-2 ratio were determined in maternal plasma immediately after delivery. In addition morphological characteristics of placenta were assessed.

Results: There was a two-fold increased of PAI-1/PAI-2 ratio in preeclamptic pregnancies compared to control group. This parameter was negatively correlated with either gestational age and fetal growth in all analysed pregnancies ($r = (-)0.63$ and $(-)0.70$; $p < 0.05$). Placental trophoblast of pathological pregnancies showed an increased extent of apoptosis compared to normal placentae.

Conclusion: These data suggest that PAI-1/PAI-2 ratio is a risk factor of pathological pregnancies that associates with fetal size, gestational age at delivery and placental damage.

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Sonographic 'jelly like' placenta and pregnancy outcome

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Objective: An atypical sonographic appearance of the placenta may be a sign of failed placentation and is often associated with an increased incidence of adverse pregnancy outcome. The aim of the following study was to investigate the clinical importance of the observation of a "jelly like" placenta at sonography.

Methods: During a 3-year period, 15 cases diagnosed to have a "jelly like" placenta at sonography were observed. A "jelly like" placenta was defined as a thick placenta with a patchy decrease of echogeneity, which quivered like jelly to sharp abdominal pressure. The pregnancy course and the neonatal outcome were reviewed. All patients delivered at the department were the ultrasonographic diagnosis was made.