Global Metabolomics of Complications in Pregnancy

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Introduction

In 2011, the fourth leading cause of infant mortality was maternal complications during pregnancy.[1] Babies born to mothers with gestational diabetes have an increased risk of developing diabetes, obesity, or metabolic syndrome, and women with gestational diabetes are more likely to experience a stillbirth compared to women without.[2] Previous work from the Keller-Wood lab has shown that maternal increases in cortisol can cause fetal mortality at term, delivery, or immediately after birth in a pre-clinical model of human pregnancy in ewes. Transcriptomic analysis revealed changes in heart metabolism, and these changes along with observed heart failure, bradycardia, lactic acidosis, and premature fetal mortality mimic human babies born to diabetic mothers.[3]

Experimental

High-resolution magic angle spinning (HR-MAS) was conducted on fetal heart tissue from septum, left ventricle, and right ventricle of fetuses from cortisol infused ewes and control, saline infused ewes. The Avance III 600 MHz spectrometer at the University of Florida Advanced Magnetic Resonance Imaging and Spectroscopy facility was used.

Results and Discussion

PCA revealed differences in fetal heart tissue metabolites from fetuses that died in utero and those that went through birth. (Figure 1.) These metabolites are listed in Table 1 ($p<<0.001$ for each metabolite.) PLS-DA revealed differences between fetal heart tissue from cortisol infused ewes and saline infused ewes in fetuses that underwent birth. Phosphoethanolamine was significantly increased in fetal heart tissue of control fetuses ($p=0.013$) while creatine was significantly increased in fetal heart tissue from fetuses of ewes treated with cortisol ($p=0.018$). The significance of these metabolic findings is being determined.

Conclusions

These preliminary findings will be further validated with additional animal samples. Metabolomics findings will be integrated with phenotypic and genomic data to create a systems biology perspective of pregnancy with the ultimate goal being the identification of possible therapeutic targets that will ameliorate harm to the fetus.

Acknowledgements

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References

[1] Hoyert D.L., et al**.** National vital statistics reports, **61**, (2012).
[2] Malcolm, J. Diabetes/Metabolism Research and Reviews, **28**, 307–311 (2012).
[3] Bradley R.J, et al. Diabet Med, **8**, 464-468 (1991).

Table 1

Metabolite	Concentration
Isoleucine	↑ born
3-Hydroxybutyrate	↑ born
Glutamine	↑ unborn
Lactate	↑ unborn

Fig. 1

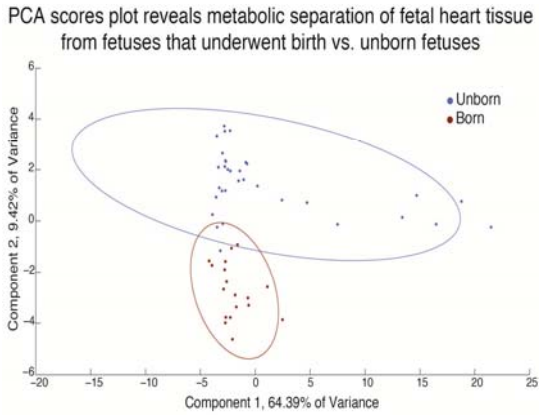

Fig.1: PCA scores plot of reveals separation of fetal hearts from fetuses that underwent birth (red) vs. fetuses that did not undergo birth (blue). Loadings plot from PCA component 2 was used to identify metabolites in Table 1.

Fig. 2

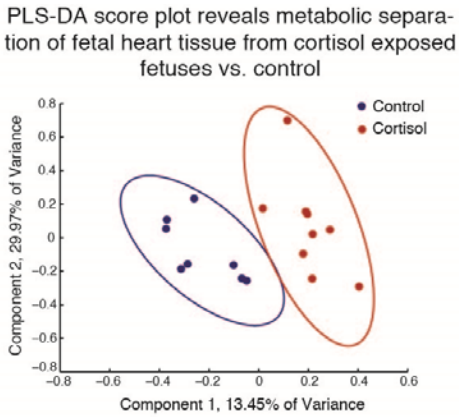

Fig. 2: PLS-DA scores plot of fetuses that underwent birth reveals separation of heart tissue from fetuses exposed to cortisol (red) compared to control (blue.)