## Fetal sex specific differences in the maternal renin-angiotensin system: implications for pregnancy outcome

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The rates of spontaneous preterm labour and premature rupture of membranes are higher in women with male infants. The causes of this sex difference are unknown but the intrauterine tissues have been suggested to regulate fetal growth and survival in a sex-specific manner. We have demonstrated that decidua from women carrying a female baby produce higher levels of prorenin during pregnancy (Wang *et al.*, 2012; Wang *et al.*, 2015). We are focussing on the role(s) of the decidual renin-angiotensin system (RAS) in maintaining the fetal membranes and how sex-specific alterations in decidual RAS expression contribute to the increased risk of preterm birth in male babies. The renin-angiotensin system is known to stimulate fibrosis in organs like the heart and kidney.

We have demonstrated that before labour, there are lower levels of expression of prorenin in decidua from women carrying male babies and a decreased ability of decidual explants from these 'male' pregnancies to produce prorenin (Wang *et al.*, 2012; Wang *et al.*, 2015). Since we have identified fetal trophoblasts in late gestation decidua, we propose that this sex-specific difference in prorenin secretion is regulated by paracrine secretions from these placental cells and begins early in pregnancy. This may explain the increased susceptibility of the male fetus to preterm birth.

In addition, we have demonstrated that female amnion shows higher expression of the prorenin receptor ((P)RR) (Pringle *et al.*, 2015), which we propose is necessary for activation of pro-fibrotic pathways within the amnion since there is a strong correlation between (P)RR and the pro-fibrotic factor TGF-β1 (Pringle *et al.*, 2015).

Our findings demonstrate that there are strong interactions between prorenin, (P)RR and TGF-β1 and that this system has a greater capacity in female amnion to stimulate fibrosis. More research is needed to investigate whether this pathway and other pro-fibrotic molecules (collagen, PAI-1 and fibronectin) play a functional role in regulating membrane integrity and if this pathway is dysregulated in women with preterm premature rupture of membranes.

Pringle KG, Conquest A, Mitchell C, Zakar T, Lumbers ER. (2015). Effects of fetal sex on expression of the (pro)renin receptor and genes influenced by its interaction with prorenin in human amnion. *Repro Sci* **22,** 750-7.

Wang Y, Pringle KG, Sykes SD, Marques FZ, Morris BJ, Zakar T, Lumbers ER. (2012). Fetal sex affects expression of renin-angiotensin system components in term human decidua. *Endocrinology* **153,** 462-468.

Wang Y, Lumbers ER, Sykes SD, Pringle KG. (2015). Regulation of the renin-angiotensin system pathways in the human decidua. *Repro Sci* **22,** 865-72.