**Title:** Liraglutide improves cardiac outcomes in a pre-pregnancy mouse model

**Background:** Obesity during pregnancy increases cardiovascular disease risk due to the physiological demands of foetal growth, including increased blood volume and reduced cardiac output. These changes can exacerbate cardiac dysfunction, often persisting postpartum. Current recommendations advise pre-pregnancy weight loss. GLP-1 receptor agonists, e.g. liraglutide, show promise in weight management and improving cardiovascular outcomes, but their use in women of reproductive age remains understudied.

**Aim:** To explore the impact of liraglutide used pre-pregnancy on maternal cardiovascular health in a murine model.

**Methods:** Female C57BL/6 mice were fed a high-fat diet (HFD), and they received either subcutaneous injections of liraglutide (0.3 mg/kg) or saline for 4 weeks. A subset of dams was sacrificed pre-pregnancy. Prior to mating, liraglutide was ceased for 1 week and mice continued on HFD. The remaining dams were cohoused with a male until pregnancy was confirmed. Following birth and weaning of offspring, dams were sacrificed. Proteomic analysis was completed on pre- and post-pregnancy cardiac tissue using data-independent acquisition, liquid chromatography mass spectrometry. Statistical analysis was completed in R.

**Results:** Over-representation analysis of biological processes revealed increased enrichment of nucleoside triphosphate, purine nucleoside phosphate, and ribose phosphate pathways in the liraglutide-treated group compared to HFD alone (adjusted p<0.0001), suggesting enhanced nucleotide metabolism and energy-related processes. These effects were diminished post-pregnancy, with only Atp5po (log₂ fold change = 1.22) remaining elevated relative to HFD. Conversely, Fv1 (log₂ fold change = -0.591, p<0.001) and Ighm (log₂ fold change = -0.888, p<0.001) were significantly suppressed. Liraglutide treatment enriched triglyceride storage (adjusted p<0.001), suppressed ATP-dependent activity and positively regulated fatty acid metabolism (both adjusted p<0.01).

**Conclusion:** These findings underscore the potential of liraglutide as a strategy for pre-pregnancy weight management and cardioprotection. The loss of cardioprotective effects post-pregnancy highlights the need for tools to sustain cardiovascular health and weight management through pregnancy.