

Highlights from 112th Abbott Nutrition Research Conference

- Drs Lucilla Poston and Susan Ozanne, (UK), noted that nutrition in pregnancy can have lasting epigenetic effects, ie, the mother's nutritional status changes gene expression in ways that alter the health of her child and her grandchildren too.
- Examples of epigenetic mechanisms are methylation of DNA and deacetylation of histones. Drs Mark Hanson, (UK), Yuan-Xiang Pan, (USA), and others discussed how such chemical modifications can suppress or activate gene expression without changing the gene's DNA sequence.
- Dr Berthold Koletzko, (Germany), predicted the long-term consequences of today's maternal obesity pandemic. He noted, "Changes in body composition in the last 2 decades have been greater than those seen in the prior 1000 years."
- According to Dr Patrick Catalano, (USA), 3%-5% of pregnant women in the US have gestational diabetes mellitus. With proposed lower thresholds for fasting and postprandial glycemia, the proportion will be even greater.
- Perinatal nutrition not only affects the baby's body weight, but it also impacts development of the brain, bones, and immune system, as discussed by Drs Cristina Campoy, (Spain), Stephanie Atkinson, (Canada), and Susanna Cunningham-Rundles, (USA).
- In countries such as India, China, and Chile, healthcare professionals are particularly challenged to meet the nutritional needs of both underweight and overweight mothers, as reviewed by Dr CS Yajnik, Prof Chunming Chen, and Dr Francisco Mardones.
- "Pregnancy is a teachable moment. With education, we can change behaviors that will have effects in the womb and beyond," noted maternal health expert Dr Barbara Abrams, (USA).

112th Abbott Nutrition Research Conference

Pregnancy Nutrition and Later Health Outcomes

Robert Miller, PhD, (Divisional Vice President, R&D and Scientific Affairs) welcomed 15 internationally acclaimed maternal and infant nutrition researchers and more than 100 local and global participants to the 112th Abbott Nutrition Research Conference on Pregnancy Nutrition and Later Health Outcomes. The meeting took place from July 26 to July 28, 2011, at Ross Park, Columbus (Ohio, USA).

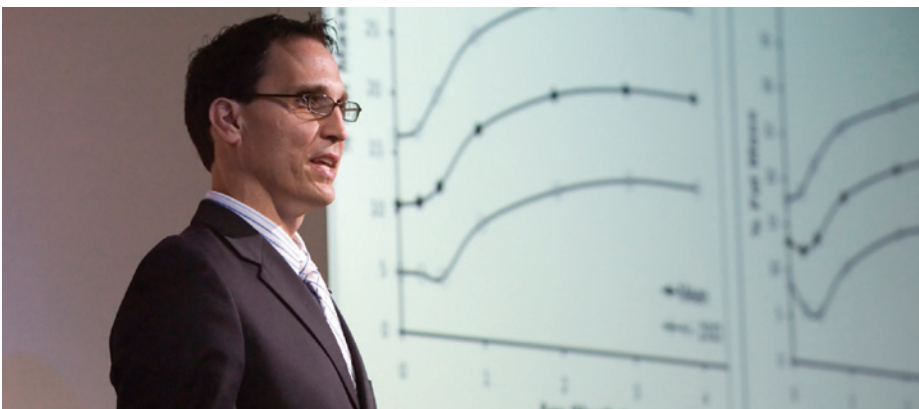
Dr Miller opened the conference, "We gathered a team of worldwide experts to discuss their most recent research findings as a way to stimulate more discussion and research. Together our goal is to improve healthcare for mothers and their babies."

Meeting of many minds

An important feature of this conference was that it gathered global experts from many disciplines—molecular biology, immunology, physiology, developmental biology, neurology and cognitive medicine, anthropometrics, obstetrics, pediatrics, endocrinology, epidemiology, public health, and global disease control and prevention—to discuss the common theme of nutrition in pregnancy. As a result, all participants got a broad perspective on the myriad ways nutrition influences the long-term health of the offspring.

"We gathered a team of worldwide experts to discuss their most recent research findings... our goal is to improve healthcare for mothers and their babies."

- Robert Miller, PhD, Abbott Nutrition



David Fields

Overview of the conference program

The 2.5 day conference program included 4 key topics that viewed pregnancy nutrition from a molecular level to a global health perspective:

1. Molecular mechanisms and biochemical pathways for effects of nutrients on maternal and child health
2. Gestational obesity and diabetes and their effects on later health outcomes for the mother and child
3. Functional outcomes when the mother's food intake is inadequate or inappropriate before or during pregnancy
4. Emerging trends in health and nutrition during pregnancy in the US and around the world

Nutritional effects on health outcomes: Molecular and biochemical regulation

Lucilla Poston, PhD, (UK), opened the meeting with an overview of how the challenges of under- and overnutrition during pregnancy bring serious health consequences to both the mother and her child (Figure 1).¹⁻³ Deficiencies in the mother's intake of macro- or micronutrients can lead to inadequate weight gain by the mother and child. Shortfalls of iron, iodine, folate, or vitamin D can cause specific abnormalities in the child. At the other end of the spectrum, excessive maternal weight gain in pregnancy can predispose the mother to thromboembolism, pre-eclampsia, gestational diabetes, and obesity, while the child is at increased risk for macrosomia, spina bifida, and some heart defects.

The offspring of mothers who were poorly nourished in pregnancy are more likely to experience obesity, diabetes, cardiovascular disease, cognitive disorders, cancer, and osteoporosis in adulthood and sometimes even earlier. Some of these changes are even passed on to the next generation—the child's children.

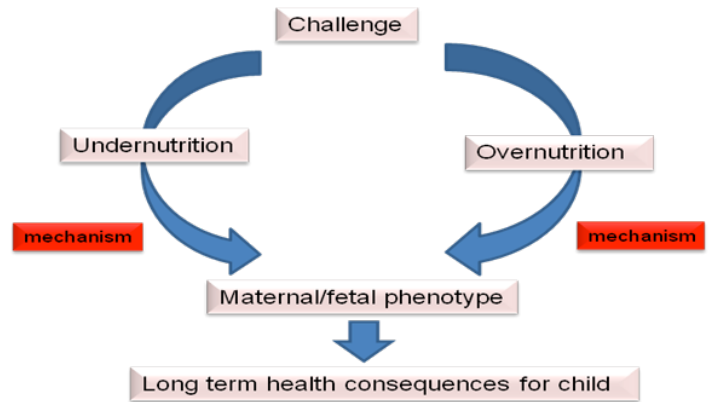


Figure 1. Poor nutrition in pregnancy has long-term consequences. Figure by L Poston.

With such serious and enduring consequences, Dr Poston advised, “Pregnancy is an ideal time to change health behaviors for the next generation. Women accept health advice more in pregnancy than in other times.”

How is it possible that a pregnant mother's diet can affect the health of her children and grandchildren? According to **Dr Susan Ozanne, (UK)**, the answer lies in *early life programming*.⁴ Studies of identical twins, of individuals who were *in utero* during periods of famine, and of animals have provided strong evidence that the early environment affects both fetal development and disease later in life. Such effects are based on the new science of epigenetics.

Epigenetics is the study of changes in gene expression caused by mechanisms other than alteration of the underlying DNA sequence. Inappropriate diet—such as calorie and protein shortfall or dietary excess as in obesity and high-fat intake—can lead to persistently altered expression of certain genes. One such example would be low levels of nutrients in fetal life leading to decreased mass in the beta cells of the pancreas, which in turn increases risk for type 2 diabetes in later life.⁵



Robert Miller, Mark Hanson, C.S. Yajnik, Stephanie Atkinson

What is epigenetics?

Epigenetics is the study of changes in gene expression caused by mechanisms other than changes in the underlying DNA sequence. The Greek prefix *epi* refers to *on top of or in addition to*.

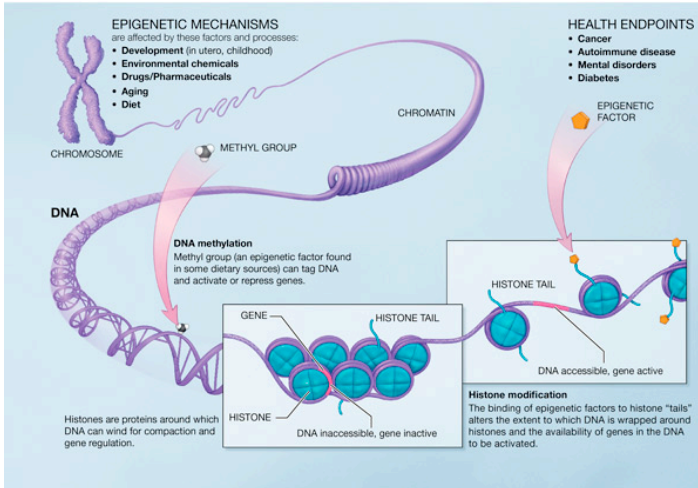


Figure 2. Epigenetic mechanisms for altered gene expression (from US National Institutes of Health).

Dr Mark Hanson, (UK),^{6,7} and **Dr Yuan-Xiang Pan, (USA),⁸⁻¹⁰** and others, described the molecular mechanisms of epigenetic programming. Methylation of DNA and acetylation of histones can respectively suppress or activate expression of specific genes (Figure 2). In turn, such changes in gene expression can alter cellular growth, function, and aging and have long-term effects on development of diseases such as diabetes and cancer in adult life.

For example, Pan's research in animal models demonstrates that *in utero* exposure to a high-fat diet has the potential to program the gluconeogenic capacity of the offspring through epigenetic modifications which could potentially lead to excessive glucose production and altered insulin sensitivity in adulthood.

Hanson posed a key question: "Can postnatal nutrition reverse prenatal changes in gene expression?"

An animal study did show that post-weaning supplementation with folic acid could correct expression of some genes in some tissues, but the effect was not consistent across all changes attributed to maternal nutrition.¹¹

Nutrition-related physiological changes: Gestational obesity and diabetes

Up from the molecular level, experts next discussed how physiological changes such as maternal obesity and diabetes can impair the development of an unborn child in ways that influence the child's later health outcomes.

Dr Keith Godfrey, (UK), described study designs used to identify maternal lifestyle factors, dietary habits, and body compositions that alter fetal development and later child development. Godfrey compared prospective cohort studies with randomized interventional studies.

A *cohort study* is a type of observational study used to assess risk factors for noncommunicable diseases. For a prospective study, the cohort is identified before the disease develops and is often followed over a long time period. Although time consuming and costly, cohort studies can yield good quality exposure information. For example, in a study of a Native American cohort followed for 24 years, childhood obesity was associated with a doubling of adult mortality before age 55 years.¹² Another cohort study, the Southampton Women's Survey, found that pre-pregnant women with poor dietary habits did not later follow recommendations for feeding their children.¹³⁻¹⁵

An *interventional study* is the next step to confirm and extend an observation from a cohort trial. An interventional study randomly assigns subjects to treatment or control groups in order to directly test a hypothesis, eg, results of an interventional study showed that supplementing the mother's prenatal diet with fish oil led to improvement in neurological outcomes in the children 5 years later.¹⁶

Epidemiological studies reflect population trends.

Dr Bert Koletzko, (Germany), noted, "Changes in body composition in the last 2 decades have been greater than those seen in the prior 1000 years."

In his presentation, Koletzko reported that obesity before and during pregnancy has become increasingly common in many populations around the world, including the Middle East, Australia, and countries of Europe. In the United States, one in three women aged 20-39 years is obese (body mass index, BMI ≥ 30 kg/m²).¹⁷ Health risks for obese, pregnant women are markedly higher than for women of normal weight,

"There is a worldwide pandemic of overweight and obesity among women of childbearing age, which is associated with increased birth complications and lifelong health risks among their children. Such risks can be lowered by weight loss, as shown by studies of mothers who underwent bariatric surgery."

- Berthold Koletzko, MD, PhD (Germany)

eg, spontaneous first trimester and recurrent miscarriage, cardiac disease, pre-eclampsia, dysfunctional labor, gestational diabetes, thromboembolism, cesarean section, post-cesarean wound infection, postpartum hemorrhage, overall severe morbidity, and maternal deaths. A recent UK review found that about half of all cases of maternal mortality occurred in women who were overweight or obese.¹⁸ Further, a high maternal prepregnancy BMI was found to predict high-fat body mass in her child at 9 years.¹⁹ This association appears to be at least partly caused by the intrauterine environment; children born after an obese mother's bariatric surgery/weight loss had a lower birth weight, greater insulin sensitivity, and a markedly reduced likelihood of being obese in follow-up compared to those born before such surgery.²⁰

Dr Patrick Catalano, (USA), extended the discussion to women with gestational diabetes mellitus (GDM) and their children.²¹⁻²³ Catalano advised that 3%-5% of pregnant women are estimated to have GDM, although newly proposed criteria for diagnosis would include 10% or more women in this category (Table 1; International Association of Diabetes and Pregnancy Study Groups, IADPSG).²⁴

Table 1. Proposed IADPSG plasma glucose thresholds for GDM diagnosis

Glucose measure*	mg/dL	mM/L
FPG	92	5.1
OGTT, 1h	180	10.0
OGTT, 2h	153	8.5

FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; GDM, gestational diabetes mellitus. *GDM diagnosis with 1 or more values \geq threshold

Studies have shown that increases in the mother's glucose and triglyceride levels are normal consequences of the physiology of pregnancy. However, among women with obesity prior to pregnancy and/or GDM, these physiological changes are exaggerated and are associated with insulin resistance in both the mother and the fetus, infant macrosomia, and increased neonatal fat mass.²³ Such changes are associated with increases in circulation of inflammatory cytokines, which appear to be derived from

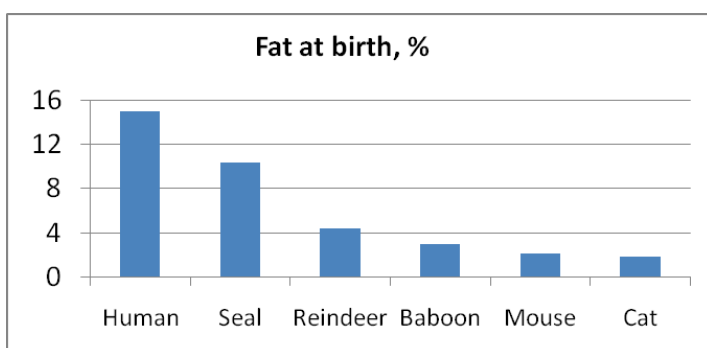


Figure 3. Humans have greater *in utero* fat deposition than any other mammalian species.

adipose tissue and from the placenta. Dr Catalano reported that his group and others are now examining lifestyle and dietary factors related to decreasing inflammation in pregnancy and, thereby, improving maternal insulin sensitivity and fetal growth.

David Fields, PhD, (USA), opened, "Compared to many other species, humans, have the greatest percentage of body fat at birth." (Figure 3)²⁵ While numerous studies have associated maternal obesity to childhood overweight and to diabetes in adulthood, exciting new technology now allows noninvasive measurement of whole body composition in infants.

Fields reported that it is now possible to measure fat mass in infants as young as 72 hours old using methods such as air-displacement plethysmography and dual-energy X-ray absorptiometry (DXA).²⁶ Compared to infants of leaner mothers, babies of obese mothers have a greater percentage of body fat as well as a greater absolute fat mass.²⁷ According to Fields, use of such measurement techniques may lead to insights that will help avert neonatal fat accumulation and prevent later development of diabetes.

The mother's diet in pregnancy influences functional outcomes in infants

While the total quantity of perinatal macronutrients affects a baby's body weight, intake of specific nutrients impacts development of the brain, bones, and immune system, as discussed by Drs Cristina Campoy (Spain), Stephanie Atkinson (Canada), and Susanna Cunningham-Rundles (USA).

Dr Cristina Campoy, (Spain), opened, "An infant's brain triples in weight during the first 3 years of life—from 400 grams to 1200 grams." (Figure 4)

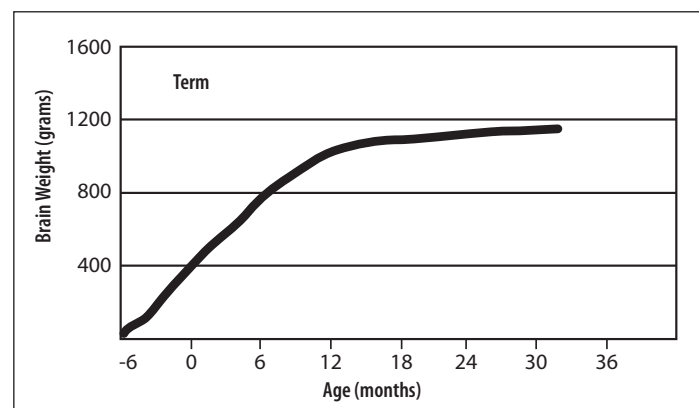


Figure 4. The human brain triples in weight during the first 3 years of life. Figure courtesy of Dr C. Campoy 2011.



Susan Ozanne, Yuan-Xiang Pan

A new research study showed that 4,000 IU/day supplemental vitamin D for pregnant women was safe and effective in achieving vitamin D sufficiency in all women and their neonates. By contrast, the traditional vitamin D supplement of 400 IU/day was comparatively ineffective, especially in African Americans.

In addition to structural growth, maturation of brain function (vision, motor activity, memory, language) is also important. Adequate perinatal supplies of the nutrients iron, folic acid, and especially long-chain polyunsaturated fatty acids (docosahexaenoic acid DHA and arachidonic acid AA) are key to normal and rapid brain development.^{16,28} Recent studies suggest that mutations in maternal genes encoding enzymes important to synthesis of DHA and AA (fatty acid desaturase enzymes, FAD) can alter supplies of these long-chain fatty acids during pregnancy and in human milk with consequences on cognitive development of the fetus or infant.²⁹ This cutting-edge area of study shows the fascinating interplay between genetics and diet in control of infant brain development.

Dr Stephanie Atkinson, (Canada), reviewed pre- and postnatal factors that influence childhood bone mass. While many factors affect childhood bone mass, including genetics and exercise of both the pregnant mother and the infant/child, the most-discussed factors today are dietary intake of calcium and vitamin D during the mother's pregnancy. Atkinson reported that maternal vitamin D status is recognized to influence fetal and child femur length, as well as birth length and weight and bone mass up to 16 years later.

In 2010, the United States and Canada updated Recommended Dietary Allowance (RDA) values for calcium to 1000 mg/day for pregnant or lactating women (ages 19-50) and 1300 mg/day for pregnant or lactating adolescents (ages 14-18); RDA for vitamin D was set at 600 IU/day regardless of age or lactation status (see Web site at <http://www.hc-sc.gc.ca/fn-an/nutrition/reference/table/index-eng.php>). Despite these recent recommendations, Atkinson noted that the necessity, safety and effectiveness of vitamin D supplementation during pregnancy still remain controversial. In fact, current recommendations for pregnant/lactating women vary widely among nutritional advisory groups—from 400 IU/day in the UK to 2000 IU/day by the Canadian Pediatric Society.

Results of a newly published US study by Hollis et al showed that even higher levels of supplemental vitamin D may be desirable.³⁰ In this randomized, controlled study, the research team found that 4,000 IU/day supplemental vitamin D for pregnant women was safe and effective in achieving vitamin D sufficiency in all women and their neonates. By contrast, the traditional vitamin D supplement of 400 IU/day was comparatively ineffective, especially in African Americans.

Dr Susanna Cunningham-Rundles, (USA),^{31,32} began her conference presentation, "The neonatal immune system is shaped by fetal life and undergoes postnatal development." Newborn babies encounter environmental antigens as foods, colonizing bacteria in the gut, and potential pathogens. Each exposure leads to an immunological change such as antibody-based clearance, suppression by innate immune response, or appropriate development of tolerance. On the other end of the spectrum, abnormal responses to environmental antigens include atopy and allergy. Adequate dietary supplies of micronutrients such as zinc, vitamin D, and vitamin A are well known to be necessary for development of the immune system.

Dr Cunningham-Rundles invited attendees to consider new evidence supporting a role for omega-3 fatty acids in the newborn diet on lessening incidence of allergies and inflammation. Polyunsaturated omega-3 fatty acids such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in the diet have anti-inflammatory properties. Cunningham-Rundles and colleagues conducted *in vitro* studies with newborn cord blood; findings showed that pretreatment of cells with DHA can reduce harmful cytokine responses elicited by a bacterial lipopolysaccharide antigen—evidence that omega-3 supplies can help reduce inflammation.

“This conference has shown us that we still have many dots to connect. Abbott Nutrition has a great opportunity to be at the front end of research.”

- Ryan Frank, Abbott Nutrition

National and global evidence linking pregnancy nutrition and health outcomes

While overweight and obesity are major problems in the United States and elsewhere in the Western world, healthcare professionals in countries such as India, China, and Chile are particularly challenged to meet the nutritional needs of both underweight and overweight mothers, as reviewed by Dr CS Yajnik, Prof Chunming Chen, and Dr Francisco Mardones.

Barbara Abrams, DrPH, RD, (USA),³³ asked the question, “What is a healthy amount of gestational weight gain (GWG)?” It depends on the starting weight of the mother, but there is still much debate about how much is good and how to successfully limit gain in mothers who are obese. Interventions that can help limit excessive weight gains include adopting a low-calorie and nutrient-dense diet, engaging in moderate physical activity, setting goals for gestational weight gain, educating mothers, using behavior modification strategies, and encouraging self-monitoring. Despite many possible interventions, Dr Abrams reported that recently published reviews provide only limited evidence of success in limiting excessive weight gain.³⁴⁻³⁶ Abrams discussed her collaborative *FIT for Delivery Program* as a model for personal intervention. Early results suggest that counseling and follow-up can help limit excessive gestational weight gain and support return to pregravid weight, but such benefits were much more difficult to achieve in mothers who were overweight or obese before their pregnancy than in normal-weight women.

The table below provides guidelines on weight gain from the US Institute of Medicine 2009 update (Table 2).³⁷ Because of differences in body structures around the world, these guidelines are not considered relevant to all populations.

Dr CS Yajnik, (India),^{38,39} conducted a study in India showing the first direct evidence that a mother’s abnormal micronutrient levels (low vitamin B12 and high folate) can predict newborn adiposity (thin Indian babies with a high level of intra-abdominal fat) and a child’s increased risk for developing diabetes later in life.⁴⁰ The low B12 level is attributed to the common practice of vegetarianism in India, while high folate may be due to prescription of high-dose folate in obstetric practice. This apparent epigenetic effect shows how India must deal with both under- and overnutrition in pregnancy.

Prof Chunming Chen, (China),⁴¹⁻⁴³ found that fewer than half of pregnant women in China take prenatal nutrient supplements. Professor Chen and colleagues will work on better educating pregnant women about the importance of nutrition as a way to improve the health of their children.

Francisco Mardones, MD, (Chile),^{44,45} summarized problems facing public health caregivers in Chile and other Latin American countries. Because of the short stature of Chilean women, perinatal weight gain can accumulate with multiple pregnancies and lead to obesity. At the same time, micronutrient deficiencies in pregnant women are also common. As a result, Chilean public health programs are challenged to deal with both under- and overnutrition during pregnancy.

Conference conclusion

At the conclusion of the conference, Ryan Frank, (Director of Global Innovation) reflected on the challenges and excitement raised by the meeting. “This conference has shown us that we still have many dots to connect. Abbott Nutrition has a great opportunity to be at the front end of research.”

Table 2. US 2009 IOM guidelines for weight gain and rate of weight gain for women with singleton pregnancies*

Prepregnancy (BMI, kg/m ²)	Total weight gain (lb)	Rate of weight gain in 2nd, 3rd trimesters (lb/wk)
Underweight (< 18.5)	28-40	1.0 (1.0-1.3)
Normal weight (18.5-24.9)	25-35	1.0 (0.8-1.0)
Overweight (25.0-29.9)	15-25	0.6 (0.5-0.7)
Obese (≥30.0)	11-20	0.5 (0.4-0.6)

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Abbott Nutrition has a long tradition of convening research conferences addressing emerging issues in adult and pediatric nutrition science. The first research conference took place in 1950. Today, we are continuing that tradition with the 112th Abbott Nutrition Research Conference, and we plan to build upon this rich tradition in the years ahead.

Coming soon to www.ahn.org:
Videos and other downloadable materials based on presentations at the 112th Abbott Nutrition Research Conference on Pregnancy Nutrition and Later Health Outcomes.

Table 3. Presenters at 112th Abbott Nutrition Research Conference: Pregnancy Nutrition and Later Health Outcomes

Lucilla Poston, PhD, (UK)	<i>Pregnancy nutrition—the impact of under- and overnutrition during pregnancy</i>
Susan Ozanne, PhD, (UK)	<i>Overview of mechanisms of early programming during pregnancy</i>
Mark Hanson, PhD, (UK)	<i>Epigenetic markers</i>
Yuan-Xing Pan, PhD, (USA)	<i>The role of the placenta in early programming</i>
Keith Godfrey, PhD, FRCP, (UK)	<i>Optimal design of cohort studies for maximum learning</i>
Bert Koletzko, MD, PhD, (Germany)	<i>Impact of maternal obesity on long-term health outcomes</i>
Patrick Catalano, MD, (USA)	<i>Impact of maternal GDM and obesity on mother and fetus</i>
David Fields, PhD, (USA)	<i>Insight from body composition studies</i>
Cristina Campoy, MD, PhD, (Spain)	<i>Impact of pregnancy nutrition on cognition</i>
Stephanie Atkinson, PhD, FCAHS, (Canada)	<i>Impact of pregnancy nutrition on offspring bone development</i>
Susanna Cunningham-Rundles, PhD, (USA)	<i>Impact of perinatal nutrition on neonatal immune response</i>
Barbara Abrams, DrPH, RD, (USA)	<i>Lifestyle intervention trials during pregnancy</i>
CS Yajnik, MD, FRCP, (India)	<i>Under- and overnutrition during pregnancy in India: dual teratogenesis</i>
Chunming Chen, Professor, (China)	<i>Nutritional status of pregnant women in China</i>
Francisco Mardones, MD, (Chile)	<i>Challenges of addressing over- and undernutrition in Chile/Latin America</i>



Ricardo Rueda, Francisco Mardones, Lucilla Poston, Susanna Cunningham-Rundles



Barbara Abrams, Raanan Shamir

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