

Intrauterine Hyperglycemia Is Associated With an Earlier Diagnosis of Diabetes in HNF-1 α Gene Mutation Carriers

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OBJECTIVE — In animals, experimentally induced maternal hyperglycemia during pregnancy results in hyperglycemic offspring. Similarly, Pima Indian offspring with mothers who are diabetic at the time of pregnancy have increased risk of early-onset diabetes. We hypothesized that exposure to hyperglycemia in utero would decrease the age at diagnosis of diabetes in patients with maturity-onset diabetes of the young (MODY) due to a mutation in the hepatocyte nuclear factor 1 α (HNF-1 α) gene.

RESEARCH DESIGN AND METHODS — We analyzed the affect of maternal diabetes on age at diagnosis of diabetes in 150 HNF-1 α gene mutation carriers from 55 families.

RESULTS — Age at diagnosis in HNF-1 α mutation carriers was younger when the mother was diagnosed before pregnancy compared with when the mother was diagnosed after pregnancy (15.5 ± 5.4 vs. 27.5 ± 13.1 years, $P < 0.0001$). This is unlikely to represent a generalized familial decrease in age at diagnosis due to a more severe mutation, because no difference was seen in age of the offspring at diagnosis of diabetes when the father was diagnosed at a young age, and a similar trend was seen when only the single common mutation, P291fsinsC, was analyzed.

CONCLUSIONS — We conclude that maternal hyperglycemia during pregnancy probably increases the penetrance of HNF-1 α mutations. The potential role of exposure to hyperglycemia in utero in a monogenic diabetic subgroup warrants prospective study.

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Age at onset of diabetes in humans and animal models is altered by both genetic and environmental factors. Established risk factors include racial origin, parental diabetes, BMI, diet, birth weight, and prenatal exposure to hyperglycemia in utero (1,2).

The effect of exposure to a hyperglycemic environment in utero has been studied extensively in animal models. Female offspring of rats with streptozocin-induced diabetes have higher blood glucose concentrations during pregnancy compared with control subjects (3). Fe-

male rats (F1) born from dams (F0) rendered hyperglycemic by continuous glucose infusion during the last week of pregnancy exhibit glucose intolerance and impaired insulin secretion in vivo at adulthood (4). Offspring from the F1 female rats (F2) are hyperglycemic, hyperinsulinemic, and macrosomic. As adults, they remain hyperglycemic with defective glucose tolerance and insulin secretion (4). An increased prevalence of glucose intolerance in F1 offspring has also been seen in mice rendered hyperglycemic by consumption of betel nuts (5).

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Abbreviations: FPG, fasting plasma glucose; HNF-1 α , hepatocyte nuclear factor-1 α ; IFG, impaired fasting glycemia; MODY, maturity-onset diabetes of the young; NGT, normal glucose tolerance.

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

In human studies, maternal hyperglycemia predisposes the offspring to type 2 diabetes. This is seen in the Pima Indians, in whom prevalence of diabetes is among the highest reported in the world (6). The risk of type 2 diabetes in offspring is significantly higher when the mother rather than the father has diabetes and is further increased when diabetes is diagnosed in the mother before or during pregnancy (7,8). At 20–24 years of age, offspring of diabetic women (diagnosed before or during pregnancy) have a 45% prevalence of type 2 diabetes compared with 8.6% for prediabetic women (normal glucose tolerance [NGT] during and immediately after pregnancy but becoming diabetic on follow-up) and 1.4% for nondiabetic women (NGT during and after pregnancy). These differences persist after taking into account paternal diabetes, age at onset of diabetes in parents, and offspring weight relative to height (7). Studies in Pima Indian children have shown that the strongest single risk factor for type 2 diabetes was exposure to diabetes in utero (odds ratio 10.4, 95% CI 4.31–25.12) (9). The evidence for a predisposing effect of maternal hyperglycemia to type 2 diabetes is less strong in non-Pima Indian populations. There is an increased risk of diabetes and a younger age at onset of diabetes in offspring of mothers in whom diabetes was diagnosed at <50 years of age (10). Studies of the offspring of patients with gestational diabetes and pregestational diabetes have shown them to be more obese and insulin resistant throughout childhood (11).

Maturity-onset diabetes of the young (MODY) is a subtype of diabetes characterized by young age (typically <25 years) at onset of non-ketosis-prone diabetes, autosomal-dominant inheritance, and β -cell dysfunction. Mutations in six genes have been shown to cause MODY: the glycolytic enzyme glucokinase and the transcription factors and hepatic nuclear factor 1 α (HNF-1 α), HNF-4 α , HNF-1 β , insulin promoter factor-1 (IPF-1), and Neuro-D1(12,13). Mutations in

the transcription factor HNF-1 α are the most common cause of MODY in European Caucasians (14,15). Patients with HNF-1 α mutations have normal glucose tolerance in early childhood. However, progressive β -cell failure leads to increasing hyperglycemia due to reduced insulin secretion in response to hyperglycemia (16). Patients typically present in their teens or early adult life with symptomatic diabetes and have increasing glycemia and treatment requirements throughout life (17,18).

The mean age at diagnosis in patients with HNF-1 α mutations is 20.4 years in the U.K., but age at onset shows considerable variation both between and within families (range 4–74 years) (14). Diabetes has developed in 63% of patients by age 25 years, but a number of cases are not diagnosed until middle age (19). The reason for the considerable variation in age at diagnosis has yet to be closely studied.

It is unlikely that a significant part of the variation is explained by differences in the mutations in HNF-1 α , because no relationship has been found between age at diagnosis and position or type of HNF-1 α mutation or with in vitro functional characteristics (14,20). The strongest evidence that factors other than the characteristics of the HNF-1 α mutation are important is the considerable variation in age at diagnosis of diabetes (4–74 years) seen in the 17 U.K. families with the common mutation P291fsinsC (14). Conventional type 2 risk factors influence age at onset; unaffected HNF-1 α mutation carriers were thinner and younger than diabetic mutation carriers in a large Scandinavian series (21), and parental history of type 2 diabetes in the non-MODY parent decreases age at diagnosis (22).

MODY due to HNF-1 α mutation is a good diabetes model in which to study the effect of diabetic pregnancy, because there is considerably more homogeneity of phenotype than seen in type 2 diabetes or gestational diabetes. Young age at diagnosis means that it will be possible to identify offspring who have been exposed to maternal diabetes during pregnancy. Changes in age at diagnosis are easier to detect than in type 2 diabetes, in which diabetes develops in middle or old age. We studied the effect of diabetes during pregnancy in the mother on age at diagnosis in patients with HNF-1 α mutations.

RESEARCH DESIGN AND METHODS

Subjects

We studied 352 subjects from 59 families with HNF-1 α mutations from the Exeter Diabetes U.K. MODY collection. These families were referred to Exeter with a family history of type 2 diabetes inherited in an autosomal-dominant pattern. Data were available on 211 mutation carriers and 141 nonmutation carrier family members.

Methods

HNF-1 α mutations were identified by direct sequencing (15). Details about anthropometry, affection status, treatment, history of parental diabetes, and age at onset of diabetes in the patient and their parents (as ascertained from the patient) were taken from the patient directly or from records collected from patients, their physicians, and their medical records.

Fasting plasma glucose (FPG) and HbA_{1c} were measured by routine laboratory methods. Patients were classified as having NGT, impaired fasting glycemia (IFG), or diabetes according to World Health Organization (WHO) and American Diabetes Association (ADA) criteria (23,24).

Calculations

Offspring were compared depending on whether they had inherited a HNF-1 α mutation from the mother or father. Offspring of mothers with the mutation were divided into two groups according to the timing of diagnosis of diabetes in the mother; diabetic mothers were those in whom diabetes was diagnosed before or during pregnancy, whereas prediabetic mothers were those in whom diabetes was not diagnosed until after pregnancy. Mothers that were not mutation carriers were not known to have gestational diabetes or to subsequently develop type 2 diabetes. Offspring of fathers with the mutation were divided into two equal groups according to whether diabetes was diagnosed in the father before or after the median age of 33 years.

Statistical analysis

Data are presented as means \pm standard deviation (SD). Means were compared using the unpaired Student's *t* test. Matched pairs were compared using the matched Student's *t* test. Group frequencies were

compared using the χ^2 test. Correlations were compared using Pearson's correlation. All tests were two-tailed and significance was defined as $P < 0.05$.

RESULTS

Clinical characteristics of diabetic and nondiabetic mutation carriers: effect of age, BMI, and sex

Information was available on 352 family members from 59 families with a mutation in the HNF-1 α gene (37 different mutations). A total of 211 family members had a mutation in the HNF-1 α gene and 141 did not. Of the mutation carriers, 186 had diabetes, 4 had IFG (FPG 6.1–7.0 mmol/l), and 21 were unaffected (FPG < 6.0 mmol/l and HbA_{1c} $< 6\%$ [Diabetes Control and Complications Trial-corrected]) at the time of data collection. The four subjects with IFG were excluded from further analysis. The 141 family members without a mutation in the HNF-1 α gene did not have IFG or diabetes. The clinical characteristics of the subjects are shown in Table 1. HbA_{1c} was similar in nonmutation carriers and unaffected mutation carriers ($P = 0.29$).

Unaffected mutation carriers were significantly younger (mean \pm SD 20.7 \pm 6.4 vs. 44.0 \pm 17.3 years, $P < 0.0001$) and had a lower BMI (21.3 \pm 3.2 vs. 24.3 \pm 3.6 kg/m², $P = 0.002$) than affected mutation carriers. BMI was directly related to age in the HNF-1 α mutation carriers ($r = 0.371$, $P < 0.01$); therefore, the difference in BMI was not independent of the age difference. As such, we individually matched all nondiabetic mutation carriers with age- (limits within 3 years) and sex-matched diabetic subjects and analyzed as matched pairs. There was then no significant difference in BMI between unaffected and affected mutation carriers (21.3 \pm 3.2 vs. 22.5 \pm 3.6 kg/m², $P = 0.37$).

Female diabetic mutation carriers were more prevalent than male diabetic mutation carriers (66% female versus 34% male), which was significantly different from the predicted 50% ($P = 0.022$). In the nondiabetic mutation carriers, 52% of subjects were female and 48% were male.

Affection status of parents of diabetic and nondiabetic mutation carriers

Details about affection status of parents were available in 131 affected mutation

Table 1—Clinical characteristics of patients from families with a hepatocyte nuclear factor-1 α gene mutation

	N (% male)	Age at sampling (years)	BMI (kg/m ²)	HbA _{1c} (%)	Mother diabetic (%)	Father diabetic (%)
Affected NM	186 (63)	44.0 \pm 17.3	24.3 \pm 3.6	6.70 \pm 1.54	60.3	39.7
Unaffected NM	21 (10)	20.7 \pm 6.4	21.3 \pm 3.2	4.56 \pm 0.83	47.4	52.6
NN	141 (69)	43.6 \pm 19.6	25.4 \pm 4.1	4.32 \pm 0.85	66.2	33.8
Affected versus unaffected NM		$P < 0.0001$	$P = 0.002$	$P < 0.0001$	NS	NS

Data are means \pm SD. Affected NM, affected mutation carriers; unaffected NM, unaffected mutation carriers; NN, patients without a mutation; NS, not significant.

carriers and 19 unaffected mutation carriers (in other family members, it was not possible to test the parents because they were dead or unavailable). A higher proportion of affected mutation carriers had inherited the mutation from their mother (mother versus father, 60.3 vs. 39.7%), whereas unaffected mutation carriers were more likely to have inherited the mutation from their father (47.4 vs. 52.6%), but these differences did not reach significance ($P = 0.28$).

Age at diagnosis: the effect of parent of origin and exposure to maternal diabetes

When all cases were examined together, age at onset in offspring was not significantly different if the mutation was inherited from the mother compared with the father (20.8 \pm 11.1 vs. 23.2 \pm 10.8 years, $P = 0.2$). When offspring were divided into two groups according to maternal diabetic status in pregnancy, offspring born to diabetic mothers were diagnosed with diabetes significantly earlier than offspring born to prediabetic mothers (15.5 \pm 5.4 vs. 27.5 \pm 13.1 years, $P < 0.0001$) (Fig. 1).

To assess whether the difference between a mother being diabetic before or after pregnancy reflected a generally earlier diagnosis of diabetes within the family (as might be seen with a more penetrant mutation) rather than a specific effect of exposure to hyperglycemia in utero, we also looked at age at diagnosis in the offspring of families with an affected father. The offspring were divided into two equal groups on the basis of the age of the father at diagnosis (≤ 33 and > 33 years). There was no significant difference in age at diagnosis of offspring in these groups (22.1 \pm 8.5 vs. 23.2 \pm 9.7 years, $P = 0.77$) (Fig. 1).

To remove the effect of different mutations, a further analysis was performed, which was confined to the 20 families with the common C-insertion mutation,

P291fsinsC. The offspring of diabetic mothers showed a trend to being diagnosed earlier than prediabetic mothers (15.9 \pm 5.7 vs. 21.3 \pm 9.9 years). However, this was not statistically significant ($P = 0.13$) due to small numbers ($n = 14$ versus $n = 6$). The offspring of fathers showed no significant difference in age at diagnosis if diabetes was diagnosed in the fathers before or after 33 years of age (24.8 \pm 11.3 vs. 21.0 \pm 13.4 years, $P = 0.66$) (Fig. 2). If offspring of mothers with diabetes during pregnancy were compared with offspring who were not exposed to hyperglycemia in utero (offspring of prediabetic women and all fathers), the former group were diagnosed at an earlier age (15.9 \pm 5.7 vs. 22.4 \pm 10.7 years, $P = 0.05$).

We compared the phenotype in those born to diabetic and prediabetic mothers with HNF-1 α mutations. Treatment requirements were not different for the offspring of diabetic women compared with offspring of prediabetic women (diet/oral hypoglycemic agents/insulin 9/9/11 vs. 4/12/7, $P = 0.27$). Similarly, HbA_{1c} was

not significantly different between the two groups (6.5 \pm 1.6 vs. 7.1 \pm 1.5, $P = 0.2$) (Table 2). BMI was significantly higher in the offspring of diabetic mothers compared with prediabetic women (26.0 \pm 4.1 vs. 23.5 \pm 3.4 kg/m², $P = 0.025$). Offspring of fathers in whom diabetes was diagnosed before 33 years of age also tended to have a higher BMI than offspring of fathers in whom diabetes was diagnosed after 33 years of age, but this did not reach statistical significance (26.0 \pm 3.3 vs. 23.4 \pm 3.4 kg/m², $P = 0.09$) (Table 2).

CONCLUSIONS— We have shown that in MODY associated with mutations in the HNF-1 α gene, a greatly reduced age at diagnosis is associated with exposure to diabetes in utero. This suggests that nongenetic effects are important determinants of age at diagnosis, even in HNF-1 α MODY, a genetic disorder.

Our study has some limitations, because subjects were not studied prospectively. Age at diagnosis, therefore, may not reflect age at onset either in the moth-

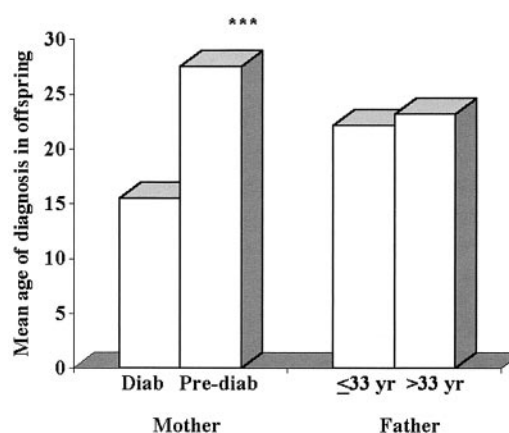


Figure 1—Mean age at diagnosis of diabetes in offspring according to diagnosis of diabetes in affected parent. Mother: diab = diabetic during pregnancy, pre-diab = diabetes diagnosed after pregnancy. Father: ≤ 33 years = diabetes diagnosed in father at or before 33 years of age, > 33 years = diabetes diagnosed in father after 33 years of age. *** $P < 0.0001$ for age at diagnosis of offspring diabetic versus prediabetic mother.

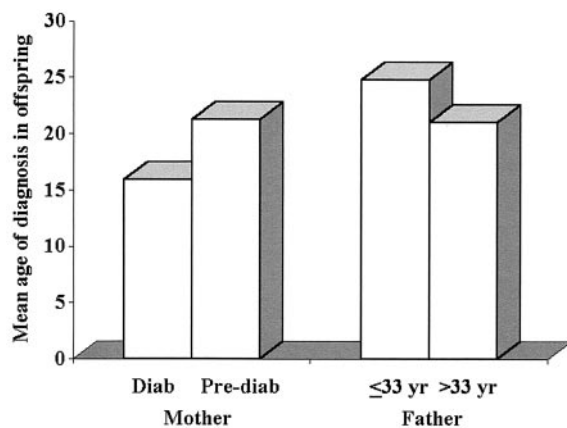


Figure 2—Mean age at diagnosis of diabetes in offspring according to age at diagnosis of diabetes in affected parent in families with common mutation, P291fsinsC. Mother: diab = diabetic during pregnancy; prediab = diabetes diagnosed after pregnancy. Father: ≤ 33 yr = diabetes diagnosed in father at or before 33 years of age, > 33 yr = diabetes diagnosed in father after 33 years of age.

ers or the offspring. A younger age at diagnosis in offspring could be due to increased testing by mothers in whom diabetes was diagnosed at a young age. However, individuals diagnosed at an older age do not have increased treatment requirements or more severe diabetes. This suggests that there is a genuine reduction in age at onset of diabetes within these families. Prospective study is required to address these issues.

We have shown a reduction in age at diagnosis by 12 years in offspring who were exposed to maternal diabetes in utero when compared with offspring whose mothers developed diabetes after pregnancy. A more severe mutation resulting in earlier diagnosis in both mothers and offspring is unlikely, because fathers in whom diabetes was diagnosed at a young age did not have children who were diagnosed earlier and a similar trend was seen when the analysis was confined to the subset of patients with the common C-insertion mutation (P291fsinsC).

This confirms previous in-depth

studies in Pima Indians suggesting that intrauterine exposure to hyperglycemia alters age at diagnosis of diabetes. Offspring of diabetic mothers are at higher risk for diabetes than offspring of diabetic fathers (8). Offspring of diabetic mothers have a much higher prevalence of type 2 diabetes compared with offspring of prediabetic or nondiabetic women (7) due to the hyperglycemic environment in utero. Studies on the children of parents with type 1 diabetes have not shown clear evidence of increased prevalence of type 2 diabetes. This may be because the effects of the hyperglycemic environment are most marked in those who are genetically predisposed (e.g., Pima Indians or HNF-1 α mutation carriers).

Recent work with the Pima Indians has shown that the acute insulin secretory response was lower in individuals whose mothers were diabetic during pregnancy than in those whose mothers developed diabetes at a young age but after the birth of the subject (25). This β -cell dysfunction is also found in offspring of rats

rendered hyperglycemic (4). This has led to the hypothesis that intrauterine exposure to hyperglycemia affects subsequent insulin secretory function by “re-setting” the pancreas at a critical stage of development. However, there are few human studies on the effect of hyperglycemia in utero on insulin secretion and action in offspring (26,27). Possible mechanisms for β -cell function may be suggested by our study. Recently, it has been shown that early development of the pancreas is altered by reduction of HNF-1 α in the pancreas (28). It is possible that maternal hyperglycemia alters pancreatic transcription factor levels and this effect combines with the reduced levels as a result of the genetic mutation to produce a more severe β -cell defect. It is possible that the younger age at diagnosis seen in successive generations (“anticipation”) could be explained, in part, by exposure to maternal diabetes in utero, decreasing age at onset of diabetes in any affected daughters who are then more likely to have diabetes when they are pregnant themselves.

Other environmental factors may have a limited role in alteration of age at onset in MODY. Work with the Pima Indians has found that children of diabetic mothers had an increased incidence of obesity compared with offspring of prediabetic mothers (29). We also found that offspring of diabetic mothers had a higher BMI than offspring of prediabetic mothers, which may contribute to the early diagnosis of diabetes. However, when differences in age were taken into account, nonpenetrance of mutations was not clearly associated with BMI.

In conclusion, we have shown a clear association between exposure to maternal diabetes in utero and an early diagnosis of diabetes in MODY caused by mutations in the HNF-1 α gene. This shows that the homogeneity seen in monogenic diabetes

Table 2—Clinical characteristics of affected mutation carriers according to timing of diagnosis of diabetes in parents

Parent affected	n	BMI (kg/m ²)	HbA _{1c} (%)	Treatment: Diet/OHA/Insulin
Mother (all)	79	24.1 \pm 3.9	6.75 \pm 1.51	21/24/24
Diabetic mother	33	26.0 \pm 4.1	6.54 \pm 1.62	9/9/11
Prediabetic mother	24	23.5 \pm 3.4	7.11 \pm 1.48	4/12/7
Father (all)	52	24.6 \pm 3.1	6.36 \pm 1.38	12/28/11
Father diagnosed at ≤ 33 years	13	26.0 \pm 3.3	5.96 \pm 1.35	3/6/4
Father diagnosed at > 33 years	13	23.4 \pm 3.4	6.84 \pm 1.71	5/8/0

Data are n or means \pm SD. Diabetic mothers were those diagnosed with diabetes before or during pregnancy. Prediabetic mothers had normal glucose tolerance during pregnancy but subsequently developed diabetes. OHA, oral hypoglycemic agent.

make it a good potential model for studying the environmental effects as well as demonstrating genetic effects such as low birth weight (30). We propose that prospective study is now required to confirm that there is an earlier age at onset in offspring of diabetic mothers as well as earlier age at diagnosis and to define associated pathophysiology.

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