

for the evaluation of the lean mass (lean area of the arm and lean area of the thigh) and the fat mass (abdominal fat thickness, subscapular fat thickness, fat area of the arm and fat area of the thigh).

Results. Fat mass growth shows an exponential curve throughout gestation in all studied pregnancies. The lean mass growth curve, representing the muscle and the bone, has also an exponential trend. Differently, the traditional biometric parameters on femur length and size of the fetal head present a nearly linear growth curve. Fetuses of GDM mothers show a tendency for greater growth, at the same gestational age, for each lean and fat non traditional parameter, in comparison to N pregnancies. Multivariate factorial analysis, carried out on all six non traditional ultrasound parameters simultaneously, showed that fetuses from GDM pregnancies not only are larger than those from normal pregnancies ($p<0.001$), but also have a higher fat mass / lean. mass ratio ($p<0.05$).

Conclusions. This study shows characteristic growth curves for each fetal tissue in the second part of gestation. Moreover a different pattern of growth has been identified in fetuses from GDM pregnancies, both for lean and fat mass. A non invasive, repeatable evaluation of fetal body composition in utero could represent both a useful method for the early detection of growth abnormalities and an indirect but comprehensive indicator of the fetal metabolic status.

91

CARBOHYDRATE AND LIPID ABNORMALITIES IN ADULT OFFSPRING OF INTRAUTERINE GROWTH RESTRICTED (IUGR) NEWBORNS. Mina Desai,* Dave A Gayle,* Jooby Babu,* Michael G Ross. *Dept. of Ob/Gyn, Harbor-UCLA Med. Ctr., Torrance, CA, USA.*

OBJECTIVE: Epidemiologic studies have shown that IUGR newborns have an increased risk for the development of adult metabolic syndrome (diabetes, obesity and cardiovascular disease), though the precise mechanisms are unknown. We sought to determine if IUGR rat pups demonstrate similar patterns of carbohydrate and lipid homeostasis at birth and as adults.

METHODS: Pregnant Sprague Dawley rats and offspring were studied. Control dams received ad libitum ($n=12$) food, whereas study dams were 50% food-restricted ($n=12$) from pregnancy day 10 to 21 to produce IUGR newborns. At birth, litter size was culled to 4 males and 4 females. All pups were nursed by dams fed ad libitum and were weaned at 3 weeks to ad libitum feed. At ages, 3 weeks and 9 months, percentage body fat was determined by DEXA, and fasting blood glucose, plasma triglycerides, cholesterol and insulin levels were determined. Additionally, 9 month old IUGR and Control offspring underwent glucose tolerance test (GTT) as follows: After an overnight fast, D-glucose (1mg/g body weight) was injected intraperitoneally in conscious rats. Blood was taken from tail vein prior to (time 0) and 15, 30, 60, 120 and 180 min after glucose injection. Values (means \pm SEM) are presented for male offspring.

RESULTS: IUGR offspring at 3 weeks of age had significantly decreased blood glucose (90 ± 2 vs 100 ± 2 mg/dl) and plasma triglycerides (32 ± 3 vs 44 ± 4 mg/dl) and insulin (0.28 ± 0.03 vs 0.45 ± 0.08 ng/ml) levels as compared to controls. Percentage body fat was similar in both groups. In contrast, 9 month old IUGR offspring had significantly increased blood glucose (115 ± 2 vs 104 ± 2 mg/dl), plasma triglycerides (97 ± 8 vs 52 ± 6 mg/dl) and insulin levels (0.83 ± 0.08 vs 0.62 ± 0.05 ng/ml) with greater percentage body fat (20 ± 2 vs 12 ± 2 %). IUGR offspring demonstrated significantly increased plasma glucose area under the GTT curve (Figure 1). IUGR female offspring showed similar changes as males.

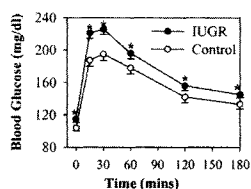


Figure 1: GTT in 9 month old IUGR and Control offspring. * $P<0.05$ vs control.

CONCLUSION: With adult maturity, IUGR pups transit from relative hypo- to hyper- glycemia, insulinemia, and triglyceridemia state associated with insulin resistance. The timing and mechanisms of this metabolic transition may be dependent upon the rate of body fat acquisition.

92

HIGH FAT, WESTERN DIETS EXACERBATE PROGRAMMED OBESITY IN INTRAUTERINE GROWTH RESTRICTED (IUGR) NEWBORNS. Mina Desai,* Dave A Gayle,* Jooby Babu,* Linda Day,* Stacy Behare,* Michael G Ross. *Dept. of Ob/Gyn, Harbor-UCLA Med. Ctr., Torrance, CA, USA.*

OBJECTIVE: Maternal food-restriction (FR) during pregnancy results in IUGR rat pups with altered levels of appetite regulating hormones, and a propensity to adult obesity when fed normal rat chow diets. Increased rates of obesity in Western society have been attributed in part to higher fat diets. However, there is little data on the interaction of higher fat diets and infant growth status at birth. We sought to examine the effects of higher fat (cafeteria) diets on offspring obesity among IUGR and control newborn pups.

METHODS: Pregnant Sprague Dawley rats were 50% food-restricted (FR; $n=12$) from pregnancy day 10 to 21 (term) to produce IUGR newborns. Control ($n=12$) dams received ad libitum food. At birth, litter size was culled to 4 males and 4 females and all pups were nursed by dams fed ad libitum. At 3 weeks of age, pups from both FR and control litters were randomized to diets of either normal laboratory chow (9% fat calorie) or cafeteria diet (16% fat calorie). At 9 months of age, percentage body fat was determined using DEXA, and fasting plasma leptin and ghrelin levels were determined. Values (means \pm SEM) are presented for male offspring.

RESULTS: At 9 months of age, IUGR offspring on normal chow were markedly heavier (742 ± 15 vs 647 ± 18 g, $p<0.001$) with greater percentage body fat (20.3 ± 1.6 vs 12.4 ± 1.5 %, $p<0.001$) and elevated plasma leptin levels (6.1 ± 0.8 vs 3.3 ± 0.5 ng/ml, $p<0.001$) as compared to the control pups on normal chow. Importantly, IUGR offspring on cafeteria diet demonstrated a further significant increase in body weight (816 ± 20 g), body fat (29 ± 2.2 %) and plasma leptin levels (13.7 ± 1.3 ng/ml). Control offspring fed cafeteria diet demonstrated similar body weight (664 ± 18 g), though elevated body fat (19.6 ± 1.7 %) and plasma leptin levels (7.5 ± 1.1 ng/ml) as compared to control offspring fed normal chow.

CONCLUSION: Higher fat diets among control pups results in offspring with similar weight, though increased body fat as compared to pups fed normal chow. However, higher fat diets provided to IUGR pups results in massively obese offspring with morbid levels of body fat and leptin levels. These results indicate that the effects of higher fat, Western diets may be modified or exacerbated by the infants' status at birth.

93

DIFFERENTIAL IMPACT OF LOW BIRTH WEIGHT ON PPAR γ AND LEPTIN EXPRESSION IN PERIRENAL FAT IN MALE AND FEMALE LAMBS. Jaime A Duffield,¹ Tony Vuocolo,² Ross Tellam,² Jim R McFarlane,³ Kate G Kauter,³ Beverly S Muhlhauser,¹ I Caroline McMillen.¹ (SPON: David M Olson). ¹*Discipline of Physiology, The University of Adelaide, Adelaide, SA, Australia;* ²*CSIRO Livestock Industries, Brisbane, QLD, Australia;* ³*Department of Animal Science, University of New England, Armidale, NSW, Australia.*

Objective: Epidemiological studies have shown that a low birth weight coupled with a rapid postnatal growth rate is associated with an increased adiposity in adult life. We have investigated the impact of low birth weight and gender on the expression of genes that regulate the differentiation (PPAR γ , RXR α), insulin sensitivity (adiponectin) and lipid metabolism (leptin, LPL, G3PDH) of perirenal adipocytes in lambs at 21d of life. **Methods:** Lambs were separated into low birth weight (LBW, <4.4 kg, $n=9$) and average birth weight (ABW, >4.5kg, $n=15$) groups. An Insulin RIA and competitive ELISA for leptin were used for plasma analyses. The relative quantity of PPAR γ , RXR α , leptin, adiponectin, LPL, and G3PDH mRNA in the perirenal fat depot was determined by qRT-PCR, and the mean size of adipocytes was determined using standard image analysis. **Results:** There was no difference between LBW and ABW lambs in the relative perirenal adipose tissue (PAT) mass at 21d. Plasma insulin concentrations during the first 24h after birth were strongly correlated with size of perirenal adipocytes at 21d ($r^2=0.57$, $P<0.0002$). PPARg ($P<0.05$) and leptin ($P<0.001$) expression in PAT was lower in LBW compared with ABW male lambs. There were also significant relationships between both PPAR γ and leptin expression in PAT and birth weight in males. In contrast, birth weight did not influence PPAR γ and leptin expression in female lambs. Female lambs had lower plasma insulin concentrations and higher relative PAT mass ($P<0.05$).

than males, and in females PPAR γ expression was directly related to mean plasma insulin ($r^2=0.41$, $P<0.05$) and the size of perirenal adipocytes ($r^2=0.64$, $P<0.01$). In females, leptin expression in PAT was also related to the size of perirenal adipocytes ($r^2=0.50$, $P<0.05$). Plasma leptin was not different between LBW and ABW lambs, or between male and female lambs, and was not related to any measure of fat mass at 21d. There was no effect of birth weight or gender on RXR α , adiponectin, LPL or G3PDH expression in perirenal fat. **Conclusions:** There are differences in the effects of birth weight on adipose gene expression in male and female lambs. We postulate that the reduced expression of PPAR γ and leptin in perirenal fat of LBW male lambs may be related to an impaired insulin sensitivity, when compared with female lambs. The differential effect of birth weight on adipocyte gene expression in male and female lambs may be important in gender specific programming of an increase in visceral fat mass in adult life.

94

A LOW PLACENTAL GROWTH FACTOR CONCENTRATION IN MATERNAL PLASMA AT 23-24 WEEKS OF GESTATION IN PATIENTS WITH AN ABNORMAL UTERINE ARTERY DOPPLER VELOCIMETRY INCREASES THE RISK OF FETAL GROWTH RESTRICTION. Jimmy Espinoza,¹ Jyh Kae Nien,¹ Samuel S Edwin,¹ Luis Medina,² Ricardo Gomez,² Moshe Mazor,³ Roberto Romero.¹ ¹Perinatology Research Branch, NICHD, NIH, DHHS, Bethesda, MD, USA; ²CEDIP, Dept of OB/GYN, Sotero del Rio Hospital, Puente Alto, Santiago, Chile; ³Dept of OB/GYN, Wayne State University, Detroit, MI, USA.

Objective: Intrauterine growth restriction is a syndrome which may be caused by chronic uterine ischemia and/or defective placentation. An anti-angiogenic state has been implicated in the pathophysiology of preeclampsia (PE). However, PE and small for gestational age (SGA) share some pathophysiologic features. The objective of this study was to determine if changes in placental growth factor (PIGF) and soluble vascular endothelial growth factor receptor-1 (sVEGFR-1) occur prior to the diagnosis of SGA and whether these changes are related to Doppler abnormalities in the uterine artery.

Methods: A longitudinal study was performed to examine the relationship among uterine artery Doppler velocimetry (UADV), the maternal plasma concentration of PIGF and sVEGFR-1 and the occurrence of SGA. PIGF and sVEGFR-1 plasma concentrations were measured in samples collected at 23-24 weeks using immunoassays.

Results: 1) The prevalence of SGA was 9.5% (323/3,455); 2) An abnormal UADV was detected in 11% (379/3,455) of the study population, and 13.5% (47/347) delivered SGA neonates; 3) Patients with an abnormal UADV who delivered SGA neonates had lower plasma PIGF concentrations and higher plasma sVEGFR-1 concentrations than those who delivered AGA neonates (for PIGF: SGA median: 242 pg/ml, range: 0-1,270 vs. AGA median: 362pg/ml, range: 0-2,040; $p<0.001$; for sVEGFR-1: SGA median: 859 pg/ml, range: 407-3,019 vs. AGA median: 804 pg/ml, range: 0-2,550; $p=0.03$); 4) Among patients with an abnormal UADV and a low PIGF concentration, the prevalence of SGA was double than that of patients with a PIGF ≥ 280 pg/ml [19.1% (29/152) vs. 8.5% (18/213); $p=0.009$]; 5) The diagnostic indices for abnormal UADV, PIGF + UADV and sVEGFR-1 + UADV are displayed.

Conclusion: A low plasma concentration of PIGF in patients with high impedance to flow in the uterine artery at 23-24 weeks increases the risk of delivering a SGA neonate.

Diagnostic indices for the prediction of SGA

	Sensitivity	Specificity	PPV	NPV	LR(+)	LR(-)
Uterine Doppler	17.2% (50/291)	89.6% (2835/3164)	13.2% (50/379)	92.2% (2835/3076)	1.65 (1.26-2.17)	0.21 (0.7-1.21)
Uterine Doppler + PIGF <280 pg/ml	10.1% (29/288)	97.2% (2853/2936)	25.9% (29/112)	91.7% (2853/3112)	3.56 (2.38-5.34)	0.93 (0.62-1.39)
Uterine Doppler + sVEGFR-1 >90 pg/ml	8% (23/288)	96.5% (2833/2936)	18.3% (23/126)	91.4% (2833/3098)	2.28 (1.47-3.52)	0.95 (0.62-1.47)

95

MATERNAL S100B LEVELS PREDICT PERINATAL BRAIN DAMAGE IN INTRAUTERINE GROWTH RETARDATION.

Pasquale Florio,¹ Diego Gazzolo,² Emanuela Marinoni,³ Romolo Di Iorio,³ Mario Lituania,³ Matteo Bruschetti,² Filiberto M Severi,¹ Michela Torricelli,¹ Felice Petraglia.¹ ¹Pediatrics, Obstetrics & Reproductive Medicine, University of Siena, Siena, Italy; ²Department of Pediatrics, G. Gaslini Children's University Hospital, Genoa, Italy; ³Laboratory of Perinatal Medicine and Molecular Biology, University "La Sapienza", Rome, Italy. Intrauterine growth retardation (IUGR) still accounts for most cases of perinatal mortality and for about 40% of neurologically handicapped children. In this age-matched (30-40 weeks) study we evaluated serum levels of S100B, a marker of central nervous system damage, in: a) 212 women whose newborns had birth-weight appropriate for gestational age (controls); b) 106 pregnancies complicated by IUGR. According to the presence of abnormal cerebral ultrasound patterns suggestive of intraventricular hemorrhage (IVH), IUGR group was subdivided in: Group A (n=46): without brain sparing effect, without IVH and normal neurological examination; Group B (n=34): with brain sparing effect, without IVH and normal neurological examination; Group C (26): with brain sparing effect and IVH. Cerebral ultrasound scanning was assessed within the first 72 hours and at 7th day from birth. Neurological examination was daily performed and neonatal neurological conditions were classified using a qualitative approach as described by Prechtl et al. (1982).

Results: Group C had the highest (1.52 ± 0.24 mg/L) maternal blood S100 B levels, significantly ($P<0.001$) higher than controls (0.1 ± 0.007 mg/L), Group A (0.06 ± 0.007 mg/L), Group B (0.26 ± 0.04 mg/L). S100 B concentrations in Group B were significantly ($P<0.001$) higher than group A and control whilst no significant difference was found between group A and controls. By using the ROC curve, the S100B cut-off value of 0.72 mg/L achieved a sensitivity of 100% and a specificity of 98.4% as a single marker for prediction of IVH in IUGR (area under the curve: 0.998), with a positive and negative likelihood ratio of 62 and 0, respectively. Twenty-six out of 274 patients developed IVH, giving an overall prevalence of the disease in the study population of 9.5% (pretest probability). When S100B levels were found above the thresholds defined by the ROC curve analysis, the probability of developing IVH (positive predictive value) was as high as 93%, whilst if they were found unaltered the probability of developing IVH (100 - negative predictive value) was 0%. This study first shows that in pregnancies complicated by IUGR, S100B levels are higher in mothers carrying a fetus who later will develop a brain damage, than those did not at follow up. S100B measurement may represent a reliable marker of brain damage before birth at a stage when postnatal ultrasound and other diagnostic procedures were still silent.

96

EFFECTS OF EARLY MATERNAL UNDERNUTRITION AND REALIMENTATION ON KIDNEY DEVELOPMENT IN THE BOVINE FETUS.

Stephen P Ford,^{1,2} Britney E Burt,^{1,2} Bret W Hess,^{1,2} Min Du,^{1,2} Peter W Nathanielsz,^{1,3} Mark J Nijland.^{1,3} ¹Center for the Study of Fetal Programming, Laramie, WY; ²Department of Animal Science, University of Wyoming, Laramie, WY; ³Department of Obstetrics and Gynecology, University of Texas Health Science Center, San Antonio, TX.

Evidence from animals and humans indicates that impaired maternal nutrition during early gestation has deleterious effects on renal development, and may alter blood pressure in the offspring. **OBJECTIVE:** This study evaluated the impact of a global undernutrition from early to mid-gestation followed by realimentation through late gestation on fetal growth and renal development in the bovine fetus. **METHODS:** Multiparous beef cows (n=110) were synchronized for estrus and bred via artificial insemination to the same bull. On day 30 of gestation, cows were divided in equal numbers and fed to either meet NRC requirements (control; C) to gain weight (average = + 4.25% body weight) or fed below NRC requirements (nutrient restricted; NR) to lose weight (average = - 6.80% body weight) from day 30 to 125 of gestation (gestation length = 280 days). Fetal sex was determined by real-time ultrasonography on day 80 of gestation, and 30 cows (15 NR and 15 C) carrying only female fetuses were utilized in this study. On day 125, five C and five NR cows were necropsied, and the remaining 10 C and 10 NR cows were realimented to 100% NRC until necropsy on day 250 of gestation. **RESULTS:** On day 125, weights were reduced ($P<0.05$) for fetuses of NR versus C cows