5 LONG-TERM NEURODEVELOPMENTAL OUTCOME IN TWIN-TO-TWIN TRANSFUSION SYNDROME IN THE EUROFOETUS TRIAL

LISA ÖRTQVIST[1], SYLVIE CHEVRET[2], LAURENCE BUSSIERES[3], STEPHANIE STARACI[1], FABIENNE HUARD[1], YVES VILLE[1], [1]Paris-Ouest University VSQ, Department of Gynecology and Obstetrics, Paris, France, [2]Université Paris 7, INSERM 444, Statistics, Paris, France, [3]Délégation Régionale à la Récherche Clinique, Hopital Saint-Louis, Clinical Research, Paris, France

OBJECTIVE: To investigate long-term neuro-developmental outcome of children born in the Eurofoetus RCT comparing endoscopic laser surgery and serial amnioreduction in twin-to-twin transfusion syndrome (TTTS).

STUDY DESIGN: Survivors beyond 6 months were followed-up and evaluated by standardized examination (Amiel-Tison and Gosselin) and by the Ages and Stages questionnaires (ASQ). Primary outcome was the incidence of severe neurological abnormalities leading to permanent disability. In addition children were subjected to cognitive evaluation using Wechsler Intelligence Scale for Children (WISC-IV) at the age of 6.

RESULTS: 120 children (73 treated with laser (L) and 47 with amnioreduction (A)) survived beyond 6 months. Six were lost to follow-up. 114 children (69 L and 45 A) were examined at a median (25-75 percentile) of 5.3 (4.4-6.1) years. Incidence of major neurological problems was 15/114 (13.1%). Univariate analysis is summarized in Table 1. Multivariate analysis showed that only gestational age at delivery, 1-minute Apgar score and Quintero staging were predictive factors. Neurological evaluation changed over time with improvement or worsening in 4/114 and 5/114 cases but remained stable from the age of 2. Normal ASQ scores were found in 72% and 89% and in 72% and 80% of cases at 2 and 4 years in the L and A groups respectively (NS). IQ was below 85 in 0/10 and 2/9 children in L and A groups at the age of 6.

CONCLUSION: Among TTTS survivors, the risk of developing long-term major neurological impairment depends upon perinatal factors but not of fetal treatment.

Table 1: Prediction of severe neurological impairment

Variable	Odd Ratio	p-value
Donor/Recipient	0.54	0.23
Laser/amnio reduction	0.94	0.92
Quintero Staging (3-4/1-2)	3.17	0.0170
Gestation at delivery, (weeks)	0.76	0.0024
Birthweight, SD	1.01	0.98
Apgar 1min	0.69	0.0018
Apgar 5min	0.59	0.0106
Arterial pH	0.05	0.51

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6 THE EFFECT OF SFLT-1 OVER-EXPRESSION IN PREGNANT MICE ON BLOOD PRESSURE OF THE OFFSPRING LATER IN LIFE

FANGXIAN LU[1], EGLE BYTAUTIENE[1], ESTHER TAMAYO[1], PHYLLIS GAMBLE[1], GARLAND D. ANDERSON[1], GARY D. V. HANKINS[1], MONICA LONGO[1], GEORGE SAADE[1], [1]University of Texas Medical Branch, Obstetrics & Gynecology/Maternal Fetal Medicine, Galveston, Texas

OBJECTIVE: sFlt-1 has been implicated in the etiology of preeclampsia, and over-expression of sFlt-1 in rodents results in a preeclampsia-like condition. Our objective was to determine if fetal programming of adult blood pressure is altered in a previously characterized mouse model of preeclampsia induced by sFlt-1.

STUDY DESIGN: As previously established, CD-1 mothers at day 8 of gestation were injected with an adenovirus carrying Flt (1-3) [AdFlt(1-3); 10^9PFU] or with an adenovirus carrying mFc as control (10^9PFU). The resulting pups were followed until 6 months of age (average life span 1.5 years), at which time blood pressure (BP) catheters were inserted through the left carotid artery into the aortic arch and connected to a telemetric transmitter. BP was recorded continuously for 6 days in the conscious unrestrained offspring. Daily mean blood pressures over 6 hours' intervals and its diurnal variation were calculated. The offspring weight was also recorded from weaning (4 wks old) until adulthood (10 wks old). One-way ANOVA followed by Newman-Keuls post hoc test were used for statistical analysis ($p<0.05$).

RESULTS: Mean BP was significantly higher during the entire measurement period in the offspring born to sFlt-1-treated mothers (D1: 146.33 ± 4.98 and D6:136.54 ± 2.17mmHg) compared with offspring born to mFc-treated mother (D1:120.76 ± 2.88 and D6:113.54 ± 2.17mmHg). This difference was also present considering day versus night. However within each group BP was similar between day and night. In addition, the offspring from sFlt-1-treated mothers were significantly smaller from weaning until adulthood.

CONCLUSION: Over-expression of sFlt-1 in the mother leads to hypertension in the offspring later in life. Our findings highlight the role of the intrauterine environment in the developmental origin of adult disease, and the impact of preeclampsia on future health of the offspring. Furthermore, this mouse model of hypertension during pregnancy provides a novel approach for studying fetal vascular programming.

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7 LOW BIRTH WEIGHT AMONG ADULTS WITH A FAMILY HISTORY OF DIABETES DECREASES THE RISK OF METABOLIC SYNDROME

BETTINA PAEK[1], KATHERINE EASTWOOD[1], KRISTINA UTZSCHNEIDER[2], JENNY TONG[2], FERNANDO GERCHMAN[2], DREW ROBILIO[1], WILFRED FUJIMOTO[2], STEVEN KAHN[2], DARCY CARR[1], [1]University of Washington, Obstetrics and Gynecology, Seattle, Washington, [2]University of Washington, Medicine, Seattle, Washington

OBJECTIVE: Having a low weight at birth (LBW) or macrosomic weight (MBW) have been linked to cardiovascular risk factors and type 2 diabetes (T2D) later in life. We hypothesized that the risk of obesity, hypertension (HTN), the metabolic syndrome (MS), and T2D would be increased in subjects who weighed <2500g (LBW) or 4000g (MBW) at birth and had a first-degree relative with T2D.

STUDY DESIGN: We performed a cross sectional analysis on 1148 mother-child pairs who participated in the GENetics of Non-Insulin dependent Diabetes (GENNID) to compare the frequencies of the MS and T2D in adult offspring with reported LBW (n=120) or MBW (n=122) compared to normal BW (NBW: n=906). The MS was defined by the revised National Cholesterol Education Program Adult Treatment Panel III. T2D was determined by medical history or fasting and 2 hour glucose values.

RESULTS: The groups had similar age (mean$\pm$SE: LBW 45.2 ± 1.12 vs NBW 44.2 ± 0.39 vs MBW 43.4 ± 1.07 years,$p=0.5$), sex distribution (female: 63 vs 59 vs 56%, $p=0.6$) and smoking status (48 vs 49 vs 57%, $p=0.1$). LBW subjects were more likely to be African American (25 vs 14 vs 9%, $p=0.001$). Adjusting for age, sex, smoking, and race, LBW were less obese than NBW (BMI 28.4 ± 0.64 vs 31.3 ± 0.28 kg/m^2, $p<0.0001$ and had lower waist circumference 92 ± 2 cm vs 101 ± 1 cm, $p<0.0001$), whereas MBW had higher BMI (33.6 ± 0.87 vs 31.4 ± 0.28 kg/m^2, $p=0.02$) and a trend to higher waist circumference (105 ± 2 vs 101 ± 1 cm, $p=0.09$). LBW also had lower blood pressures (systolic 119 ± 2 vs 123 ± 1 mmHg, $p=0.006$) and insulin levels (13.9 ± 1.3 vs 17.6 ± 0.7 iU/ml, $p=0.007$). Consistent with this, LBW had a decreased risk of the MS (LBW 58 vs NBW 70%, OR .54, 95% CI .30-.95, $p=0.03$). However, the risk of T2D was not different (LBW 61 vs NBW 60 vs MBW 60%, $p=0.9$).

CONCLUSION: Among individuals with a family history of T2D, having LBW decreased the risk of obesity, central adiposity, HTN, and the MS later in life. Thus, in this high-risk population, LBW appears protective for future metabolic risk; whereas MBW did not confer additional risk of MS or T2D over NBW.

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8 FETAL ORIGINS OF DISEASE: ESSENTIAL NUTRIENT SUPPLEMENTATION PREVENTS ADULT METABOLIC DISEASE IN A TRANSGENERATIONAL MODEL OF IUGR

KJERSTI AAGAARD-TILLERY[1], WILLIAM HOLLAND[2], ROBERT MCKNIGHT[3], SHANNON JENKINS[3], XING YU[3], SCOTT SUMMERS[2], WARE BRANCH[4], ROBERT LANE[3], [1]University of Utah, Obstetrics and Gynecology, Salt Lake City, Utah, [2]University of Utah, Biochemistry and Molecular Biology, Salt Lake City, Utah, [3]University of Utah, Division of Neonatology, Salt Lake City, Utah, [4]University of Utah, Obstetrics and Gynecology, SLC, Utah

OBJECTIVE: Adult metabolic diseases, such as obesity and diabetes, result from in utero constraints; these morbidities have been shown to extend across generations. Development of the metabolic phenotype is associated with fetal alterations in one-carbon metabolism, which manifest as persistent changes in hepatic gene expression accompanied by epigenetic modifications in DNA methylation. We hypothesized that supplementation of essential nutrients (ENS) serving as intermediates in the one-carbon pathway would prevent adult metabolic disease. We therefore sought to characterize the effects of ENS in a transgenerational model of IUGR.

STUDY DESIGN: Sprague-Dawley P1 dams underwent bilateral uterine artery ligation (n 8) or sham surgery (n 8) on e19, and resultant F1 litters yielded IUGR (n 64) or control lineages (n 64), respectively. On d21, weaned F1 were allocated to ENS (Teklad8640+folic acid, choline, B12, betaine, L-methionine, L-arginine, zinc) or control diet (Teklad8640). F1 pairs were mated by d80, and resultant F2 (n 512) were weaned to their parental diet. F2 body composition was determined by pDEXA, and glucose and insulin tolerance tests with hyperinsulinemic euglycemic [^{14}C]glucose clamps were performed.

RESULTS: Significant differences in mean birthweight were observed among F2 offspring of IUGR lineages (maternal 6.1 g, paternal 6.5 g, both 5.6 g) when compared with shams (8.0 g), regardless of maternal diet (6.0 g vs 6.1 g). However, by d160 these progeny of IUGR animals on control diet exceeded sham body weights (496 g vs 411 g) while ENS fed had not (340 g vs 390 g). Central fat mass was significantly less among ENS fed IUGR lineages (7.9 g vs 53.5 g, $p=.02$). Furthermore, male offspring from the IUGR lineages on control diet developed hepatic insulin resistance (HGO 9.5 vs $-.2$ mg/kg/min, $p=.02$), whereas the ENS diet prevented this adult morbidity (1.5 mg/kg/min, $p=.047$).

CONCLUSION: Diet supplemented with essential nutrients, yet unaltered in its caloric content, prevents adult obesity and insulin resistance in a heritable transgenerational model of IUGR.

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