Developmental programming following prenatal alcohol exposure: models and mechanisms of disease

K.M. Moritz, School of Biomedical Sciences The University of Queensland St Lucia 4067. (Introduced by Caroline McMillen)

Chronic prenatal exposure to high doses of alcohol can cause a range of developmental abnormalities but whether alcohol causes detrimental effects in the fetus following short term exposure or at low doses is somewhat controversial. Many women cease drinking upon pregnancy recognition but many continue to drink during pregnancy with the pattern of drinking varying from occasional drinking to routine consumption of a low amount of alcohol on a daily basis. In this study we hypothesized that the dose and timing of exposure may be critical in determining both the short and long term effects of alcohol on fetal development and outcomes in offspring.

Thus, we have used the following three rat models of alcohol exposure to explore the immediate and/or long term consequences for the fetus and offspring:

1. High dose binge (HD) in which rats are administered 1mg/kg alcohol (or saline as a control) by oral gavage on days 14 and 15 of pregnancy.
2. Chronic low dose exposure (CL) in which the dam has *ab lib* access to a liquid diet containing 6% alcohol (~15% calories derived from alcohol) or a control diet throughout pregnancy.
3. Periconceptional exposure (PC) where the dam has *ad lib* access to a liquid diet containing 12% alcohol (~30% calories derived from alcohol) from 4 days prior to mating and then for the first 4 days of pregnancy.

Maximal blood alcohol content (BAC) reached approximately 0.11%, 0.03-0.05% and 0.1% in the HD, CL, and PC models respectively. Offspring in the HD model were born growth restricted and remained small throughout lactation but experienced catch up growth after weaning and were of a similar weight to control animals in adulthood. Animals in the CL group were lighter at day 20 of pregnancy but were of similar weight to control animals throughout weaning and early adulthood. Animals in the PC were of a similar weight to controls at day 20 of pregnancy and have yet to be studied as offspring. As adults, both male and female offspring in the HD group had elevated blood pressure (BP, $p<0.001$) whilst BP was normal in the CL group. Renal function was altered in the HD offspring with males showing an increase in GFR ($p<0.001$) whilst females showed a decreased GFR ($p<0.01$). There were alterations in the ability of the CL offspring to concentrate urine following dehydration. Offspring in both the HD and CL groups had a reduced number of nephrons in the kidney (~20-30% reduction compared to controls) when examined using unbiased stereology. In the HD group there were significant changes in genes regulating branching morphogenesis in the fetal kidney whilst apoptosis was elevated in the fetal kidneys of animals in the CL and PC groups. This suggests that kidney development is susceptible to alcohol and that multiple mechanisms may contribute to the impairment in renal development and the subsequent low nephron number. The dose and timing of alcohol exposure is likely to be important in determining the subsequent risk of adult onset disease.