Fetal cardiac function at E15.5 is altered by maternal glucocorticoid receptor (*Nr3c1*) genotype but is unchanged by early antenatal glucocorticoid treatment

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Background

- The rise in plasma glucocorticoids levels before birth is vital to mature fetal organs[1]
- Mothers at risk of pre-term delivery are routinely administered glucocorticoid (typically dexamethasone) to improve neonatal survival[2]
- Excess exposure to glucocorticoid prenatally 'programmes' increased risk of cardiovascular disease in adulthood[3]
- Glucocorticoid action is essential for maturation of the fetal heart; glucocorticoid receptor deficiency in cardiomyocytes leads to structural and functional impairment of the fetal heart[4]
- GR haploinsufficiency in mice causes elevated plasma corticosterone levels with and increase in HPA axis activity[5]. This could impact upon fetal programming.

Aims & Hypothesis

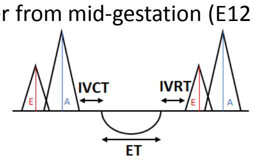
It is hypothesised that fetal cardiac function at E15.5 will depend on maternal genotype. Antenatal glucocorticoid administration will advance maturation of fetal cardiac function.

1) To establish whether fetal cardiac function depends on maternal genotype.

2) To determine whether dexamethasone administration advances fetal cardiac maturation.

Methods

- Heterozygous (GR+/-) and wild-type (GR+/+) female mice were crossed with heterozygous males generating GR+/+, GR+/- (reduced GR) and glucocorticoid resistant GR-/- fetuses.
- Glucocorticoid (dexamethasone, 100µg/kg/d) or vehicle was administered to the dam in drinking water from mid-gestation (E12.5) to E15.5.
- *In vivo* fetal cardiac function was assessed by Doppler ultrasound at E15.5.



- Myocardial Performance Index was calculated as the sum of the isovolumetric contraction and isovolumetric relaxations times (IVCT and IVRT, respectively) divided by the ejection time (ET).

Fetal cardiac function at E15.5 is altered depending on maternal genotype

Due to no significant differences in cardiac function between GR+/+ and GR+/- fetuses within a single maternal genotype, data from fetal genotypes were pooled to determine any effect of maternal genotype

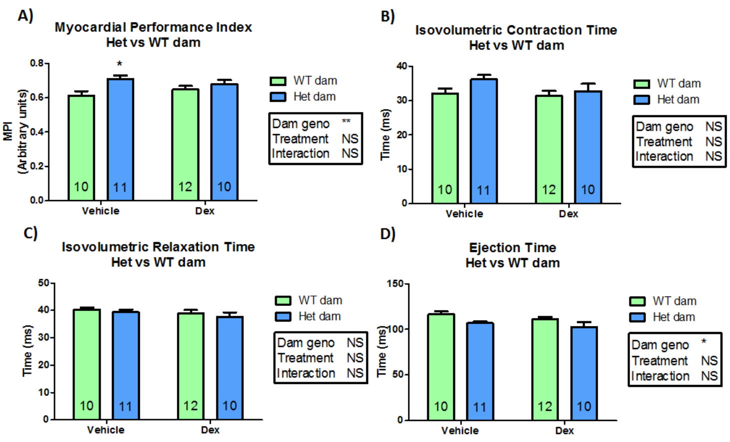


Figure 3: ***In utero*** **echocardiography measurements of fetal left ventricular function in pooled GR+/+ and GR+/- fetuses, comparing the effect of maternal genotype.** Heterozygous or WT dams were administered with dexamethasone (dex) or vehicle from E12.5-E15.5. Data were analysed by 2-way ANOVA with Bonferroni post-tests and Student's t-test. *p<0.05 ** p<0.01. n=10-12 (number of dams, mean of each fetal genotype per dam was used) (indicated in each bar of histograms).

Prenatal dexamethasone administration did not improve fetal cardiac function at E15.5 from WT dams

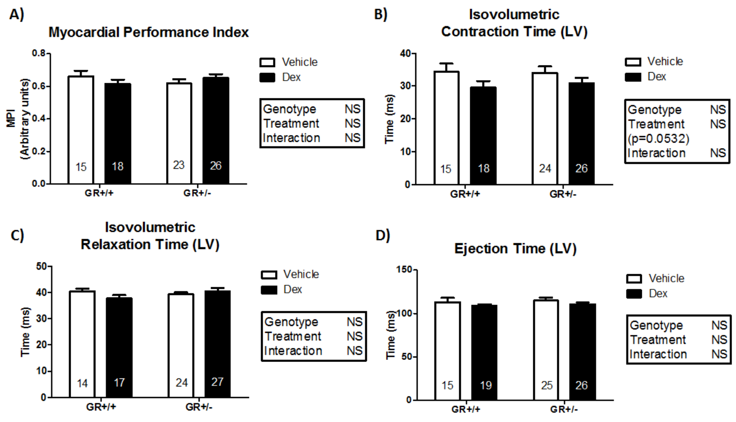


Figure 1: ***In utero*** **echocardiography measurements of fetal left ventricular function in GR+/+ and GR+/- fetuses of WT dams administered with dexamethasone (dex) or vehicle from E12.5-E15.5.** Data were analysed by 2-way ANOVA with Bonferroni post-tests and Student's t-test. *p<0.05 n=14-27 (number of fetuses) (indicated in each bar of histograms).

Prenatal dexamethasone administration did not improve fetal cardiac function at E15.5 from heterozygous dams

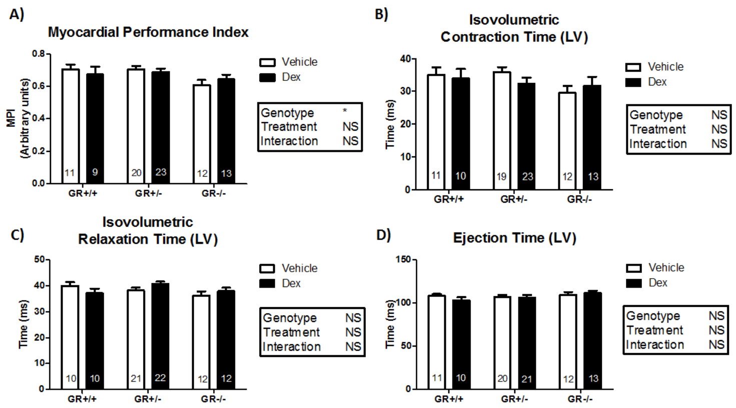


Figure 2: ***In utero*** **echocardiography measurements of fetal left ventricular function in GR+/+, GR+/- and GR-/- fetuses of heterozygous dams administered with dexamethasone (dex) or vehicle from E12.5-E15.5.** Data were analysed by 2-way ANOVA with Bonferroni post-tests and Student's t-test. *p<0.05 ** n=9-23 (number of fetuses) (indicated in each bar of histograms).

Conclusions & future directions

- Maternal genotype has an important influence on the developing fetal cardiac function.
  - -At E15.5, fetuses from heterozygous dams display impaired cardiac function compared with those from WT dams, perhaps because of precocious or excessive exposure to glucocorticoid.
- Dexamethasone administration to pregnant dams does not affect fetal cardiac function at E15.5.
  - -The level of fetal dex exposure will be established by mass spectrometry in fetal tissues.
- Although there is impaired cardiac function in GR+/- and GR-/- fetuses at E17.5, there are no impairments at E15.5, either in GR+/- or GR-/- fetuses.
- Further testing of dex administration to birth and examining the effect on postnatal cardiac structure and function may provide further insights into how precocious glucocorticoid may advance fetal cardiac development in preterm infants to lead to improved neonatal survival.

References

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