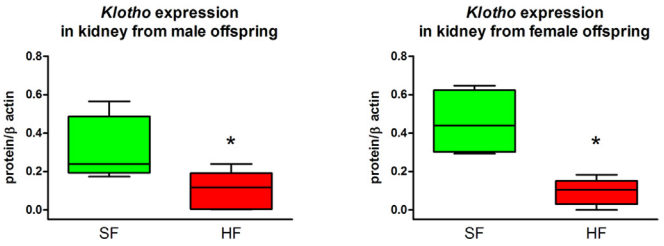
CONCLUSION: Offspring born to obese mice demonstrate an accelerated aging process. These modifications were tissue- specific. Our data demonstrates for the first time that maternal pre-pregnancy obesity resulting from high fat diet programs the offspring for the development of accelerated aging.



Box plot: median, 25th-ile, 75th-ile, max and min values. *p<0.05. SF: pups born to mothers fed standard chow, HF: pups born to mothers fed high fat diet.

46 Lipopolysaccharide (LPS)-induced perinatal inflammation increases postnatal airway reactivity

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OBJECTIVE: Antenatal inflammation can impair pulmonary maturation and potentially promote development of postnatal chronic lung disease. The purpose of our investigation is to evaluate how in utero exposure to maternal inflammation influences neonatal pulmonary function in a murine model. Our hypothesis was that inflammation leads to structural and functional airway changes that contribute to chronic diseases such as asthma.

STUDY DESIGN: Breeding colonies of C57/BL6 wild-type mice were established. On embryonic day 16 pregnant dams underwent intraperitoneal injections with sterile saline or with different concentrations of LPS (E. coli 055:B5) to induce maternal inflammation: 50 ug/kg, 200 ug/kg, 400 ug/kg. Dams spontaneously delivered and pups were monitored until postnatal day 21 when pulmonary function testing was performed using a SciReq FlexiVent system. Airway resistance, compliance and inspiratory capacity were assessed at baseline and in response to increasing concentrations of the bronchoconstrictor methacholine.

RESULTS: Intra-peritoneal LPS did not adversely influence maternal or neonatal mortality, or maternal failure to thrive during pregnancy. Neonatal pups were of comparable weight across groups. At postnatal day 21, LPS pups showed lower weight compared to controls, but there were no significant differences between the three different LPS dose groups. Airway resistance was increased with LPS, and importantly, LPS pups showed decreased airway compliance and inspiratory lung capacity compared to saline controls.

CONCLUSION: In this model of LPS-induced maternal inflammation, pulmonary function of the progeny is detrimentally impacted in terms of increased airway resistance, decreased airway compliance, and decreased inspiratory capacity. These changes represent characteristics of inflammatory reactive airway disease such as asthma. Future studies are needed to determine how antenatal inflammation alters neonatal pulmonary structure and airway function with the aim of developing novel therapeutic avenues.

47 Differential expression of Rac1 in common aneuploidies: a model for altered placentation

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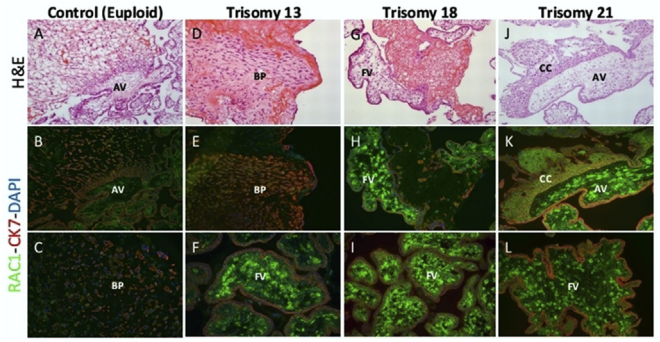
OBJECTIVE: Inadequate formation and regeneration of the placenta contribute to several pregnancy syndromes such as IUGR & preeclampsia, which may lead to iatrogenic preterm delivery with the goal of preventing fetal death and maternal complications. We investigated the effects of commonly occurring aneuploidies (Trisomy 21,18, and 13; T21,T18 and T13, respectively) on placentation. Specifically, we focused on the role of Rac1, which our microarray data showed was upregulated in all three trisomies.

STUDY DESIGN: We collected second trimester samples of the maternal-fetal (decidua-placental) interface: 20 trisomy cases (T21, n=10; T18, n=6; T13, n=4) and 4 gestational age-matched, euploid controls (14-22 weeks). Fluorescent in situ hybridization was used to confirm ploidy. Microarray approach enabled global transcriptional profiling in trisomies vs. controls. For immunolocalization, samples were fixed in 3% paraformaldehyde and embedded in OCT. Cryosections were stained with an antibody specific for Rac1 to validate its differential expression at the protein level.

RESULTS: Microarray analyses revealed upregulation of RAC1 mRNA in the trisomies that were studied (T13, T18, T21). Rac1, a small G protein, is involved in a wide variety of signaling pathways and in the migration of extravillous trophoblasts. We observed a marked increase in staining intensity for the Rac1 protein in trisomic placental biopsies as compared to control. RAC1 localized primarily to the mesenchymal cores of floating/anchoring chorionic villi, with expression generally absent from the basal plate and invasive trophoblasts (Fig 1.).

CONCLUSION: Our findings showed altered expression, in trisomy-affected pregnancies, of a protein that is involved in normal placental development. These pregnancies have increased rates of miscarriage and adverse pregnancy outcomes. Overexpression of Rac1 could explain these problems and points to the possible role of the mesenchymal compartment in the placental defects that are associated with these aneuploidies.



Differential expression of the Rac1 protein in placental villi-at 20x magnification. (A-C) Control (euploid) placental sample. A-B show an anchoring villus (AV) with invasive trophoblasts by H&E staining as well as fluorescent staining; the maternal-fetal interface. C-Basal plate (BP) portion in euploid tissue, showing minimal expression of Rac1 protein (green). (D-F) **Trisomy 13**. D-E show a section of basal plate, confirming that there is minimal expression of Rac1 in maternal tissue, even in trisomy. F shows increased presence of Rac1 protein in the villous core of a floating villi (FV). (G-I) **Trisomy 18**. G-I all show FV with increased expression of Rac1. (J-L) **Trisomy 21**. J-K show an AV with visible cell column (CC), with expression of Rac1. L also confirms the location of Rac1 protein in FV.

48 Obesity in pregnancy is associated with decreased placental estradiol biosynthesis

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OBJECTIVE: Estradiol is a critical modulator of insulin sensitivity and other key reproductive physiologic functions. Obese pregnant women (OP) have lower plasma estradiol levels compared to their normal weight counterparts (NWP). Since the placenta is the only source of estradiol (synthesized solely from cholesterol in the mitochondria), we hypothesized that maternal obesity alters placental cholesterol biosynthetic pathways (Figure 1), potentially affecting feto-placental function.

STUDY DESIGN: Placenta and maternal blood were obtained at term elective C-section delivery in 24 women with a wide BMI range and insulin sensitivity (Table 1). Cholesterol was measured in placental mitochondria by ELISA. Gene expression of key enzymes in the estradiol biosynthetic pathways (Figure 1) was measured by real-time RT-PCR and placental cholesterol transport by western blot analysis of mithochondrial transporters.

RESULTS: OP were hyperinsulinemic and insulin resistant compared to NWP. Mitochondrial cholesterol concentrations were lower in placenta of obese women (0.21 ± 0.06 vs. 0.37 ± 0.09 μg/mg protein, $p<0.05$). Several genes regulating cholesterol biosynthesis: ACAT1, ACAT2, LSS, SQLE, SC4MOL, NSDHL, CYP51A1 (Figure 1) were down-regulated ($p<0.05$) in placenta from OP compared to NWP. The expression of the primary placental cholesterol transporters, MLN64 and TSPO were both reduced by 30% ($p<0.05$). 17-beta-hydroxysteroid dehydrogenase (17βHSD), a key enzyme in estradiol production was down-regulated by 300% in placenta of OP ($p<0.05$).

CONCLUSION: Several key steps leading to cholesterol biosynthesis and estradiol production are altered in pregnancy associated with obesity and insulin resistance. These data highlight for the first time that obesity alters a major endocrine function of the feto-placental unit by decreasing its capacity to synthesize estradiol. We speculate that decreased placental estradiol function may relate to adverse pregnancy outcomes such as stillbirth, preterm delivery and glucose intolerance in OP compared with NW.

Schematic representation of placental steroid hormone biosynthetic pathways showing the down regulated genes in cholesterol biosynthesis, cholesterol transporters and genes involved in steroid hormone production.

Characteristics of the study cohort (mean + SEM)

Group	Mat. pre BMI	Insulin µU/mL	Glucose mg/dl	HOMA	Baby wt.	Placenta wt.
Lean (n=12)	22.93 ± 0.85	7.86 ± 0.85	68.04±1.41	1.29 ± 0.15	3.12 ± 0.08	644.9 ± 68.66
Obese (n=12)	42.58 ± 1.5	38.10 ± 3.72	79.62 ± 3.51	7.74 ± 0.84	3.43 ± 0.13	706.85 ± 47.16
p value	<0.01	<0.01	<0.01	<0.01	0.02	0.23

IR, insulin resistance; *Mat*, maternal; *wt*, weight.

49 Arterial cord blood (ACB) lactate correlates with brain lactate in non-encephalopathic term infants

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OBJECTIVE: Brain lactate is a biomarker for injury in infants with HIE. Recent data indicate ACB lactate may be superior to pH and base excess as a marker of neonatal morbidity risk. Advanced magnetic resonance imaging (MRI) allows detection of brain lactate without need for pathologic samples. Combining these technologies, we aimed to correlate ACB lactate with brain lactate in non-encephalopathic term infants.

STUDY DESIGN: A nested case-control study was performed within an on-going prospective cohort of over 8000 consecutive singleton term ($\geq$ 37 weeks) non-anomalous infants. Neonates underwent cerebral MRI within the first 72 hours of life. Cases (ACB pH $\leq$ 7.10) were gender- and race-matched 1:3 to controls (ACB pH $>$ 7.10). MR spectroscopy (MRS) was used to detect qualitative, and if present quantitative, lactate in the left thalamus by a single technician, blind to ACB lactate and clinical measures. The lactate peak was identified as a doublet (2 methyl groups) at 1.33 ppm resonance frequency. Integral values for MRS lactate, as well as N-acetyl aspartate (NAA) for normalization, were calculated. The ACB lactate was measured as part of the primary cord gas analysis. Linear regression was used to estimate the association between incremental change in ACB lactate and brain lactate, both directly and as a ratio with NAA, adjusting for mode of delivery, nulliparity, and maternal fever.

RESULTS: Of 178 infants who underwent MRI with spectral sequencing, 3 studies were too poor to interpret. 52 of the remaining 175 infants had detectable brain lactate. The 52 infants with MRI lactate peaks had ACB lactate values of 1.6 - 11.4 mmol/L. Among these infants, for every 1.0mmol/L increase in ACB lactate, there was an increase in MRI lactate of 0.02, which remained significant even when corrected for NAA.

CONCLUSION: MR spectroscopy measured brain lactate is significantly correlated with ACB lactate in non-anomalous term infants, which may help to explain the observed association between ACB lactate and neurologic morbidity.