Birth Weight and Parental BMI Predict Overweight in Children From Mothers With Gestational Diabetes

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OBJECTIVE — To investigate the growth of children from pregnancies with gestational diabetes mellitus (GDM) and its association with antenatal maternal, fetal, and recent anthropometric parameters of mother and father.

RESEARCH DESIGN AND METHODS — In 324 pregnancies of Caucasian women with GDM, BMI before pregnancy, maternal glycemic values, and measurements of the fetal abdominal circumference were recorded. The weight and height of infants were measured at birth and at follow-up at 5.4 years (range 2.5–8.5). In addition, somatic data from routine examinations at 6, 12, and 24 months and the BMI of parents at follow-up were obtained. BMI standard deviation scores (SDSs) were calculated based on age-correspondent data.

RESULTS — At all time points, BMI was significantly above average (+0.82 SDS at birth; +0.56 at 6, +0.35 at 12, and +0.32 at 24 months; and +0.66 at follow-up; $P < 0.001$). BMI at birth was related to BMI at follow-up ($r = 0.27$, $P < 0.001$). The rate of overweight at follow-up was 37% in children with birth BMI ≥90th percentile and 25% in those with normal BMI at birth ($P < 0.05$). Abdominal circumference of third trimester and postprandial glucose values were related to BMI at follow-up ($r = 0.22$ and $r = 0.18$, $P < 0.01$). Recent maternal, paternal, and birth BMI were independent predictors of BMI at follow-up ($r = 0.42$, $P < 0.001$). Sixty-nine percent of children of parents with BMI ≥30 kg/m^2 were overweight at follow-up compared with 20% of those with parental BMI <30 kg/m^2 ($P < 0.001$).

CONCLUSIONS — Children of mothers with GDM have a high rate of overweight that is associated both with intrauterine growth and parental obesity.

G estational diabetes mellitus (GDM) reflects a metabolically altered fetal environment due to an increased maternal supply of carbohydrates leading to fetal hyperinsulinism. Stimulation of the insulin-sensitive tissue results in increased fetal growth, predominantly of the abdomen, and delivery of large-for-gestational-age newborns. Clinical and experimental studies have shown that the implications of fetal hyperinsulinism reach far beyond delivery. Children of mothers with diabetes in pregnancy may develop an increased disposition for obesity and glucose intolerance through a nongenetic "fuel-mediated" mechanism (1–8).

Disposition for obesity could be influenced by many factors other than maternal diabetes in pregnancy. To our knowledge, there are no studies that evaluate the contribution of maternal hyperglycemia to childhood overweight in comparison to other antepartum maternal and fetal confounders and the influence of the postnatal environment. The present large longitudinal study of infants of mothers treated for GDM aimed to evaluate the association of the level of maternal hyperglycemia during pregnancy, fetal (as assessed by ultrasound) and neonatal obesity, and childhood obesity, as well as maternal and paternal obesity in pregnancies complicated by GDM.

RESEARCH DESIGN AND METHODS — The study cohort was recruited from children of mothers who had GDM and attended the Diabetes Prenatal Care Clinic of the Department of Obstetrics at the Vivantes Medical Center Berlin, a tertiary community hospital, from 1995 through 2000. The infants were selected from an ongoing database where clinical, glycemic, fetal ultrasound, and delivery data of all women attending the clinic were prospectively entered. Inclusion criteria were as follows: *1*) at least one maternal glucose profile after diagnosis of GDM, *2*) availability of data regarding maternal obstetrical history and anthropometry, *3*) singleton pregnancy, *4*) accurate gestational age at delivery confirmed by an ultrasound examination before 20 weeks of gestation, *5*) at least one complete fetal biometry after diagnosis of GDM, and *6*) age ≥2 years at the time of study. The study protocol was approved by the institutional review board. In-

formed written consent was obtained from the parents.

Diabetes care

Diagnosis of GDM was established by a 75-g oral glucose tolerance test (OGTT) with determination of capillary blood glucose levels using a glucose oxidase method (Beckman Glucose Analyzer, Brea, CA). Diagnostic criteria for GDM valid in Germany at the time of study were fasting blood glucose ≥90 mg/dl (5.0 mmol/l), 1-h blood glucose ≥165 mg/dl (9.1 mmol/l), and 2-h blood glucose ≥145 mg/dl (8.0 mmol/l) (9). Diagnosis of GDM required at least two abnormal values. Testing had been performed selectively in women with risk factors for GDM.

After GDM diagnosis, women were put on a 25– to 30–kcal · kg^{-1} · day^{-1} diet based on their prepregnancy weights. All women were taught self-monitoring of blood glucose by performing daily glucose profiles (three preprandial and three 2-h postprandial measurements) twice per week or daily if insulin therapy was required, respectively, using memory-based glucometers (Roche Diagnostics, Grenzach-Wyhlen, Germany). Insulin therapy was initiated when either the mean of all capillary glucose values of a profile exceeded 100 mg/dl (5.5 mmol/l) or fasting glucose exceeded 95 mg/dl (5.3 mmol/l) and/or when 2-h postprandial values exceeded 120 mg/dl (6.6 mmol/l) after a 2-week trial of diet. HbA1c (A1C) was determined at the first visit.

Data collection

Data were obtained from three different sources. Maternal clinical and antenatal glycemic data as well as fetal and somatometric data at birth were obtained from the database. Ultrasound examination with complete fetal biometry had been scheduled in conjunction with diabetes clinic visits. The fetal abdominal circumference measurements were taken at the standard cross-section view (10). Fetal macrosomia was defined as abdominal circumference >90th percentile. Birth weight and length were determined immediately after delivery.

Anthropometric data in childhood were prospectively obtained. All parents of infants who qualified for the study were contacted. When parents were interested in joining the study, the actual weight and height of their children were taken. Body weight was measured using a digital scale (Soehnle, Murrhardt, Germany) to the nearest 0.1 kg, and standing height was measured with a wall-mounted stadiometer (Sena, Witten, Germany). Additionally, the actual weight and height of mother and father were obtained, and the BMI was calculated.

Furthermore, prior anthropometric data were retrospectively obtained from routine examinations at 6, 12, and 24 months, which are offered to all children within the German health care system. The examinations were performed by outside pediatricians and documented in a special booklet given to parents at delivery.

Data analysis

Birth weight and BMI were transformed into percentiles according to gestational age at delivery (11). Large-for-gestational-age birth weight was assessed on the basis of BMI ≥90th percentile. The standard deviation score (SDS) of BMI at follow-up examinations was calculated by Cole's transformation using age-correspondent data of a normal German population (12). Overweight in childhood was defined as BMI ≥90th percentile (12,13). BMI was analyzed in the total group and separately in children with age less than and ≥6 years using *t* test or Wilcoxon and Kruskal-Wallis when appropriate. The Kolmogoroff-Smirnov test was used to assess BMI deviation from normal population. Differences between groups were tested by *t* test (continuous variables) or by χ^2 analysis (categorical variables).

For comparison of intrauterine growth with anthropometric data at last follow-up, we used the ultrasound measurement of the fetal abdominal circumference obtained close to the time of entry to diabetes care (abdominal circumference at diagnosis) and of the last examination during the third trimester of pregnancy (abdominal circumference at third trimester). Abdominal circumference measurements were transferred into categories (percentiles) according to gestational age (10); abdominal circumference >90th percentile was defined as fetal overweight. Associations with BMI were assessed by Spearman correlation analyses.

For comparison of maternal glycemic values with anthropometric data, correlation coefficents were calculated for each of the three glucose values of the OGTT and for average values of fasting and 2-h postprandial glucose measurements during gestational weeks 28–40. Finally, stepwise multivariate linear regression analysis was performed to determine independent predictors of BMI at follow-up.

RESULTS — A total of 771 children qualified for the study. Between May 2003 and January 2004, examinations were performed on 324 children (54.0% boys, 46.0% girls). The remaining families either did not respond (n = 322) or were not interested in an examination of their child (n = 125). Antenatal maternal, fetal, or neonatal data of the children without follow-up examination were not significantly different from those who could be examined.

Neonatal and childhood BMI

The rate of large-for-gestational-age newborns was 17.0%, while 7.1% of the newborns had a birth weight <10th percentile. Birth BMI ≥90th percentile was found in 30.9% of the newborns and a BMI <10th percentile in 4.6%. Mean gestational age at delivery was 39.2 ± 1.5 weeks.

The mean age at follow-up was 5.4 ± 1.6 years (range 2.5–8.5). Of the children, 40.4% were at least 6 years old. At follow-up, a BMI >90th percentile was found in 92 of 324 children (28.4%) without significant difference in sex or age at follow-up (Table 1). The highest BMI was seen at birth with an SDS of 0.82 ± 1.14. Subsequently, SDS values continuously decreased toward 0.32 ± 1.13 at 24 months but increased again to 0.66 ± 1.06 at last follow-up. At follow-up, SDS values of the two subgroups of children aged less than and ≥6 years were 0.58 ± 1.00 and 0.76 ± 1.16, respectively (P = 0.154). At each time point, the BMI was significantly elevated (P < 0.001) compared with normal population values (Fig. 1).

BMI SDS at follow-up was significantly related to BMI SDS at birth (r = 0.27, P < 0.001). At follow-up, 37.0% of children with neonatal overweight maintained their BMI ≥90th percentile. In contrast, only 25.4% of children with normal birth BMI were overweight at follow-up (P < 0.05). The rate of overweight at follow-up increased with increasing birth weight (Fig. 2). In children with birth BMI <10th percentile, the rate of overweight at follow-up was 6.7% (1/15).

Table 1—*Antenatal maternal, fetal, and neonatal parameters of GDM pregnancies in 324 children with BMI < or ≥90th percentile at follow-up examination*

	Total cohort (n = 324)	BMI <90th percentile at follow-up (n = 232)	BMI ≥90th percentile at follow-up (n = 92)	χ^2/t test P value
Maternal				
History of GDM	43 (13.3)	31 (13.4)	12 (13.0)	0.939
History of macrosomia (>4,000 g)	41 (12.7)	27 (11.6)	14 (15.2)	0.382
Parity	2.0 ± 1.1	1.9 ± 1.1	2.0 ± 1.2	0.578
Age at delivery (years)	30.8 ± 5.5	31.0 ± 5.6	30.3 ± 5.4	0.252
Prepregnancy BMI (kg/m²)	27.1 ± 5.6	26.4 ± 5.3	28.8 ± 6.2	0.003
Weight gain during pregnancy (kg)	11.7 ± 5.7	11.6 ± 5.2	12.0 ± 6.7	0.589
Diabetes-related parameters				
Gestational age at diagnosis (weeks)	26.5 ± 6.1	26.5 ± 5.9	26.5 ± 6.8	0.929
OGTT (mg/dl)				
Fasting	91.4 ± 20.1	90.7 ± 19.9	93.3 ± 20.8	0.308
1 h	195.4 ± 33.8	194.2 ± 33.8	198.3 ± 33.9	0.345
2 h	145.8 ± 38.1	145.5 ± 37.5	146.6 ± 39.9	0.832
Mean fasting glucose, third trimester	78.3 ± 12.2	77.9 ± 11.9	79.2 ± 13.0	0.429
Mean 2-h postprandial, third trimester	104.0 ± 17.0	102.6 ± 16.7	107.2 ± 17.4	0.043
A1C at diagnosis (%)	5.9 ± 1.3	5.8 ± 1.4	6.1 ± 1.2	0.209
Insulin use	27 (8.8)	19 (8.4)	8 (9.1)	0.855
Fetal and neonatal				
Fetal AC at diagnosis ≥90th percentile	53 (21.5)	35 (19.7)	18 (26.5)	0.245
Fetal AC third trimester ≥90th percentile	38 (15.4)	22 (12.7)	16 (21.6)	0.076
Gestational age at delivery (weeks)	39.2 ± 1.5	39.3 ± 1.5	39.0 ± 1.6	0.121
Sex (male)	175 (54.0)	125 (53.9)	50 (54.3)	0.939
Birth weight ≥90th percentile	55 (17.0)	33 (14.2)	22 (23.9)	0.036
Neonatal BMI ≥90th percentile	100 (30.9)	63 (27.2)	37 (40.2)	0.022

Data are *n* (%) or means ± SD. AC, abdominal circumference.

Antenatal, parental parameters, and childhood BMI

Antenatal maternal and fetal parameters of children stratified according to their BMI at follow-up are presented in Table 1. Maternal and child's BMI at follow-up were significantly related ($r = 0.31$, $P < 0.001$). In women with prepregnancy BMI >30 kg/m², the rate of overweight infants was 42.0% compared with 24.1% in nonobese mothers ($P = 0.004$). The vast majority of the children (294/324) were from families with Caucasian origin without significant difference between the rate of non-Caucasian mothers (9.3%) in children with BMI less than or ≥90 at follow-up.

The average of postprandial glucose values ($n = 260$) derived from daily profiles during the third trimester was the only maternal glycemic parameter that was significantly related to the infant BMI at follow-up ($r = 0.18$, $P = 0.003$).

Ultrasound examinations performed at entry of diabetes care ($n = 246$) revealed a fetal abdominal circumference ≥90th percentile in 21.5% of the fetuses (mean gestational age at examination 27.4 ± 6.1 weeks). The rate was higher, although not significantly, in children with increased BMI than in those with normal BMI at follow-up (Table 1). However, as assessed by correlation analysis, abdominal circumference at diagnosis proved to be significantly associated with both the BMI at birth ($r = 0.24$, $P < 0.001$) and at follow-up ($r = 0.16$, $P < 0.01$). The fetal abdominal circumference of the third trimester ($n = 247$) had a slightly closer relation to the BMI at birth ($r = 0.36$, $P < 0.001$) and follow-up ($r = 0.22$, $P < 0.001$) than the abdominal circumference at diagnosis.

At follow-up examination, BMI SDSs of children were significantly correlated with the recent maternal ($r = 0.324$, $P < 0.001$) and paternal ($r = 0.169$, $P = 0.003$) BMI. The association of parental obesity with the BMI of the child at follow-up is depicted in Fig. 3. When both parents had a BMI <30 kg/m², 20.4% of the infants were overweight; the rate increased to 34.1% with one parent and to 69.2% with both parents being obese

($P < 0.001$). The same association was found in the subgroup of children with normal BMI at birth ($n = 213$), with 18.5% overweight children when both parents had a BMI <30 kg/m² and 66.7% overweight when both parents were obese ($P < 0.05$). Neonatal BMI was positively correlated with maternal BMI ($r = 0.222$, $P < 0.001$) but not with paternal BMI ($r = 0.089$, $P = 0.120$).

Independent predictors of childhood BMI

Parameters entered in the multivariate regression analysis were BMI at birth, fetal abdominal circumference at diagnosis and third trimester, maternal prepregnancy BMI, recent BMI of mother and father, age at follow-up, sex, OGTT values, and fasting and postprandial glucose values during the third trimester. Independent predictors were neonatal BMI (standardized regression coefficient $\beta = 0.195$, $P < 0.001$), recent maternal BMI ($\beta = 0.248$, $P < 0.001$), and recent paternal BMI ($\beta = 0.137$, $P = 0.011$), with $r = 0.418$ ($P < 0.001$). Thus, 17.4% of
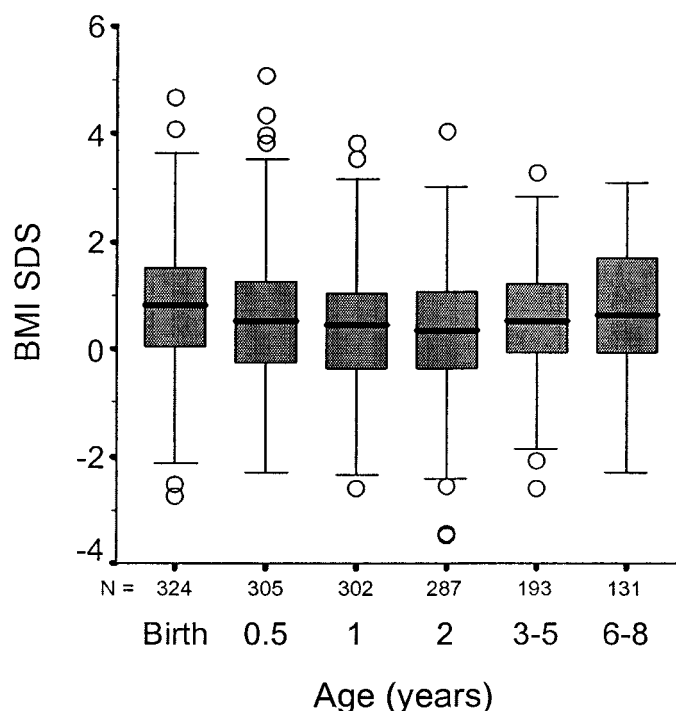
Figure 1—*SDS of BMI in 324 children at birth and during observation time up to 8 years of age. Data are presented as box-and-whisker plots with interquartile range (box), 95th percentile range (whisker), and median value (line within box). BMI SDS was significantly different from zero at each time point (P < 0.001).*

the variance of the BMI at follow-up could be explained by three independent factors. If BMI at birth was excluded from the model, abdominal circumference at diagnosis ($r = 0.406$) or alternatively abdominal circumference at third trimester ($r = 0.385$) stayed in the model as an independent factor. Likewise, prepregnancy BMI stayed in the model ($r = 0.422$) if the recent BMI of the mother was excluded.

CONCLUSIONS — In a population of 324 children from Caucasian women with GDM, we demonstrated that these children have consistently increased BMI at various time points up to 8 years of age compared with the average German population. Independent predictors of the children's BMI were BMI at birth (or the fetal abdominal circumference), recent maternal BMI, and recent paternal BMI. Infants from GDM pregnancies eventually born with normal weight still had a rate of 67% childhood overweight when both parents were obese in contrast to 19% overweight children when both parents had a BMI <30 kg/m². This demonstrates that both pre- and postnatal environment contributes to childhood overweight.

Our results are based on a study co-

hort that represents 40% of the eligible group of patients treated in our institution. This raises the question of the generalizability of our findings. However, neither birth weight nor maternal BMI were different in the study and in the complementary group. Thus, we don't have any indication that there was a selec-

tion of children with overweight in our study cohort.

Birth weight and childhood overweight
In the infants of mothers with GDM we studied, overweight developed in a biphasic pattern as previously described by Silverman et al. (4). Overweight at birth was attenuated in the 1st year of life and recurred later at 2–3 years of age. We observed a tight relationship between overweight at birth and childhood overweight. Several long-term observations in offspring of diabetic and nondiabetic pregnancies have demonstrated an increased risk for adolescent or adult obesity, type 2 diabetes, and insulin resistance associated with birth weights <2.5 kg and >4.5 kg alike (3,14–17). Similar to a prior study by Plagemann et al. (7), in our GDM offspring cohort, low birth weight was not associated with childhood obesity.

The focus of most studies of diabetic pregnancies has been on preexisting type 1 or type 2 diabetes (4,6,18,19), or populations with preexisting and gestational diabetes were combined (20,21,4). Here, we explicitly excluded women with preexisting diabetes because diabetic vascular disorders may cause placental dysfunction and intrauterine growth retardation. Second, we wanted to demonstrate that even mild maternal glucose intolerance in Caucasian women has long-term effects on the offspring. In the GDM pregnancies studied, average ma-
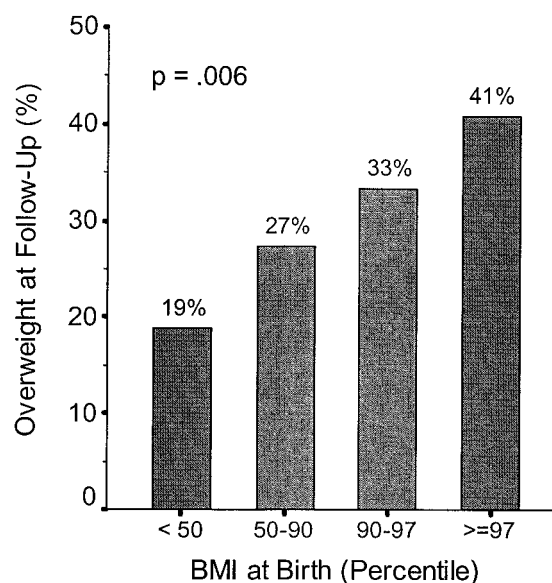

Figure 2—*Rate of children with BMI ≥90th percentile at follow-up examination at ages 2–8 years according to percentiles of BMI at birth.*
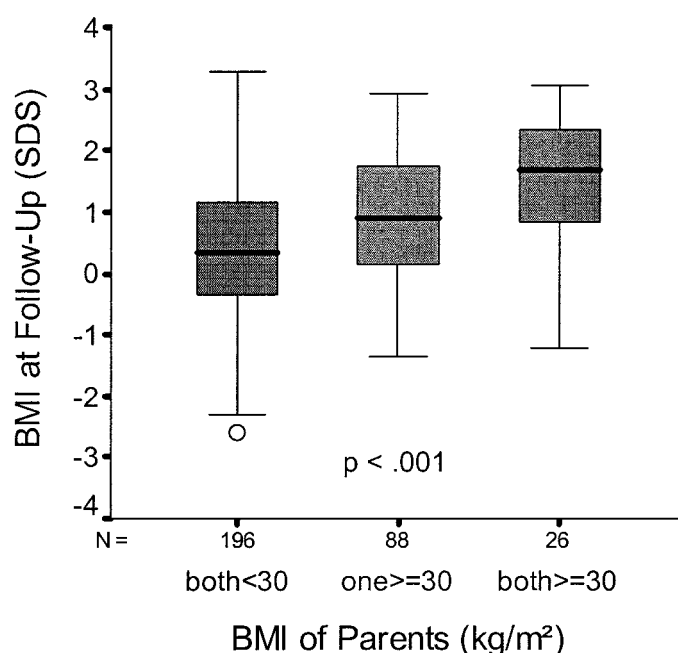
Figure 3—*BMI SDSs of the children at follow-up examination according to recent parental BMI.*

ternal hyperglycemia was moderate. Although we found that neonatal BMI is an independent factor of later overweight in childhood, we cannot conclude due to our study design that adverse intrauterine metabolic environment is an independent risk factor, since accelerated fetal growth is not a specific marker for intrauterine exposure to hyperglycemia. The association between birth weight and later overweight has been reported in most studies, except for a cohort with a 50% neonatal macrosomia rate (4) and in Pima Indians, in whom childhood obesity develops regardless of birth weight (22).

Maternal glycemia and childhood overweight
This report shows the predictive value of postprandial but not fasting glucose measurements obtained by self-monitoring of glucose during the third trimester for long-term outcome. This supports the current policy to rely on postprandial instead of preprandial glucose values to monitor glucose control in pregnancy. To our knowledge, this is the first study that used data of glucose measurements obtained by self-monitoring in all pregnant women. Prior studies (8) reported an association of the 2-h glucose value of the OGTT with skinfold thickness at age 1 year in children of GDM mothers or with relative weight at ages 5–7 years in Pima

Indians (3); others used biweekly obtained fasting plasma glucose and demonstrated no or very limited correlation with adolescent or childhood body habitus (2,23). The extent of maternal hyperglycemia within a treated population of women with GDM appears to act as a risk factor for childhood obesity, but it does not seem to be the major determinant. However, studies in siblings have shown that the intrauterine environment of maternal diabetes conveys a risk for obesity and diabetes (5), and measurements of amniotic fluid insulin have demonstrated a tight relation between fetal hyperinsulinism and childhood obesity independently from maternal BMI (1). The nonlinear relationship of measures of maternal glucose with fetal hyperinsulinism (24) may explain the weak predictive power of maternal glycemic values. Additionally, the small variation in maternal glucose values resulting from strict glycemic control may be a reason why an independent effect of the level of the maternal hyperglycemia on offsprings' BMI was not noted.

Parental BMI and childhood overweight
In addition to overweight at birth, the postnatal environment of the infants has a strong impact on childhood overweight. Both the recent BMI of mother and father

at follow-up were independent predictors for an increased BMI of the child. Maternal obesity before pregnancy is associated with increased fetal growth during late gestation (25) and postnatal somatic development (4,8,23,26). In the women with GDM studied here, the recent BMI of the mother was even more predictive than the prepregnancy BMI as judged by stepwise regression analysis. Our effort to normalize fetal growth to avoid long-term sequelae of diabetic pregnancies seems to be diminished by the postnatal environment. In the present study, even children born with normal weight were placed at a highly elevated risk of overweight when both parents were obese.

Clinical implications
First, effective preventive intervention has to start at the earliest possible age. Accelerated intrauterine growth is a major antenatal factor for later overweight, and fetal growth–based GDM management has been successfully implemented (27,28). Second, in offspring of mothers with GDM who are already at increased risk for later obesity, shared familial dietary and physical activity habits may strongly influence the risk of childhood obesity. Therefore, promoting a healthy lifestyle in families with offspring of GDM mothers combined with a close follow-up of the somatic development of the children may reduce the risk of obesity. For long-term prevention of obesity and diabetes, GDM management should not stop after delivery.

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