Congenital Anomalies in Offspring of Maternal Glucokinase–Maturity-Onset Diabetes of the Young: A Case Report

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A 24-year-old white European woman with diet-treated diabetes since 15 years of age presented prior to her first pregnancy. Her prepregnancy HbA_{1c} was 5.8% (40 mmol/mol), and HbA_{1c} at 12 weeks' gestation was 6.0% (42 mmol/mol). She received insulin therapy from 13 weeks (up to 0.3 units/kg/day) and had a vaginal delivery of a boy weighing 3,205 g (84th centile) at 37 weeks. He had neonatal jaundice and bilateral vesicoureteral reflux requiring reimplantation surgery (Table 1).

Her second pregnancy was managed similarly, with insulin therapy from 4 weeks' gestation (up to 0.7 units/kg/day). The HbA_{1c} was 5.5% (37 mmol/mol) at 8 weeks. She had a vaginal delivery of a healthy girl weighing 3,235 g (33rd centile) following induction of labor at 40 weeks.

Postpartum, the mother's persistent fasting hyperglycemia, small increment on a 75-g oral glucose tolerance test (6.2, 7.7, and 6.3 mmol/L [fasting, 1 h, and 2 h, respectively]), and two-generation family history of diabetes suggested glucokinase–maturity-onset diabetes of the young (GCK-MODY), which was confirmed on genetic testing (heterozygous *glucokinase* (*GCK*) mutation c.952G>A, p.Gly318Arg).

Her third pregnancy was managed at another institution with diet alone. The HbA_{1c} was 6.5% (48 mmol/mol) at 5 weeks' gestation. Third trimester fetal ultrasounds suggested accelerating abdominal circumference (50th to 95th centile). She developed obstructed labor at 40 weeks and delivered a boy weighing 4,200 g (97th centile) via cesarean section. He has trivial pulmonary valve stenosis.

Subsequent genetic testing of all three children demonstrated that the second child had inherited the *GCK* mutation, whereas the first and third children did not have the *GCK* mutation.

GCK-MODY is an autosomal dominant condition caused by heterozygous inactivating mutations in the *GCK* gene. For individuals with GCK-MODY, the glucose threshold for insulin release is set 1.0–2.5 mmol/L higher than that of normal subjects. As a result, they have mild fasting hyperglycemia (5.5–8.0 mmol/L), and glucose perturbations are regulated to the higher set point. Diabetes-related complications are relatively uncommon, so treatment of the hyperglycemia is not usually indicated, except in pregnancy.

The management approach for GCK-MODY in relation to pregnancy is designed to improve neonatal outcomes. As in type 1 and type 2 diabetes, maternal GCK-MODY can increase the risk of macrosomia and attendant complications. However, whether maternal GCK-MODY increases the risk of congenital anomalies is unclear.

Table 1—Details of GCK-MODY pregnancies in this case report

Pregnancy	Maternal age (years)	HbA_{1c} % (mmol/mol)	Gestation HbA_{1c} (weeks)	Fetal inheritance of *GCK* mutation	Birth weight centile at delivery	Congenital anomaly
1st	25	6.0 (42)	12	No	84th	Bilateral vesicoureteral reflux
2nd	32	5.5 (37)	8	Yes	33rd	None
3rd	35	6.5 (48)	5	No	97th	Trivial pulmonary valve stenosis

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It is well documented that maternal GCK-MODY can increase fetal growth. For each pregnancy, there is a 50% chance that the fetus will inherit the *GCK* mutation. Fetal growth is predominantly determined by fetal genotype, more so than by treatment of maternal hyperglycemia (1). If the fetus inherits the *GCK* mutation, the fetus will regulate its blood glucose levels to the same elevated set point as its mother and normal fetal growth ensues (1), as demonstrated in the second child in the present case. Treatment of maternal hyperglycemia could adversely reduce fetal growth and therefore is not recommended. Conversely, if the fetus does not inherit the *GCK* mutation, maternal hyperglycemia will stimulate insulin-mediated fetal growth, which increases the risk of macrosomia, cesarean section, and neonatal hypoglycemia, as demonstrated in the first and third children in the present case, and insulin treatment is recommended (1). The fetal genotype is usually unknown during pregnancy, so serial fetal ultrasounds are recommended to monitor fetal growth and guide management. For the third child, acceleration of the fetal abdominal circumference suggested that the fetus had not inherited the *GCK* mutation and should have prompted intensive insulin therapy (>1 unit/kg/day).

For offspring of mothers with type 1 or type 2 diabetes, the rate of congenital anomalies increases linearly with increasing maternal HbA_{1c} >6.3% (45 mmol/mol), with no difference in risk by type of diabetes (2). However, at lower early pregnancy HbA_{1c} >5.6% (38 mmol/L), there is also evidence for an increased risk (3). For individuals with GCK-MODY, the HbA_{1c} is typically 5.6–7.6% (38–60 mmol/mol) (4). It is, therefore, plausible that maternal hyperglycemia secondary to GCK-MODY, while relatively mild, may be sufficient to contribute to congenital anomalies in offspring who have not inherited the *GCK* mutation.

Recently, a case of sacral agenesis in a fetus of a woman with GCK-MODY was reported (5). However, the fetal genotype was unknown. In the present case, the fetal *GCK* genotype of all three children was confirmed. Congenital anomalies occurred in the two offspring who had not inherited the *GCK* mutation. Although the co-occurrence of maternal GCK-MODY and congenital anomalies does not establish causality, it raises the possibility that GCK-MODY could contribute to pathogenesis in offspring who have not inherited the *GCK* mutation. Consideration should be given for preconception high-dose folic acid in women with GCK-MODY and establishment of an international GCK-MODY register to monitor pregnancy outcomes.

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References

1. Spyer G, Macleod KM, Shepherd M, Ellard S, Hattersley AT. Pregnancy outcome in patients with raised blood glucose due to a heterozygous glucokinase g ene mutation. Diabet Med 2009; 26:14–18

2. Bell R, Glinianaia SV, Tennant PW, Bilous RW, Rankin J. Peri-conception hyperglycaemia and nephropathy are associated with risk of congenital anomaly in women with pre-existing diabetes: a population-based cohort study. Diabetologia 2012;55:936–947

3. Suhonen L, Hiilesmaa V, Teramo K. Glycaemic control during early pregnancy and fetal malformations in women with type I diabetes mellitus. Diabetologia 2000;43:79–82

4. Steele AM, Wensley KJ, Ellard S, et al. Use of HbA1c in the identification of patients with hyperglycaemia caused by a glucokinase mutation: observational case control studies. PLoS One 2013;8:e65326

5. Taylor RAM, Mackie A, Mogra R, Pinner J, Rajendran S, Ross GP. Caudal regression syndrome in a fetus of a glucokinase-maturity-onset diabetes of the young pregnancy. Diabet Med 2019;36:252–255