The 112th Abbott Nutrition Research Conference: Selected Summaries

July 26-28, 2011

Columbus, Ohio

Pregnancy Nutrition and Later Health Outcomes

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Welcome

Abbott Nutrition welcomes the opportunity for you to explore the Selected Summaries from the Proceedings of the 112th Abbott Nutrition Research Conference, entitled “Pregnancy Nutrition and Later Health Outcomes.”

The purpose of this conference was to explore the impact of maternal nutrition and health on near-term growth and development of the offspring as it relates to the propensity for cardiometabolic diseases later in life. Developmental programming is an area of research that has gained, and continues to gain, momentum. This model asserts that the choices pregnant women make and the conditions their offspring face prenatally and in the immediate postnatal period potentially have great impact on health and disease in later years.

This publication highlights 4 of the 15 conference presentations, which focus on the impact of under- and overnutrition during pregnancy, mechanisms of early programming during pregnancy, impact of maternal gestational diabetes and obesity on mother and fetus, and lifestyle intervention trials during pregnancy. These topics and others will be addressed in detail in the Full Conference Proceedings, which will be available later in 2012. We hope you find these summaries insightful in your practice, and that they reinforce the critical impact of proper nutrition on the short- and long-term health of the mother and child.

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Pregnancy Nutrition and Later Health Outcomes

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Pregnancy Nutrition and Later Health Outcomes

The 112th Abbott Nutrition Research Conference was held in Columbus, Ohio, on July 26–28, 2011. This Report contains summaries of presentations given by the following contributors:

Pregnancy Nutrition: The Impact of Under- and Overnutrition During Pregnancy

Lucilla Poston, PhD
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Nutrition in pregnancy presents a window of opportunity to influence the health of the mother as well as that of her child in infancy and later in life. Dr Poston offers an overview of the adverse effects of both undernutrition and overnutrition (ie, obesity) on mother and child. With respect to obesity interventions, Dr Poston suggests that approaches that focus on improvement of maternal glucose tolerance and consequent reduction of macrosomia may be more effective than strategies to limit gestational weight gain.

Overview of Mechanisms of Early Programming During Pregnancy

Susan Ozanne, PhD
University of Cambridge, UK
Department of Clinical Biochemistry

Extensive studies during the last 20 years have revealed that both low birth weight (especially when followed by accelerated postnatal growth) and high birth weight are associated with metabolic disease later in life. Dr Ozanne describes three categories of mechanisms by which a phenomenon that occurs in early life can have long-term effects on the function of a cell and therefore metabolism of an organism years later. The main goals now in the early programming field are to build on these findings and to translate them into ways to improve human health through development of preventative and intervention strategies.

Impact of Maternal GDM and Obesity on Mother and Fetus

Patrick Catalano, MD
Case Western Reserve University, USA
Department of Reproductive Biology

The worldwide increase in obesity among women of reproductive age signals a shift of the global disease burden from acute infectious disease to chronic diseases such as diabetes and atherosclerotic vascular disease, with their associated increase in health care costs. Dr Catalano discusses the causes and outcomes of the pattern of obesity/insulin resistance/gestational diabetes in pregnant women. Citing inflammation as a contributing factor in this pattern, Dr Catalano indicates that current research is examining lifestyle and dietary factors relating to decreasing inflammation in pregnancy and thereby improving maternal insulin sensitivity and fetal growth.

Lifestyle Intervention Trials During Pregnancy

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Understanding the physical, psychological, social, cultural, and financial barriers that women face in addressing weight control during pregnancy and designing appropriate responses to women's experiences and concerns will improve future behavioral interventions for pregnant women. A variety of intervention strategies, including counseling and education about weight gain, healthy eating, physical activity, and monitoring of weight gain, are utilized to improve maternal dietary intake and physical activity. Dr Abrams discusses the results of the Fit for Delivery Study and other behavioral intervention trials that suggest that it is possible to moderate gestational weight gain through methods that are implemented in the clinical setting.

Contents

Acronyms and Abbreviations

BMI . . . . . .body mass index

CRP . . . . . .C-reactive protein

GDM . . . . . .gestational diabetes mellitus

HNF4α . . . . . .hepatocyte nuclear factor 4 alpha

HPL . . . . . .human placental lactogen

IL . . . . . .interleukin (eg, IL-6, IL-8, IL-10)

MLR . . . . . .multiple logistic regression

OR . . . . . .odds ratio

PDX1 . . . . . .pancreatic and duodenal homeobox 1

SGA . . . . . .small for gestational age

TNF-alpha . . . . . .tumor necrosis factor alpha

TOBEC . . . . . .total body electrical conductivity

Pregnancy Nutrition: The Impact of Under- and Overnutrition During Pregnancy

Lucilla Poston, PhD

Optimization of maternal nutritional and fetal status has been a public health goal since records began. The association of low-calorie intake with low birth weight is perhaps best evidenced by reports from the famine-stricken populations of Leningrad and southern Holland during World War II.[1,2] Since the beginning of the 20th century, with the awareness that gestational weight gain was a proxy for maternal nutrition, efforts have been made to ensure adequate gestational weight gain. The effects of fetal nutritional excess also are exemplified by excessive fetal growth in response to suboptimal glucose control in women with gestational diabetes, but recently increasing trends in maternal dietary caloric excess and obesity have led to considerable concern over the myriad of associated adverse maternal and fetal health outcomes. Importantly, we are now aware that maternal nutritional status may have unforeseen influences on the developing child that extend to increased risk of disease in later life. This association, embodied in the Developmental Origins of Disease Hypothesis, has given renewed vigor to investigations of maternal nutritional status in pregnancy.

Protein-Energy Malnutrition

Women in developing countries remain at risk of protein-energy malnutrition and associated low birth weight, major causes of neonatal mortality and morbidity. A recent meta-analysis of women from developed and developing countries suggests that balanced protein-energy supplementation can lead to a 31% (95% CI 15%–44%) reduction in delivery of infants who are small for gestational age.[3] Data from some of the studies in the meta-analysis are shown in Fig 1.

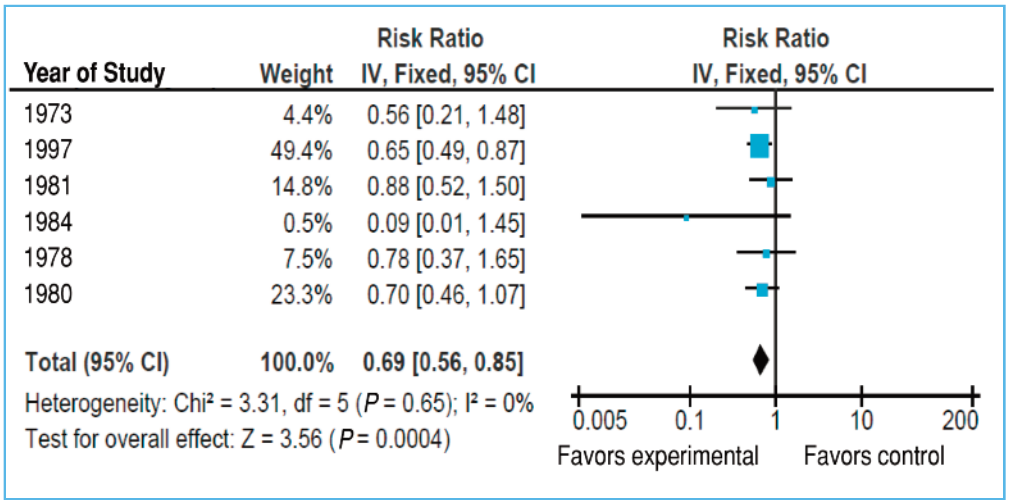

Fig 1. Effect of balanced protein energy supplementation during pregnancy on risk of small-for-gestational age births.[3]

Source: Imdad A, Bhutta ZA. Effect of balanced protein energy supplementation during pregnancy on birth outcomes. *BMC Public Health*. 2011;11(suppl 3):S17.

These findings suggest that this intervention should be scaled up in developing countries. There is hitherto no information, however, as to whether these benefits may reduce risk of disease in the child in later life.

Micronutrient Deficiencies

Pregnant women in both developed and developing countries are at risk of micronutrient deficiency. In developing countries where the incidence of anemia is high, iron/folate supplementation is an effective treatment, but iron and multivitamin supplements have only a modest influence on reducing low birth weight.[4] Iodine deficiency, which is associated with adverse influences on cognitive development and increased infant mortality and morbidity, remains a problem in some parts of the world.[5]

The influence of inadequate periconceptual folate intake on risk of neural tube defects is well known, but increasing evidence for the role dietary folate insufficiency plays in fetal growth restriction, for example, in pregnancy in adolescents,[6] (Fig 2) and in preeclampsia[7] suggests that folate supplementation should be considered throughout pregnancy.

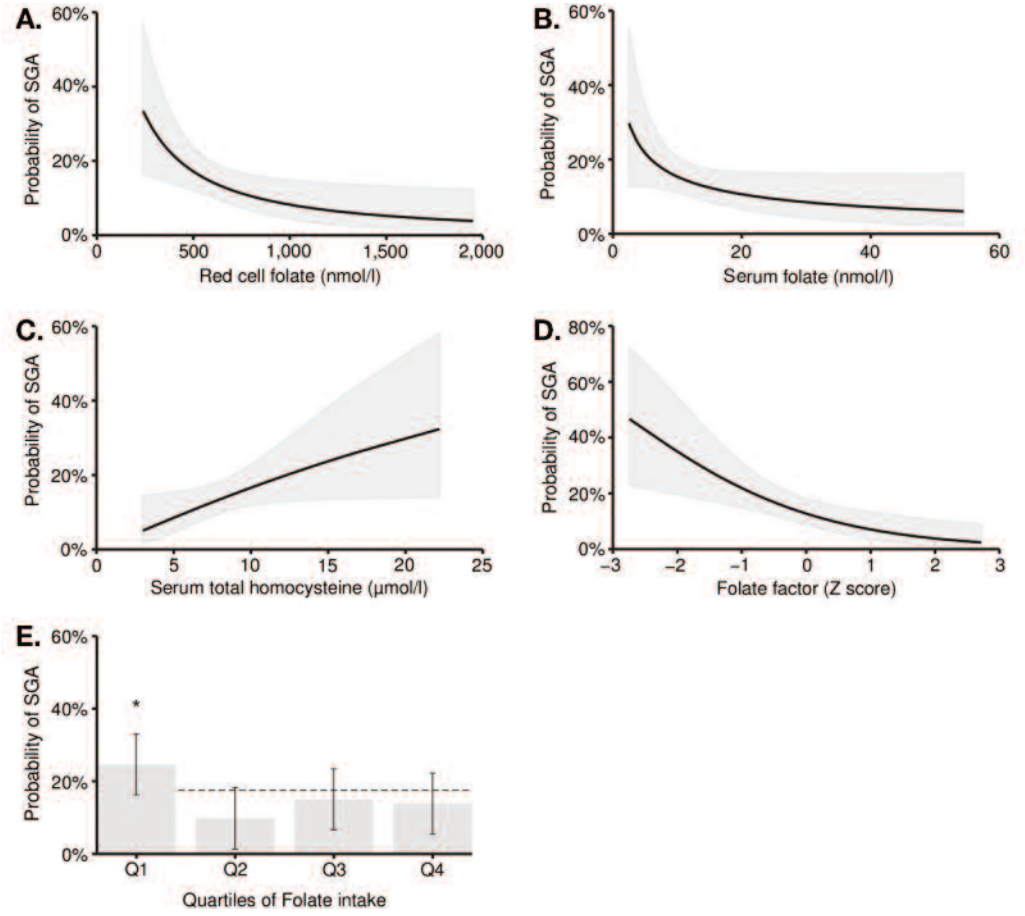

Fig 2. Folate status and folate intake measured in pregnant adolescents during the 3rd trimester and relations with small-for-gestational age (SGA) birth.[6] Shaded areas represent 95% CIs. Data adjusted for confounding variables (multiple logistic regression). A: Relation between red blood cell folate and SGA birth (n=263). Curve obtained by multiple logistic regression (MLR) of log-transformed biomarkers. B: Relation between serum folate and SGA birth (n=280). Curve obtained by MLR of log-transformed biomarkers. C: Relation between serum total homocysteine and SGA birth (n=290). Curve obtained by MLR of log-transformed biomarkers. D: Relation between folate factor score and SGA birth (n=290). Folate factor score defined by factor analysis of red blood cell folate, serum folate, and serum total homocysteine. Curve obtained by MLR of log-transformed biomarkers. E: Relation between quartiles of folate intake and SGA birth (n=288). Subjects in the lowest quartile of folate intake (<187 µg/day) were more likely to deliver an SGA infant than were subjects with higher intakes (odds ratio: 2.71; 95% CI: 1.28, 5.71; *P*=0.009, energy-adjusted). Columns represent the probability of SGA birth, determined by MLR of folate intake and SGA birth, adjusted for energy intake. Error bars represent 95% CIs. The dashed line indicates the incidence of SGA birth in the sample as a whole.

Source: Baker PN et al. A prospective study of micronutrient status in adolescent pregnancy. *Am J Clin Nutr.* 2009;89:1114-1124. Reprinted by permission of the American Society for Nutrition.

A new randomized controlled trial (the FACT trial) is addressing the potential for prevention of preeclampsia by folate supplementation in early pregnancy. Although there is little evidence of a prolonged effect of folate on childhood risk of disease, a recent study of Indian mothers and their children suggests that folate status in pregnancy may have an independent influence on cognitive function in young children.[8] Since folate metabolism plays an important role in gene methylation status and epigenetic regulation of gene expression, influences of maternal dietary folate on later risk of disease may occur through persistently altered gene methylation status in the child. Further studies are required to address the genome-wide or candidate gene methylation status of children born to folate-deficient and folate-replete women.

Vitamin D insufficiency in pregnant women is prevalent worldwide and observational studies have suggested links with gestational diabetes and preeclampsia.[9] While a relationship between vitamin D insufficiency and increased risk of infant rickets is well established, it now appears that maternal vitamin D status may have consequences for a child's bone density in later life.[10,11]

Obesity

Obesity in pregnancy represents an increasing challenge to health care professionals. Obesity is associated with increased risk of miscarriage, thromboembolism, preeclampsia, gestational diabetes, and a high cesarean section rate, among many other problems (Table). An infant born to an obese mother is more likely to develop congenital malformations, to be born large for gestational age, and to die in stillbirth.[12]

Table. Maternal and Fetal Risks Associated With Maternal Obesity

Maternal Risk	Fetal/Infant Risk
Gestational diabetes	Macrosomia
Preeclampsia	Shoulder dystocia
Venous thromboembolism	Brachial plexus damage
Genital infection	Intrauterine death
Urinary tract infection	Spina bifida
Wound infection	Heart defects
Postpartum hemorrhage	
Induction of labor	

An intervention is needed that reliably reduces the risk of these complications, in both mother and child. One approach is to devise strategies to limit gestational weight gain in obese pregnant women; however, a meta-analysis of recent small studies suggests that the strategies that have been tried have been unable to achieve the weight-gain restrictions recommended by the USA Institute of Medicine (5–9 kg).[13] However, approaches that specifically concentrate on improvement of maternal glucose tolerance and consequent reduction of macrosomia may be more apposite, although these require much larger studies to achieve adequate power. Such a study, the UPBEAT Trial, is now underway in the United Kingdom.

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Overview of Mechanisms of Early Programming During Pregnancy

Susan Ozanne, PhD

More than 20 years ago the first epidemiological studies revealed a relationship between patterns of early growth and subsequent risk of diseases such as type 2 diabetes, cardiovascular disease, and the metabolic syndrome. Extensive studies during this time have revealed that both low birth weight (especially when followed by accelerated postnatal growth) and high birth weight were associated with metabolic disease later in life.

Evidence also shows not just that metabolic conditions are associated with patterns of early growth but also that similar relationships exist between birth weight and nonmetabolic parameters such as mental health and immune function. Studies of identical twins, individuals who were in utero during periods of famine, discordant sib pairs, and animal models have provided strong evidence that the early environment, including nutrition during fetal life, plays an important role in mediating these relationships.[1] The concept of early life programming therefore is widely accepted.

However, the mechanisms by which a phenomenon that occurs in early life can have long-term effects on the function of a cell and therefore metabolism of an organism many years later are only starting to emerge. Insight into these molecular mechanisms has primarily come from the study of animal models including those established in nonhuman primates, sheep, pigs, rats, and mice. A major strength of studying a range of diverse species is that it allows the identification of molecular mechanisms that are conserved between species and therefore likely to represent fundamental mechanisms that are likely to be important in humans. However, most studies have been carried out in rodents as these allow mechanisms to be addressed across the life course of an organism.

It has become increasing apparent that a single mechanism cannot explain all the observed programming phenomena. Based on current knowledge, the potential mechanisms can be categorized into three groups. These three mechanistic categories clearly are not mutually exclusive, and there is likely to be interaction among them (Table).

Overview of Mechanisms of Early Programming During Pregnancy

Table. Proposed Mechanisms of Early Programming

Programming Mechanisms
1. Permanent structural changes
2. Epigenetic programming of gene expression
3. Accelerated cellular aging

One of the earliest proposed mechanisms was related to effects mediated by permanent changes in the structure and consequently the function of critical organs. It was suggested that during a critical period of development of an organ, exposure to a suboptimal level of a nutrient or hormone that is essential for appropriate development of that organ would permanently alter the structure and function of that tissue. Examples are low levels of nutrients early in life leading to a permanent reduction in pancreatic beta cell mass and renal nephron numbers, which can influence risk of type 2 diabetes and hypertension respectively.[2,3] Suboptimal levels of the hormones insulin and leptin in early life also can permanently influence the structure and, consequently, function of the hypothalamus, which plays a key role in regulation of energy balance and thus can influence risk of obesity.[4,5]

More recently focus has been directed toward the potential role of persistent alterations in epigenetic modifications (eg, DNA methylation and histone modifications) leading to programmed changes in gene expression that form the basis of cellular memory.[6] Several transcription factors including hepatocyte nuclear factor 4 alpha (HNF4α), pancreatic and duodenal homeobox 1 (PDX-1), and peroxisome proliferators-activated receptor alpha are susceptible to programmed changes in gene expression through such mechanisms. Fig 1 illustrates the role of HNF4α in the beta cell and consequently type 2 diabetes.

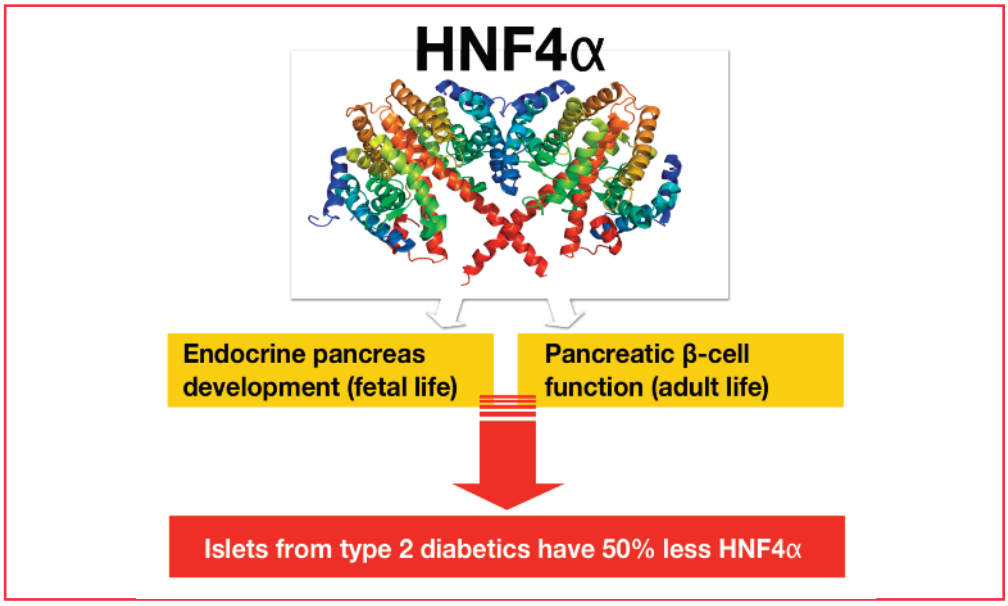

Fig 1. Mechanisms of programmed changes in gene expression through persistent alterations in epigenetic modifications: hepatocyte nuclear factor 4 alpha (HNF4α)→type 2 diabetes.

Source: http://en.wikipedia.org/wiki/File:Protein_HNF4A_PDB_1m7w.png.

Transcription factors are particularly attractive targets of developmental programming because a whole network of other genes can be modulated through modulation of their expression.

A permanent effect of early exposures on the regulation of cellular aging has been suggested as another mechanism that can link a suboptimal early environment and long-term health. Increases in oxidative stress leading to macromolecular damage, including that to DNA and specifically telomeres, can contribute to such effects by leading to premature cell senescence.[7] Mitochondrial dysfunction resulting from either defects in mitochondrial copy number or defects in mitochondrial complex activities could provide the source of the oxidative stress.[8]

The main goals now in the programming field are to build on these findings and to translate them into ways to improve human health through development of preventative and intervention strategies. However, there are still major challenges that need to be addressed to achieve such goals. It is clear, certainly from animal models, that maternal overnutrition and undernutrition during pregnancy can affect not only the health of the mother but also the long-term health of the baby. However, modulation of diet during human pregnancy is not straightforward and it

should be noted that maternal diet does not equate to fetal diet. Therefore, in many instances an apparently well-nourished or overnourished mother can deliver an undernourished baby as a result of poor placental function. Furthermore, although initial focus in human studies was directed toward high or low birth weight as a proxy for exposure to a suboptimal in utero environment, it is now apparent that birth weight is a very crude index of in utero experiences and that not every suboptimal environment influences fetal growth. Therefore, a need exists to identify at-risk individuals through good molecular markers (see strategies in Fig 2). These could be genetic, protein, or epigenetic factors, which to be clinically useful would have to be present in clinically accessible material such as blood, urine, placenta, or umbilical cord. The latter two are particularly attractive because they are available very early in life, thus providing the maximum time for intervention.

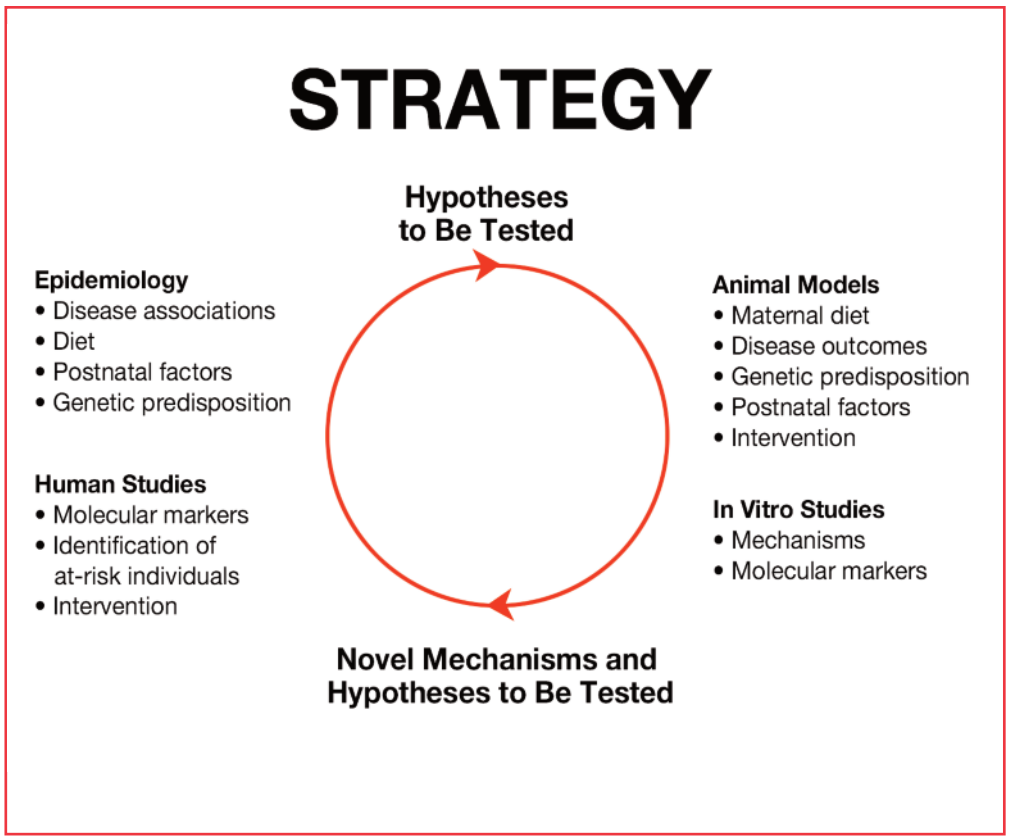

Fig 2. Strategies for identifying individuals at risk for certain metabolic diseases.

The insight gained from mechanistic studies may enable the design of targeted intervention studies and ultimately personalized medicines. Most of the diseases associated with a suboptimal environment are heterogeneous conditions. For example, type 2 diabetes is a phenotype that can result from a wide variety of factors that influence pancreatic beta cell function and/or insulin action. Therefore, it may be naïve to assume that the same medication will be suitable for all causes of type 2 diabetes. Mechanistic insight into the pathways that mediate the effects of a suboptimal early environment on type 2 diabetes risk could help identify rational drug targets.

Understanding environmentally driven processes provides more tractable targets for intervention than those driven by genetic processes. Therefore, further progress on understanding the pathways and mechanisms underlying early life programming offers the potential to help combat the burden of many common diseases faced by modern society.

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Impact of Maternal GDM and Obesity on Mother and Fetus

Patrick Catalano, MD

Over the last 2 decades, the incidence of obesity in reproductive-age women has increased significantly. The increase has been observed not only in developed areas of the world, but possibly more important in developing countries as well.[1] The increase in worldwide obesity is a harbinger of a shift of the global disease burden from acute infectious disease to chronic diseases such as diabetes and atherosclerotic vascular disease, with their associated increase in health care costs.

One of the primary metabolic abnormalities associated with obesity and diabetes is increased insulin resistance. During pregnancy, obese women are at increased risk of the "metabolic syndrome" of pregnancy, ie, gestational diabetes mellitus (GDM) and hypertensive disorders such as preeclampsia.[2] Women developing GDM have both increased insulin resistance and impaired beta cell function, whereas obese women often have increased insulin resistance but are able to compensate with increased beta cell response resulting in normoglycemia.[3] The insulin resistance of pregnancy not only affects glucose metabolism but also lipid and amino acid metabolism, ie, "fuel mediated teratogenesis" as described by Freinkel.[4]

In one study, we examined longitudinal changes in maternal insulin sensitivity with a hyperinsulinemic-euglycemic clamp in women with a pregravid body mass index (BMI) <25, 25–30, and >30. We found that obese women were significantly less insulin sensitive (ie, more insulin resistant) than lean women (P=0.0001) and overweight women (P=0.004), particularly pregravid and in early gestation (Fig).[5]

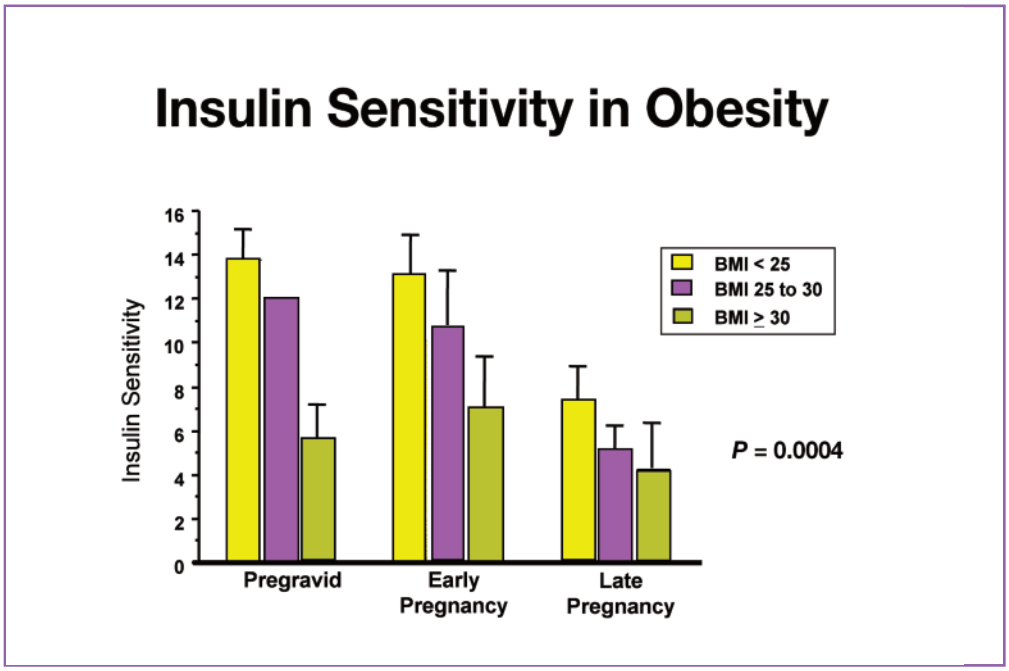

Fig. Longitudinal changes in insulin sensitivity in lean, overweight, and obese women, before conception (pregravid) and in early (12–14 weeks) and late (34–36 weeks) gestation.[5]

Source: Catalano P, Ehrenberg H. The short- and long-term implications of maternal obesity on the mother and her offspring. *BJOG*. 2006;113:1126–1133. Reproduced with permission of Blackwell Publishing Ltd.

Our research has focused on estimates of body composition to assess fetal growth, using anthropometrics, stable isotopes, total body electrical conductivity (TOBEC) and most recently air-displacement plethysmography (PEA POD®). At birth, infants of women with GDM often are larger than those of women with normal glucose tolerance because of increased fat and not lean body mass, even with the same weight.[6] Similarly, infants of obese women are larger at birth because of increased fat and not lean body mass.[7] Both GDM and maternal obesity are risk factors for later childhood obesity and related problems such as insulin resistance, glucose intolerance, and elevated blood pressure.[8]

Over 50 years ago, Jorgen Pedersen hypothesized that increased maternal glucose, which crosses the placenta in a concentration-dependent manner from mother to fetus (facilitated diffusion), results in increased fetal glucose concentrations and insulin response.[9] The combination of these two factors in women with diabetes results in fetal overgrowth, or macrosomia. More recently, investigators have

reported that maternal triglycerides are correlated with increased fetal growth and more specifically, adiposity.[10]

The increase in glucose and triglycerides during pregnancy are normal consequences of the physiology of pregnancy, ie, increased insulin resistance. However, when insulin resistance increases before conception, as seen in GDM and obesity, the physiologic changes in pregnancy are exaggerated. This results in greater nutrient availability to the fetus and subsequent fetal overgrowth. What then are the mechanisms by which insulin resistance increases progressively during pregnancy?

The insulin resistance of pregnancy improves significantly after delivery; therefore, placental factors are most likely responsible. Previously, placental hormones such as human placental lactogen (HPL) were assumed to be a factor. However, more recent research in both pregnant and nonpregnant women points to inflammation as the mechanism, resulting in dysfunction in postreceptor insulin signaling.[11-13] We studied 53 lean and 68 obese women who had a scheduled cesarean delivery to measure insulin resistance and inflammatory markers in the mothers and in umbilical cord blood.[14] Table 1 shows that obese women were significantly more insulin resistant and had significantly higher levels of several inflammatory markers than lean women.

Table 1. Maternal Systemic Inflammation in Obesity[14]

	Lean n=53	Obese n=68	*P* value
Pregravid BMI	22.0 ± 1.9	38.4 ± 6.3	0.0001
Plasma insulin (µU/mL)	11.8 ± 5.6	26.0 ± 14.6	0.006
Plasma glucose (mg/dL)	74 ± 7	79 ± 11	ns
Adiponectin (µg/mL)	10.7 ± 4.6	9.7 ± 4.0	0.0001
Leptin (ng/mL)	31.9 ± 20	72.1 ± 34.7	0.0001
IL-6 (ng/mL)	2.4 ± 1.4	4.6 ± 3.4	ns
TNF-alpha (pg/mL)	1.4 ± 0.9	1.3 ± 0.5	0.004
CRP (ng/mL)	8074 ± 6467	12433 ± 7918	

BMI=body mass index, IL-6=interleukin 6, ns=not sigificant, TNF-alpha=tumor necrosis factor alpha, CRP=C-reactive protein

Evidence indicates that in obese nonpregnant individuals increased inflammatory cytokines derived from adipose tissue may play an important role in insulin resistance.[11] During pregnancy the placenta is another potential source for cytokine production.

Preliminary data have shown that maternal circulating monocytes may be the source of cytokine production. In the placenta, macrophages also may contribute to the inflammatory milieu of obese pregnancy.[15] In gene array studies of placenta from women with obesity/GDM and type 1 diabetes, there is a differential expression of genes related to lipid and glucose metabolism.[16] These data support our hypothesis that both maternal glucose and lipids can be the substrate source of adipose tissue in the developing fetus, depending on the mother's metabolic profile.

As noted previously, at birth infants of obese women have increased body fat. Fetal adiposity is strongly correlated with fetal insulin resistance, as estimated by umbilical cord blood measures of glucose and insulin in women undergoing scheduled cesarean delivery.[14] The increases in fetal adiposity and insulin resistance are related to the increase in obesity and insulin resistance in later childhood. In a regression analysis, maternal pregravid obesity was the strongest risk factor for fetal obesity at birth and in childhood, even in women with well-controlled GDM (Table 2).[8]

Table 2. Maternal Pregravid Obesity as a Predictor of Childhood Obesity[8]

Pregravid BMI >30

OR 5.45 (95% CI 1.62–18.4, *P*=0.0006)

Including gender and group (GDM)

OR 7.75 (95% CI 1.51–37.74, *P*=0.01)

Maternal obesity

Accounts for 17.6% of the variance in childhood obesity

Treated GDM appears to be less of a risk factor for childhood obesity than maternal pregravid obesity

BMI=body mass index, (weight [k]/height [m]^2), GDM=gestational diabetes mellitus, OR=odds ratio

However, more research is needed in the time between birth and childhood in order to understand the effect of the modifiable factors on the individual's growth and development.

Finally, is there anything we can do during pregnancy to interrupt the cycle of maternal obesity and GDM that begets childhood problems of obesity and related metabolic dysfunction? Recently, two randomized controlled trials in women with GDM have shown improved neonatal outcomes at birth.[17,18] There is evidence that treatment of mild GDM can decrease the risk of macrosomia, fetal adiposity, and other related perinatal outcomes. However, only short-term studies have been conducted in children up to 5 years of age, without evidence of long-term benefit.[19,20]

The treatment of maternal obesity during pregnancy is not as well defined. All would agree that avoidance of excessive gestational weight gain during pregnancy is important for both mother and fetus.[21] Although the Institute of Medicine has recently revised the guidelines for gestational weight gain, many feel the guidelines do not go far enough, particularly in the 30+% of pregnant women who are obese.[22] Much research needs to be done in this area to determine both the short-term and long-term benefits of limited weight gain or loss in overweight and obese pregnant women. In the interim, our research group and others are examining lifestyle and dietary factors relating to decreasing inflammation in pregnancy and thereby improving maternal insulin sensitivity and fetal growth. Because of the effects of maternal metabolism on placental growth and gene expression, prevention—which ideally should begin before a planned pregnancy—by necessity should be initiated as early in pregnancy as possible.

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Lifestyle Intervention Trials During Pregnancy

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Recent data from the US Centers for Disease Control indicate that the prevalence of excessive gestational weight gain (Table) approaches 40% among women with a normal prepregnancy body mass index (BMI), and is even higher among women who are overweight.[1] Excessive maternal gestational weight gain is an established risk factor for increased risk of cesarean delivery, fetal macrosomia, and maternal weight retention in the immediate postpartum period and is possibly related to a wider array of other adverse pregnancy outcomes.[1]

Table. Cutoff Values for Excessive Gestational Weight Gain Based on 2009 Institute of Medicine Recommendations[1]

Pregravid BMI Category	Total Weight Gain (lb)	Rate/Week (lb)*
Underweight (<18.5 kg/m^2)	>40	>1.3
Normal weight (18.5–24.9 kg/m^2)	>35	>1
Overweight (25.0–29.9 kg/m^2)	>25	>0.7
Obese (≥30.0 kg/m^2)	>20	>0.6

*2nd and 3rd trimester
Source: Adapted from the National Academy of Sciences, 2009.

Growing evidence also exists to show that high maternal gestational weight gain increases the risk of child and adolescent obesity.[2,3] To address the health risks associated with excessive gestational weight, the 2009 Institute of Medicine Report, *Weight Gain During Pregnancy: Reexamining the Guidelines,* recommended that "those who provide prenatal care to women should offer counseling, such as guidance on dietary intake and physical activity, that is tailored to their life circumstances."[1]

In theory, this is an excellent idea. Unlike preexisting obesity, gestational weight gain is potentially modifiable during the course of pregnancy, with the potential to reduce negative in utero influences on the fetus that could persist over the child's life.[4] Pregnant women are concerned about having healthy babies and are perhaps

more motivated to change their behavior during pregnancy than at other points of time.[5] It is possible that intervention during pregnancy could correct or improve habits related to weight management that could translate into better health for women and their families over the long term.

The consistent contact with the medical care system through prenatal care could provide an ideal vehicle for delivery of behavioral interventions to women. However, current prenatal care systems are not set up to provide these services. In order to change the medical care system, research-based evidence is required to determine effective intervention strategies to promote healthy gestational weight gain in the clinical setting.

Interventions to Improve Maternal Diet and Physical Activity

In the past year, six different groups have published critical literature reviews comprised of approximately 12 trials investigating how behavioral interventions to improve maternal dietary intake and/or physical activity reduce excess gestational weight gain. One review focuses only on women who began pregnancy overweight or obese,[6] while five reviews include a wider range of prepregnancy BMI.[7-11] Three groups conducted meta-analysis.[7,8,12] and three did systematic reviews. Only controlled studies were included, and most were randomized controlled trials. Conducted in Australia, Belgium, Denmark, Norway, Sweden, and the United States, the sample size of these trials ranged from 41–560.

Researchers used a variety of intervention strategies, including counseling and education about weight gain, healthy eating, and physical activity and/or monitoring of weight gain, with or without feedback. The intensity and frequency of interventions and the number and combination of different components are variable. Even though all reviews used high-quality methodology to assess the evidence and all looked at the same accumulation of data, the conclusions vary. Three of the reviews conclude that interventions can effectively reduce gestational weight gain, although results are inconsistent,[8,10,11] two conclude that interventions are ineffective,[6,7] and one concludes that the quality of the studies is too weak to consider their findings for evidence-based guidelines.[9] Overall, these reviews demonstrate a clear need for more definitive research on which to base clinical practice.

The Fit for Delivery Study, conducted by Dr Suzanne Phelan and a multidisciplinary team and published in April 2011, adds to the knowledge summarized by these reviews.[13] Informed by Social Learning Theory, this randomized, assessor-blinded, controlled trial tested an intervention that included the following:

- Nutritional counseling provided by a dietitian at enrollment, with a diet prescription of 20 kcal/kg
- A book to aid women in reducing fat and calorie intake
- Three telephone calls with the dietitian during the course of the study to assess progress
- Encouragement to moderately exercise, supported by a supplied pedometer with the ultimate goal of walking 10,000 steps/day, and the request that women keep a record of their progress
- Provision of a gestational weight-gain goal for each woman, based on the 1990 Institute of Medicine Recommendations,[14] as well as a scale and directions to monitor and record weight gain
- Feedback on weight-gain progress by postcard after each prenatal visit
- A "stepped-up care" approach for women who gain too much weight, with more frequent contacts and structured meal plans and behavioral goals
- Regularly mailed educational materials and "challenge" cards to strengthen motivation to healthfully control weight

Controls received one 15-minute meeting with the study dietitian to discuss general principles of diet and physical activity during pregnancy, as well as newsletters throughout the study that covered aspects of pregnancy unrelated to weight management. Both groups received standard prenatal care and pamphlets from the American College of Obstetricians and Gynecologists and the March of Dimes. The study randomized 401 women—200 to standard care and 201 to the intervention. Half of each group had a normal and half an overweight/obese BMI. Fig 1 shows that the intervention significantly reduced excessive gestational weight gain among those with normal BMI, but not those who began the study overweight or obese.

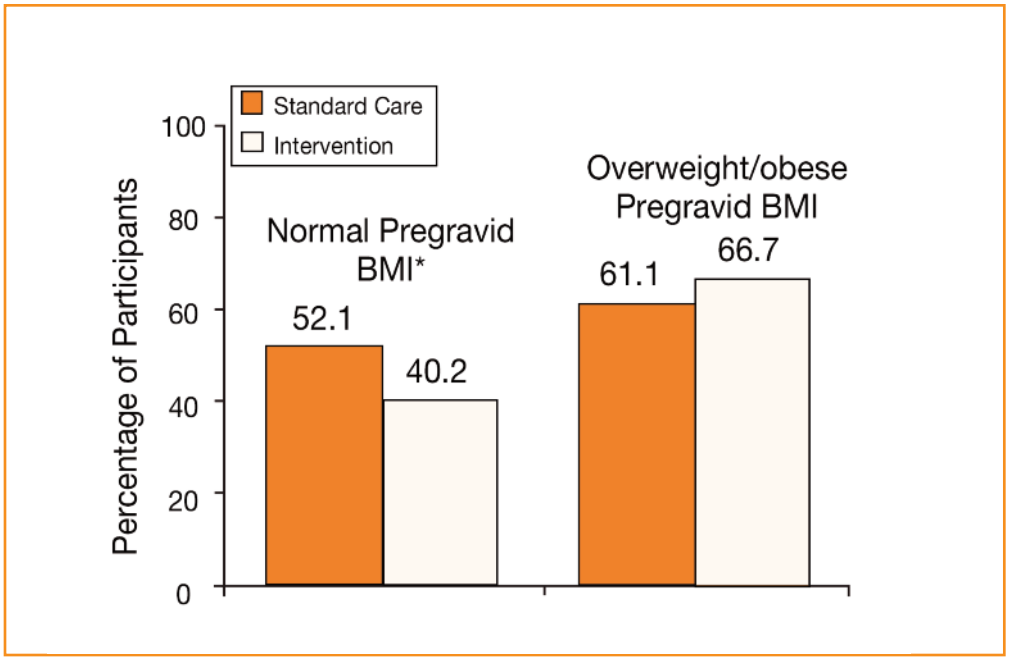

Fig 1. Excessive weight gain† in the Fit for Delivery Study women.[13] Results were based on an intention-to-treat analysis.

**P*<0.05
†Total pregnancy weight gain >35 lb for normal weight women and >25 lb for overweight/obese women

Source: Phelan S et al. Randomized trial of a behavioral intervention to prevent excessive gestational weight gain: the Fit for Delivery Study. *Am J Clin Nutr*. 2011;93:772-779. Reprinted with permission of the American Society for Nutrition.

However, at 6 months after delivery, the prenatal intervention increased the proportion of women who returned to their prepregnancy weight (defined as retaining <1 kg) in both groups (Fig 2), despite the fact that no additional intervention was provided after delivery.

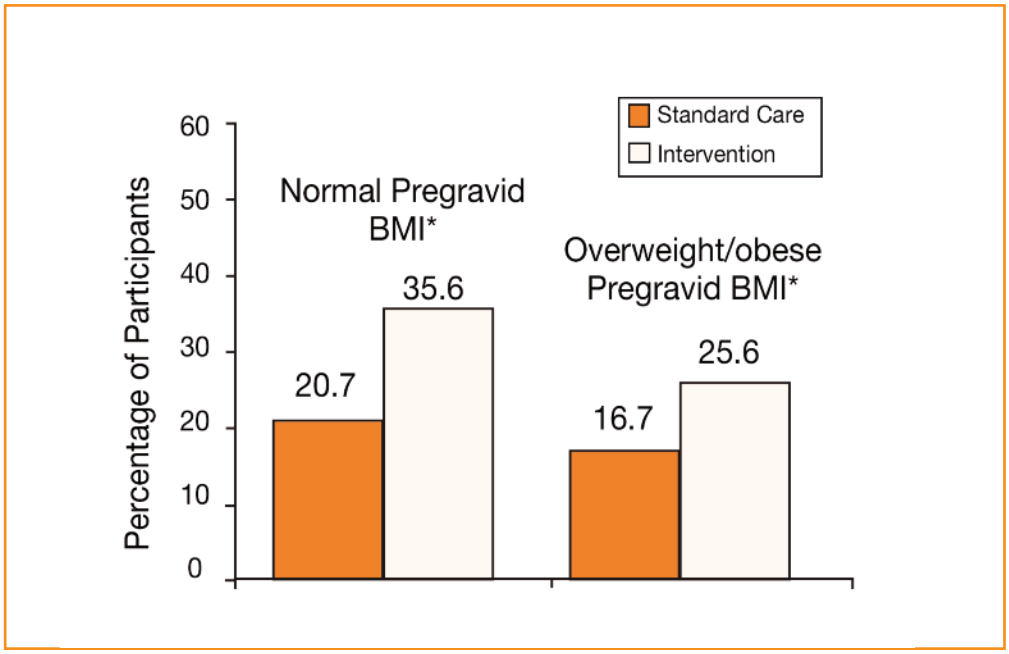

Fig 2. Postpartum weight status† 6 months after birth in Fit for Delivery Study women.[13]
Results based on an intention to treat analysis.

*$P<0.05$
†±0.9 kg or below prepregnancy weight

Source: Phelan S et al. Randomized trial of a behavioral intervention to prevent excessive gestational weight gain: the Fit for Delivery Study. *Am J Clin Nutr.* 2011;93:772-779. Reprinted with permission of the American Society for Nutrition.

These results, in addition to those from other trials, suggest that it is possible to moderate gestational weight gain through methods that are implemented in the clinical setting. Echoing previous results, Fit for Delivery intervention did not reduce excessive gestational weight gain in overweight/obese women, the group at highest risk for poor pregnancy outcomes. However, our finding of some effect on weight in this group postpartum is encouraging, suggesting that the prenatal intervention may have had longer term impact. Although a step in the right direction, the finding that 40% of normal-weight women in the intervention group still gained weight excessively indicates that even in normal-weight women, more effective strategies are needed.

Future Research and Improved Behavioral Interventions

Reviewers suggest a number of important ways to improve the study of behavioral interventions for pregnant women.[7-10] In addition to strengthening and standardizing study methodologies and reports to allow comparability, a fresh look at the interventions themselves is needed. Virtually all studies to date focus solely on changing each individual woman's diet and physical activity, but pregnant women do not live in a vacuum. It is likely that excessive gestational weight gain is a function of the same neighborhood and environmental factors that cause obesity in children and other adults, thus multilevel interventions are needed.[15] Still, we need to better understand the physical, psychological, social, cultural, and financial barriers that women face in addressing weight control during pregnancy and design interventions responsive to women's experiences and concerns. Evidence also shows that women receive contradictory messages from family, friends, the media, and clinicians about weight management during pregnancy. Use of a mixed-method research design, which combines qualitative and quantitative approaches, could help inform new strategies based on established behavioral theories.

Finally, studies in nonpregnant populations suggest that successful weight control is possible through more intensive lifestyle treatments than those that are typically used in pregnancy, such as a calorie prescription supported by structured meal plans and meal replacements, high levels of physical activity (60–90 minutes/day), daily monitoring of weight and food intake, behavior therapy, and continued patient-provider contact.[16] The safety, acceptability, and efficacy of these approaches in pregnancy, as well as application of these methods before and after pregnancy, deserve serious study.

As researchers augment current knowledge with new perspectives, there is every reason to believe that future research will yield the keys to utilizing the "teachable moments" of pregnancy to promote health in mothers and their children.

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