Background

Maternal obesity and gestational diabetes (GDM) are common pregnancy complications that cause significant maternal and neonatal morbidity.[1] Offspring of obese/diabetic mothers are at increased risk of adult-onset diseases.[2] Obesity and pregnancy are states of relative insulin resistance (IR) associated with elevated sympathetic tone.[3,4] Low-frequency electroacupuncture (EA) is increasingly recognised as a treatment for IR outwith pregnancy.[5,6] Glucose-lowering effects have been shown in >30 clinical and animal studies, mostly in T2DM and PCOS.[7] Acupuncture and related techniques modulate autonomic function via somatovisceral reflexes[8] and can exert neuroendocrine effects via GLUT4/MAPK/pERK upregulation.[9-11] Low-frequency EA normalizes insulin sensitivity in rats with polycystic ovary syndrome via effects mediated by the sympathetic nervous system.[12] EA effects *in vivo* are similar to aerobic and resistance exercise but independent of body composition.[13] Of note, EA acts synergistically with metformin, suggesting a potential adjunctive role to standard care.[14] Given the favorable safety profile of acupuncture in pregnancy,[15] the possible efficacy of EA for pregnancy-induced IR deserves further evaluation.

Overall Aim

- To determine whether or not EA can improve whole-body insulin sensitivity in rat pregnancies complicated by maternal obesity/GDM

Interval Events

- Moved from St George's University of London to University of Vermont (USA)
- Successfully gained local ethical approval (with self as principal investigator)
- Identified laboratory with relevant expertise in experimental endocrinology (including hyperinsulinemic euglycemic clamp procedure) to host project
- Based on local husbandry requirements, changed experimental diet from the cafeteria-style diet detailed in original BMFMS application to a standardized commercial diet proven to induce obesity/IR and fetal programming effects
- Successfully applied for additional funding from University of Vermont and the British Medical Acupuncture Society to expand scope of project from feasibility study (designed initially only to facilitate power calculation for more definitive experiment) to adequately powered proof-of-principle study

Methods

Sixty female Wistar rats (230±3g, 76±1d old) were housed under controlled conditions. Fifty were fed an obesogenic high-fat high-sugar (HFS) diet (TestDiet 58V8, 20% sucrose, 45% fat) for 44d [27-47] pre-mating and throughout pregnancy, and randomized to receive 12-14 sessions EA (10mA intensity, 3/15Hz alternating frequency, 30min each) of rectus abdominis (T6-L1), tibialis anterior (L4) and triceps surae (L5), vs. no intervention, daily under isoflurane anesthesia from embryonic day (E)1-4. Pregnancy (P) was confirmed by ultrasound in 19 treated and 19 untreated HFS rats (HFS+EA-P/HFS-P groups); on E18±1d, after an 18h fast, whole-body insulin sensitivity was quantified by terminal hyperinsulinemic-euglycemic clamp (by investigators blind to treatment group) prior to dissection. Clamps were performed during estrus in the remaining non-pregnant treated/untreated HFS rats (HFS+EA/HFS groups, n=6 each) and 10 unmated rats receiving standard chow (control group).

Results

At mating HFS-fed rats weighed 19% more than controls (330±3 vs. 277±6g, p<0.001) and 2SD above genotype mean for age. Glucose infusion rate (Figure 1) was reduced in HFS-P vs. control groups (reflecting IR) but restored in the HFS+EA-P group. Pancreatic weight was unaffected by diet alone (HFS vs. control p>0.05) but increased 24% in the HFS-P group; EA abolished this effect (Figure 2). Body weight and fat mass at necropsy were 6% and 15% lower, respectively, in HFS-P+EA vs. HFS-P groups (383±7 vs. 408±5g, p=0.007; 39±3 vs. 46±2g, p=0.047). Fetal/placental weight ratio was higher (4.09 vs. 3.79, p=0.034) and residual uterine weight lower (3.8±0.3 vs. 5.0±0.3g, p=0.003) after EA.

Conclusion

EA improves whole-body insulin sensitivity, decreases body weight and adiposity, and impacts pancreatic weight and placental efficiency in pregnant rats with diet-induced obesity. EA may have potential as a preventive treatment for gestational diabetes.

Future Directions

Having recently secured a 50:50 academic/clinical fellowship in Maternal-Fetal Medicine at the University of Vermont, I plan to apply for a 5-year NIH program grant to support further work moving towards clinical translation, including *in vivo* mechanistic experiments (using selective vagotomy and pharmacological inhibition of autonomic function), safety (maternal/fetal), programming effects (studying metabolic function of adult offspring of treated mothers) and a clinical study of acceptability/feasibility in patients with maternal obesity and/or GDM.

Figure 1

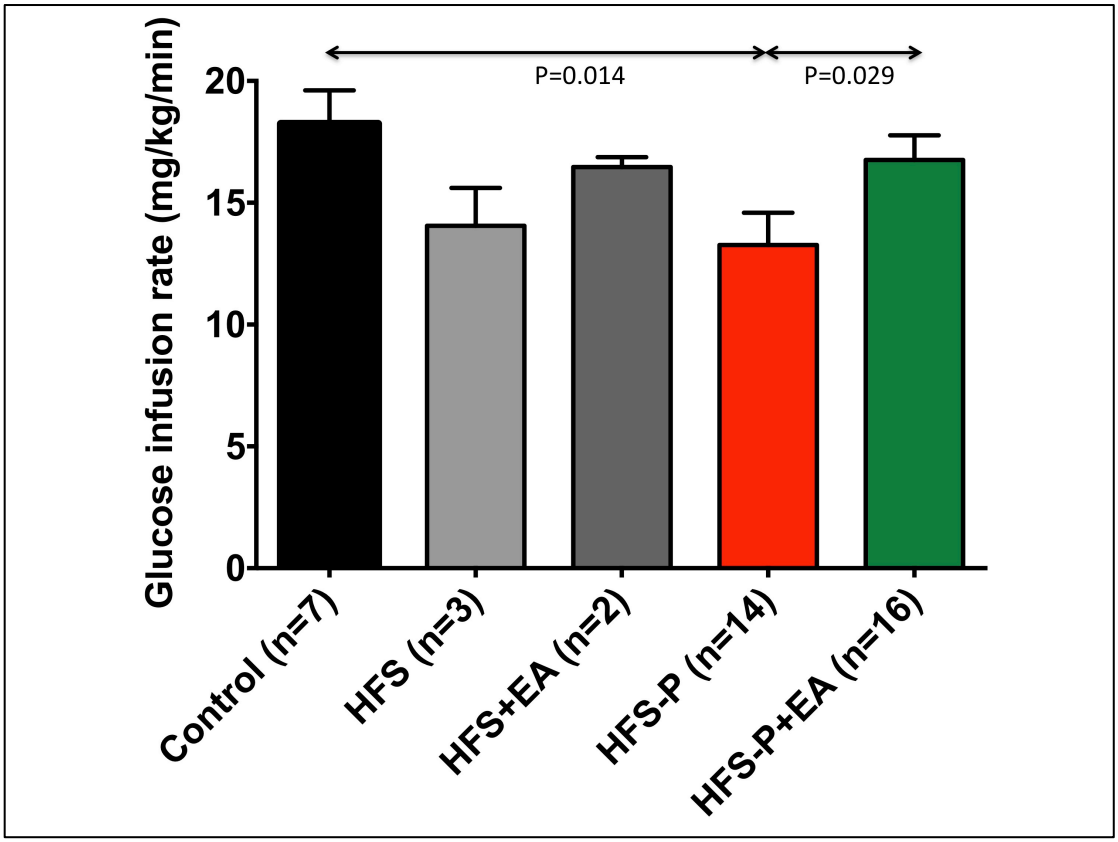
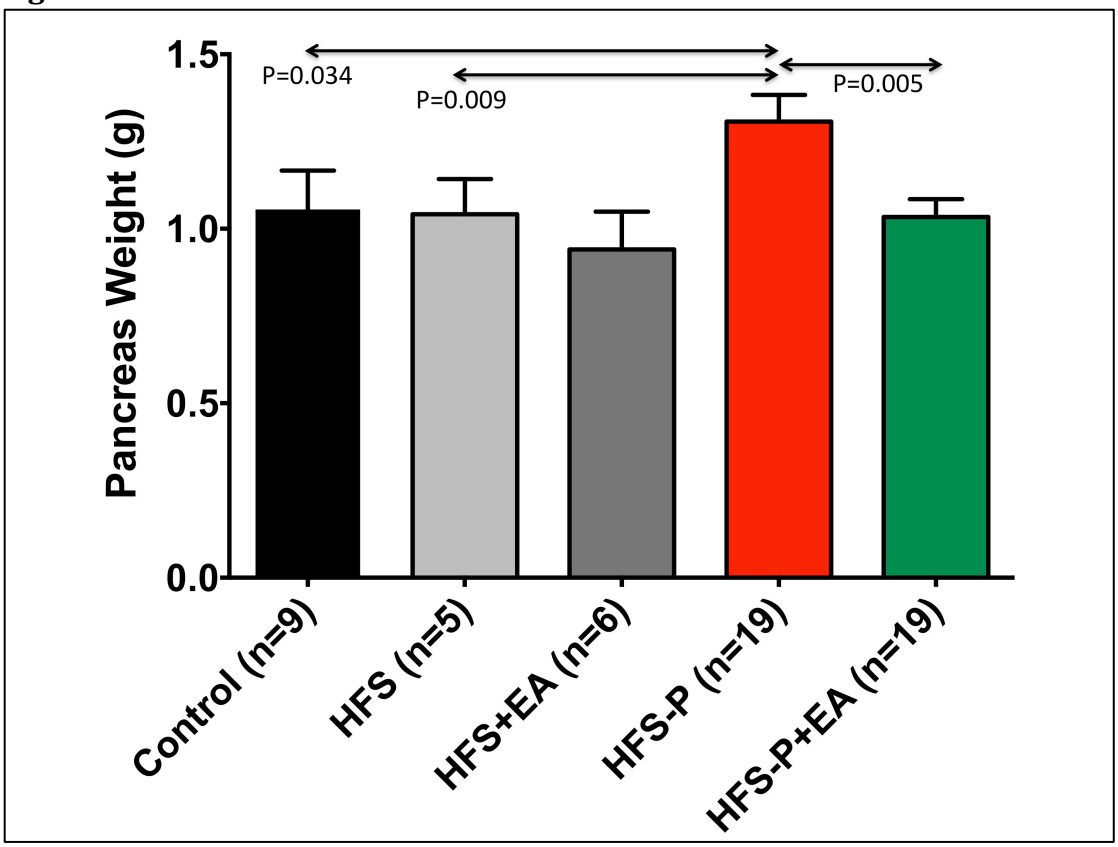


Figure 2



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