Sex specific effect of preterm birth on mRNA expression of drug transporters in guinea pig liver

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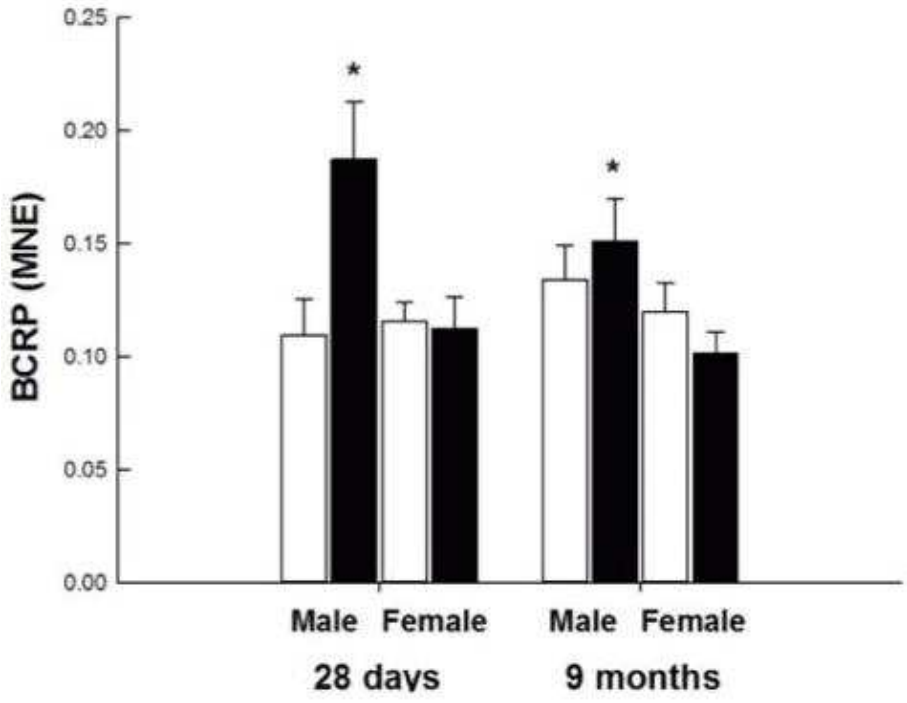
Introduction: Preterm birth affects ~10% of live births every year and these babies are likely to be treated with drugs during their lifetime. Due to advancements in perinatal medicine, more preterm babies are surviving into adulthood; however, little is known regarding the ex-preterm's ability to clear medication from its system in later life because there is limited data on neonatal drug disposition in this population.

Methods: Guinea pigs were mated and randomised to term and preterm groups. Standard clinical care for women at risk of preterm delivery was replicated by administration of two doses of betamethasone 48 and 24 hours before induction of preterm delivery at day 62 (Term=69d) in the preterm group. Liver tissue was collected at 28d after euthanasia (Term males, n=5; Term females, n=8, Preterm males, n=6, Preterm females, n=6), representing pre-adolescent juveniles, and 9 months (Term males, n=9; Term females, n=8, Preterm males, n=8, Preterm females, n=6), representing adulthood. qRT-PCR was used to determine the mRNA expression of drug transporters (Breast cancer resistant protein (BCRP) and P-glycoprotein (P-gp)) as well as factors that can regulate the expression or function of drug transporters (Glucocorticoid bioavailability (Glucocorticoid receptor (GR), 11-Beta hydroxysteroid dehydrogenase-1 (11βHSD1) and -2 (11βHSD2)), Pregnane X Receptor (PXR) and the most common active dimer complex of NF-κB (p50 and p65).

Results: We found an increase in BCRP mRNA expression in the liver of preterm males at 28 days and this effect persisted into adulthood. The figure shows that preterm birth resulted in increased mRNA expression of BCRP in male guinea pigs at 28d and 9 months, but not in female guinea pigs. *P<0.05, effect of preterm; white bars, term; black bars, preterm; error bars show SEM. Interestingly, preterm birth had no effect on BCRP mRNA expression in females. There was no effect of preterm birth on P-gp mRNA expression. Although, preterm birth had no effect on GR mRNA expression, males had higher GR mRNA expression compared to females. Interestingly, at both ages preterm birth resulted in an increase in 11βHSD1 mRNA expression in males, but a decrease in females. There was no effect of preterm birth on mRNA expression of Pregnane X Receptor, and the most common active dimer complex of NF-κB, p50 and p65.



Conclusions: This preliminary data shows that preterm birth may affect drug disposition in later life. In addition there appears to be differential effects of sex.