

Embryonic and fetal genomes considered 'most sensitive' to environmental effects

SIG's winter symposium puts emphasis on prenatal factors in determination of subsequent health and disease

The 'hypothesis' proposed by the epidemiologist David Barker in the early 1990s - that intrauterine and early postnatal nutrition are in part responsible for the risk of non-communicable diseases in later life - is now widely accepted as biological fact. He particularly noted that those with a low birth weight are at greater risk of coronary heart disease. The acceptance of the hypothesis now explains the 'life course' approach to health policy, whereby interventions at the maternal/infant stage of life, when developmental plasticity is at its greatest, are considered just as effective in disease prevention as interventions during adolescence and adulthood.

Such thinking lay behind most of the presentations at the Winter Campus Symposium of the SIG Early Pregnancy, which was organised jointly with the Task Force Basic Science and titled 'From early pregnancy to later in life'. There was indeed little disagreement that health in maturity is the consequence of a continuum that begins with the oocyte (and sperm cell) and that the embryonic and fetal genomes are most sensitive to environmental effects. Lurking in the background of this continuum were the mechanisms of epigenetics, whose modifications are assumed to mediate environment-gene interactions which cause persistent changes in gene regulation and metabolic pathways.

There was, therefore, a strong emphasis in this Campus programme on the effects exerted on the oocyte and embryo at their very earliest formative stages: genes expressed by cumulus cells (those predictive of competence); freeze-thawing and its damaging effects on 'trans-zonal' processes during antral follicle growth; optimal culture after freezing and thawing; oocyte vitrification (evidence so far that survival rates are better than after slow-freezing, without negative impact on oocyte integrity); and embryo culture in IVF (a 'real possibility' of an effect). These observations thus strongly implied that ART - with which all these functions are associated - is taking place at a very sensitive time for epigenomic reprogramming in the germline and early embryo.

'We should,' said Thomas Haaf from Wurzburg, 'be much more concerned about the long-term consequences of a sub-optimal environment around the time of conception and during pregnancy . . . The adaptive response of the fetus to the intrauterine environment influences the lifelong risk of metabolic and other diseases.'

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However, while most presentations concentrated on the germ-cell, periconceptual, prenatal and perinatal stages of development, there was also good evidence presented during the symposium that these effects may even have lasting consequences over several generations. Thus, while recent studies suggest, for example, that mothers with gestational diabetes and obesity have babies with epigenetic changes conducive to metabolic disease later in life, the well known and evolving Dutch famine cohort study now suggests that the effects of diet restriction 'might' be passed down to subsequent generations.

The proposal - that 'you are what your (grand)mother ate' - came from Dutch investigator Tessa Roseboom, principal investigators of the Fetal Origins Research group at the Academic Medical Center in Amsterdam, who confirmed from data from the Dutch famine study that 'prenatal nutrition has a 'huge influence on lifespan'.

The study was based on the consequences of food

During the Dutch famine of 1944-1945 the Netherlands suffered from substantial undernutrition (of around 1000 calories per day). The limited food intake of mothers who were pregnant during this period has been associated with direct effects on body weight, diabetes and cardiovascular disease. Some effects of the famine - epigenetic changes, for example - have been observed 60 years later.



shortages during the winter of 1944-45 and the full birth records later found in the Wilhelmina Gasthuis in Amsterdam (which would later become the AMC). The records covered the births of 2500 babies, all of whom have been traced by investigators. Inevitably, there have been many studies based on this natural experiment, but the single finding to emerge with consistency is that undernutrition caused by the famine did have a direct effect on birth weight, especially among those whose exposure to malnutrition was later in the famine period. As early as 1997 a study showed that second born babies in the cohort weighed less than first borns, and third borns even less again. Even then, said Roseboom, there appeared an intergenerational effect of famine.

More recently, when examined at the age of 50 by her group, the late and medium term exposures in the cohort had higher rates of obesity, diabetes, atherosclerosis and cardiovascular disease than those exposed early (or controls). Examined ten years later,



the incidence of CVD mortality was also higher.

Right now, the investigators are seeing for the first time a fourth generation of subjects whose pedigrees trace back to the famine. But, said Roseboom, it's too early yet to see what the direct effects - if any - will be.

Nevertheless, the evidence from this Campus meeting pointed unequivocally to a critical effect of lifestyle and environmental factors during the pre-pregnancy, conception and early pregnancy stages. And in the debate which closed the meeting there was clearly an overwhelming view that as a biomarker of successful pregnancy the embryo is far more predictive than the endometrium. Despite the emphatic case of the SIG's Deputy Co-ordinator Siobhan Quenby (that the endometrium determines implantation), it was the prevailing opinion of this meeting that the outcome of conception, whether pregnancy or later life health, was more dependent on factors affecting the oocyte and embryo in their formative stages, where intervention for disease prevention now seemed likely to be effective.

Evidence search next for the SIG's diagnostic and management guidelines for recurrent miscarriage

Our joint Campus meeting reported above was attended by a variety of reproductive scientists, clinical embryologists, reproductive gynaecologists, and reproductive physicians. Indeed, the concept of developmental origins of health and disease are now attracting an increasing amount of attention, and speakers made it obviously clear that the pre-pregnancy, early implantation and early pregnancy stages are critical periods in which environmental or lifestyle factors may adversely affect pregnancy outcomes and health in later life.



Steering committee SIG EP, l to r: Ole B Christiansen (DK) Past Co-ordinator, Emma Kirk (GB) Deputy Co-ordinator, Mariëtte Goddijn (NL) Co-ordinator, Siobhan Quenby (GB) Deputy Co-ordinator, Robbert van Oppenraaij (NL) Junior Deputy

New evidence has been reported on the treatment of women with recurrent miscarriage, which now demands an update of our 2006 guideline. The new version will be revised and updated according to ESHRE's latest guideline protocols. Our aim is to provide statements systematically developed to assist professional and patient decisions on appropriate care for couples with recurrent miscarriage. A guideline team has been established (with many European experts) and 20 key questions formulated. Following a literature search, evidence will be graded and recommendations formulated.

Guidelines

Our current ESHRE guidelines project involves the diagnostics and management of couples with recurrent miscarriage. New medical tests should be thoroughly evaluated before routine introduction, thereby avoiding erroneous diagnoses or the initiation of potentially harmful therapy. In addition, the increasing costs of healthcare demand the elimination of ineffective medical testing. In addition, women with recurrent miscarriage are vulnerable and easily attracted to unproven therapies to apparently increase their future chance of a healthy liveborn child.

Future activities

Our precongress course in Munich will be held in collaboration with the SIG Reproductive Endocrinology on **The contribution of endocrinology and early pregnancy management to the success of an ART centre.**

Later in the year, our traditional winter symposium, organised with the Paramedical Group in December in Copenhagen, will be on the evidence-based management of early pregnancy.

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