

Impaired Glucose Tolerance in Adolescent Offspring of Diabetic Mothers

Relationship to fetal hyperinsulinism

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OBJECTIVE — To test the hypothesis that long-term postnatal development may be modified by metabolic experiences in utero.

RESEARCH DESIGN AND METHODS — We enrolled offspring of women with pregestational diabetes (this included insulin-dependent diabetes mellitus [IDDM] and non-insulin-dependent diabetes mellitus [NIDDM]) and gestational diabetes in a prospective study from 1977 through 1983. Fetal β -cell function was assessed by measurement of amniotic fluid insulin (AFI) at 32–38 weeks gestation. Postnatally, plasma glucose and insulin were measured yearly from 1.5 years of age after fasting and 2 h after 1.75 g/kg oral glucose. Control subjects had a single oral glucose challenge at 10–16 years.

RESULTS — In offspring of diabetic mothers, the prevalence of impaired glucose tolerance (IGT) (2-h glucose concentration >7.8 mmol/l) was: 1.2% at <5 years, 5.4% at 5–9 years, and 19.3% at 10–16 years. The 88 offspring of diabetic mothers (12.3 ± 1.7 years), when compared with 80 control subjects of the same age and pubertal stage, had higher 2-h glucose (6.8 ± 1.4 vs. 5.7 ± 0.9 mmol/l, $P < 0.001$) and insulin (660 ± 720 vs. 455 ± 285 pmol/l, $P < 0.03$) concentrations. The 17 subjects with IGT at >10 years of age (9 boys and 8 girls) include one girl with NIDDM. IGT was not associated with the etiology of the mother's diabetes (gestational versus pregestational) or macrosomia at birth. IGT was found in only 3.7% (1 of 27) of adolescents whose AFI was normal (≤ 100 pmol/l) and 33.3% (12 of 36) of those with elevated AFI ($P < 0.001$). Although most of the children with IGT are obese, AFI and obesity are independently associated with IGT by multiple logistic analysis.

CONCLUSIONS — In confirmation of our original hypothesis, IGT in the offspring is a long-term complication of maternal diabetes. Excessive insulin secretion in utero, as assessed by AFI concentration, is a strong predictor of IGT in childhood.

Freinkel (1) proposed that maternal fuel metabolism might exert long-term effects on the offspring. The hypothesis of fuel-mediated teratogenesis is that maternal fuels may influence development of the fetus by modifying phenotypic gene expression in terminally differentiated, poorly replicating cells. The

long-range effects depend on the cells undergoing differentiation, proliferation, and/or functional maturation at the time of the disturbances in maternal fuel economy. It was postulated that pancreatic β -cells and adipose tissue would be among the tissues vulnerable to functional alterations during later life.

The Diabetes in Pregnancy Center Study was established at Northwestern University to determine the effects of maternal diabetes on anthropometric development of the fetus and glucoregulation in later life of the offspring. Previous reports from this ongoing study have shown a link between the intrauterine environment and obesity in childhood (2,3). Maternal diabetes (exclusively non-insulin-dependent diabetes mellitus [NIDDM]) is associated with an increased risk of both obesity and the development of NIDDM in young adults (4,5) in the highly inbred Pima Indian population. Among women with gestational diabetes mellitus (GDM) we have observed maternal histories of diabetes more frequently than expected (6). Cross-sectional, epidemiological studies in Britain (7) and France (8) have found that individuals with NIDDM more often have had a diabetic mother than a diabetic father. The development of diabetes in the offspring of diabetic rats is influenced by perturbed maternal carbohydrate metabolism, as well as by genetic factors (9,10).

We have investigated, in a prospective study, the relationships between insulin secretion in the fetus and glucose tolerance in adolescence in offspring of diabetic mothers (11,12).

RESEARCH DESIGN AND METHODS

Mothers

Women with glucose intolerance diagnosed during pregnancy (GDM) and with known diabetes before pregnancy (pregestational diabetes mellitus [PGDM]) were recruited from September 1977 to February 1983 for detailed longitudinal

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AFI, amniotic fluid insulin; BMI, body mass index; CI, confidence interval; FPG, fasting plasma glucose; GDM, gestational diabetes mellitus; IDDM, insulin-dependent diabetes mellitus; NIDDM, non-insulin-dependent diabetes mellitus; OGTT, oral glucose tolerance test; PGDM, pregestational diabetes mellitus.

characterizations of maternal metabolism and long-term evaluation of their offspring. We excluded women who chronically required medication other than insulin. All of the women with PGDM (predominantly insulin-dependent diabetes mellitus [IDDM]) received insulin. Of those women with GDM, 28% received insulin for the first time during pregnancy; the others were treated by diet only. All participating women gave written informed consent.

All women were seen at the outpatient clinic at least biweekly before 30 weeks gestation and weekly thereafter. The details of antepartum care, including routine hospitalization, have been previously reported (13). Every 1–2 weeks, blood samples were drawn after an overnight fast for measurement of fasting plasma glucose (FPG). HbA_{1c} was measured monthly. The mean values for FPG and HbA_{1c} for the 2nd and 3rd trimesters were calculated.

Offspring

At the time women were enrolled in this study, amniocentesis was carried out every 2 weeks starting at 32–38 weeks gestation until term, and amniotic fluid was sampled to monitor fetal lung maturation in all pregnancies complicated by diabetes (when possible). This was not a research procedure; however, in 63 of the subjects enrolled in this study, aliquots were frozen for later measurements of immunoreactive insulin concentrations. Insulin secreted by fetal β -cells is cleared by the fetal kidney and fractionally excreted into the amniotic fluid, thereby providing a unique integrated index of fetal insulin secretion (14). We found no association between insulin concentration and gestational age during this period of sampling. Thus, when two or more measurements were available, the mean value was used.

After detailed evaluation at birth, the study population was seen at 6 months and then yearly for physical examination including measurements of height and weight. Newborn obesity, or macrosomia, was defined as a relative

weight-to-height ratio of >1.20 after adjustment for gestational age (2). The body mass index (BMI) (weight/height [kg/m²]) was calculated. Glucoregulation was evaluated by a modified oral glucose tolerance test (OGTT) yearly from 1.5 years onward. Pubertal stage was assessed by the method of Tanner (15), in addition to measurement of testicular volume in boys. Morning fasting glucose and insulin were measured followed by an oral glucose load of 1.75 g/kg body wt with a maximum dose of 75 g. A second sample was drawn at 2 h for estimations of glucose and insulin. Consistent with the National Diabetes Data Group (16) criteria for children and adolescents, impaired glucose tolerance (IGT) is defined as a 2-h glucose concentration >7.8 mmol/l, and diabetes is defined as symptoms of diabetes (polyuria and polydipsia) with a random glucose concentration >11.1 mmol/l or fasting glucose concentration >7.8 mmol/l with a 2-h and intervening glucose concentration ≥ 11.1 mmol/l.

Among the 88 adolescent offspring of diabetic mothers studied at 10–16 years, 49% were Caucasian, 23% African-American, 19% Hispanic, and 9% other ethnic groups.

Control subjects

Control subjects represent a broad cross-section of a much larger group of normal subjects in whom we have assessed anthropometric developments in childhood. This population of healthy children was recruited from pediatricians' offices and public health clinics at the time of routine yearly physical examinations and inner city school and after school programs. Children 10–16 years of age without any history of maternal diabetes were offered the opportunity to participate. Subjects with acute illness or chronic disorders affecting carbohydrate metabolism or those taking medications were excluded. Of the control subjects, 63% were Caucasian, 31% African-American, and 6% Hispanic. Control subjects were weighed, measured on a stadiometer, ex-

amined for pubertal stage, and given a single modified OGTT.

Laboratory research

Glucose was measured by a hexokinase-glucose-6-phosphate dehydrogenase coupled assay (Gilford, Oberlin, OH). Insulin was measured by a polyclonal double-antibody radioimmunoassay (17). HbA_{1c} determinations were made as previously described (18).

Statistical analysis

A test of normality was applied to all the study variables with a continuous scale. Most of the variables were normally distributed, with the exception of insulin. Therefore, insulin values were log-transformed before analysis. Data are expressed as means \pm SD. All statistical comparisons are two-tailed with $P < 0.05$ considered significant. Comparisons between the control group and offspring of diabetic mothers are by χ^2 test with Yate's correction, Student's t tests, or Mann-Whitney U test as appropriate; 95% confidence intervals (CI) were calculated. Multiple logistic regression analysis was also applied to examine the relationship between fetal hyperinsulinism and IGT independent of obesity.

RESULTS—The age-related frequency of IGT in our cohort of offspring of diabetic mothers is displayed in Fig. 1. Data were obtained from 168 children <5 years of age, 111 aged 5–9, and 88 aged 10–16 years. Before the age of 5 years, IGT was a rare event, with 1.2% (CI 0.2–3.9%) of the children having a 2-h glucose concentration >7.8 mmol/l. From ages 5 to 9, 5.4% (CI 2.2–10.9%) demonstrated IGT, similar to literature reports in normal children (16). However, after age 10 we found a marked increase in the frequency of IGT, with 17 of 88 (19.3%, CI 12.1–28.6%) subjects having an elevated 2-h plasma glucose concentration.

Three of the offspring of diabetic mothers have developed diabetes. One islet cell antibody-positive boy developed

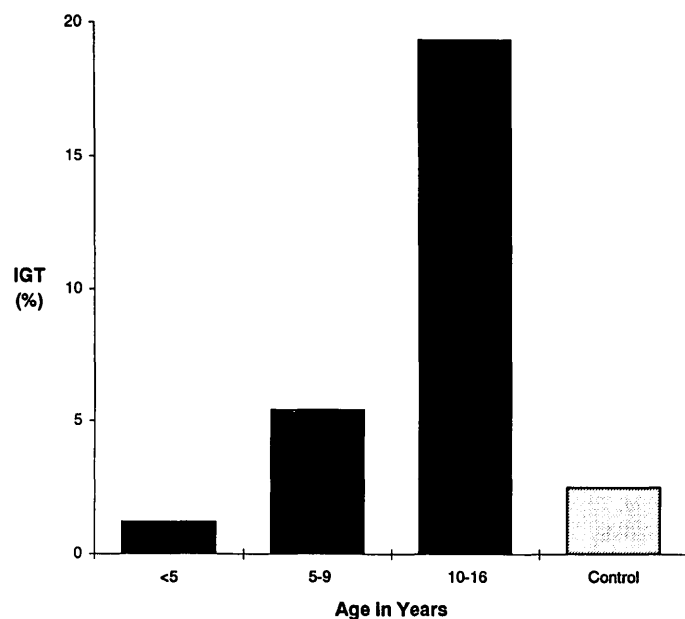


Figure 1—The prevalence of IGT in offspring of diabetic mothers in 3 age-groups are plotted in the solid bars and compared with control subjects aged 10–16 years in the gray bar. The age-related increase is highly significant ($P < 0.001$) by χ^2 test, as is the difference between the offspring of diabetic mothers at 10–16 years and the control subjects ($P < 0.005$).

IDDM, presenting as ketoacidosis, at age 12 years. After birth, he did not participate in the study and never had an OGTT. Therefore, he is not included in any of the above statistics. Two girls have developed NIDDM at ages 7 and 11, both initially detected on a yearly OGTT. By age 10, the younger of these girls was being treated with insulin and did not have another OGTT. Although both girls are included in the IGT frequency data above, only the 11-year-old is included in the comparison of our cohort with control subjects aged 10–16 below. All of the subjects with IGT and NIDDM have been islet cell antibody-negative.

Although the prevalence of IGT in this group of adolescent offspring of diabetic mothers is higher than that observed in any previous reports of OGTTs in children, we elected to recruit a cohort of children whose mothers had no history of abnormal carbohydrate metabolism during gestation. We did this for the following reasons: 1) as adolescence is a time of relative insulin resistance, it is important

to compare offspring of diabetic mothers with subjects of similar age and degree of sexual maturation; and 2) a number of reports have suggested that there is a secular trend toward increasing obesity, making the older literature reports less appropriate for comparison. Thus, direct comparison between our group of offspring of diabetic mothers and a group of contemporary normal children was essential.

In Table 1, we compared the general characteristics and OGTT results in the control subjects with the entire group of offspring of diabetic mothers. The sex distribution is not different. The control subjects are slightly, but not significantly, older. There were no significant differences between the offspring of diabetic mothers and control subjects in either testicular volume in boys or Tanner stage of breast development in girls. Of the 88 adolescent offspring of diabetic mothers, 49% were Caucasian, 23% African-American, 19% Hispanic, and 9% other ethnic groups. Of the control subjects 63% were

Caucasian, 31% African-American, and 6% Hispanic. The control adolescents had a lower mean BMI than the offspring of diabetic mothers. In the fasting state, glucose and insulin concentrations and the insulin:glucose ratio are almost identical. However, 2 h after an oral glucose load, the offspring of diabetic mothers manifest significantly higher glucose and insulin concentrations. The criteria for IGT (2-h glucose concentration >7.8 mmol/l) were met in 19.3% of the offspring of diabetic mothers but in only 2.5% of the control subjects ($P < 0.005$) (Fig. 1). This frequency of IGT in control subjects is consistent with the published literature for oral glucose tolerance testing in normal children (19).

Within the group of offspring of diabetic mothers, we sought to determine whether the development of IGT could be predicted by perinatal factors or characteristics measured in childhood. Comparisons between the 71 subjects with normal glucose tolerance after 10 years of age and the 17 with IGT at last testing are shown in Table 2. The incidence of IGT is the same in offspring of mothers with GDM compared with offspring of mothers with PGDM. Treatment of GDM with insulin was not related to development of IGT in the offspring. IGT developed both in subjects who were macrosomic and in those who were normal size at birth. There is no significant effect of sex. The subjects with IGT are similar in age to those with normal glucose tolerance but heavier, with BMIs of 25.0 ± 7.3 kg/m², compared with 22.3 ± 4.8 kg/m² in those with normal glucose tolerance. This difference in BMI persists after covariant correction for age and sex. Fasting insulin concentrations and insulin:glucose ratios were slightly higher in subjects with IGT. There was no difference in FPG. In the group with IGT, the 2-h glucose concentrations are higher by definition, and the 2-h insulin concentrations are markedly elevated in concert with the greater hyperglycemia.

To examine the relationship between glucose tolerance in adolescence in

Table 1—Comparison of control subjects and offspring of diabetic mothers

	Control	ODM	P value
Subjects (n)	80	88	
Age (years)	12.8 ± 1.7	12.3 ± 1.7	0.06
Sex (M/F)	41/39	49/39	NS
BMI (kg/m ²)	20.3 ± 4.0	22.8 ± 5.4	0.001
Sexual development			
Testicular volume <12 ml (%)	73	62	NS
Breast: Tanner stage I/II–III/IV–V (%)	13/46/41	13/36/51	NS
OGTT			
Fasting glucose (mmol/l)	5.5 ± 0.4	5.6 ± 0.4	NS
2-h glucose (mmol/l)	5.7 ± 0.9	6.8 ± 1.4	<0.001
Fasting insulin (pmol/l)	130 ± 80	135 ± 80	NS
2-h insulin (pmol/l)	455 ± 285	660 ± 720	0.03
Fasting insulin:glucose (pmol/mmol)	23.6 ± 13.8	23.4 ± 13.0	NS
2-h insulin:glucose (pmol/mmol)	78.1 ± 42.7	93.6 ± 90.7	NS
IGT (%)	2.5 (0.4–8.1)	19.3 (12.1–28.6)	0.005

Data are means ± SD or means (95% CI). Sexual development for girls: comparison of pubertal development is made between prepuberty (Tanner stage I), early puberty (Tanner stages II and III), and late puberty (Tanner stage IV), on the basis of breast development. For fasting insulin, although means ± SD are shown, insulin values were log-transformed for statistical calculations. IGT is defined as a 2-h glucose concentration >7.8 mmol/l. The one subject with NIDDM presenting after age 10 is included in the group with IGT.

the context of the Pedersen and Freinkel hypotheses, we divided our population on the basis of islet function during intra-uterine life, which was available for 63 of 88 subjects. In nondiabetic pregnancies, studied concurrently, the mean + 2 SD for amniotic fluid insulin (AFI) was 100 pmol/l (2). As shown in Table 3, those mothers with elevated AFI (>100 pmol/l) had poorer metabolic control, documented by significantly higher HbA_{1c} concentrations in midgestation, and higher average FPG in the 3rd trimester of gestation. Among the 27 subjects who had concentrations of AFI similar to those in nondiabetic pregnancies, the frequency of IGT in adolescence is only 3.7%. The remaining 36 subjects, with elevated AFI levels in utero, had a frequency of IGT of 33.3% ($P < 0.01$). This represents a 13-fold increased frequency (CI 1.6–107.7, $P < 0.01$).

We have previously reported that elevated AFI is correlated with obesity in childhood (2,3). Obesity itself is associated with insulin resistance in both adults (20) and children (21). However, after

correction for age, sex, and BMI by multiple logistic regression analysis, the estimated relative risk of IGT in those with elevated AFI is 3.6 (CI 1.25–10.5, $P < 0.02$).

Table 2—Comparison of offspring of diabetic mothers with normal glucose tolerance and IGT to oral glucose challenge

	Normal	IGT	P value
Subjects (n)	71	17	
Age (years)	12.3 ± 1.7	12.3 ± 1.5	NS
Sex (M/F)	40/31	9/8	NS
GDM/PGDM	34/37	9/8	NS
Macrosomia/normal size at birth	35/36	11/6	NS
BMI (kg/m ²)	22.3 ± 4.8	25.0 ± 7.2	NS
OGTT			
Fasting glucose (mmol/l)	5.6 ± 0.4	5.7 ± 0.5	NS
2-h glucose (mmol/l)	6.3 ± 0.9	8.8 ± 1.6	<0.001
Fasting insulin (pmol/l)	125 ± 65	155 ± 120	NS
2-h insulin (pmol/l)	575 ± 665	975 ± 845	<0.01
Fasting insulin:glucose (pmol/mmol)	22.5 ± 11.4	27.1 ± 18.2	NS

Data are means ± SD. Macrosomia is defined as a relative weight: relative height ratio >1.2 at birth (3). For fasting insulin, although means ± SD are shown, insulin values were log-transformed for statistical calculations.

CONCLUSIONS—Four decades ago, Pedersen (22) proposed that maternal hyperglycemia induces fetal hyperglycemia and hyperinsulinemia and that this premature activation of fetal islets is responsible for macrosomia and neonatal hypoglycemia. Pedersen's hypothesis has been well established and confirmed again in our cohort. The finding of poorer metabolic control in the 2nd, as well as the 3rd, trimester in those with fetal hyperinsulinemia has been reported previously (23,24). Freinkel (1) postulated that this abnormal fetal metabolic milieu would, in addition, have long-term effects on growth and metabolic development. In support of this hypothesis of fuel-mediated teratogenesis, we found a remarkably high frequency of IGT in adolescent offspring of diabetic mothers. Studies in normal children and adolescents have consistently reported frequencies of <5% (16,25,26), similar to what we found in our control subjects.

An increased risk of IGT and even diabetes in offspring of diabetic mothers has been reported by others (27–29). In general, populations with a high prevalence of IGT later become populations with high prevalences of NIDDM (30).

Table 3—Comparison between groups of offspring of diabetic mothers with normal and elevated concentrations of amniotic fluid insulin

	Amniotic fluid insulin		P value
	Normal (≤ 100 pmol/l)	Elevated (> 100 pmol/l)	
<i>n</i>	27	36	
2nd trimester			
HbA _{1c} (%)	5.3 \pm 1.1	6.1 \pm 1.1	0.02
Fasting glucose (mmol/l)	6.2 \pm 1.7	6.9 \pm 2.0	NS
3rd trimester			
HbA _{1c} (%)	5.5 \pm 1.0	5.9 \pm 0.8	NS
Fasting glucose (mmol/l)	5.2 \pm 0.7	6.0 \pm 1.14	0.001
Adolescence			
IGT	1 of 27 (3.7)	12 of 36 (33.3)	0.01

Data are means \pm SD or *n* (%). In four subjects with IGT, AFI was not measured. Maternal values are shown for the 2nd and 3rd trimesters of pregnancy. The prevalence of IGT in the offspring is shown at adolescence.

Studies in the Pima Indians, a native American tribe with the highest reported prevalence of NIDDM in the world, have shown that offspring of diabetic mothers are at increased risk for development of both IGT and NIDDM (31). In this population, NIDDM begins to appear after 15 years of age in offspring of diabetic mothers. In Pima Indians, the risk of development of NIDDM is greater if the mother had diabetes during pregnancy, rather than developing it after pregnancy. This implies that there is a component of abnormal metabolic milieu in addition to the genetic risk. Further evidence is provided by cross-sectional epidemiological studies in Britain (7) and France (8). In each study, individuals with NIDDM have mothers who are twice as likely to have NIDDM as these individuals' fathers.

Numerous factors may contribute to the high prevalence of altered glucose regulation in offspring of diabetic mothers. The Pimas are an inbred population with a very high prevalence of NIDDM. It could be argued that exposure to maternal diabetes during intrauterine development simply leads to earlier expression of a genetic trait. When strains of rats with spontaneous NIDDM and non-diabetic rats were crossed, a greater degree of glucose intolerance was observed

in the offspring as young adults when the mother was diabetic than when the father carried the diabetes (9). A rare form of NIDDM linked to mutations in mitochondrial DNA and associated with severe hearing loss is also maternally transmitted (32). Similarly, maturity-onset diabetes of the young, which is associated with defects in the glucokinase gene in some kindred, particularly of French descent, could present as GDM in mothers and IGT or NIDDM in adolescence (33).

Each of the uncommon forms of diabetes could contribute to heterogeneity of NIDDM in general, as well as in a population such as our cohort. However, even in the aggregate, such rare syndromes would represent a small minority. We find the increased risk of IGT in an American population of mixed racial/ethnic composition among offspring of diabetic mothers with both PGDM (predominately but not exclusively IDDM) and GDM. In our cohort, the predisposition to IGT is linked to prenatal metabolism, but not the genetic form of the mother's diabetes. As a group, a large majority of these adolescents are displaying characteristics associated with NIDDM, not IDDM, regardless of the mother's diabetes. It would be expected that 1–3% of the children would develop IDDM (34),

and indeed, only one case of IDDM has been observed. Rather, the children of mothers with IDDM are developing IGT at the same rate as offspring of mothers with GDM. We postulate that in addition to the inherited risk of IDDM, offspring of mothers with IDDM carry an additional burden of an increased risk of IGT, and likely NIDDM, as a result of abnormal prenatal fuel exposures.

Our data suggest the following sequence of events. As shown in Table 3, maternal hyperglycemia is associated with fetal hyperinsulinism (the Pedersen hypothesis [22]). Fetal hyperinsulinism (documented by measurement of the concentration of insulin in amniotic fluid) predisposes to obesity and IGT in adolescence (the Freinkel hypothesis [1]). Offspring of diabetic mothers with normal AFI concentrations have an incidence of IGT similar to that of the general population. But those offspring of mothers with the highest concentrations of AFI in utero have a 13-fold increased risk of developing IGT by 10–16 years of age. Rhesus monkeys made hyperinsulinemic by infusion of insulin into the fetus, while remaining in utero, develop abnormal glucose tolerance as pregnant adults (35). Together, these data from humans and primates implicate exposure to excess insulin action in utero in the predisposition to IGT, and putatively to NIDDM.

Recent evidence from animal models and epidemiological studies suggests that a disturbance in islet function, which may develop during intrauterine or early postnatal life, produced by a variety of mechanisms, predisposes to metabolic disturbances and IGT in later life. Thus, offspring of rats with streptozotocin-induced diabetes during pregnancy develop IGT and GDM, which is transmitted transgenerationally (10). When pregnant rats without a genetic predisposition to diabetes are made mildly hyperglycemic by glucose infusion in late pregnancy, the offspring develop IGT (36). Rats whose mothers were protein-deprived during pregnancy have IGT as young adults (37). In studies of men born

between 1920 and 1930, Hales et al. (38) found that those with IGT or NIDDM by age 60 were more likely to have been of low birth weight and to have had poor growth over the 1st year of life.

In aggregate, these observations suggest that fetal and neonatal β -cell development may be vulnerable to a variety of disturbances in maternal and/or infant fuel economy, consistent with the hypothesis of fuel-mediated teratogenesis. Thus, an abnormal metabolic environment, through whatever mechanism—PGDM, GDM, impaired placental function, or protein-calorie malnutrition—is associated with altered islet function in utero or in infancy. This, in turn, is associated with altered glucoregulation later in life.

Many of the offspring of diabetic mothers in our study are approaching childbearing age. If this propensity for glucose intolerance becomes manifest during pregnancy as GDM in the second generation, the pattern of perpetuation from generation to generation will be established. This suggests that diabetes can predispose to more diabetes, which may contribute to an overall increasing burden of diabetes in the population. However, this process is potentially preventable by minimizing fetal hyperinsulinism by optimal metabolic control throughout gestation in women with PGDM and by early diagnosis and correction of the metabolic disturbances of GDM.

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