Antenatal Diagnosis of Fetal Genotype Determines if Maternal Hyperglycemia Due to a Glucokinase Mutation Requires Treatment

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OBJECTIVE—In women with hyperglycemia due to heterozygous glucokinase (*GCK*) mutations, the fetal genotype determines its growth. If the fetus inherits the mutation, birth weight is normal when maternal hyperglycemia is not treated, whereas intensive treatment may adversely reduce fetal growth. However, fetal genotype is not usually known antenatally, making treatment decisions difficult.

HISTORY AND EXAMINATION—We report two women with gestational diabetes mellitus resulting from *GCK* mutations with hyperglycemia sufficient to merit treatment.

INVESTIGATION—In both women, DNA from chorionic villus sampling, performed after high-risk aneuploidy screening, showed the fetus had inherited the *GCK* mutation. Therefore, maternal hyperglycemia was not treated. Both offspring had a normal birth weight and no peripartum complications.

CONCLUSIONS—In pregnancies where the mother has hyperglycemia due to a *GCK* mutation, knowing the fetal *GCK* genotype guides the management of maternal hyperglycemia. Fetal genotyping should be performed when fetal DNA is available from invasive prenatal diagnostic testing.

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Heterozygous mutations in the glucokinase (*GCK*) gene result in mild, lifelong fasting hyperglycemia (1), typically 5.5–8.0 mmol/L. The latest International Association of Diabetes and Pregnancy Study Groups' recommendations reinforce the advice to treat hyperglycemia in pregnancy and defines gestational diabetes mellitus (GDM) as a fasting glucose ≥5.1 mmol/L (2). Therefore, patients with *GCK* mutations meet the criteria for GDM and account for 1–3% of the GDM population (3). For offspring of mothers with a *GCK* mutation and untreated hyperglycemia, birth weight is normal if the fetus inherits the mutation but is increased by 550–700 g if the fetus is not affected (4,5). Diet has little impact on the raised maternal fasting glucose. Insulin treatment is indicated if the fetus is not affected. However, if the fetus is affected, growth is normal if the mother is not treated, and achieving maternal euglycemia may result in reduced fetal growth, so maternal treatment is not recommended (6). Usually fetal genotype is not known antenatally; therefore, regular assessment of fetal growth is recommended with acceleration of fetal abdominal circumference >75th percentile, a prudent surrogate basis for the decision of whether to treat maternal hyperglycemia (5,7).

We describe the first two cases of fetal diagnosis of a *GCK* mutation, which altered gestational management of maternal hyperglycemia. Both patients provided consent to publication of their case.

CASE 1

History and examination

A white, European, 33-year-old woman was diagnosed with GDM at 32 weeks' gestation in her first pregnancy (75-g oral glucose tolerance test [OGTT] = 5.8, 9.9, and 8.0 mmol/L [fasting, 1 h, and 2 h, respectively]). Insulin treatment was given from 35 weeks' gestation. She delivered a healthy girl, weighing 3,405 g (50th percentile), at 39 weeks' gestation.

A heterozygous *GCK* mutation (c.1340G>A, p.Arg447Gln) was found in the mother on sequencing performed because of a three-generation paternal history of diabetes, persistent fasting hyperglycemia, and small glucose increment in a postpartum OGTT (7.0, 7.5, and 7.9 mmol/L) (8). During her second pregnancy, her initial self-monitored blood glucose levels were ≈6 mmol/L, fasting, and 6–8 mmol/L, 1-h postmeal. Her HbA_{1c} was 46 mmol/mol at 12 weeks' gestation. The hyperglycemia was managed with diet alone during the first two trimesters.

Investigation

Chorionic villus sampling (CVS) had been undertaken at 13 weeks' gestation after high-risk first-trimester aneuploidy screening (normal result). Urgent sequencing of DNA from this sample at 18 weeks' gestation found the fetus to be heterozygous for the *GCK* mutation. Thus, insulin treatment was not initiated in the second or third trimester despite fasting and postprandial hyperglycemia on self-monitoring (Fig. 1*A*) and the fetal abdominal circumference being in the 94th percentile. The patient's

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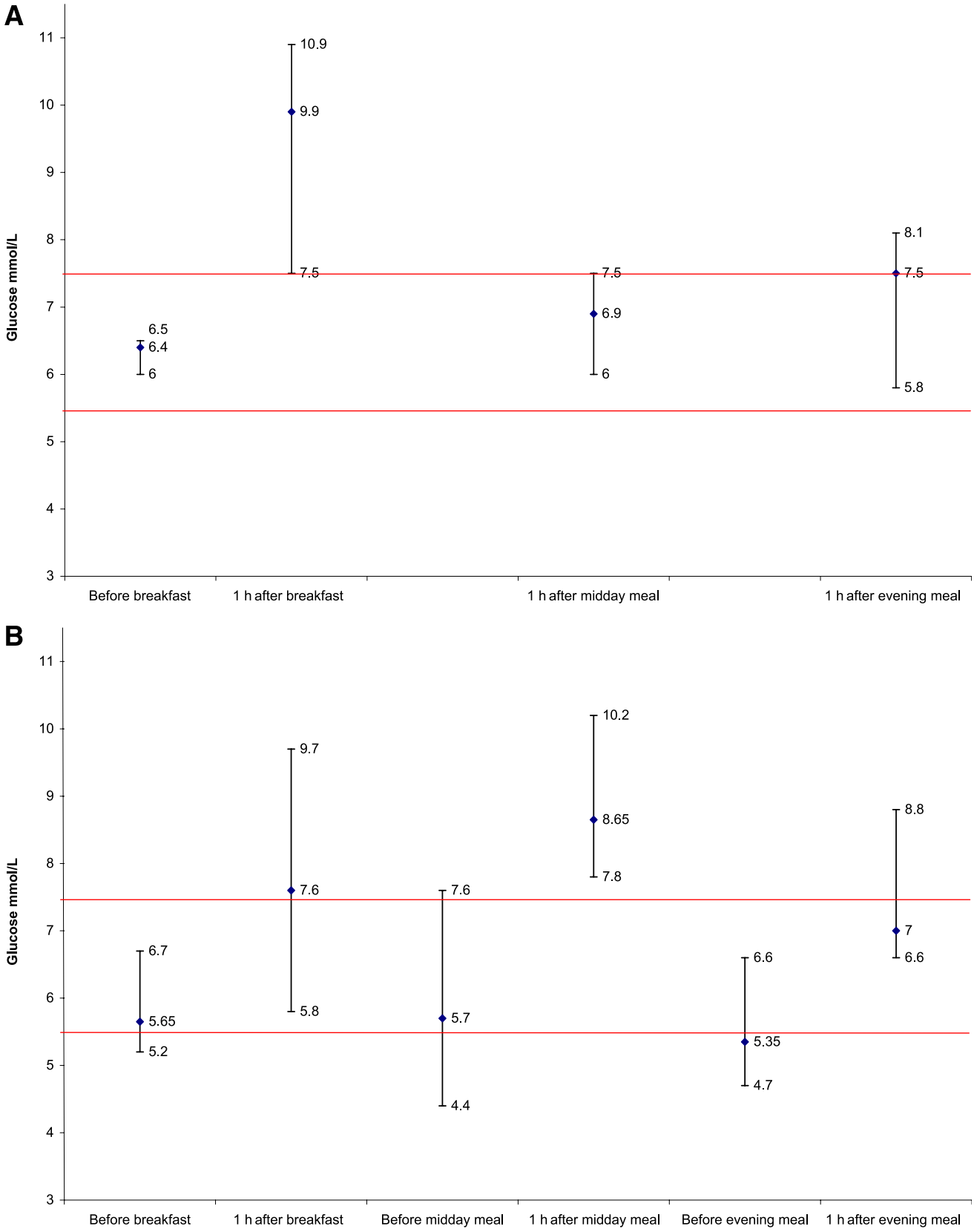

Figure 1—A: *Median and range of capillary glucose by time of day for patient 1 showing hyperglycemia above conventional treatment targets from 29 to 31 weeks' gestation. Horizontal lines indicate fasting and postprandial capillary glucose targets.* B: *Median and range of capillary glucose by time of day for patient 2 showing hyperglycemia above conventional treatment targets from 29 to 31 weeks' gestation. Horizontal lines indicate fasting and postprandial capillary glucose targets. (A high-quality color representation of this figure is available in the online issue.)*

HbA_{1c} was 41 mmol/mol at 36 weeks' gestation. She delivered a normal boy, weighing 3,415 g (51st percentile), at 39 weeks' gestation. There was no neonatal hypoglycemia or peripartum complication.

CASE 2

History and examination

In her first pregnancy, a white, European, 43-year-old woman had selective fetocide at 17 weeks' gestation for dichorionic twins discordant for trisomy 21. She delivered a healthy boy at 38 weeks, weighing 3,000 g (21st percentile). She was diagnosed with GDM in her second pregnancy. The pattern of glucose values (OGTT at 28 weeks = 5.5 and 8.3 mmol/L [fasting and 2 h]) (8), paternal, diet-treated diabetes, and BMI = 22.7 kg/m^2 suggested a diagnosis of GCK hyperglycemia, which was confirmed on sequencing (heterozygous *GCK* mutation c.370G>A, p.Asp124Asn).

Self-monitored glucose levels were 5.2–6.7 mmol/L, fasting, and 5.8–10.2 mmol/L, 1-h postmeal (Fig. 1*B*). The fetal abdominal circumference was in the 88th percentile. The patient's HbA_{1c} was 34 mmol/mol at 33 weeks' gestation. Treatment with insulin was considered in line with conventional guidelines of the management of GDM (2).

Investigation

CVS had been undertaken at 12 weeks' gestation after high-risk first-trimester aneuploidy screening (normal result). Urgent sequencing of DNA from this sample confirmed the fetus had inherited the *GCK* mutation. Therefore, insulin treatment was not commenced.

The patient delivered a normal boy, weighing 3,590 g (55th percentile), at 38 weeks' gestation. There was no neonatal hypoglycemia or peripartum complication.

CONCLUSIONS—In these two cases of GDM, due to a mutation in the *GCK* gene, antenatal genetic testing showed the fetuses had inherited the *GCK* mutation. As a result, neither mother received insulin treatment for established maternal hyperglycemia. The children had normal birth weights (51st and 55th percentiles) and did not have any metabolic complications.

Normal birth weight is the usual outcome of GDM resulting from a *GCK* mutation if the fetus inherits the mutation and maternal hyperglycemia is not treated (5). Heterozygous *GCK* mutations cause a regulated rise in fasting plasma glucose, typically 5.5–8.0 mmol/L (1). This raised glucose results in appropriate fetal insulin secretion because the affected fetus has the same homeostatic glucose set point as its mother (5). Insulin is not recommended for pregnancies in which the fetus has inherited the mutation because it can result in low birth weight (6). In contrast, when the fetus is unaffected, macrosomia is common, and treatment with insulin to achieve maternal euglycemia is appropriate.

The clinical dilemma of managing pregnant women with *GCK* mutations is due to uncertainty about the fetal genotype. Although unreliable (9), current advice is to measure fetal growth using serial ultrasound scans as a surrogate for fetal genotype, to guide diabetes and obstetric management. In pregnancies with accelerating fetal growth (abdominal circumference >75th percentile), it is assumed that the fetus has not inherited the mutation. Intensive insulin treatment should be initiated, aimed at lowering elevated blood glucose levels to normal pregnancy ranges. Large insulin doses of >1 U/kg/day (6) may be required to overcome maternal glucose homeostasis, which can be difficult to achieve without causing symptoms of hypoglycemia.

In these two cases, knowledge that the fetuses had inherited the *GCK* mutation allowed the maternal hyperglycemia in pregnancy to remain untreated. We recommend that if a pregnant woman with a *GCK* mutation has a CVS or amniocentesis for another reason, the fetal DNA should be tested for the *GCK* mutation. However, the 1% miscarriage rates associated with these procedures (10) means they are not routinely warranted for fetal genetic diagnosis in this situation. In the future, noninvasive prenatal diagnosis using cell-free fetal DNA or fetal cells in maternal blood (11) has the potential to determine fetal genotype and therefore influence the management of GCK-MODY (maturity-onset diabetes of the young) in pregnancy without the attendant risks associated with invasive prenatal testing.

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