to test the hypothesis that placental DNA is able to stimulate a robust proinflammatory cytokine response after enzymatic cleavage of telomere regions.

STUDY DESIGN: Genomic DNA was obtained from maternal, fetal and placental tissues from pregnant CD-1 mice (DNA extraction kit from Roche). The DNA was then incubated with the exonuclease BAL-31 (which cleaves the telomere ends of the chromosomal DNA). The BAL-31 treated DNA was incubated with mouse peritoneal macrophages (RAW 264.7 cells from ATCC) to assess TLR9 stimulation. Positive control incubations were performed using ODN2395 (a TLR9 agonist). IL6 concentration in the incubation media was assayed by ELISA (BioLegend), normalized for cellular protein, and reported as picograms (pg) per milligram (mg) protein. Each experiment N = 4.

RESULTS: The optimal BAL-31 digestion time was 2 hours. The maximal stimulation occurred with 1 - 5 mcg/mL BAL-31 treated placental DNA (result = 11,431 - 15,140 pg IL6/mg protein); results significantly ($p< 0.01$) higher than found with untreated DNA (= 5.7 pg/mg) or ODN2395 (= 944 pg/mg). Timed studies demonstrated increased IL6 at 6 hours which peaked at 24 hours after the DNA addition. Compared to placental DNA, BAL-31 treated fetal DNA produced a similar robust IL6 response (= 13,654 pg/mL), whereas BAL-31 treated DNA from maternal liver produced a significantly lower IL6 response (= 6,313 ng/mg, $p< 0.01$).

CONCLUSION: During apoptosis, DNA undergoes degradation, including removal of telomere sequences. These studies have demonstrated that placental DNA depleted of telomeres stimulates robust IL6 production by macrophage cells. Inflammation appears to plays a key role during the onset of spontaneous parturition; these studies have provided additional support for the hypothesis that cell-free fetal DNA, generated during placental apoptosis, is able to trigger these events. (Funded by VCRB at MGH)

205 Maternal outcomes in pregnancies with pulmonary hypertension: A cohort of 89 cases

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OBJECTIVE: Maternal pulmonary hypertension (pHTN) has historically been associated with prohibitively high maternal morbidity and mortality. However, data is limited to case reports and case series of the most severe cases, restricting our ability to adequately counsel and care for these patients. We sought to examine maternal outcomes in a large cohort of women with pHTN of various etiologies and severity.

STUDY DESIGN: We performed a retrospective cohort study of all pregnancies in women with pHTN delivering at a single tertiary center over a 10 year period (2004-2014). pHTN was defined as pulmonary artery systolic pressure $\geq$ 40mmHg prior to or during pregnancy estimated by Echocardiography or directly measured by right heart catheterization. Patients with pHTN due to congenital heart disease (CHD) were compared to those with pHTN from other causes. Additionally, patients were compared according to degree of pHTN (mild, moderate, or severe). Primary outcomes were intensive care admission (ICU), hospital readmission after delivery, heart failure, respiratory failure, pre-eclampsia, arrhythmia during pregnancy, death, and a composite of severe morbidity/mortality. Overall results were analyzed in three ways: 1) as a whole, 2) including only births after 20 weeks, 3) including only first pregnancy since diagnosis of pHTN.

RESULTS: Our cohort included 89 pregnancies in 68 women. 16 cases were associated with CHD, while 73 were due to other causes. The cohort included 58 mild, 19 moderate, and 12 severe cases of pHTN. There were only three cases of maternal death, all during the first pregnancy since diagnosis. In continuing pregnancies, rates of heart failure, respiratory failure, and ICU admission were 21.1%, 23.7%, and 29% respectively. Composite severe morbidity and mortality was 42.1% overall in continuing pregnancies and increased to 50% in patients with severe pHTN.

CONCLUSION: In the largest cohort of pHTN cases to date, we identified that the risk for major maternal morbidity is high, 40.7% among those with mild disease up to 50% for those with severe disease. Two of the three deaths occurred in women with mild disease.

	Overall*	Overall†	Overall§	pHTN-CHD associated	pHTN-Other etiology	Mild (PASP 40-54)	Moderate (PASP 55-69)	Severe (PASP ≥ 70)
	N=89	N=76	N=68	N=16*	N=73*	N=54†	N=14†	N=8†
ICU	25.8% (23)	29.0% (22)	27.9% (19)	18.8% (3)	27.4%(20)	27.8% (15)	35.7%(5)	25%(2)
Readmission	21.4% (19)	23.7% (18)	22.1%(15)	12.5% (2)	23.3%(17)	24.1%(13)	28.6%(4)	12.5%(1)
Heart failure	19.1% (17)	21.1% (16)	25%(17)	12.5% (2)	20.1%(15)	25.9%(14)	7.1%(1)	12.5%(1)
Respiratory failure	20.2% (18)	23.7% (18)	23.5%(16)	18.8% (3)	20.1%(15)	24.1%(13)	28.6%(4)	12.5%(1)
Pre-Eclampsia	20.2% (18)	23.7% (18)	19.1%(13)	25% (4)	19.2%(14)	18.5%(10)	42.9%(6)	25%(2)
Arrhythmia	6.7% (6)	7.9% (6)	5.9%(4)	12.5% (2)	5.5%(4)	7.4%(4)	7.1%(1)	12.5%(1)
Maternal Death	3.4% (3)	2.6% (2)	4.4% (3)	6.3% (1)	2.7% (2)	3.5%(2/58)*	0%(0/19)*	8.3%(1/12)*
Composite morbidity/mortality‡	38.2% (34)	42.1% (32)	42.7% (29)	31.3% (5)	39.7% (29)	41.4% (24/58)* 40.7% (22/54) †	31.6% (6/19)* 42.9% (6/14) †	33.3% (4/12)* 50% (4/8) †

Data is presented as % (n)
* Including all cases
† Including all births after 20 weeks
§ Including only first pregnancy since diagnosis of pHTN
‡ Composite of maternal death, heart failure, respiratory failure, intensive care unit admission, and invasive cardiac procedure required during pregnancy or 6 weeks post-partum.

206 Sex-specific effects of maternal obesity on embryo size and fetal brain oxidative stress

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OBJECTIVE: Maternal obesity (MATOB) is associated with adverse neurodevelopmental outcomes in children, including autism spectrum disorder, developmental delay, and ADHD. Underlying mechanisms remain unclear. In amniotic fluid of obese women, we previously identified gene expression patterns consistent with dysregulated fetal brain development and significant upregulation of *APOD*, a CNS-specific gene implicated in response to oxidative stress,. Here, we directly examined fetal brains in a mouse model of maternal diet-induced obesity.

STUDY DESIGN: Female (F) C57BL/6J mice were fed a 60% fat high-fat diet (HFD) or a 10% fat control diet (CD) for 10-12 weeks prior to mating. In pregnancy, obese dams continued on the HFD (HFD/HFD), or transitioned to a CD (HFD/CD). Lean dams stayed on the CD (CD/CD). On embryonic day 17.5, fetal brains were snap frozen. RNA and protein were extracted from 25-35 embryonic brains/diet group. Quantitative RT-PCR was performed for *apod*. Fetal brain maldionaldehyde (MDA), a marker of oxidative stress, was quantified using HPLC. Kruskal-Wallis and Mann-Whitney testing determined significant differences between groups ($p<0.05$).

RESULTS: Embryos of HFD/HFD dams were significantly smaller than controls, with males (M) more severely affected than Fs ($p<0.001$, Fig 1A). Brain *apod* expression was significantly decreased in F embryos of HFD/HFD dams compared to controls ($p=0.003$, Fig 1B). When obese dams were switched to a CD in pregnancy, brain *apod* expression in Fs increased to levels similar to controls ($p=0.04$). These changes were not observed in M brains. F brains