**Abstract Title**

The effects of maternal smoking and BMI on the first and second trimester human fetal kidney.

**Background**

Maternal lifestyle has life-long health consequences for the offspring. In-utero exposure to maternal smoking (at least 20% of Scottish pregnancies) is linked to a wide range of fetal developmental abnormalities including low birth weight and smaller kidneys. We have demonstrated changes to human fetal ovaries, testes, and liver, but less is known about smoking effects on the fetal kidney. Similarly, the obesity epidemic worldwide currently affects one-third of women in reproductive age, giving rise to higher prevalence of obesity in pregnancy. Children born to overweight or obese mothers (BMI ≥25) are at an increased risk of developing childhood obesity and type 2 diabetes, which in turn predisposes individuals to chronic kidney disease. Although clear associations have been demonstrated between maternal smoking or maternal obesity and long-term consequences on offspring health, the mechanisms underlying the effects remain largely unknown.

**Methods**

We aimed to characterize and identify phenotypic and molecular changes to the human fetal kidney in relation to either maternal smoking or pregnancy BMI status. A total of 112 human fetal kidneys were collected from elective terminations of normally-progressing pregnancies (7-20 weeks of gestation, Scottish Advanced Fetal Research Study, REC 15/NS/0123). All 112 kidneys were weighed and whole kidney extracts prepared from 58 fetuses. 23 transcripts of key renal developmental genes, renin-angiotensin system (RAS), and kidney injury markers were quantified by qPCR. 27 whole kidneys were processed for histomorphological analysis to assess gross phenotype and podocyte density. Statistical analysis was performed by ANOVA, linear regression and non-parametric tests as appropriate. Because maternal smoking status and BMI are not associated in our population, in this pilot study we were able to analyses the data sequentially for maternal smoking and maternal weight.

**Results**

Smoke-exposed kidneys tend to weigh less by 14-16 weeks in both sexes (p=0.026). Expression of 11/23 transcripts (5 renal developmental genes, 4 components of RAS, 1 kidney injury marker and 1 hypoxic marker) significantly increased with fetal age, while the erythropoietin (EPO) transcript was undetectable. VEGF-A and HIF1A, normally induced by hypoxia, were significantly increased in male fetuses. BMP7, NPHS1 and NPHS2, involved in podocyte development were dysregulated in kidneys of smoke-exposed female fetuses. These findings are suggestive of slowed developmental expression patterns in smoke-exposed fetuses. High maternal BMI significantly increases the relative ratio of kidney weight to total fetal body weight in male fetuses (p=0.02), but maternal BMI has no significant association with overall podocyte density in fetuses. The renal renin encoding gene, *REN*, involved in blood pressure and fluid balance control was significantly increased in fetal male kidneys if maternal BMI was ≥25 (p < 0.04).

**Conclusions**

Human nephrogenesis begins from 4 weeks of gestation and continues into the late fetal period (gestation week 34-35). Our population sample includes fetuses up to 20 weeks of gestation, hence the final stages of podocyte development cannot be quantified in our study. Maternal smoking leads to smaller kidneys and our data suggests that this manifests as early as 14-16 weeks of gestation. Retarded renal development is a known major contributor to hypertension in adulthood. Moreover, sex-specific patterns of transcript expression may lead to sex differential susceptibility to renal injuries. These findings are also suggestive of altered kidney development, particularly the renin-angiotensin system in male fetuses carried by women with high maternal BMI.