Decreased passive compliance in the uterine arteries of late pregnant relaxin gene knockout mice is exacerbated by ageing

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Failure of the maternal uterine vascular system to adapt to pregnancy gives rise to serious complications such as gestational hypertension, intrauterine growth restriction and pre-eclampsia (PE). These complications affect ~10% of all pregnancies and are a leading cause of maternal death. The peptide hormone relaxin (RLX) is a potent vasodilator of renal and systemic arteries, and regulates the essential maternal renal vascular adaptations in early pregnancy[1]. Relaxin concentrations increase 6-7 days after ovulation, but highest RLX levels are measured in the first trimester. Pregnant women with lower than normal serum RLX concentrations during the first 13 weeks of gestation are 7 times more likely to develop PE (Conrad, 2011). Our hypothesis is that low circulating concentrations of RLX in pregnancy result in inadequate uterine vascular remodelling and contribute to vascular complications of pregnancy.

Aims: To: i) examine passive mechanical wall properties of the uterine artery in late pregnant RLX-deficient ($Rln^{-/-}$) mice, and ii) investigate the additional effects of ageing on uterine artery remodelling.

Methods: Pregnant $Rln^{+/+}$ and $Rln^{-/-}$ mice aged 3 (young) and 7 (old) months were used in this study. Uterine arteries were collected from anaesthetized (inhalation isofluorane, AEEC: 0911478.1) mice on day 17.5 gestation (19 days term) and mounted on a pressure myograph cannula (100-150μm) and bathed in Ca^{2+}-free physiological saline containing 5mM EGTA. Arteries were pressurised in 10mmHg steps and vessel dimensions recorded at each step to construct stress-strain curves. RNA was also extracted from uterine arteries to compare expression of elastin (*Eln*), collagen (*Col1a1* and *Col3a1*) and RLX receptor (*Rxfp1*) genes by qPCR between genotypes and ages.

Results: There was no significant effect of genotype on passive compliance in the uterine arteries of young pregnant mice. In contrast, older pregnant $Rln^{-/-}$ mice had significantly stiffer uterine arteries, indicated by a shift in the stress-strain curve to the left of $Rln^{+/+}$ mice. There were no differences in *Col1a1* and *Col3a1* between genotypes or ages, but there was a significant increase in *Eln* in the uterine arteries in the aged, $Rln^{-/-}$ mice. A key finding was the dramatic up-regulation in Rxfp1 in the uterine arteries of young $Rln^{-/-}$ mice, which was completely absent in the aged mice.

Summary: These data demonstrate increased vessel stiffness in the uterine arteries of old pregnant $Rln^{-/-}$ mice, which may affect blood flow to the placenta. We also identified increased *Eln* and decreased *Rxfp1* as two potential mechanisms to explain this phenotype in older $Rln^{-/-}$ mice.

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