

Notes from the GDM Pasadena II: An International Conference on Gestational Diabetes

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DAY 1 - 4/8/10

Pathophysiology of glucose intolerance and obesity

Nutritional Dynamics and GDM in Primates: Impact on Early Origins of Disease

Jacob E. Friedman, PhD; Professor of Pediatrics and Biochemistry & Molecular Genetics, University of Colorado, Denver

Currently 2/3 of US mothers are obese overweight at the time of conception. While maternal-fetal glucose clearly affects infant growth and body composition, much less is known about the role of fatty acid supply to the fetus. Despite the growing trend in maternal obesity and exposure on the fetus, there is very little information about the underlying mechanisms controlling metabolic and gene regulatory responses in the fetus in response to excess maternal lipid exposure.

His group studied the effect of High Fat Diet (HFD) on primate infants. The infants were smaller but had increased liver triglycerides and oxidative stress. When the infants were given a normal diet the lipid levels were lower but not down to normal. The infants were studied to 1 year of age and they showed persistent liver changes.

HYPOTHESIS: HFD contributes to insulin resistance in juvenile monkeys and their livers show increased inflammation and glucose output and impaired nutrient sensing.

Current Strategies to Manipulate Beta Cell Mass

David Hill, MD, PhD; Scientific Director, Lawson Health Research Institute, Professor of Physiology, University of Western Ontario, Canada

The pancreatic beta cells have a low intrinsic proliferation rate, making regeneration of beta cell mass following diabetes-associated loss a challenge. Yet during pregnancy, maternal beta cell mass transiently increases by both neogenesis and beta cell replication showing that plasticity of the beta cell is a normal physiological mechanism.

Beta cells show an inducible plasticity and altered beta cell mass in the mother and fetus following GDM which may be open to modification

Obesity – Metabolic Priming for GDM?

Dilys Freeman, PhD; Senior Lecturer, Reproductive and Maternal Medicine, University of Glasgow, UK

Lipid Metabolism can highlight potential pathological pathways in type 2 DM.

	Type 2 DM	
Central obesity	Insulin Resistance	Metabolic Syndrome & b-Cell failure with increased insulin
Excess fat in diet = limited capacity of hypertrophied adipocytes to store non-esterified fatty acids (NEFA)	Fatty acid “spillover” and accumulation of fat in liver muscle and potentially pancreatic beta cells	Oxidative stress and may cause beta cell failure
	GDM	
Central obesity with adipose hypertrophy	NEFA increase due to poor diet and lack of exercise	Reduced capacity to store NEFA -susceptible to type 2 DM later in life
NEFA in excess pregnancy can lead to maternal beta cell failure	Endothelial dysfunction	Placental insufficiency
		May contribute to offspring obesity

Inflammation and endothelial activation is evident at birth in offspring of mothers with type 1 diabetes

Scott Nelson, PhD, MRCOG; Professor of Obstetrics and Gynecology, University of Glasgow, UK

Maternal obesity and gestational weight gain have a significant impact on maternal metabolism and offspring development.

Insulin resistance, glucose homeostasis, fat oxidation and amino acid synthesis are disrupted by maternal obesity and contribute to adverse outcomes.
Modification of lifestyle is an effective intervention strategy to improve maternal metabolism and prevent type 2 DM and potentially GDM

Offspring of mothers with DM are at risk of obesity and glucose intolerance later in life.

In adults markers of subclinical inflammation include:

C-reactive protein (CRP)

Interleukine-6 (IL-6)

Endothelial activation (intracellular adhesion molecule (ICAM)-1)

All are associated with obesity and higher risk for the incidence of Type 2 DM

Inflammatory markers are increased in OT1DM and are related to measures of fetal adiposity, particularly leptin, and maternal glycemia. Subclinical inflammation is a novel component of the diabetic intrauterine environment and should be considered a potential etiological mechanism for in utero programming of disease

Diabetes Genetics and the Legacy of James Neel

Richard M. Watanabe, PhD; Associate Professor, Preventive Medicine & Physiology & Biophysics University Southern California, Los Angeles

>30 susceptible loci for the DM2 but no single “gene” identified.

Thrifty Gene Hypothesis: In earlier times when there were feast and famine we needed to store fat but not in modern life. Genes haven’t caught up.

Do T2DM and GDM have the same genetic basis?

Alterations in DNA Methylation Associated with Abnormal Fetal Growth

Francine H. Einstein, MD; Assistant Professor, Division of Maternal-Fetal Medicine, Dept. OB/GYN, Albert Einstein College of Medicine, New York

Perturbations of the intrauterine environment can have major effects in determining susceptibility to what was once considered adult or age-related disease, such as type 2 diabetes. Fetal life is a critical period of developmental plasticity in which the same genotype can produce more than one phenotype in response to environmental conditions. While the precise mechanism of this biological memory remains unclear, mounting evidence suggests an epigenetic basis. The concept of "fetal origin of adult disease" has largely been focused on fetal growth restriction, but paradoxically, the relationship between birth weight and risk for age related disease is U-shaped, resulting in increased risk for all cause mortality in those born with the lowest and highest birth weights. The induced phenotypic traits associated with both intrauterine growth restriction (IUGR) and large for gestational age (LGA) vary among individuals, but share altered activity of metabolic pathways, homeostatic control processes and tissue structure/function. The commonality of susceptibility to chronic disease and involvement of multiple organ systems is analogous to the normal decline of resistance to disease that occurs with aging. All cells, including non-embryonic stem cells, accumulate unrepaired cellular and molecular damage with normal aging and repetitive replication. While the cumulative environment over the course of a lifetime can induce increasing epigenetic dysregulation, adverse events that occur during early development may induce significant additional dysregulation of the epigenome, marked by defects in phenotypic plasticity and susceptibility to age-related disease.

Maternal Obesity, Nutrition, & Environmental Exposures: Programming the Fetal Epigenome

Kjersti Aagaard-Tillery, MD, PhD: Assistant Professor of Obstetrics and Gynecology, Baylor University, Houston, Texas

A high fat diet alters fetal metabolites and after return to a normal diet the fetal liver triglycerides do not completely return to normal but do improve.

Metaflammation at the Maternal Fetal Interface

Sylvie Haugel-de Mouzon, PhD; Professor of Cell Biology, Case Western University, Cleveland; Senior Scientist, INSERM, Paris, France

Obesity and type 2 diabetes generate a complex array of chronic alterations linking the metabolic and the immune systems into a situation of metabolic inflammation or meta-inflammation. Profound modifications of the adipose tissue secretome with increased synthesis of adipo-cytokines represent the core of the inflammatory response leading to the resistance to insulin action. During pregnancy, the placenta makes an additional contribution to the systemic inflammatory changes because of its capacity to deliver cytokines in the maternal circulation and the strong similarity between the placenta and adipose tissue secretomes. Increased insulin resistance and inflammation in pregnant women are associated with adverse outcomes for both the mother and her fetus. In addition to an increased insulin resistance and adiposity at birth, the offspring of obese or diabetic women is at higher risk of developing metabolic diseases in adulthood. This may be caused by specific adaptations during the prenatal period which translate into impaired metabolic function later in life (developmental origin of adult disease).

Evidence produced during the past decade have started to identify several factors which could be causative of meta-inflammation in pregnancy: pre-gravid obesity, diet, environmental pollutants. In this respect, it is essential to emphasize that the placenta is the primary target of any change elicited in the maternal environment. Eventually, placental dysfunction yielding to excess nutrient transfer to the fetus will be the impetus for abnormal nutrition during fetal life and the associated short and long term consequences.

Placental Lipid Handling in Diabetes

Gernot Desoye, PhD; Professor of Obstetrics and Cell Biology, University of Graz, Austria

Research on lipids in pregnancy has focused on fatty acids and triglycerides and recently, cholesterol has gained interest.

Evidence suggests an increased maternal-to-fetal transfer of cholesterol in maternal diabetes. Along with diabetes-associated oxidative stress the fetal hypercholesterolemia may contribute to fatty streak formation in the fetus. In addition, the local cholesterol homeostasis in the placental vasculature may be modified in the wake of the fetal diabetic environment.

Potential Role of Maternal Triglycerides as a Fuel for Fetal Fat Accretion

Linda Barbour, MD, MSPH; Professor of Medicine & OB/GYN, Division of Endocrinology & Maternal-Fetal Medicine, University of Colorado, Denver

- Fat stores increase early in pregnancy and lean women store more fat than obese women
- Babies on high fat diets gain weight faster, low fat diets may result in failure to thrive
- Fetal-placental glucose and amino acid utilization highest 22-26 weeks
- Later in pregnancy there is a shift from anabolic to catabolic state
- 90% of calories in the last 10 weeks gestation go to fetal fat (they gain 7 grams of fat/day at term)
- The human placenta is capable of transporting FFA by diffusion and selectively increases the transport of essential fatty acids (EFA) by fatty acid carrier proteins (FACP) so that these essential LC-PUFA are at a higher concentration in the fetus than in the mother.
- The activity of placental lipases, especially LPL, increases from 1st to 3rd trimester and can hydrolyze TG from either VLDL or chylomicrons (CM) from the maternal diet.
- Placental LPL activity appears to be stimulated by hyperinsulinemic and hyperglycemic conditions favoring hydrolysis of maternal fatty acids for transport across the placenta and some data suggests that it is increased in LGA babies of women with Type 1 DM.

Programmed Metabolic Syndrome: Appetite and Adipose

Michael Ross, MD, MPH: Professor and Chair of Obstetrics, Harbor-UCLA, Los Angeles, California

Born small – high rate of metabolic syndrome as an adult

Leptin and insulin enhance neural development

Rats fed a high fat diet had offspring programmed to eat more

In rodent studies SGA fetuses exhibit an alteration of cellular nutrient sensors that may have reduced neural stem cell pool and brain development.

Prevent programmed adiposity!!!

Maternal Obesity; Short- and Long-term Implications for the Fetus

Pat Catalano, MD: Professor and Chair of Obstetrics, Metropolitan Health System, Case Western University, Cleveland, Ohio

The *in utero* maternal metabolic environment is important relative to the short and long term development of the offspring. Although poor fetal growth remains a significant factor relative to long-term outcome, fetal overgrowth is assuming greater importance because of the increase in obesity in the world's populations. Maternal obesity is the most common metabolic complications of pregnancy related to fetal overgrowth and more specifically adiposity.

Due to pending publication, Dr. Catalano declines allowing the research data to be included. References for his presentation are listed below.

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Metabolic Programming of Hypothalamic Neuronal Circuits Perinatal Programming of Hypothalamic Connectivity

Richard Simerly, PhD; Professor of Pediatrics & Biology, Keck School of Medicine/University of Southern California, Los Angeles

Memory is an anatomical event due to the development of neural networks

Once the brain is wired up it follows you through life

Leptin is needed for development of circuits and helps neurons grow axons and medial fibers but not lateral fibers. It helps you know when to stop eating. Leptin acts during development to specify patterns of hypothalamic neural circuitry that impact distinct aspects of neuroendocrine regulation.

Mice studies: Both groups had more obesity

Small litters were over nourished

Large litters were SGA but rapidly caught up. Abolished the normal postnatal surge in leptin and had increased adiposity, rapid catch up growth after weaning, and increased insulin resistance and changes in brain circuits (neural projections from the arcuate nucleus of the hypothalamus (ARH) Implications for the emphasis we currently have on premies and the need to rapidly gain weight.