form a unique population of cells in the arcuate nucleus (ARC) of the hypothalamus and play a critical role in GnRH/LH pulse generation. Based on recent evidence from our lab that chronic feed restriction reduces kisspeptin and NKB protein expression in young male sheep, we hypothesized that nutrient restriction would inhibit mRNA abundance for kisspeptin and NKB in the same animals. Fourteen wethers were placed into a fed to maintain body weight group (n=6; Fed) or a feed-restricted to lose 15-20% of pre-study body weight group (FR; n=8). Weekly blood samples (every 12 minutes for 4.5 hours) were taken via jugular venipuncture and plasma was stored at -20°C until the time of radioimmunoassay. Weekly body weights were recorded and feed amounts were adjusted to achieve desired body weights. At Week 13, animals were euthanized following blood collection, brain tissue was perfused with 4% paraformaldehyde, and tissue containing the hypothalamus was collected. Following submersion in 20% sucrose for at least four weeks, hypothalamic blocks were sectioned at 50 μm on a freezing microtome, and stored in a cryopreservative solution until processing. At Week 13, the average percent change in body weight was clearly evident (Fed, 6.79 + 3.4% vs FR, -19.82 ± 1.6%), and mean LH was significantly lower in FR wethers (13.41 + 3.7 ng/ml) compared to Fed controls (26.43 + 2.5 ng/ml). To assess changes in mRNA abundance, we used a relatively new *in situ* hybridization technique, RNAscope, to quantify mRNA for kisspeptin and NKB in the ARC with probes that were ovine-specific. Results showed that feed restriction reduced the number of kisspeptin mRNA-expressing cells (Fed, 231.2 + 14.4 vs FR, 100.3 + 35.9) and NKB mRNA-expressing cells (Fed, 192.7 + 18.4 vs FR, 97.3 + 21.7) per hemi-section. Furthermore, analysis of kisspeptin and NKB co-expressing cells (30 cells/animal) revealed that feed restriction significantly reduced the average mRNA integrated density for NKB, but not kisspeptin, compared to Fed controls. Together, these findings further support a role for kisspeptin and NKB in the central mechanism governing GnRH/LH secretion during undernutrition in male sheep.

Reproductive Endocrinology

CHALLENGES IN REPRODUCTIVE ENDOCRINOLOGY: LATE BREAKING INSIGHTS

Effect of Preconception Intensive vs. Standard Lifestyle Intervention on Birth Outcomes in Obese Women With Unexplained Infertility: A Multicenter Randomized Trial

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Effect of Preconception Intensive vs Standard Lifestyle Intervention on Birth Outcomes in Obese Women with Unexplained Infertility: A Multicenter Randomized Trial

We hypothesized that weight loss with an intensive preconception lifestyle (IL) intervention of caloric restriction with meal replacements, daily orlistat and increased physical activity in women with obesity and unexplained infertility (UI) was more likely to result in Good Birth Outcome than a standard lifestyle modification (SL) with increased physical activity alone. The 16 week period of lifestyle modification was followed by an open label empiric infertility treatment regimen of 3 cycles of ovarian stimulation with clomiphene, ovulation triggering with hCG and intrauterine insemination. We randomized 379 obese women 18-40y with UI (regular menses, normal ovarian reserve, patent reproductive tract and normal male factor). A Good Birth Outcome (GBO) was the primary outcome, defined as a live birth of an infant born at ≥37wks with a birthweight between 2500-4000g and no major congenital anomaly. Key secondary outcomes were live birth, pregnancy loss and pregnancy complication rates. The study had 80% power and an alpha of 0.05 to detect an absolute 15% difference in GBO. An Intention-to-Treat analysis was used. Both groups (SL N=191, IL N =188) were well matched at baseline(e.g. weight (kg), mean ± SD, SL:107±21, IL: 108 ±23). Women in the IL arm lost significantly more weight preconception than SL (SL -0.3±3.4 vs IL -7.3±6.6 kg, P<.001) with similar decreases in associated biometric and biochemical parameters. Overall 59.4% of the IL group lost >5% weight vs 6.5% in SL group(P<.001). Despite achieving the targeted weight loss, GBO rate between groups was not significantly different (IL12.2% vs SL 15.2%, IL Rate Ratio, 95% CI: 0.8, 0.5-1.3) or in live birth (IL 20.2% vs SL 22.0%, IL RR: 0.9, 0.6-1.4). Pregnancy loss among women who conceived trended higher in the IL group (IL 38.1% vs SL 23.7%, IL RR:1.6, 0.9-2.8) but miscarriage rates (loss after visualized intrauterine pregnancy), were significantly higher in IL (IL 20.6% vs SL 3.4%, IL RR: 6.1, 1.4-25.8, P=0.005). Birthweights were similar in both groups (IL: 3199±712 vs SL: 3106±794g). Major pregnancy complications trended lower in IL: Preterm Labor (IL 3.2% vs SL 10.2%), Pre-eclampsia (IL 6.3% vs SL 11.9%), Gestational DM (IL 9.5% vs SL 16.9%). Adverse events were more common in the IL group, i.e. increased GI side effects of bloating, flatulence, diarrhea and steatorrhea, likely related to use of orlistat. Moderate weight loss prior to conception does not improve live birth or GBO rates compared to exercise alone in obese women. Of concern, early pregnancy loss is more common when conception occurs after IL intervention. However a benefit to IL modification preconception may be lower perinatal morbidity, although further larger studies are necessary to confirm this potential benefit.