

nuclear atypia in endometrial glands. We hypothesized that hyperinsulinemia and unopposed estradiol have a synergistic effect on inducing abnormal architecture and DNA damage in the endometrium, than either alone.

At 8-10 weeks old, cohorts of MKR (n=20) and WT (n=20) mice underwent ovariectomy and placement of either an estradiol (E2) or placebo (P) pellet. Metabolic profiling included insulin tolerance testing and MR for body composition. At 3 months post-implantation, mice received a partial hysterectomy and second pellet replacement. At 6 months, the remaining uterus was bisected into pieces. A blinded histological analysis was conducted by a gynecology pathologist. A marker of DNA damage due to oxidative stress, 8-oxoguanine-DNA-glycosylase (8-OHdG), was quantified by ELISA. Data was analyzed using Kruskal-Wallis test with multiple test correction, or Fischer's exact test.

By 6 months, MKR-E2 treated mice had a 27% lower body weight than MKR-P mice ($p<0.05$), and 31% lower than WT-E2 mice ($p<0.01$). WT-E2 and WT-P had similar weight, and were similar to MKR-P ($p=ns$). Percent body fat was similar across all 4 cohorts of mice ($p=ns$). Since placebo-treated mice had small, atrophied uteri with minimal gland formation, E2 pellet failure was determined by the presence of small, atrophied uteri and occurred in 4 MKR and 3 WT mice at either 3 or 6 months. All other MKR and WT E2 treated mice had enlarged uteri. The frequency of endometrial gland dilation was similar in MKR-E2 and WT-E2 uteri ($p=ns$), but all MKR mice had moderate-severe dilation, whereas WT mice had 50% mild and 50% moderate-severe dilation ($p=0.07$). Focal hyperplasia was present in one MKR-E2 mouse, and nuclear atypia was present in one WT-E2 mouse. MKR-P uteri had a 7-fold higher mean 8-OHdG relative to MKR-E2 uteri (5.0 ± 3.7 vs 0.7 ± 1.6 , $p<0.002$). WT-E2 and WT-P uteri had similar 8-OHdG (1.6 ± 0.8 vs 1.8 ± 0.6 , $p=ns$), as did MKR-E2 and WT-E2 uteri ($p=ns$).

Our findings show that hyperinsulinemia exacerbates the cystic dilation induced by chronic unopposed estradiol, indicating a synergy of insulin and estradiol in promoting abnormal glandular growth in the endometrium. Surprisingly, uterine DNA damage was highest in the setting of hyperinsulinemia alone, in a hormonal state mimicking post-menopause. Further work is needed to understand the effect of estradiol on intrauterine oxidative stress-induced damage.

Reproductive Endocrinology

IMPLANTATION AND PREGNANCY: IMPACT ON MATERNAL AND FETAL HEALTH

Long-Term Effects of Late Gestation in Utero Hypoxic Stress on Mood Disorders: Sex and Age Differences

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Introduction: *In utero* insults have been linked with increased fear and anxiety in progeny. *In utero* hypoxic stress is associated with a multitude of gestational complications such as pregnancy-associated hypertensive disorders and

intrauterine growth restriction. Maternal hypertension during pregnancy is also associated with increased mood and anxiety disorders in progeny. However, it is unknown if these associations are due to *in utero* hypoxic stress. We hypothesized that exposure to late gestational hypoxia will have a long-term impact on anxiety in progeny. **Methods:** Timed pregnant female Long-Evans rats were exposed to five days (gestational days: 15-20) of chronic intermittent hypoxia (CIH) or room air (normoxia - 21% O₂) for 8 hours during their sleep phase. Each CIH cycle was 6 min of 3 min hypoxia (10% O₂) and 3 min normoxia (21% O₂) for a total of 10 CIH cycles/hour. At weaning (PND 28), progeny was pair-housed with a conspecific of same sex and similar weight. To examine mood and anxiety disorders, we quantified anxiety-related behaviors (time spent in the center of open field arena, marble burying test, social and anti-social behaviors with conspecifics) along with quantifying food intake and circulating sex hormone levels during puberty (postnatal day, PND 40-45) and young adulthood (PND 60-65) in male and female progeny. **Results:** Gestational CIH did not impact circulating sex hormones or food intake, regardless of sex or age of progeny. However, gestational CIH increased anxiety related behaviors in pubertal females. These effects of gestational CIH on anxiety in pubertal females were not maintained, as these behaviors resolved in young adulthood. Gestational CIH did not impact male progeny, regardless of age. **Conclusion:** Exposure to CIH during gestation resulted in increased anxiety related behaviors in pubertal female progeny. *In utero* hypoxia during late gestation may temporarily increase the risk for mood and anxiety disorders in pubertal females.

Reproductive Endocrinology

IMPLANTATION AND PREGNANCY: IMPACT ON MATERNAL AND FETAL HEALTH

Long-Term Effects of Late Gestation in Utero Hypoxic Stress on Neurodegeneration: Sex and Age Differences

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Introduction: *In utero* insults have been proposed to lead to the onset of neurodegenerative diseases later in life, such as Parkinson's disease (PD). *In utero* hypoxia is associated with a multitude of conditions, such as maternal sleep apnea, preeclampsia, gestational diabetes, and maternal hypertension. Exposure to *in utero* hypoxia may impact male progeny more than female progeny, which may underlie the male biased sex differences in PD. It is currently unknown whether late gestational hypoxic stress has a long-term effect on brain regions associated with PD, such as the nigrostriatal pathway. We hypothesized that exposure to late gestational hypoxia will result in nigrostriatal impairment in adult male progeny compared to adult female progeny. **Methods:** Timed pregnant female Long-Evans rats were exposed to five days (gestational days: 15-20) of chronic intermittent hypoxia (CIH) or room air (normoxia - 21% O₂) for 8 hours during their sleep phase. Each CIH cycle was 6 min of 3 min hypoxia