Paternal transmission of metabolic dysfunction to offspring born to a growth restricted father

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Introduction. Being born small increases metabolic disease risk, with males exhibiting more severe phenotypes than females. These disease risks are not limited to the first generation (F1) but can be transmitted to the next generation (F2) with limited evidence of paternal line transmission. We characterized metabolic phenotype of F2 offspring born to normally grown and growth restricted (F1) fathers.

Methods. Late gestation rat uteroplacental insufficiency was induced (Restricted) or sham (Control) surgery in F0. F1 males were mated with normal females. Rats were anaesthetized with 4% isoflurane and 650ml.min^{-1} oxygen flow (reduced to 3.2% isoflurane and 250ml.min^{-1} oxygen flow when suturing). F2 body weights were measured from birth and metabolic function characterized by fasting intraperitoneal glucose tolerance test (IPGTT) and insulin challenge at 6 and 12 months. All data were analysed by t-test within a gender.

Results. F2 offspring body weight was not different at birth. Male offspring had higher body weight at 4, 5 and 6 months of age indicative of accelerated growth (+5-6%). There were no differences in adipose depots at 6 nor 12 months. There were no differences in plasma glucose response to an insulin challenge at 6 nor 12 months. Males, but not females, from Restricted fathers had altered glucose control following an IPGTT at 6 months (higher area under glucose curve; reduced first phase insulin secretion). At 12 months of age, first phase insulin secretion was increased in Restricted males indicative of insulin resistance. Female offspring from a growth restricted father had normal metabolic function. β-cell mass quantification is in progress.

Conclusions. F2 offspring, born to F1 growth restricted fathers are not programmed to be born of low birth weight but males demonstrated accelerated early adulthood growth but did not develop obesity. Males had altered glucose control at 6 months and developed insulin resistance with the exacerbation of age to 12 months. Our findings provide novel evidence of transmission of metabolic dysfunction with aging in F2 males *via* the paternal line in an uteroplacental insufficiency model of growth restriction. Females were protected from these programmed disease risks.