Identifying the pattern and prevalence of alcohol consumption in pregnancy
– Dr Elizabeth Henderson

Aims:

Alcohol consumption in pregnancy has well recognised adverse consequences for the developing fetus, but is typically under-reported. Measuring alcohol metabolites in infant meconium has potential to identify prenatal alcohol exposure; pilot data suggested an incidence of significant alcohol consumption in pregnancy in Glasgow of 15%. We sought to confirm this finding and, with a much larger sample, to identify any demographic factors associated with alcohol consumption in pregnancy.

Methods:

Mothers of singleton infants delivering during every 4th 24 hour period were invited to provide a sample of their newborn infant’s meconium for analysis of fatty acid ethyl esters (FAEEs) and ethyl glucuronide (EtG), and to undergo confidential interview. Meconium samples were collected into plain containers, frozen at -20°C and transported to Italy for analysis. All mothers provided written informed consent.

Results:

1013 eligible mothers were identified over 71 collection days, of whom 905 were approached for consent. 843 mothers agreed to participate (93.1%; 79.5% of all eligible mothers). 741 samples of meconium were collected, of which 730 were suitable for analysis. 114 (13.5%) mothers admitted to consuming alcohol at any point after 20 weeks’ gestation, of whom only 8 declared >3 units on any one occasion. FAEEs were measurable in all meconium samples, and were >600ng/l in 39.5%. EtG was detected above the LOQ in 205 samples and was >30ng/l in 14.5%. Maternal smoking was the only demographic factor predictive of (lower) FAEE concentration (>600ng/l, 28.4% smokers; <600ng/l, 22.2% smokers (p=0.056); this result was confirmed for EtG (p=0.021).

Conclusions:

Collecting infant meconium is a feasible way to study alcohol consumption in pregnancy. Confidential interview underestimates the amount, but not the prevalence of alcohol consumption.
High-resolution MRI Imaging Of Bone-Muscle-Fat In Glucocorticoid Treated Boys With Duchenne Muscular Dystrophy: Results from the ScOT-DMD study – Dr Shuko Joseph

**Background:**

The pathophysiological mechanism of skeletal fragility in Duchenne Muscular Dystrophy (DMD) is unclear. Objective: To compare trabecular bone microarchitecture, cortical geometry, muscle area and fat fraction at distal femur and vertebral bone marrow adiposity (BMA) in DMD and controls.

**Method:**

Bone-muscle and muscle fat fraction (FF) were assessed using 3T MRI and quantitative Dixon. BMA was assessed using 1H-MRS. Results expressed as median(range). Cortical parameters were compared following adjustment for femur length, muscle area and age.

**Results:**

Sixteen boys with DMD, median age of 11.7 years (8.8 to 18.9) treated with median of 5.9 years (1.8 to 10.5) of glucocorticoid (GC), were compared with 22 healthy boys, median age of 12.6 years (8.1 to 17.0). Median muscle area in DMD and controls was 3000 mm$^2$ (889, 12295) and 5400 mm$^2$ (33234, 10847), respectively [p=0.0004]. Median muscle FF in DMD and controls was 52% (3.5, 93.1) and 1.5% (0.4, 4.9), respectively [p<0.0001]. Median apparent trabecular bone volume/total volume (appBV/TV) in DMD and controls was 0.54 (0.51, 0.62) and 0.56 (0.51, 0.60), respectively [p=0.0027]. Median apparent trabecular thickness (appTb.Th) in DMD and controls was 0.25 mm (0.23, 0.30) and 0.28 mm (0.25, 0.31), respectively [p<0.0001]. Trabecular appBV/TV (r= 0.35, p=0.19) and appTB.Th (r=-0.29, p=0.32) were not associated with duration of GC. However, appTBTh in non-ambulant DMD boys (n=9/16) were significantly lower than ambulant boys. Boys with DMD had significantly lower cortical thickness (β=-0.67, 95% CI: -0.95 to -0.39). Moreover, cortical thickness (r=0.01, p=0.97) was not associated with duration of GC. Median BMA in DMD and controls was 49.6% (28.7, 78.9) and 21.1% (8.0, 52.3), respectively [p<0.0001]. BMA was not associated with muscle FF (r=-0.20, p=0.56), appBV/TV (r=0.58, p=0.07), appTb.Th (r=-0.16, p=0.65), nor cortical thickness (r=0.27, p=0.42).

**Conclusion:**

This first study using high-resolution MRI identified several abnormalities in trabecular microarchitecture and cortical geometry in DMD. The lack of a relationship of bone microarchitecture and geometry to the duration of GC raises the possibility that some of these deficits may not be solely due to GC. The novel finding of increased BMA in DMD and its role in osteoporosis requires further exploration.
Stillbirth in pre-gestational diabetes: defining associated maternal and neonatal characteristics in the Scottish population – Dr Sharon Mackin

Aims:

National data has shown stillbirth rates 4- and 5-fold higher in mothers with type 1 (T1DM) and type 2 diabetes (T2DM) compared with non-diabetes populations. We aimed to define maternal and fetal characteristics associated with stillbirth in pregnancy complicated by diabetes.

Methods:

Scottish obstetric and diabetes databases were linked and data collected on 3778 T1DM mothers and 1614 T2DM mothers delivering singletons >24 weeks from 1998-2016.

Results:

Stillbirth rates were 16.1 per 1,000 births in T1DM (n=61) and 22.9 per 1,000 in T2DM (n=37). In T1DM, mothers who suffered stillbirth had a shorter duration of diabetes (11.4 years vs 14.1 years P<0.05) but were of similar age, deprivation and smoking history. Mothers with T2DM with stillbirth had similar age (33.8±6.0 vs 33.2±5.6 years), duration of diabetes (4.4±4.0 vs 4.2±4.2 years), deprivation and smoking history (30.3% vs 21.0%). Stillborn infants were delivered earlier: T1DM (33.8±4.2 weeks vs 36.6±2.2 weeks; P<0.0001) and T2DM (33.7±4.7 weeks vs 37.2±2.3 weeks; p<0.0001). The majority of stillbirths were delivered preterm (T1DM 62%, T2DM 66%). Absolute risk increased through pregnancy and was highest in the 38th week in T1DM (7.0 per 1000 ongoing pregnancies) and 39th week in T2DM (9.3 per 1000). Corrected birthweight was similar between groups (Z-scores: T1DM 1.38± 1.68 vs 1.37±1.30; T2DM 1.08±1.82 vs 0.83 ±1.36). Mean pre-conceptual HbA1c was 88±22 mmol/mol in the stillbirth group versus 68±19 mmol/mol in the livebirth group (p<0.0001) and remained higher in each trimester (p<0.001). Significant association with maternal glycaemia and stillbirth was only found preconceptually in T2DM (74±23 versus 60±20mmol/mol, p=0.018).

Conclusion:

With the exception of glycaemia, mothers experiencing stillbirth are similar to those with livebirths. Although absolute risk increased with gestational age, the majority of stillbirths occur pre-term and all occurred before 40 weeks. More accurate detection of those at risk near term is needed.
Maximal therapeutic benefit from the neuroblastoma-targeting radiopharmaceutical 131I-MIBG may be obtained by its combination with chemotherapy. Aberrant mitochondrial metabolism is a common trait among cancers. The synthetic glucose analogue 2-deoxyglucose (2-DG) and the anti-diabetic drug metformin both target mitochondrial metabolism following inhibition of glycolysis and the electron transport chain, respectively.

Both 2-DG and metformin have shown potential as radio- and chemosensitisers. Our purpose was to investigate the potential of 2-DG and metformin to enhance the efficacy of X-radiation or 131I-MIBG in the treatment of neuroblastoma. Single agent 2-DG or metformin treatment (≤1 mM) had negligible effect on the clonogenic survival of SK-N-BE(2c) neuroblastoma cells or UVW glioma cells transfected with the noradrenaline transporter (UVW/NAT cells).

However, 2-DG acted as a radiosensitiser when administered at 10 mM. The radiation dose required to sterilise 50% of SK-N-BE(2c) clonogens was significantly reduced from 2.23 Gy to 1.32 Gy (p<0.01). Metformin failed to radiosensitise SK-N-BE(2c) or UVW/NAT cells when administered at concentrations ≤3 mM. However, triple agent therapy consisting of metformin, 2-DG and X-irradiation enhanced the cell kill achieved by either single agent modality administered alone to UVW/NAT cells.

Furthermore, we determined that irradiating cells 6 h prior to treatment with 2-DG and metformin was the most effective treatment regimen. This schedule produced the greatest G2/M cell cycle arrest and also killed the greatest number of UVW/NAT clonogens. The glycolytic inhibitor 2-DG sensitised neuroblastoma and glioma cells to external beam ionising radiation. Moreover, the efficacy of 2-DG was further enhanced by its combination with the anti-diabetic drug, metformin.

We hypothesise that the mechanism of 2-DG radiosensitisation entails the onset of apoptosis following the prolonged accumulation of cells in G2/M of the cell cycle. Disruption of cancer cell metabolism using glycolytic inhibitors is expected to improve the treatment of neuroblastoma using 131I-MIBG targeted radiotherapy.
Altered vascular function in boys with hypospadias- role of reactive oxygen species
– Dr Angela Lucas Herald

Background:

Hypospadias in boys may be associated with a lack of androgen exposure during the masculinisation programming window. As testosterone has effects on the vasculature, we assessed whether boys with hypospadias show any evidence of vascular dysfunction.

Methods:

Excess foreskin tissue was obtained from boys undergoing hypospadias repair (cases) or circumcision (controls) and small arteries dissected from this. Vascular contractility was assessed by wire myography. Generation of reactive oxygen species (ROS) was measured in vascular smooth muscle cells (VSMCs) by amplex red and chemiluminescence. mRNA expression was measured by qPCR. Results: 19 cases and 22 age-matched controls were enrolled in this study (median age 1.9 (range 1.3, 12.2) years). There were 8(42%) cases of distal, 4(21%) of midshaft and 7(37%) of proximal hypospadias. Endocrine and genetic evaluation did not reveal an underlying disorder of sex development in the cases and there were no differences in clinical cardiometabolic or biochemical parameters between the groups. Arteries from cases demonstrated increased constriction (Emax: 175.6 vs 66.3 p<0.001), an effect inhibited by the ROS scavenger N-acetylcysteine (NAC). VSMC superoxide anion (5.3 fold) production and H202 (3.3 fold) levels were increased in cases (p<0.05). Expression of Nox5, a major ROS-generating oxidase in vascular cells, was also increased (2.6 fold, p<0.05). Exposure of vessels to testosterone increased vasoconstriction (Emax: 66.3 to 124.6 p<0.001) in controls only. Incubation with NAC abolished the testosterone-induced vascular effects. Vascular hypercontractility in boys with hypospadias was associated with reduced endothelium-dependent and –independent vasorelaxation.

Conclusions:

These novel data, from a unique cohort of patients, demonstrate that small arteries from boys with hypospadias exhibit increased vascular contractility and decreased vasorelaxation with associated increased Nox-derived ROS generation. The functional significance of vascular dysfunction in these boys is unclear, but may play a role in immediate surgical outcome as well as altered long-term cardiovascular risk.