The Predisposition to Obesity and Diabetes in Offspring of Diabetic Mothers

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The hypothesis of fuel-mediated teratogenesis (1) proposes that intrauterine exposure to an excess of fuels (for example, glucose) causes permanent fetal changes. In pregnancies complicated by diabetes, this would lead to malformations, greater birth weight, and an increased risk of developing type 2 diabetes in later life. Recently, obesity in the offspring has been included as an outcome in pregnancies complicated by diabetes. The hypothesis is now widely accepted, although the relatively few studies that have examined the question are poorly comparable and focus almost exclusively on growth and glucose regulation.

This article reviews the evidence that intrauterine exposure to maternal diabetes conveys high risks for obesity and type 2 diabetes in the offspring, in addition to genetic predisposition, and regardless of maternal diabetes type. It also discusses potential mediators as well as possible public health consequences of fuel-mediated teratogenesis driven by maternal hyperglycemia in utero.

LONG-TERM ANTHROPOMETRIC AND METABOLIC CONSEQUENCES OF EXPOSURE TO DIABETES DURING PREGNANCY

Development in a diabetic intrauterine environment results in excess fetal growth. While maternal glucose freely crosses the placenta, maternal insulin does not (1). The developing fetal pancreas responds to this increased glucose load by producing additional insulin, which in turn, acts as a fetal growth hormone promoting growth and adiposity (1). Only two studies have prospectively examined the role of exposure to diabetes in utero on childhood growth, later obesity, and risk for type 2 diabetes in the offspring: the Pima Indian Study and the Diabetes in Pregnancy Study at Northwestern University in Chicago.

Growth and risk for obesity

Researchers at the Diabetes in Pregnancy Center at Northwestern University in Chicago have reported excessive growth in a multiethnic population of offspring of women with diabetes during pregnancy, including both gestational diabetes mellitus (GDM) and insulin-treated preexistent diabetes (2). Children were examined at birth, at age 6 months, and annually to age 8 years. The symmetry index (an obesity index with a normal value of 1.0) was normal at 1 year of age, but increased during follow-up, so that by age 8 years, the mean symmetry index was almost 1.3, i.e., the children were on average 30% heavier than expected for their height.

The offspring of Pima Indian women with preexistent type 2 diabetes and GDM were larger for gestational age at birth and, at every age, were heavier (adjusted for height) than the offspring of prediabetic or nondiabetic women (3–5). Even in normal birth weight offspring of diabetic pregnancies, childhood obesity was still more common than among offspring of nondiabetic pregnancies (6).

Using total body electrical conductivity estimates of body composition, Catalano et al. (7) showed that newborn infants of women with mild glucose intolerance (i.e., GDM) have 20% higher body fat than infants of women with normal glucose tolerance, regardless of birth weight. Fasting glucose level at the time of maternal oral glucose tolerance test was the strongest single correlate of neonatal adiposity. Taken together, these findings may be regarded as evidence of early effects of exposure to diabetes in utero on obesity risk, effects that seem to be amplified during further development.

Other studies have failed to show clear associations between maternal GDM and offspring obesity (8,9), perhaps because they studied populations with lower diabetes risk. Therefore, most information relating exposure to diabetes in utero and childhood outcomes is based on special populations: the Pima Indian study and a specialized pregnancy clinic population in Chicago without an internal comparison group. There is a need to evaluate the effects of exposure to diabetes in utero on childhood growth and body size among ethnically diverse youth. This issue is critical to resolve, as programming of offspring adiposity by maternal glucose-insulin metabolism could lead to a "vicious cycle" of increasing childhood obesity and later GDM over each subsequent generation (10).

Abnormal glucose tolerance and risk for type 2 diabetes

For >30 years, Pima Indian women have had oral glucose tolerance tests during pregnancy, as well as outside pregnancy approximately every 2 years (5). Consequently, extensive maternal diabetes information based on glucose testing rather than on assessment of family history of diabetes is available for the offspring of women who had diabetes before or during pregnancy (diabetic mothers), for those mothers who developed diabetes only after pregnancy (pre-diabetic mothers), as well as for those who remained nondiabetic.

Figure 1 shows the prevalence of type 2 diabetes by age-group in offspring of diabetic, pre-diabetic, and nondiabetic mothers (11). By age 5–9 and 10–14 years, diabetes was present almost exclusively among the offspring of diabetic women. In all age-groups, there was significantly more diabetes in the offspring of diabetic women than in those of prediabetic and nondiabetic women. There

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Abbreviations: GDM, gestational diabetes mellitus.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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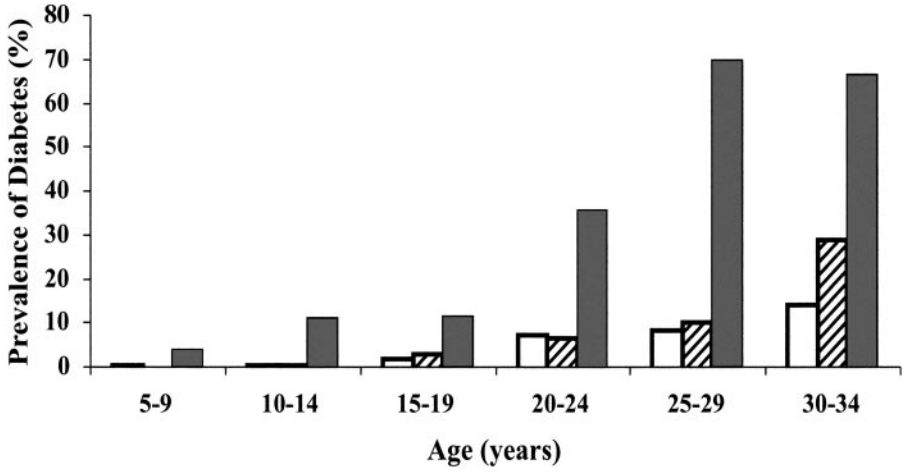

Figure 1—*Prevalence of type 2 diabetes, by mother's diabetes during and after pregnancy in Pima Indians aged 5–34 years. Reprinted with permission from Dabelea and Pettitt (11). □, Offspring of nondiabetic mothers; ▨, offspring of pre-diabetic mothers; ■, offspring of diabetic mothers.*

were much smaller differences in diabetes prevalence between offspring of pre-diabetic and nondiabetic women. These small differences may be due to differences in the genes inherited from the mothers, whereas the large difference in prevalence between the offspring of diabetic and pre-diabetic mothers, who have presumably inherited the same genes from their mothers, is the consequence of exposure to the diabetic intrauterine environment (3). These differences persisted after adjusting for presence of diabetes in the father, age at onset of diabetes in either parent, and obesity in the offspring.

The Diabetes in Pregnancy Study at Northwestern University in Chicago enrolled offspring of women with pregestational diabetes (both insulin-dependent and non-insulin dependent) and GDM from 1977 to 1983. Plasma glucose and insulin were measured fasting and after a glucose load yearly from age 1.5 years in offspring of diabetic mothers and one time at ages 10–16 years in control subjects (12). On their most recent evaluation (average age 12.3 years), offspring of diabetic mothers had a significantly higher prevalence of impaired glucose tolerance than the age- and sex-matched control group (19.3 vs. 2.5%, Fig. 2).

Cardiovascular abnormalities

Animal studies have shown that diabetes can induce cardiovascular dysfunction in adult offspring (13). Few human studies have examined cardiovascular risk factors in offspring of diabetic pregnancies. By 10–14 years, offspring of diabetic pregnancies enrolled in the Diabetes in Pregnancy follow-up study in Chicago had significantly higher systolic and mean arterial blood pressure than offspring of nondiabetic pregnancies (2). Manderson et al. (14) reported higher concentrations of markers of endothelial dysfunction (ICAM-1, VCAM-1, E-selectin), as well as cholesterol-to-HDL ratio among offspring of mothers with type 1 diabetes compared with offspring of nondiabetic pregnancies, independent of current BMI. Recently, the Pima Indian investigators have shown that, independent of adiposity, 7- to 11-year-old offspring exposed to maternal diabetes during pregnancy have significantly higher systolic blood pressure than offspring of mothers who did not develop type 2 diabetes until after the index pregnancy (15). These data suggest that in utero exposure to diabetes confers risks for the development of cardiovascular disease later in life that are independent of adiposity and may be in addition to genetic predisposition to diabetes.

OBESITY AND TYPE 2 DIABETES IN OFFSPRING OF DIABETIC MOTHERS ARE NOT DUE TO GENETIC FACTORS ALONE

— The attribution of congenital abnormalities to excess maternal fuel exposure in utero may be confounded by genetic factors. Women who develop diabetes at an early age might carry more diabetes susceptibility genes than those who develop the disease later in life and, therefore, they might transmit greater genetic susceptibility to their offspring. Thus, the greater frequency of diabetes and obesity in the offspring of diabetic pregnancies might be due to greater genetic susceptibility in such offspring.

Evidence that excess growth experienced by offspring of diabetic mothers is not due to genetic factors alone comes from several areas. First, obesity is no more common in the offspring of women in whom diabetes developed after delivery than in those of nondiabetic women (4,16). Second, obesity in the offspring of diabetic women cannot be accounted for by maternal obesity (4,6). Third, the excessive growth seen in the offspring of diabetic mothers is not found in offspring of diabetic fathers in either the Joslin Clinic or the Pima Indians series (17). The comparison between offspring of diabetic and pre-diabetic women is an attempt to con-

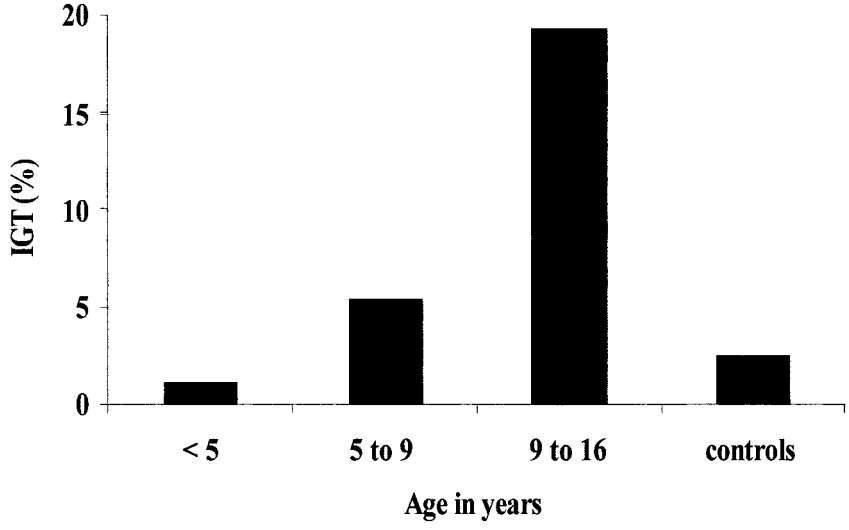

Figure 2—*Prevalence of impaired glucose tolerance (IGT) in offspring of diabetic mothers in three age-groups and in control subjects aged 10–16 years. Reprinted from Silverman et al. (12).*

trol for any potential confounding effect of a genetic predisposition to obesity and diabetes on the relationship between exposure to the maternal diabetic environment and obesity and diabetes in the offspring.

The ideal way to approach this question is to examine sibling pairs in which one sibling is born before and one is born after the onset of their mother's diabetes (18). The mean BMI in the 62 Pima Indian nondiabetic siblings born after the onset of the mother's diabetes, i.e., the offspring of the diabetic woman, was significantly higher (mean BMI difference 2.6 kg/m^2) than among the 121 nondiabetic siblings who were not exposed to diabetes in utero, e.g., born before the onset of the mother's diabetes. In contrast, there was no significant difference between siblings born before or after their father was diagnosed with type 2 diabetes (mean BMI difference 0.4 kg/m^2) (18). These data support the hypothesis that exposure to diabetes in utero has effects on offspring body size that are in addition to genetic susceptibility to obesity.

Recent data in 9- to 14-year-old non-Hispanic white children in the Growing Up Today Study (8) showed that the association between a history of maternal GDM and adolescent overweight was substantially attenuated after adjustment for reported maternal BMI, a surrogate for genetic susceptibility for obesity. These findings suggest that "genetics" may account for part of the observed association in this population. The authors concluded that their results were consistent with the hypothesis that GDM programmed the fetus for later postnatal influences that lead to obesity, although they did not implicate GDM as a sufficient cause of offspring obesity.

To determine the role of exposure to the diabetic intrauterine environment that is in addition to genetic transmission of diabetes susceptibility, the prevalence of type 2 diabetes was compared in Pima Indian siblings born before and after their mother developed diabetes (18). A total of 19 families with 58 siblings and 28 sib-pairs discordant both for diabetes and diabetes exposure in utero were informative for the analysis. In 21 of the 28 sib-pairs, the diabetic sibling was born after mother's diagnosis of diabetes and in only 7 of the 28 pairs was the diabetic sibling born before (odds ratio 3.0, $P < 0.01$, Fig. 3). In contrast, among 84 siblings and 39 sib-pairs from 24 families of diabetic fathers, the risk for type 2 diabetes was similar in the sib-pairs born before and after father's diagnosis of diabetes (Fig. 3). Since siblings born before and after a diabetic pregnancy are believed to carry a similar risk of inheriting the same susceptibility genes, the different risk likely reflects the effect of intrauterine exposure associated with or directly due to hyperglycemia and/or other fuel alterations of a diabetic pregnancy.

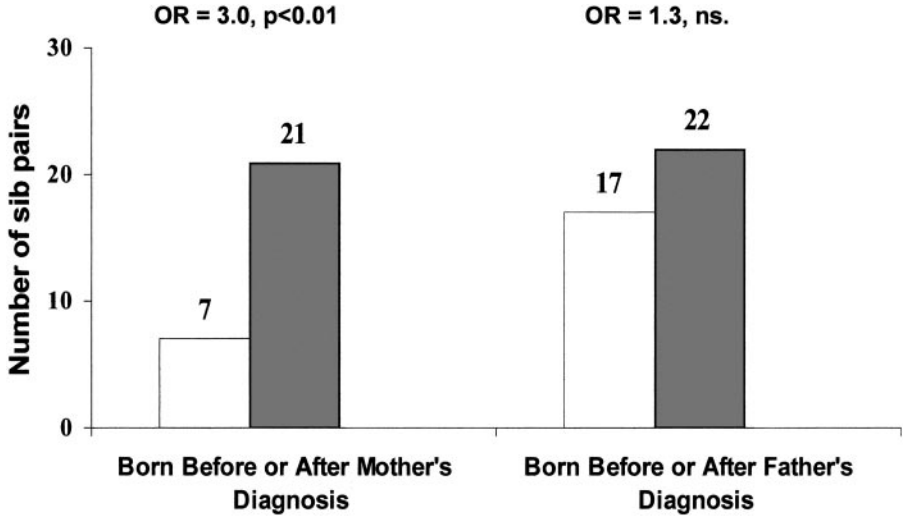

Figure 3—*Pima Indian sib-pairs discordant for diabetes and exposure to diabetes in utero. Reprinted with permission from Dabelea and Pettitt (11).* Left*: Of 28 sib-pairs born before or after their mother was diagnosed with diabetes, the diabetic sibling was born* after *the mother was diagnosed with diabetes* (■) *in 21 sib-pairs and* before (□) *in 7 sib-pairs; odds ratio (OR) 3.0,* $P < 0.01$*, for the association between being born before or after the mother was diagnosed with diabetes and diabetes in the offspring.* Right*: Of 39 sib-pairs born before or after their father was diagnosed with diabetes, the diabetic sibling was born* after *the father was diagnosed with diabetes* (■) *in 22 sib-pairs and before* (□) *in 17 sib-pairs; OR 1.3, NS, for the association between being born before or after the father was diagnosed with diabetes and diabetes in the offspring.*

THE EFFECTS OF EXPOSURE TO MATERNAL DIABETES DURING PREGNANCY ARE SIMILAR REGARDLESS OF MATERNAL DIABETES TYPE —

There is evidence that the long-term consequences of exposure to diabetes in utero on future obesity are independent of mother's diabetes type (2,5,20). Weiss et al. (20) studied the offspring of women with type 1 diabetes and reported that by age 5–15 years, they also had a significantly higher BMI than the offspring of control women. The measures of obesity were significantly positively correlated with maternal levels of fasting and postload blood glucose.

In the cohort of adolescent offspring of diabetic mothers studied by Silverman et al. (12), the predisposition to impaired glucose tolerance was associated with maternal hyperglycemia and not with the type of diabetes in the mother. In a study in Germany, the prevalence of impaired glucose tolerance was similarly increased in infants (ages 1–4 years) and children (ages 5–9 years) of mothers with pregestational type 1 diabetes and in those of mothers with GDM (21). Recently, Sobngwi et al. (22) showed that adult offspring of women who had type 1 diabetes during pregnancy are more likely to have impaired glucose tolerance than the off-

spring of diabetic fathers, although there were no differences between groups with respect to adiposity. These data support the hypothesis that the effects of maternally transmitted diabetes genes are modified by intrauterine influences, regardless of the type of diabetes present in the mother. The metabolic effects of the diabetic intrauterine environment on the fetus might therefore be similar regardless of whether the mother has gestational, type 1, or type 2 diabetes.

MECHANISMS UNDERLYING A POTENTIAL ROLE OF MATERNAL DIABETES ON CHILDHOOD RISK FOR OBESITY AND TYPE 2 DIABETES

Adipoinsular axis

The mechanisms by which exposure to diabetes in utero increases the risk of offspring obesity are not fully understood. Exposure to maternal diabetes is associated with excess fetal growth in utero (23), possibly mainly due to an increase in fetal fat mass (7), and alterations of fetal hormones. Concentrations of insulin are raised (1) and, more recently, increases in fetal leptin levels have been reported (24,25).

There is some suggestion that relative hyperinsulinemia may be a precursor to childhood obesity. At age 5–9 years, Pima offspring of women with diabetes or impaired glucose tolerance during pregnancy have higher fasting insulin concentrations than the offspring of women with better glucose tolerance during pregnancy (26). Although this difference is not apparent at older ages, a follow-up of children and adolescents found that the fasting insulin concentration at ages 5–9 years was significantly positively correlated with the rate of weight gain during follow-up (27).

The Chicago study measured amniotic fluid insulin at 32–38 weeks of gestation. The symmetry index was used to categorize obesity of the offspring at age 6 years. Among children who had a symmetry index of <1.0, the mean amniotic fluid insulin concentration in the mothers was 86.1 pmol/l; among those with a symmetry index between 1.0 and 1.2, it was 69.9 pmol/l. These levels were only half of the levels that were measured in the mothers of more obese children who had a symmetry index >1.2 (140.5 pmol/l; $P < 0.05$ for each comparison). Amniotic fluid insulin is of fetal origin and is directly correlated with the amount of fetal insulin produced. Fetal insulin, in turn, is correlated with the amount of the circulating glucose, which is of maternal origin and is directly correlated with mother's diabetes control. Thus, this study demonstrates a direct correlation between an objective measure of the diabetic intrauterine environment and the degree of obesity in children and adolescents (2).

Leptin, a hormone secreted by adipocytes and by the placenta, also seems to be associated with fetal growth (28). Leptin measured at birth was positively related to birth weight (24,29,30) and with the amount of fetal adipose tissue (31). In both animals and humans, inefficient leptin action leads to hyperphagia, decreased fat oxidation, increased tissue triglyceride levels, insulin resistance, and obesity (32–34). This endocrine loop has been termed the "adipoinsular axis," linking the brain and endocrine pancreas with other peripheral insulin- and leptin-sensitive tissues in the control of feeding behavior, metabolic regulation, and energy balance (34).

Elevated cord blood leptin concentrations were found in both infants of type 1 diabetic (24.7 ng/ml) and GDM mothers (29.3 ng/ml), compared with control subjects (7.9 ng/ml) (35), even after controlling for differences in birth weight. This suggests a direct influence of maternal hyperglycemia on fetal fat mass and leptin levels. In two other studies, exposure to GDM was associated with both hyperleptinemia and hyperinsulinemia in the newborn (36,37). This suggests that GDM may lead to increased insulin secretion and adiposity in the fetus, despite the rising plasma leptin concentrations, which are unable to control the release of insulin and the increase in fetal adiposity (37). Induction of leptin resistance in utero may therefore be hypothesized as a potential mechanism for later development of obesity in offspring exposed to diabetes in utero. Fetal overnutrition may result in a resetting of the adipoinsular axis leading to adiposity during childhood, a hypothesis that requires further testing.

Fetal malprogramming of hypothalamic neurons: "functional teratogenesis"

An interesting hypothesis relating hormonal changes present at birth in offspring exposed to diabetes in utero with later risks for obesity and type 2 diabetes has been formulated by Plagemann (38). When present in nonphysiological concentrations during critical ontogenetic periods, hormones (such as insulin and leptin) can act as "endogenous functional teratogens" (38). For example, untreated diabetes in pregnant rats leads to "malprogramming" of hypothalamic neuropeptidergic neurons in offspring, leading to increased orexigenic neuropeptide Y and agouti-related peptide, which could contribute to hyperphagia and later development of overweight. Islet transplantation in pregnant GDM rats normalizes blood glucose and prevents these acquired alterations (39).

Defective insulin secretion in offspring exposed to maternal diabetes

In GK rats, the diabetic syndrome is produced by streptozotocin injection or glucose infusion. These rats do not have any genetic predisposition for diabetes, nor can their diabetes be classified as type 1 or 2. In these studies, hyperglycemia in the mother during pregnancy leads to impairment of glucose tolerance and decreased insulin action and secretion in adult offspring (40,41).

Impaired insulin secretion (42) has also been observed in human studies. Among 104 normal glucose tolerant Pima Indian adults, the acute insulin response was ~40% lower in individuals whose mothers had diabetes during pregnancy than in those whose mothers developed diabetes at an early age but after the birth of the subject (43). Recently, Sobngwi et al. (22) showed that adult offspring of women with type 1 diabetes during pregnancy had a significantly decreased insulin secretory response to glucose when compared with offspring of type 1 diabetic fathers, whereas there were no differences between groups with respect to insulin action. Based on the observation made in rats and supported by the human findings, it may be hypothesized that exposure to hyperglycemia during critical periods of fetal development "programs" the developing pancreas in a way that leads to a subsequent impairment in insulin secretion.

PUBLIC HEALTH IMPLICATIONS OF INCREASING EXPOSURE TO MATERNAL DIABETES IN UTERO

— In Pima Indian children age 5–19 years, the prevalence of type 2 diabetes has increased two- to threefold over the last 30 years (44). The percent of chil-

dren who have been exposed to diabetes in utero has also increased significantly over the same time period, which was associated with a doubling of the amount of diabetes in children attributed to this exposure (from 18.1% in 1967–1976 to 35.4% in 1987–1996). The "epidemic" of type 2 diabetes in Pima Indian children was almost entirely accounted for, statistically, by the increase in exposure to diabetes during pregnancy and the resultant increase in obesity, a demonstration of the postulated vicious cycle.

Increases in GDM over the past decade among non-Indian populations have recently been reported, suggesting that GDM is an increasingly important childhood exposure. Two studies of Kaiser Permanente Health plan members showed significant increases in the cumulative incidence of GDM: ~3.5% per year in Northern California (45) and 11% annually (1994–2002) in Colorado (46). Important and disturbing, both studies show increasing rates of GDM among all racial/ethnic groups. It is, therefore, possible that the vicious cycle of diabetes in pregnancy initially described among Pima Indians is also operating among other racial/ethnic groups.

FUTURE DIRECTIONS FOR RESEARCH

— The effects of maternal diabetes during childhood and over the life course may be viewed as a vicious cycle (10). Children whose mothers had diabetes during pregnancy are at increased risk of becoming obese and developing diabetes at young ages. Many of these female offspring already have diabetes or abnormal glucose tolerance by the time they reach their childbearing years, thereby perpetuating the cycle. Whether the vicious cycle of the diabetic pregnancy is operating in racial/ethnic groups other than American Indians is possible, but has not yet been adequately investigated. An important research need is to derive risk estimates for childhood obesity, impaired glucose tolerance, and type 2 diabetes that are attributable to maternal diabetes in utero, in populations other than American Indians.

There is recent debate over whether exposure to maternal obesity during pregnancy, in the absence of frank GDM, is also associated with long-term effects on the offspring above and beyond genetic susceptibility. If the hypothesis that maternal obesity during pregnancy drives fuel-mediated teratogenesis is correct, the public health consequences are enormous, since obesity is widespread and increasing. Studies are needed to disentangle the relative contribution of various altered fuels, in addition to glucose, in pregnancies complicated by obesity, to the long-term effects on childhood risks for obesity and impaired glucose metabolism.

Finally, future research is needed to determine whether better glucose control can be achieved throughout pregnancy that would prevent the long-term consequences on the offspring described here. If this is achievable, it will in turn probably reduce the prevalence of diabetes in the next generation of pregnancies and, therefore, be beneficial for future generations as well as for the immediate offspring.

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