

Diagnosis and management of glucokinase monogenic diabetes in pregnancy: current perspectives

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Abstract: Glucokinase–maturity-onset diabetes of the young (GCK-MODY) is an autosomal dominant disorder caused by heterozygous inactivating *GCK* gene mutations. GCK-MODY is one of the most common MODY subtypes, affecting 0.1% of the population and 0.4–1% of women with gestational diabetes mellitus. Glucokinase is predominantly expressed in pancreatic beta cells and catalyzes the phosphorylation of glucose to glucose-6-phosphate. The unique kinetics of glucokinase enable it to change the rate of glucose phosphorylation according to the glucose concentration, thereby regulating insulin secretion. Individuals with GCK-MODY have mildly elevated fasting blood glucose levels (5.5–8.0 mmol/L) and regulate glucose perturbations to a higher set-point, resulting in a relatively flat glucose profile on a 75 g oral glucose tolerance test. The hyperglycemia is usually subclinical and may only be detected on incidental glucose testing. It is important to correctly identify GCK-MODY as the clinical course and management differs substantially from other types of diabetes. Diabetes-related complications are relatively uncommon, so glucose-lowering treatment is not usually required. The exception is pregnancy, where fetal growth and therefore glucose-lowering treatment are predominantly determined by whether or not the fetus inherits the *GCK* mutation. The fetal genotype is not usually known but can be inferred from serial fetal ultrasound measurements. If there is evidence of accelerating fetal abdominal circumference on serial ultrasounds, the fetus is assumed to not have the *GCK* mutation and treatment of maternal hyperglycemia is indicated to reduce the risk of macrosomia, Caesarean section and neonatal hypoglycemia. If there is no evidence of accelerating fetal growth, the fetus is assumed to have inherited the *GCK* mutation and will have a similarly elevated glucose set-point as their mother, so maternal hyperglycemia is not treated. With recent advances in genetic technology, such as next-generation sequencing and noninvasive fetal genotyping, the detection and management of GCK-MODY in pregnancy should continue to improve.

Keywords: GCK, MODY, genetics, mutation, gestational diabetes, fetal

Introduction

Monogenic diabetes encompasses several types of diabetes that are caused by single gene mutations. Overall, monogenic diabetes accounts for <5% of all cases of diabetes. One subtype of monogenic diabetes that has particular relevance in pregnancy is glucokinase–maturity-onset of the young (GCK-MODY). The population prevalence of GCK-MODY is 1.1 in 1000 (0.1%).¹ GCK-MODY is the most common MODY subtype in Japan² and the second most common MODY subtype in Chinese³ and Anglo-Celtic⁴ populations. However, due to its subtle clinical presentation and limited availability of diagnostic molecular genetic testing, GCK-MODY is often undiagnosed.⁵ It is important to diagnose GCK-MODY,

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particularly in relation to pregnancy, because the clinical course and management differs substantially from other types of diabetes, including gestational diabetes mellitus (GDM).

This review focusses on the genetics and physiology, clinical features, and diagnosis and management of GCK-MODY, with particular reference to pregnancy.

Genetics of GCK-MODY

GCK-MODY is caused by heterozygous inactivating mutations in the *glucokinase* (*GCK*) gene, which is located on chromosome 7p. The *GCK* gene consists of 12 exons that span 45,168bp and encode for a 465 amino acid protein.⁶ There are three *GCK* isoforms, based on different-sized exon 1. Exon 1a is expressed in the pancreatic beta cell. Exons 1b and 1c are expressed in the liver. *GCK* mutations have been identified in the promoter⁷ and exons 1a, 2–10 of the pancreatic beta cell *GCK* isoform.⁶ The majority of *GCK* mutations are missense or nonsense mutations, followed by small deletions and splice site mutations. Partial or whole gene deletions, which may not be detected by sequencing, account for 3.5% of GCK-MODY cases in the UK.⁸ There are no common mutations.

Despite substantial variation in the type and severity of the *GCK* mutation, the clinical phenotype of GCK-MODY is relatively constant.⁹ The stable phenotype may be explained by overexpression of the normal allele, potentially via post-translational mechanisms,¹⁰ which may partly compensate for the mutant allele.¹¹

GCK-MODY has an autosomal dominant mode of inheritance. Therefore, for women with GCK-MODY, there is theoretically a 50% chance with each pregnancy that the child will inherit the *GCK* mutation. In addition to inherited *GCK* mutations, *de novo* *GCK* mutations have been reported.¹²

Physiology of GCK-MODY

Glucokinase is a hexokinase isoenzyme that catalyzes the phosphorylation of glucose to glucose-6-phosphate, which is the first rate-limiting step in glucose metabolism.¹³ Glucokinase is predominantly expressed in pancreatic beta cells, where it regulates insulin secretion by altering the rate of glucose phosphorylation according to the glucose concentration. Glucokinase is, therefore, the glucose sensor for the pancreas. Glucokinase has unique kinetics that distinguish it from other hexokinases and enable it to function as an effective glucose sensor, including its lower

affinity for glucose ($K_m \sim 10$ mmol/L), moderate cooperative binding with glucose and lack of inhibitory feedback by glucose-6-phosphate.¹⁴

Functional studies have demonstrated that heterozygous inactivating mutations in the *GCK* gene decrease the ability of the glucokinase enzyme to phosphorylate glucose to glucose-6-phosphate, which causes hyperglycaemia.⁶ Individuals with GCK-MODY have mild fasting hyperglycemia, typically in the range of 5.5–8.0 mmol/L.¹³ Studies investigating insulin secretion rates following intravenous glucose infusions have demonstrated that the first-phase insulin response is preserved in individuals with GCK-MODY.¹⁵ However, there is a right shift in the glucose to insulin secretion rate dose-response curve, such that, for any given glucose, individuals with GCK-MODY have a reduced insulin secretion rate.¹³ In normal subjects, the pancreatic beta cell is most sensitive to an increase in glucose at concentrations of 5.5–6.0 mmol/L. In individuals with GCK-MODY, the peak beta cell sensitivity occurs at higher glucose concentrations of 6.5–7.5 mmol/L.¹³ Therefore, the glucose threshold for insulin release is 1.0–2.5 mmol/L higher in individuals with GCK-MODY compared with normal subjects.

When individuals with GCK-MODY undergo a 75 g oral glucose tolerance test (OGTT), the shape of the glucose response curve is similar to that of normal subjects, but shifted upwards. The pattern is one of mild fasting hyperglycemia, followed by an early glucose rise with early (30 min) insulin secretion, such that glucose peaks at 30–60 mins before declining towards the elevated baseline glucose level.⁹ Unlike other types of diabetes, the shape of the glucose response curve is relatively “flat,” which results in a small increment between the 2 hr glucose and fasting glucose. UK data suggests that the increment (2 hr glucose minus fasting glucose) is <3.0 mmol/L in 70% of individuals with GCK-MODY⁹ and <4.6 mmol/L in 90% of individuals with GCK-MODY.¹⁶

Similarly, in individuals with GCK-MODY, counter-regulatory responses to hypoglycemia are activated at a higher glucose level. Following induction of hypoglycemia by a hyperinsulinemic clamp, individuals with GCK-MODY had a higher glucose threshold for increasing glucose production (5.0 vs 3.9 mmol/L) and stimulating glucagon (4.5 vs 3.7 mmol/L) compared with normal subjects.¹⁷ These counterregulatory responses restore blood glucose levels to the elevated baseline level.

In addition to pancreatic expression, glucokinase is expressed in the liver and contributes to the storage of

glucose as glycogen. In GCK-MODY, there is decreased hepatic glycogen production and increased hepatic gluconeogenesis after meals, which may contribute to the pathogenesis of hyperglycaemia.¹⁸ Interestingly, the liver does not seem to have a threshold response to glucose, so is not thought to have a major role in the determination of an individual's glucose set-point.¹⁹

Clinical features of GCK-MODY

Individuals with GCK-MODY have mild fasting hyperglycaemia, typically in the range of 5.5–8.0 mmol/L. Following a 75g OGTT, 2 hr glucose levels are relatively preserved, so the increment between the 2 hr glucose and fasting glucose is usually <4.6 mmol/L.¹⁶ The HbA1c is typically in the range of 38–60 mmol/mol (5.6–7.6%).²⁰

The hyperglycemia associated with GCK-MODY is present at birth and persists lifelong, but is usually subclinical so may only be detected on routine glucose testing. Unlike other types of diabetes, the degree of hyperglycemia only slightly worsens with increasing age and does not appear to be related to an individual's body mass index (BMI).⁹

Given the mild nature of the hyperglycemia, many individuals with GCK-MODY do not meet the diagnostic thresholds for diabetes. In one study, only 38% of individuals with GCK-MODY met the fasting glucose threshold for diabetes (≥ 7.0 mmol/L) and only 19% met the 2 hr glucose threshold for diabetes (≥ 11.1 mmol/L).⁹ A further 46% met the World Health Organization (WHO) threshold for impaired fasting glucose (≥ 6.1 mmol/L) and 53% met the threshold for impaired glucose tolerance (≥ 7.8 mmol/L).⁹ Therefore, many individuals with GCK-MODY are considered as having “normal” glucose levels, so may never be tested for GCK-MODY.

GCK-MODY has an autosomal pattern of inheritance. Therefore, a family history of “type 2 diabetes,” fasting hyperglycemia (5.5–8.0 mmol/L) or GDM is often present in a first degree relative. However, the absence of family history does not exclude the diagnosis, as *de novo* GCK mutations can occur.

Diabetes-related complications are relatively uncommon in GCK-MODY, with several studies reporting a similar rate of microvascular and macrovascular complications as that of the general population.^{12,21} The exception is the rate of retinopathy, which was detected in 30% of individuals who had GCK-MODY for a median duration of 49 years, compared with 14% of normal subjects ($p=0.007$).²¹ In that study, most cases of retinopathy in individuals with GCK-MODY were classified as mild

background retinopathy, with less than five microaneurysms.²¹ None of the GCK-MODY individuals had pre-proliferative or proliferative retinopathy, maculopathy or required laser therapy.²¹

Diagnosis of GCK-MODY

Molecular genetic testing of the *GCK* gene is expensive and not readily available. However, it is extremely important that individuals with suspected GCK-MODY undergo genetic testing in order to avoid misdiagnosis as another type of diabetes, usually type 2 diabetes. A diagnosis of GCK-MODY prevents unnecessary glucose-lowering treatment and medical review, and has been demonstrated to have a positive impact on the health and wellbeing of many individuals with GCK-MODY.²² In the UK, genetic diabetes nurses are trained as regional experts in monogenic diabetes and help identify individuals with possible monogenic diabetes who warrant genetic testing.²³ This approach has led to considerable cost savings.²³

Best practice guidelines for the molecular genetic diagnosis of GCK-MODY were developed in 2008 and remain applicable today. Screening criteria for *GCK* genetic testing include: (1) fasting glucose 5.5–8.0 mmol/L; (2) 2 hr increment <4.6 mmol/L on a 75 g OGTT; (3) family history of type 2 diabetes or GDM (although the absence of family history does not exclude the diagnosis).^{16,24}

The detection rate of monogenic diabetes is further improved by excluding individuals with probable type 1 diabetes, identified by low C-peptide and/or the presence of positive glutamic acid decarboxylase (GAD) autoantibodies, insulinoma-associated antigen-2 (IA-2) autoantibodies or zinc transporter 8 (ZnT8) autoantibodies.^{25,26}

Genetic testing of the *GCK* gene involves sequencing the promoter, exons 1a, 2–10 and splice sites of the *GCK* gene.^{6,27,28} In addition, gene dosage analysis using multiplex ligation-dependent probe amplification (MLPA) is recommended to detect large gene deletions, insertions or duplications that may be missed with sequencing alone.²⁹ Alternatively, targeted next-generation sequencing enables the simultaneous analysis of multiple monogenic diabetes genes.³⁰

Diagnosis of GCK-MODY in pregnancy

Hyperglycemia that is first detected during pregnancy is invariably diagnosed as GDM. However, some of these women will have undiagnosed GCK-MODY. The prevalence

of GCK-MODY in the GDM population is 0.4–1%.^{12,31,32} Differentiating GCK-MODY from GDM is important because the management during and after pregnancy differs.

Clinical features that suggest GCK-MODY in pregnancy include: (1) persistent fasting hyperglycemia (5.5–8.0 mmol/L) before, during and after pregnancy; (2) 2 hr increment <4.6 mmol/L on a 75 g OGTT before, during or after pregnancy; (3) history of “type 2 diabetes,” fasting hyperglycemia (≥ 5.5 mmol/L) or GDM in a first degree relative (although the absence of family history does not exclude the diagnosis).^{16,33,34}

Several studies have validated the use of the fasting glucose (≥ 5.5 mmol/L) criterion for identifying pregnant women with GCK-MODY.^{1,24,31} However, neither the 2 hr increment nor family history appear to adequately differentiate GCK-MODY from GDM.¹² A small study that screened women with GDM for GCK-MODY demonstrated that all women with GCK-MODY had a 2 hr increment <3.0 mmol/L on the 75g antepartum OGTT,³⁴ which suggests the standard increment of <4.6 mmol/L may be too generous in pregnancy.

More recently, combined criteria of fasting glucose ≥ 5.5 mmol/L and normal pre-pregnancy BMI <25 kg/m² have been proposed. These combined criteria had a 68% sensitivity, 96% specificity and number needed to test of 2.7 women with GDM to identify one case of GCK-MODY.¹ This study was conducted in a predominantly Anglo-Celtic population and the use of these combined criteria in Anglo-Celtic populations is supported by another study.³¹ However, the normal BMI criterion may exclude some cases of GCK-MODY in other ethnic populations and ethnic-specific screening criteria need to be developed.³¹

Management of GCK-MODY

The current recommendation for individuals with GCK-MODY is that they do not require treatment of their hyperglycemia, except during pregnancy. Glucose-lowering therapy, including insulin, is reported to have minimal impact on glucose levels in individuals with GCK-MODY, which is thought to be related to the rapid onset of counter-regulatory responses following a downward perturbation in glucose.^{12,17,35,36} There is also evidence of reduced endogenous insulin secretion in individuals with GCK-MODY who are receiving exogenous insulin treatment.¹² In one study, there was no difference in HbA1c between individuals with GCK-MODY who were receiving glucose-lowering treatment (oral glucose-lowering agents or

insulin) and those who were not receiving any treatment.³⁷ Further, when the glucose-lowering treatment was ceased, the HbA1c did not deteriorate,³⁷ a result that was replicated in a recent prospective study.³⁸ Therefore, the recommendation for individuals with newly diagnosed GCK-MODY, who may have been receiving glucose-lowering treatment prior to the diagnosis, is to cease this treatment.¹²

Individuals with GCK-MODY have the same background risk of type 1 and type 2 diabetes as the general population.¹² Therefore, individuals with GCK-MODY who develop symptoms of hyperglycemia or blood glucose levels that are above the range typically seen in GCK-MODY should be investigated for coexistent type 1 or type 2 diabetes. HbA1c may have a role in monitoring individuals with GCK-MODY for the development of other types of diabetes. An HbA1c of 60 mmol/mol (7.6%) represents the 95% confidence limit for GCK-MODY,¹² so an HbA1c above this level may be useful in considering coexistent type 1 or type 2 diabetes.

Family members of an individual with GCK-MODY should be counseled regarding cascade testing. Cascade testing involves screening for fasting hyperglycemia (5.5–8.0 mmol/L) unless the family member already has a diagnosis of diabetes or prediabetes, then performing limited sequencing of the exon with the known *GCK* mutation, which is less expensive than standard *GCK* genetic testing.²³ A correct diagnosis of GCK-MODY may prevent unnecessary investigations and treatment for family members, which has broader health and economic implications.²³ However, for each family member, the potential benefits of cascade testing should be balanced with the possible negative consequences of testing, such as psychosocial and insurance-related issues.³⁹

Management of GCK-MODY in pregnancy

This section on management of GCK-MODY in pregnancy applies to women with a confirmed diagnosis of GCK-MODY. If a woman with GDM is suspected of having GCK-MODY, the standard treatment approach for GDM should be continued until a genetic diagnosis of GCK-MODY is confirmed.

Preconception

The rate of congenital anomalies in pregnancies of women with GCK-MODY is unknown and difficult to ascertain given the limited availability of *GCK* genetic testing and

small numbers of women with diagnosed GCK-MODY.¹² For women with type 1 or type 2 diabetes, the rate of congenital anomalies has been reported to linearly increase with increasing hyperglycemia above an HbA1c of 45 mmol/mol (6.3%).⁴⁰ The HbA1c range for individuals with GCK-MODY is typically 38–60 mmol/mol (5.6–7.6%),²⁰ so it is biologically plausible that maternal hyperglycemia secondary to GCK-MODY may confer an increased risk of congenital anomaly.³⁹ Recently, there was a case report of a congenital anomaly in a fetus of a woman with GCK-MODY. In that case, the fetus had sacral agenesis, which is a subtype of caudal regression syndrome.³⁹ However, the fetal genotype was unknown, which raises the possibility that the sacral agenesis may have been a “chance” event.³⁹ Whilst further research and reporting is required, the possibility of an increased congenital anomaly risk in women with GCK-MODY raises the question of whether preconception high dose folic acid should be considered in these women.

Antepartum

It is well established that GCK-MODY can affect fetal growth. If either parent has GCK-MODY, there is a 50% chance that the fetus will inherit the *GCK* mutation. Fetal inheritance of the *GCK* mutation largely determines fetal growth.^{41,42}

For maternal GCK-MODY, if the fetus inherits the *GCK* mutation, the fetus will have the same elevated glucose set-point as their mother and will regulate their blood glucose levels to that higher set-point.^{41,42} As a result, neonates who inherit a maternal *GCK* mutation typically have a normal birth weight if maternal hyperglycemia is not treated.^{41,42} Treatment of maternal hyperglycemia in this situation may adversely reduce the birth weight, so is not recommended.⁴³

For maternal GCK-MODY, if the fetus does not inherit the *GCK* mutation, the fetus will be exposed to maternal hyperglycemia, which increases the risk of macrosomia, Caesarean section and neonatal hypoglycaemia.^{35,41,42} The increased fetal growth can be explained by the Pedersen hypothesis which asserts that maternal hyperglycemia stimulates fetal hyperinsulinism and insulin-mediated fetal growth.⁴⁴ Studies have demonstrated a 550–700 g increase in birth weight in neonates who do not inherit the maternal *GCK* mutation, compared to neonates who inherit the *GCK* mutation, with associated increases in birth weight centile and rate of macrosomia (Table 1).^{41,42,45} In this situation, insulin treatment is recommended, aimed at lowering maternal blood glucose levels to normal pregnancy levels in order to reduce the risk

Table 1 Studies investigating the birth weight of offspring born to women with GCK-maturity-onset diabetes of the young (MODY)

Study	Year	Offspring (n)	Region	Affected offspring		Unaffected offspring		Significance (p)
				Mean birth weight (kg)	Mean birth weight centile	Mean birth weight (kg)	Mean birth weight centile	
Hattersley et al ⁴²	1998	40	UK	3.4	53	4.0	86	<0.05
Spyer et al ⁴¹	2009	82	UK	3.2	47	3.9	85	<0.001
Hosokawa et al ⁴⁵	2019	40	Japan	2.7	41	3.4	75	<0.006

of complications.^{12,43} Supraphysiological insulin doses (>1 unit/kg/day) are usually required to overcome maternal counterregulatory mechanisms.^{35,43} Management is further challenged by maternal symptoms of hypoglycemia at “normal” glucose levels.³⁶ Delivery at 38 weeks’ gestation should be considered.¹²

For paternal GCK-MODY, fetal inheritance of the *GCK* mutation also affects fetal growth. If the fetus does not inherit the paternal *GCK* mutation, the fetus will have the same glucose set-point as their mother and will have normal fetal growth (48th vs 47th centile; $p=0.99$).⁴¹ However, if the fetus inherits the paternal *GCK* mutation, the fetus will have a higher glucose set-point than their mother, which will result in reduced fetal insulin secretion and reduced insulin-mediated fetal growth. In these neonates, birth weight is typically reduced by ~400 g, with associated reduction in birth weight centile (30th vs 47th centile; $p<0.005$).⁴¹

The clinical dilemma in the management of pregnant women with GCK-MODY is that fetal genotype is not usually known during pregnancy. The current recommendation is to use serial fetal ultrasound measurements to assess fetal growth and guide management.¹² Fetal ultrasounds should be performed every 2 weeks from 26 weeks’ gestation.¹² If there is ultrasound evidence that the fetal abdominal circumference is increasing disproportionately above the 75th centile, the fetus is assumed to not have the *GCK* mutation and insulin treatment of maternal hyperglycemia should be commenced. The use of fetal ultrasound measurements to guide management decisions may become less reliable in the future if the trend of increasing

pre-pregnancy overweight and obesity continues.^{46–48} In addition, excessive gestational weight gain is independently associated with accelerating fetal abdominal circumference in late pregnancy, which may further complicate management decisions.⁴⁹

The current management approach for pregnant women with GCK-MODY is supported by two case reports where the fetus was diagnosed with a *GCK* mutation *in utero*. Both fetuses were diagnosed with a *GCK* mutation by opportunistic genetic testing of DNA from chorionic villus sampling, which had been performed following high-risk aneuploidy screening.⁵⁰ Knowledge of the fetal *GCK* mutation dictated that the maternal hyperglycemia was not treated. Both fetuses had a normal birth weight and there were no peripartum complications, despite the maternal hyperglycemia.⁵⁰

Given that knowledge of the fetal genotype guides management, if a pregnant woman with GCK-MODY has chorionic villus sampling or amniocentesis for another reason, the fetal DNA should be tested for the *GCK* mutation.⁵⁰ However, these invasive procedures are not indicated for fetal *GCK* genotyping alone because the benefit of knowing the fetal genotype does not outweigh the miscarriage risk associated with these procedures.⁵¹ Recent advances in non-invasive fetal genotyping using cell-free fetal DNA from maternal plasma sampling are promising.^{52–54} Non-invasive fetal *GCK* genotyping would more accurately determine whether maternal hyperglycemia requires treatment and whether delivery at 38 weeks’ gestation should be considered (Table 2).

Table 2 Management of pregnant women with GCK-maturity-onset diabetes of the young (MODY) according to fetal genotype

Fetal <i>GCK</i> genotype	Maternal-fetal <i>GCK</i> genotype interaction	Predicted neonatal outcomes if maternal hyperglycemia is not treated	Recommended management
Fetus known to have <i>GCK</i> mutation	Fetus has same elevated glucose set-point as their mother	Normal birth weight	Do not treat maternal hyperglycemia Insulin treatment may adversely reduce birth weight
Fetus known to not have <i>GCK</i> mutation	Maternal hyperglycemia stimulates insulin-mediated fetal growth	Increased birth weight Increased risk of macrosomia, Caesarean section, neonatal hypoglycemia	Treat with insulin Consider delivery at 38 weeks’ gestation
Fetal genotype unknown	Unknown	Unknown	Initially withhold insulin Fortnightly fetal ultrasounds from 26 weeks’ gestation If fetal AC accelerating >75th centile, treat with insulin and consider delivery at 38 weeks’ gestation

Abbreviations: AC, abdominal circumference; *GCK*, glucokinase.

Post-partum

Post-partum, any maternal antepartum insulin treatment should be ceased immediately. Testing for neonatal hypoglycemia should be performed. Women should be advised to seek preconception counseling prior to future pregnancies. A yearly HbA1c is recommended to monitor for the development of concurrent type 1 or type 2 diabetes.

For offspring of individuals with GCK-MODY, there is currently no evidence to suggest adverse long-term outcomes. In two large studies, adult offspring had a similar BMI, irrespective of maternal or fetal *GCK* genotype.^{55,56} In addition, exposure to the relatively mild maternal hyperglycemia of GCK-MODY *in utero* did not appear to impact glucose tolerance, insulin secretion, insulin sensitivity, blood pressure or lipid profiles in adulthood.^{55,56}

Conclusion

GCK-MODY is a unique subtype of monogenic diabetes which, despite a mild clinical phenotype, has important implications for pregnancy. Understanding the maternal-fetal *GCK* genotype interactions is essential in order to optimize maternal and fetal outcomes.

Disclosure

The author reports no conflicts of interest in this work.

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