

Many studies have showed that GDM is linked to a variety of separate conditions, including: preterm labor, preeclampsia, increased cesarean section rates, macrosomia, birth injury, stillbirth, and neonatal hypoglycemia and hyperbilirubinemia. With tight maternal blood glucose controlled, pregnancy outcomes in women with GDM have been improved.

Although most women with GDM reverse to normal glucose tolerance after delivery, their insulin sensitivity and insulin secretion are different from women without GDM. More and more studies have also shown that GDM is associated with increased risk of obesity, developing Type 2 diabetes and metabolic syndrome later in life for both mothers and their babies. So, it will be very important to early diagnose and manage these women with GDM in order to improve both mothers and their infants' outcomes in China.

### Session 5E. Lactation

#### 5E-1 Human lactation: innate immune protection and nutrition

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The ability to fully nourish their young with milk in any habitat that can support adult life is a common feature of mammals. Most theories conclude that the mammary gland evolved from sweat and sebaceous glands associated with hair follicles. Recently an interesting alternate theory proposed that lactation evolved from inflammation and the highly conserved innate immune response protecting the integuments of early soft skinned animals. This response developed into mucus secreting glands that provided protection for both the skin as well as the hatchling and new born and finally to more complex glands providing innate immune protection as well as nourishment for the newborn. This progression is supported by the biochemical evidence that milk contains almost all components of the innate immune system and that two of these components; xanthine oxidoreductase and lysozyme had crucial roles in the development of the nutritional components in milk. Lysozyme was the precursor to the milk protein  $\alpha$ -lactalbumin and this protein is also essential for the synthesis of the milk carbohydrate (lactose) and xanthine oxidoreductase is essential for milk fat secretion. The composition of milk varies greatly between different species of mammal but is adapted to the specific needs of each species young. Most research in human lactation has focuses on breastfeeding and breastmilk and its role in promoting optimal growth and development for the baby. However, it is now becoming clear that there are mutual long-term outcomes both for the baby and the lactating mother.

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#### 5E-2 The impact of breastfeeding on long-term child health and development

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A World Health Organisation initiative states that breastfeeding plays an essential role in the treatment and prevention of childhood illness. The optimal duration of exclusive breastfeeding recently came under technical scrutiny during an expert consultation. The consultation recommends exclusive breastfeeding for six months, with introduction of complementary foods and continued breastfeeding thereafter. Breastfeeding is clearly a public health consideration as it provides significant protection against infections in newborns and infants. Although breastfeeding is clearly associated with lower rates of both morbidity and mortality in the developing world, evidence in the developed world has been and remains more controversial. Yet, investigations

demonstrate a protective effect of breastfeeding in early and later childhood on lower respiratory disease, asthma, cognitive development, obesity, diabetes, cancer, celiac disease and ulcerative colitis. Human milk may reduce the incidence of disease in infancy because mammalian evolution promotes a survival advantage. Furthermore breastfed babies have reduced exposure to foreign dietary antigen. In addition, factors in milk promote gastrointestinal mucosal maturation, decrease the incidence of infection, alter gut microflora, and have immuno-modulatory and anti-inflammatory functions. Hormones, growth factors and cytokines in human milk may modulate the development of disease. Following the termination of breastfeeding, there is evidence of ongoing protection against illness that may be due to biological embedding on the immune system mediated via human milk. This talk will summarise published meta-analyses on the benefits of breastfeeding.

#### 5E-3 Placental and lactational nutrient restriction and the consequences for later disease

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Intrauterine growth restriction followed by accelerated growth after birth is associated with increased adult disease risk. In Western society, a poorly functioning placenta is the major characteristic of human pregnancies complicated by IUGR. We use bilateral uterine vessel ligation (Restriction-R) or sham surgery (Control-C) to induce placental restriction in WKY rats. We have shown that dams exposed to placental restriction experience premature initiation of lactation and reduced milk quality and quantity further compromising growth. Our cross-fostering approach determined the influences of prenatal placental restriction and postnatal lactational restriction on disease outcomes. Control, Reduced (RED-litter size of Control to 5, to match Restricted) and Restricted pups were cross-fostered onto a Control or Restricted mother.

Growth-restricted R-on-R male offspring had hypertension, nephron deficit and glomerular hypertrophy without obesity. Providing a normal lactation environment (R-on-C) corrected the hypertension, nephron deficit and altered vascular reactivity. Red-on-R pups with normal prenatal, but impaired lactational environment developed hypertension without a nephron deficit. Being born small (R-on-R, R-on-C), or being born of normal weight but having slowed followed by accelerated growth (RED-on-R), reduced bone dimensions and bending strength.

The programmed hypertension, nephron deficit and vascular dysfunction were corrected by providing a normal lactational environment, highlighting the importance of postnatal nutrition in regulating cardiovascular function. Furthermore, being born small, or undergoing accelerated growth after weaning programs a reduction in bone bending strength and may increase osteoporotic bone fracture risk. We identify lactational nutrition, and its interaction with the prenatal environment, as critical for programming growth and disease development.

### Session 6A. Assisted Reproduction and Later Health

#### 6A-2 Genetic/epigenetic and environmental origins of pcos

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**Aims:** To discuss some of theories regarding the origins of polycystic ovary syndrome (PCOS), the commonest hormone condition of women in the reproductive age. PCOS occurs in 5–10% of the

population and has familial and environmental elements to its origin. The aim of this talk is to look at the aspects that suggest epigenetic modification of the familial factors that predispose to PCOS and also to discuss the environmental precipitants that may initiate PCOS in a susceptible individual.

**Study design:** The literature will be systematically reviewed to look at those papers that cover genetic and epigenetic predisposing factors to PCOS.

**Subjects:** Women with PCOS and their families as well as information derived from experimental animal studies.

**Outcome measures:** The prevalence and severity of PCOS.

**Results:** There is strong evidence that genetic factors may play a role in PCOS but in a recent paper Hickey et al were able to demonstrate epigenetic effects within families. Environmental factors such as obesity play a major role in the expression of the disease.

**Conclusions:** There are clearly familial/genetic components to PCOS and environmental factors including diet, play a significant role in expression of the disease. Epigenetic factors are still debated but there is interesting information to suggest that this may play a role.

#### **6A-3** Midnight's broken toll: the male germ cell and its role in the aetiology of genetic disease

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**Aims:** To determine the possible causes for DNA damage in the male germ line.

**Study design:** These studies involved detailed analysis of DNA integrity in human spermatozoa along with markers of oxidative stress.

**Subjects:** Unselected donors and patients attending an infertility clinic.

**Outcome measures:** DNA damage by Comet, TUNEL and mass spectrometry; ROS generation by DHE and MitoSOX Red.

**Results:** These studies have demonstrated that human spermatozoa are capable of generating reactive oxygen species from both mitochondrial and non-mitochondrial sources. The excessive generation of these toxic oxygen metabolites is associated with a state of oxidative stress that results in lipid peroxidation and oxidative DNA damage. A variety of factors have been found to trigger oxidative stress including retinoids, unesterified unsaturated fatty acids, catechol estrogens and electromagnetic radiation. We hypothesise that the aberrant repair of this oxidative DNA damage in the fertilized egg leads to the creation of genetic abnormalities in the zygote that can compromise both the viability of the embryo and the health and wellbeing of the offspring. Such events are a source of concern because it is inevitable that DNA-damaged spermatozoa are being used in assisted conception programmes, particularly where fertilization is achieved by ICSI.

**Conclusions:** DNA damage in the male germ line is associated with poor fertilization, impaired embryonic development, an increased incidence of abortion and potential morbidity in the offspring. Determining the cause of such DNA damage is a priority task for the future.

### Session 6B. Lifecourse Biology

#### **6B-1** Intergenerational predictors of fetal growth rate in generation 3 of the Cebu cohort

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**Aims:** DOHaD has emphasized the long-term effects of fetal and infant nutrition and growth on late-life risk for metabolic and other diseases. In most epidemiologic or experimental work, early nutrition – the exposure – is either manipulated (animal models) or merely observed (human epidemiology). In natural settings, fetal and infant nutrition are set by maternal physiology and metabolism and are potentially influenced by the mother's early life experiences, including her own fetal and infant nutrition and growth rate. The original offspring of the Cebu birth cohort are now having offspring of their own, creating new opportunities to explore the intergenerational predictors of fetal growth rate.

**Study design:** Community-based, prospective study of a 1983–84 birth cohort followed from the prenatal period to age 21–22, and their newborn offspring.

**Subjects:** 297 mothers and their newborns.

**Outcome measures:** recalled birth weight.

**Results:** Independent of potential confounders, we found (1) a positive relationship between maternal and offspring fetal growth rate; (2) a dose-response negative association between maternal diarrhea episodes during infancy and birth weight of her future offspring; (3) women who were breastfed as infants give birth to larger babies, but only if their mothers had favourable energy status while lactating.

**Conclusions:** These findings suggest that fetal nutrition serves as a chronic index of prior maternal nutritional experiences, and highlight the need for additional work on intergenerational influences on nutrient transfer and growth at the age when metabolic disease risk is induced in offspring.

#### **6B-2** The effects of variation in maternal and postweaning diet on the intergenerational transmission of developmentally programmed insulin resistance over five generations in a rat model

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**Aims:** To assess the transmission of developmentally programmed insulin resistance over multiple generations in rats fed energy-restricted or high fat diets.

**Study design:** Female rats (F0) were mated with controls and protein malnourished during pregnancy/lactation. In one experimental condition, F1 offspring were then weaned to adequate but energy-restricted diets into adulthood. F1 dams were fed energy-restricted diets throughout pregnancy/lactation. F2 offspring were also fed energy-restricted diets postweaning. F2 pregnant dams and F3 offspring were maintained as described for F2. In the second experimental condition, F0 dams were mated and malnourished as described above, and their F1 offspring were weaned to high fat diets. Animals were maintained on high fat diets for four (F1–F4) generations. An additional (F5) generation was bred from F4 high fat diet dams fed an energy restricted diet during pregnancy/lactation. Control animals were fed adequate diets throughout pregnancy/lactation, and postweaning.

**Subjects:** Sprague Dawley rats.

**Outcome measures:** Adult insulin sensitivity was measured by the Homeostatic Model Assessment (HOMA).

**Results:** F2 animals fed energy-restricted diets were insulin resistant, while their F3 offspring were highly insulin sensitive. Among animals fed high fat diets, insulin resistance was observed