"OPENING AND CLOSING LECTURES".

L1.
PERICONCEPTIONAL IMPAIRMENTS AND FUTURE HEALTH

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Across mammalian species and including the human the periconceptional (PC) period has been identified as vulnerable to environmental influences which may change the programme of development and have lasting effects on disease risk into adulthood. We have studied the effect of maternal undernutrition during the PC period in mice (low protein diet, LPD). Even restricting LPD to just the preimplantation period with normal nutrition thereafter and in postnatal life (Emb-LPD) is sufficient to induce increased cardiovascular, metabolic and behavioral disease in adult offspring. We have found the timeline of programming initiates through Emb-LPD diet-induced reduction in insulin and branched-chain amino acid (BCAA) concentrations within maternal serum and/or uterine fluid. These changes are sensed by blastocysts via the mTOR signal pathway. This sensing mechanism associates with altered programming even if Emb-LPD blastocysts are transferred to control mothers. Similarly, in vitro cultured embryos with reduced insulin and BCAAs and subsequent transfer lead to similar adult disease phenotype to maternal Emb-LPD treatment. Programmed embryos undergo compensatory responses within the extra-embryonic cell lineages (trophectoderm; primitive endoderm) to promote nutrient retrieval during gestation to promote fetal growth. These responses include increased proliferation, endocytosis and motility of affected tissues. However, embryonic lineages show evidence of increased apoptosis and reduced survival signalling. Derivation of embryonic stem cell lines from blastocysts from diet-treated mothers retain programming characteristics over several passages and permit mechanistic analyses and reduced use of animals. These lines have also been effective in identifying epigenetic mechanisms underlying lineage-specific programming responses. Lastly, Emb-LPD compensatory responses induced within extra-embryonic lineages cause increased perinatal growth. However, perinatal weight in programmed offspring correlates positively with disease risk in later life. These data therefore show a continuum of biological processes from maternal PC diet to adverse adult phenotype. Funded through BBSRC, EU FP7 EpiHealth and EpiHealthNet.

L2.
IMMUNOMODULATION IN IMPLANTATION

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In mammalian pregnancy, there is attenuated expression of paternal-derived alloantigens by gestational tissues. Despite this, the fetus and placenta are recognized as non-self by the maternal immune system, and are vulnerable to immunological attack. An active system to suppress inflammation and prevent rejection must exist from when conceptus and maternal tissues first come into contact at implantation. Crucial mediators of immune protection are inducible regulatory T cells (Treg cells). Unless sufficient Treg cells are present in the endometrium, successful implantation and progression to pregnancy cannot ensue. This key role of Treg cells confers to the female immune system substantial capability to influence reproductive events, particularly around the time of conception, embryo implantation and early placental development. While on the one hand this risks susceptibility to immune-based reproductive disorders, the potential evolutionary trade-off is the benefit of quality control to avoid poor reproductive outcomes. Several factors are required to establish a robust Treg cell response and an immune environment conducive to successful implantation and pregnancy. These include (a) appropriate cytokine balance; (b) correct phenotype of endometrial macrophages and dendritic cells to enable Treg cell activation; (c) sufficient estrogen and progesterone to stabilize and strengthen Treg cell phenotype, and (d) adequate male partner seminal fluid composition, including MHC antigens and immune-deviating agents, to promote priming of Treg cell populations after coitus. Compromises in the quality of this immune adaptation at conception can influence the early embryo and either prevent implantation or impair placental morphogenesis. Failure to successfully establish Treg cell-mediated immune tolerance is emerging as an important etiological pathway leading to poor fertility or imparting compromised placental function and associated pregnancy disorders, leading to adverse consequences for the fetus and offspring.

L3.
ROLE OF THE ENDOMETRIUM IN SUPPORTING EARLY DEVELOPMENT OF THE HUMAN PLACENTA

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In all mammals the initial nutritional support for the co Cambridge nceptus is provided by histiotrophe secreted from oviductal cells and endometrial glands. In the human, it was previously thought that the duration of histiotrophic nutrition is short due to our uniquely invasive form of implantation that removes the conceptus from the uterine lumen. However, it is now realized that secretions from the endometrial glands are delivered into the intervillous space during the first trimester through openings in the developing basal plate. These secretions, rich in glycogen, lipid droplets and large maternal glycoproteins such as MUC-1, are phagocytosed by the syncytiotrophoblast, where they co-localize with the lysosomal pathway suggesting their breakdown. Immunohistochemistry also indicates that these secretions contain a range of powerful mitogenic growth factors, including epidermal growth factor (EGF) and vascular endothelial growth factor. Application of EGF to first trimester explants stimulates proliferation of cytotrophoblast cells, and so the secretions may play an important role in promoting early placental development. Importantly, the pattern of glycosylation of the secretions changes between the late secretory phase and early pregnancy, with the loss of sialic acid endcaps. Consequently, any of the growth factors that reach the maternal circulation through the uterine veins will be rapidly cleared by asialoglycoprotein receptors in her liver. This arrangement allows a highly proliferative microenvironment to be created within the placenta without putting the mother at risk of excessive stimulation. Evidence from other species indicates that the conceptus signals to the glands to upregulate secretory activity and so promote its own development. In the human, the glandular epithelium undergoes characteristic morphological changes in early pregnancy indicative of hypersecretion, the Arias-Stella reaction. Experiments *in vitro* using an immortalized gland epithelial cell line indicate that chorionic gonadotropin and placental lactogen from the trophoblast and prolactin from the decidua may mediate this effect.

L4.
SEXUAL DIMORPHISM IN THE EFFECT OF MATERNAL OBESITY ON PLACENTAL MITOCHONDRIAL FUNCTION

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Maternal obesity programs the offspring for adverse outcomes in later life. In adults obesity is associated with decreasing mitochondrial function. We hypothesized that maternal adiposity would affect placental mitochondrial respiration and function. Placentas were collected at term by C section in the absence of labor from women (n=33) of pre-pregnancy BMI 18.5 – 40. Isolated villous cytotrophoblast cells were allowed to syncytialize over 72 hr. Mitochondrial respiration was measured in a Seahorse XF24. Basal, ATP-stimulated and maximal respiration and spare capacity were all significantly reduced with increasing maternal adiposity. Increasing maternal adiposity was associated with significantly increased generation of reactive oxygen species but significantly decreased ATP generation, mitochondrial biogenesis and expression of mitochondrial complexes I-V. Culture of trophoblast from lean, but not overweight or obese women in galactose as glycolytic substrate increased respiration illustrating a lack of metabolic flexibility with increasing adiposity. Expression of the hypoxamir, miR-210 was increased with greater adiposity, but only in trophoblast from a female fetus, and accompanied by decreased expression of the mitochondrial