Intrauterine Hyperglycemia Modifying the Development of (Monogenic) Diabetes?

Tiinamaija Tuomi, MD, PhD
Leif Groop, MD, PhD

During the last decade, mutations in the glucokinase and hepatic nuclear factor (HNF) genes were found to cause maturity-onset diabetes of the young (MODY), which is characterized by a dominant autosomal mode of inheritance, high penetrance, lack of cardiovascular morbidity, and defective insulin response to glucose stimulus combined with normal, or even supranormal, insulin sensitivity (1,2). Most forms of MODY are caused by mutations in transcription factors such as HNF-1α (MODY3), HNF-4α (MODY1), insulin promoter factor (IPF)-1 (MODY4), HNF-1β (MODY5), or glucokinase (MODY2) (1). Although the precise mechanisms by which mutations in these transcription factors cause diabetes are not known, they are thought to involve transcription of a number of β-cell genes (3). Despite the fact that the defects are already present at birth, diabetes is rarely manifested at birth. Instead, the monogenic forms of diabetes are in fact heterogeneous with respect to age at diabetes diagnosis and severity of the insulin secretory defect (1). It has been hypothesized that high insulin sensitivity could maintain normoglycemia, despite minimal insulin secretory capacity, and that any deterioration in insulin sensitivity could result in hyperglycemia. This is supported by frequent normoglycemic responses to an OGTT, even in their fifth decade (7).

The age at diagnosis of diabetes in the HNF-1α mutation carriers varies between 4 and 74 years (4). The youngest cases have often been diagnosed through glucosuria, which is a common feature in this condition, and the majority of patients are diagnosed at or after the onset of puberty. Most studies are cross-sectional, and the age at diagnosis is uncertain. In fact, in our early series, diabetes was diagnosed in one-third of mutation carriers at screening by the oral glucose tolerance test (OGTT) (5). Apart from MODY2, where an elevated fasting plasma glucose is part of the diagnosis, diagnosis of the other forms of MODY rely more on an elevated 2-h glucose value than on fasting glucose, which can remain normal even in the face of elevated postprandial glucose levels (6). However, although the true time of conversion is rarely known, it is undisputed that some mutation carriers have normoglycemic responses to an OGTT, even in their fifth decade (7).

Two independent studies published in the December issue of Diabetes Care show that the age at onset is affected by the mother’s diabetes during pregnancy (8,9). Among the patients of Stride et al. (8), offspring of diabetic mothers were diagnosed on average 12 years earlier than those whose mothers were nondiabetic during the pregnancy (15.5 ± 5.4 vs. 27.5 ± 13.1 years of age, P < 0.0001). Accordingly, Klupa et al. (9) found that 57% of the offspring of diabetic mothers were diagnosed with diabetes by 15 years of age, as compared with none of the carriers whose mother was diagnosed later in life. This was presumably not the consequence of earlier diagnosis of mild diabetes due to increased awareness in the families, because most children inheriting the disease from the mother had a severe insulin-requiring type of diabetes. In contrast, the age at which fathers were diagnosed had no effect on the age at diagnosis of the child (8,9).

Taken together, both studies provide compelling evidence that hyperglycemia during fetal life could accelerate diabetes onset. What could be the mechanisms? There is some evidence to suggest that intrauterine hyperglycemia could interfere with insulin secretion later in life. Offspring of diabetic Pima Indian mothers show a reduced acute insulin response (10), and offspring of diabetic rats rendered hyperglycemic during pregnancy (11) also display impaired β-cell function. Apparently, the fetal islets are very sensitive to the toxic effects of glucose. It is obvious that this is not an unspecific mechanism, since offspring of mothers with type 1 diabetes have a lower risk than offspring of fathers with type 1 diabetes. Information about these mechanisms may shed new light not only on the mechanisms by which mutations in these transcription factors provoke diabetes but also on the interplay between the islets and the intrauterine environment.

There are still some questions to answer. Why did some mothers with MODY mutations develop diabetes before or during pregnancy, whereas others escaped the diabetogenic effects of pregnancy? This is an important aspect, as age at diagnosis of diabetes in the mother also was reflected by age at diagnosis in the offspring. Could some of the mothers have inherited other modifying risk genes or have been exposed to other diabetogenic risk factors? Some answers are provided in the article by Klupa et al. (9) showing that age at onset had a strong heritability (h² = 0.47 ± 0.17), which increased (to 0.91 ± 0.20)
when parent of origin was included as a covariate. Anticipation, i.e., earlier age at diagnosis in each generation, has previously been noted in MODY (5). The studies of Stride et al. and Klupa et al. would restrict this to maternal transmissions.

Age at onset of type 2 diabetes has been dramatically decreasing during the last decades, suggesting that many pregnant mothers will already have diabetes or develop it during pregnancy. Will hyperglycemia during pregnancy have the same effect on risk of type 2 diabetes in the offspring as on the risk of MODY in offspring of MODY mothers? These two articles have emphasized the importance of the intrauterine milieu for subsequent risk of MODY diabetes. Whether hyperglycemia during pregnancy provides an extreme of the “thrifty” phenotype remains to be shown. Data on birth weight, as well as some measure of β-cell function in the offspring, would be needed. There is an obvious need for prospective studies of nondiabetic carriers of MODY mutations, which in turn increases the demand for screening at-risk individuals. Improved high-throughput tools for diagnosis of MODY mutations are required to obtain the badly needed epidemiological data on MODY.

### References