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Glucocorticoid intervention prenatally: effects on fetal heart maturation

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Glucocorticoids are routinely administered to pregnant women at risk of pre-term delivery to mature fetal organs and improve neonatal survival. We have shown that glucocorticoid action is essential to mature the fetal heart. Here, we tested the hypotheses that (i) antenatal glucocorticoid exposure, prior to the normal increase in glucocorticoid levels, will advance fetal heart maturation and (ii) this will depend on cardiovascular glucocorticoid receptor (GR).

Male SMGRKO mice, which have Sm22α-Cre mediated deletion of GR in cardiomyocytes and vascular smooth muscle cells (VSMC), were crossed with female control (Cre-) mice to generate SMGRKO and control fetuses within the same pregnancy. Dexamethasone (Dex, 100µg/kg/d) or Vehicle (Veh) was administered in the drinking water of pregnant dams from E12.5 (n=3-6 dams/group), 2d prior to the initiation of fetal glucocorticoid synthesis. In utero high frequency ultrasound was performed at E15.5.

Initial results show that dexamethasone increased isovolumetric contraction time (indicating impaired systolic function) in control fetuses (Dex, 36.3±6.1ms vs Veh, 25.1±6.6ms; p<0.05). However, there was no significant effect in SMGRKO fetuses (Dex, 31.4±10.4ms vs Veh, 28.0±9.3ms; p=0.2). Heart rate was also decreased by Dex treatment in control (Dex, 191±5bpm vs Veh, 227±15bpm, p<0.05), but not in SMGRKO mice (Dex, 214.0±7bpm vs Veh, 221±7bpm, p=0.5).

Comparison of Veh treated SMGRKO and control mice showed no differences in E/A wave ratio, a marker of cardiac maturity (SMGRKO+Veh, 0.39±0.03 vs Con+Veh, 0.43±0.06; p=0.49). However, in Dex treated mice, E/A wave ratio was lower in SMGRKO mice than in controls (SMGRKO+Dex, 0.32±0.01 vs Con+Dex, 0.41±0.01; p<0.01), suggesting greater cardiac immaturity in SMGRKO mice than controls following exogenous glucocorticoid treatment. This finding is consistent with previous findings that glucocorticoid effects on E/A wave ratio are independent of cardiovascular GR.

Precocious glucocorticoid exposure may impair fetal systolic heart function via activation of cardiovascular GR. It may also impair cardiac maturation via actions that are independent of cardiovascular GR. These could be mediated via GR elsewhere, via MR activation by endogenous corticosterone (in face of removal of competing GR) or via maternal or blood pressure effects. However, this requires further investigation and experiments are ongoing. Nevertheless, these data suggest that early exposure to potent synthetic glucocorticoids antenally, prior to the normal increase in endogenous glucocorticoids, may be detrimental to cardiovascular health.