Gestational Diabetes Mellitus: Primum Non Nocere

Maturity-onset diabetes of the young (MODY) encompasses a collection of distinct forms of diabetes, which are inherited in an autosomal-dominant mode from the maternal or paternal side of the family or occasionally occur as a de novo mutation. All the genes involved affect either β-cell sensing or insulin secretion (1). The clinical presentations of MODY are heterogeneous, reflecting the different gene mutations involved, and the glucose dysregulation observed ranges from a relatively innocent rise in the fasting glucose to frank diabetes with neurological involvement (2,3).

An exact MODY prevalence within the general diabetes population has proven difficult to assess because of underrecognition and lack of routinely available and affordable diagnostic tools. A further confounder is that the reported regional prevalence of specific MODY mutations varies considerably (4). Conservative estimates suggest that between 0.14–1.8% of all cases of diabetes could be attributable to MODY (4). It is to be expected that among women screened for gestational diabetes mellitus (GDM) the prevalence of MODY will be higher, reflecting both the proportionately lower prevalence of type 2 diabetes in women of this age group and the probability that those with undiagnosed MODY will screen positive (5). From the few population studies reported, mutations in the hepatocyte nuclear factor 1 α (*HNF1a*) gene (MODY 3) and glucokinase (*GCK*) gene (MODY 2) account for the majority of cases (6).

MODY 2 is characterized by its high penetrance, early onset, and lifelong fasting hyperglycemia. It is due to mutations in the pancreatic *GCK* gene, which acts as the β-cell glucose sensor, setting the glucose threshold at which amplification of insulin secretion occurs (7). In MODY 2, this is set at 18–45 mg/dL (1.0–2.5 mmol/L), higher than for unaffected adults (7). Glucose tolerance can remain stable over many years, provided that insulin sensitivity also remains stable (8). Although MODY 2 is associated with lifelong fasting hyperglycemia that may progressively increase with age, long-term diabetes complications are uncommon (9,10).

MODY 2 does, however, have clinical implications in pregnancy when there is discordance between the maternal and fetal genotype; statistically this occurs in 50% of all pregnancies in which the mother or father carries the MODY mutation. When the mother is affected but not the fetus, maternal hyperglycemia causes fetal hyperinsulinemia and increased birth weight (11). By contrast, when the fetus carries the paternal MODY 2 gene, the levels of maternal glycemia are insufficient to stimulate adequate fetal insulin to sustain optimal growth, and birth weight is approximately 500 g lower than for an unaffected sibling (11). When both the mother and fetus share the MODY 2 mutation, birth weight is normal, providing the mother's hyperglycemia is not treated, as the glucose threshold to trigger insulin secretion is similar in the mother and fetus, and fetal insulin levels remain normal. If, however, a mother with MODY 2 has her hyperglycemia treated in pregnancy and the fetus also carries the *GCK* mutation, birth weight can be severely compromised (12). On the basis of these observations, it has been recommended to treat hyperglycemia in the mothers with MODY 2 only when there is ultrasound evidence of accelerated fetal growth (5).

Maternal hyperglycemia at levels observed in women with MODY 2 has in observational and randomized trials been associated with adverse pregnancy outcomes (13,14). These studies have provided the evidence for the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) guidelines on the diagnosis of GDM (15). In the IADPSG guidelines, a fasting glucose value of ≥92 mg/dL (5.1 mmol/L) is considered diagnostic for GDM. As this fasting value is set lower than other commonly used diagnostic criteria, if adopted, more women with GDM would be diagnosed (16). In addition, the lower fasting value by IADPSG criteria would label all pregnant women with previously undiagnosed MODY 2 as having GDM.

If, in keeping with the IADPSG diagnostic criteria, a fasting glucose level below 92 mg/dL (5.1 mmol/L) was also adopted as a management target in GDM, this would be difficult to achieve in women with MODY 2 treated with diet alone, and would inevitably necessitate insulin therapy. More importantly these more stringent fasting glucose targets would be detrimental to fetal growth in half of all pregnancies (12).

The article by Chakera et al. (17) in this issue of *Diabetes Care* provides proof of concept that prior knowledge of the fetal genotype can help predict fetal susceptibility to maternal hyperglycemia and can therefore favorably influence treatment in women with MODY 2. The article describes two pregnancies in women with MODY 2 in whom glycemic management was tailored on the basis of fetal genotyping, performed following chorionic villus sampling undertaken for other indications. In both pregnancies, the fetuses had inherited the maternal *GCK* mutation and were therefore protected from the levels of maternal hyperglycemia they were exposed to. Both women would have warranted active glycemic management by current guidelines (18). Despite significant maternal hyperglycemia and no treatment, both infants were born at term with normal birth weights.

There are increasing numbers of maternal genes being identified that influence fasting blood glucose and fetal growth (19). Our knowledge in this field will expand with further subanalyses of maternal and fetal genes from the large Hyperglycemia and Adverse Pregnancy Outcome (HAPO) cohort for which detailed biochemical, anthropometric, and genetic data have been collected (19). In the absence of this knowledge and the ability to detect fetal genotype noninvasively during pregnancy, it must be acknowledged that universally applied treatment guidelines will not be appropriate for a minority of women with GDM. However as 15–20% of today's antenatal population has GDM using the IADPSG criteria, this minority will

still represent a sizable number of pregnancies (16).

Identifying and managing pregnancies appropriately when either the mother or the father carries the MODY2 gene requires a higher level of clinical suspicion among family physicians, diabetologists, and obstetricians and greater access to the necessary diagnostic tools. Until there are advances in the noninvasive genotyping of fetal DNA, for example using cell free fetal DNA, genotyping the fetus will require opportunistic use of CVS if undertaken for alternative indications.

The optimal treatment during pregnancy of women with other monogenic forms of diabetes has not been well evaluated. Permanent neonatal diabetes is believed to affect approximately 1 in 200,000 births; however, the condition is often misdiagnosed as type 1 diabetes. A variety of genes have been implicated including activating mutations in the gene encoding the Kir6.2 subunit of the β-cell ATP-sensitive K channel (*KCNJ11*) (20). Good glycemic control with a lower risk of hypoglycemia can be achieved in patients with the Kir6.2 mutations using treatment with sulfonylureas rather than insulin (21). However, the safety of sulfonylurea use in pregnancy has not been clearly established, and though some evidence exists on the use of glyburide, the safety of other agents such as gliclazide is unknown (22).

Gathering together sufficient numbers of women with permanent neonatal diabetes in pregnancy to establish the optimal therapy will depend on observational data from those few specialized centers that look after these women. Because of the general paucity of data, the two case reports by Gaal et al. (23) of women with *KCNJ11* mutations treated exclusively during pregnancy with the sulfonylurea glicazide, is a small but helpful contribution, which when added to other anecdotal reports (24) will begin to establish a knowledge base from which guidelines can be formed. However, until safety data on the use of gliclazide in pregnancy is established, its use cannot be routinely advocated in these circumstances.

The reports from Chakera et al. and Gaal et al. both highlight that treating all women with hyperglycemia in pregnancy using generic evidenced-based algorithmic guidelines may not necessarily be in the best interests of all mothers and their babies.

Shivani Misra, mrcp[1]
Anne Dornhorst, frcp[2]

From the [1]Department of Metabolic Medicine, Imperial Healthcare NHS Trust, London, U.K.; and the [2]Department of Medicine, Imperial College Healthcare NHS Trust, London, U.K.

Corresponding author: Shivani Misra, s.misra@imperial.ac.uk.

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