The 0.1% of the Population With Glucokinase Monogenic Diabetes Can Be Recognized by Clinical Characteristics in Pregnancy: The Atlantic Diabetes in Pregnancy Cohort

Ali J. Chakera,[1,2] Gill Spyer,[3] Nicola Vincent,[1] Sian Ellard,[1,4] Andrew T. Hattersley,[1,2] and Fidelma P. Dunne[5]

OBJECTIVE

Identifying glucokinase monogenic diabetes (GCK-MODY) in pregnancy is important, as management is different from management for other forms of gestational diabetes mellitus (GDM) and there is no increased maternal risk of type 2 diabetes. We calculated the population prevalence of GCK-MODY in pregnancy and determined the clinical characteristics that differentiate pregnant women with GCK-MODY from those with GDM.

RESEARCH DESIGN AND METHODS

We calculated the population prevalence of GCK-MODY in pregnancy by testing a subset of patients from the population-based Atlantic Diabetes in Pregnancy (Atlantic DIP) study (*n* = 5,500). We sequenced for *GCK* mutations in 247 women with a fasting glucose ≥5.1 mmol/L and 109 randomly selected control subjects with normal fasting glucose. Using data from the cases found and 40 previously identified GCK-MODY pregnancies, we analyzed whether clinical criteria could be used to differentiate GCK-MODY from GDM.

RESULTS

Four women with fasting glucose ≥5.1 mmol/L were diagnosed with GCK-MODY. No cases were identified with normal fasting glucose. The population prevalence of GCK-MODY is 1.1 in 1,000 (95% CI 0.3–2.9 in 1,000) and prevalence in GDM is 0.9% (95% CI 0.3–2.3). Fasting glucose and BMI significantly differentiate GCK-MODY from GDM ($P < 0.0001$). Combined criteria of BMI <25 kg/m^2 and fasting glucose ≥5.5 mmol/L has a sensitivity 68%, specificity 96%, and number needed to test of 2.7 women with GDM to find one case of GCK-MODY.

CONCLUSIONS

Our large population cohort of pregnant women tested estimates the population prevalence of GCK-MODY of 1.1 in 1,000. We have shown routine clinical criteria that can identify which women should be tested for GCK-MODY in pregnancy.

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[1]University of Exeter Medical School, Exeter, Exeter, U.K.
[2]Department of Diabetes and Endocrinology, Royal Devon and Exeter National Health Service Foundation Trust, Exeter, U.K.
[3]Department of Diabetes and Endocrinology, South Devon National Health Service Foundation Trust, Torbay, U.K.
[4]Department of Molecular Genetics, Royal Devon and Exeter National Health Service Foundation Trust, Exeter, U.K.
[5]Galway Diabetes Research Centre, Galway University Hospital and National University of Ireland, Galway, Ireland

Corresponding authors: Andrew T. Hattersley, a.t.hattersley@exeter.ac.uk, and Fidelma P. Dunne, fidelma.dunne@nuigalway.ie.

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It is important to identify glucokinase monogenic diabetes (GCK-MODY) in pregnancy, as it is managed differently than are other more common subtypes of gestational diabetes mellitus (GDM). People with GCK-MODY have a lifelong increased fasting glucose (5.5–8.0 mmol/L) that is regulated at this higher level (1). In contrast to GDM, the birth weight of offspring of mothers with GCK-MODY is related to whether the fetus inherits the mutation. Babies that do not inherit the mutation are exposed to their mother's hyperglycemia and have, on average, a 700 g increase in corrected birth weight (2,3). On the other hand, babies that inherit the mutation have the same homeostatic glucose set point as their mother and sense the higher glucose levels as normal, resulting in a normal birth weight (2,3).

If the baby inherits the mutation, it is recommended that the mother not receive treatment for hyperglycemia, as this will result in a normal–birth weight offspring (3,4) and treating the mother with insulin has attendant risks, is inconvenient, and can potentially lead to a reduction in birth weight (5). If the fetus does not inherit the mutation, the mother may need insulin treatment, with induction of the pregnancy at term and monitoring of the newborn baby for hypoglycemia (3,4).

A correct maternal diagnosis has wider implications: the mother does not have an increased risk of type 2 diabetes (it is the same as the general population), does not need treatment outside pregnancy, and is not at risk for the microvascular complications associated with diabetes. Furthermore, any other family members with diabetes can be tested and, if they are found to have the same *GCK* mutation, any glucose-lowering treatment can be discontinued.

Patients with GCK-MODY are frequently detected to have hyperglycemia on screening in pregnancy. The International Association of the Diabetes and Pregnancy Study Groups (IADPSG) (6) diagnostic criteria set a fasting glucose level of ≥5.1 mmol/L to define GDM based on a 1.75 increased risk of adverse neonatal outcomes. The World Health Organization (WHO)/IADPSG criteria for GDM have recently been endorsed by WHO (7). This means that pregnant women with GCK-MODY—who, by definition have a raised fasting glucose—will be misdiagnosed as having GDM. At least 50% of these women will be unnecessarily treated with insulin and exposed to the associated risks.

Knowing the prevalence of GCK-MODY and the clinical criteria that identify these women from those diagnosed with GDM, defined by WHO/IADPSG criteria, would help individualize clinical care for these women. There have been no population studies of GCK-MODY. Previous studies completed in pregnant women (8–16) have been small (9 studies: n = 15 to n = 119), often of selected patients, or requiring a postpregnancy glucose test—which negates any possibility of influencing the management of that pregnancy (see Colom et al. [4] for an overview of the studies). Furthermore, where clinical criteria have been used to identify GCK-MODY presenting in pregnancy (e.g., Ellard et al. [13]) there has been no comparison of these same characteristics in the GDM population, so they cannot be used to determine sensitivity and specificity and thus utility of these characteristics in a pregnant population.

The Atlantic Diabetes in Pregnancy (Atlantic DIP) cohort (17)—in which all pregnant women were offered an oral glucose tolerance test (OGTT) at 24–28 weeks' gestation regardless of pretest risk—allows us, for the first time, to look at the population prevalence of GCK-MODY. Use of a population-based cohort will allow us to determine the prevalence of GCK-MODY cases and thus estimate how many women are misdiagnosed. By using clinical details from case subjects and other U.K. women with GCK-MODY in pregnancy, we can estimate the clinical characteristics that can distinguish them from women with GDM.

RESEARCH DESIGN AND METHODS

Prevalence of GCK-MODY

A total of 1,543 women had clinical details and DNA available for analysis from 5,500 women recruited to the Atlantic DIP. We selected all women with WHO/IADPSG GDM (on the basis of a fasting glucose ≥5.1 mmol/L) who had DNA available (n = 247) and 109 non-GDM subjects, chosen at random, with a fasting glucose <5.1 mmol/L (Fig. 1). The subjects whose DNA was studied were representative of the whole Atlantic DIP cohort (patients studied without GDM: BMI 26.2 vs. 26.9 kg/m^2, NS, age during pregnancy 31.0 vs. 31.3 years, NS; patients with GDM: BMI 31.2 vs. 30.1 kg/m^2, age during pregnancy 33.1 vs. 32.9 years, NS).

We detected pathogenic *GCK* mutations by sequencing the coding region and β-cell promoter using previously described methods (18). We calculated the population prevalence of GCK-MODY by assuming the pickup rates in the fasting glucose–defined subgroups were applicable to all patients from the Atlantic DIP cohort.

Clinical Characteristics of GCK-MODY in Pregnancy

To study the clinical characteristics of GCK-MODY in pregnancy, with increased precision, we combined the clinical details of the four women with GCK-MODY found in the Atlantic DIP cohort and all 40 U.K. patients diagnosed with GCK-MODY in pregnancy by the Molecular Genetics Laboratory at the Royal Devon and Exeter National Health Service Foundation Trust. These 44 women with GCK-MODY were compared with women from the Atlantic DIP cohort GDM (n = 447). We compared age at pregnancy, fasting glucose, increment on OGTT, prepregnancy BMI, and family history of diabetes between the GCK-MODY, GDM, and normal glucose tolerance groups. We used a Student t test to compare means and χ^2 analysis for family history. We plotted receiver operating characteristic (ROC) curves for those clinical criteria in which there was a significant statistical difference between the GCK-MODY and GDM groups ($P < 0.01$). An area under the ROC curve (AUC) of >0.8 identified a clinical variable useful for identifying GCK-MODY in pregnancy.

For each useful clinical variable, we used the ROC curve data to determine the actual value that discriminated GCK-MODY and GDM with optimal

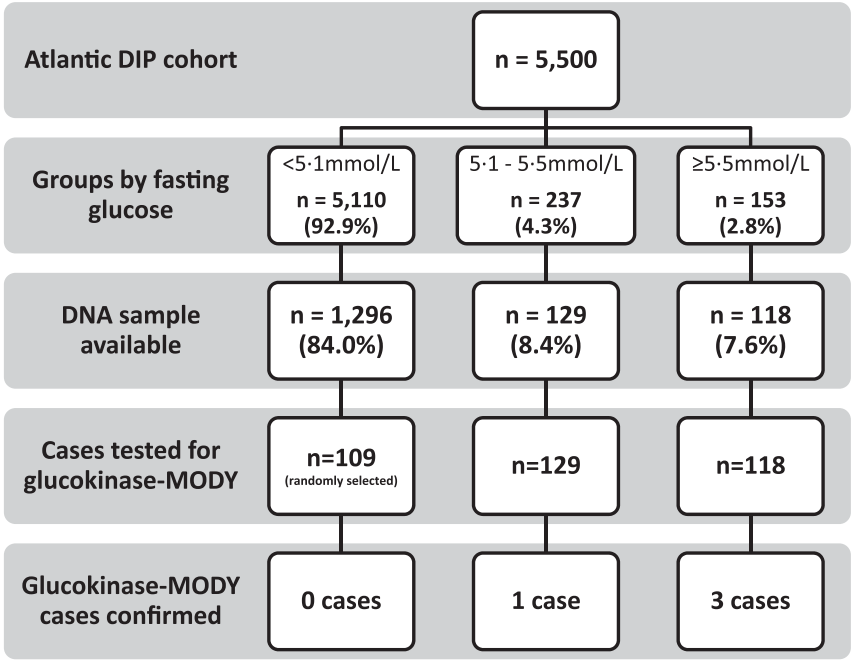

Figure 1—Breakdown of the number of cases from the Atlantic DIP cohort tested for GCK-MODY in this study. The last row identifies the number of cases of GCK-MODY identified in each group. For further details of the cases, see Supplementary Table 1.

sensitivity and specificity. Where this method resulted in noninteger values, these cutoffs were rounded up or down to clinically useful values.

We calculated the sensitivity and specificity for the ability of each combination of clinical features to discriminate GCK-MODY from GDM. Using the prevalence of GCK-MODY calculated from the Atlantic DIP cohort, we were able to calculate positive and negative predictive values for these cutoffs and thus define the number needing molecular genetic testing to find one case of GCK-MODY. As these values are a continuum, and there is no absolute value that can be said to be most useful, we repeated this process for a range of clinical cutoff points to allow us to compare the utility of achieving maximum sensitivity (i.e., finding most of the GCK-MODY cases) against the lowest number needed to test (i.e., saving on the cost of molecular genetic testing). As the sensitivity improves, the number needed to test to find one case increases.

Statistical analysis was carried out in Stata, version 12.1. Mathematical functions were performed in Excel 2007.

RESULTS

Prevalence of GCK-MODY

Four of 247 women with a fasting blood glucose ≥5.1 mmol/L were diagnosed with GCK-MODY from the Atlantic DIP cohort (Supplementary Table 1 for individual patient details). No cases were identified in the control group (n = 109) with a fasting glucose <5.1 mmol/L.

In the Atlantic DIP cohort, 390 women of the 5,500 cohort had a fasting glucose ≥5.1 mmol/L; therefore, our finding equates to a population prevalence of GCK-MODY of 0.11% (95% CI 0.03–0.29) or ~1 in 1,000. In women meeting the WHO/IADPSG criteria for GDM, the prevalence is 0.93% or 9 in 1,000 (95% CI 0.25–2.34).

Clinical Characteristics of GCK-MODY in Pregnancy

Pregnant women with GCK-MODY (n = 44), compared with those with GDM from the Atlantic DIP study (n = 447), had a higher fasting glucose (6.4 vs. 5.2 mmol/L, $P < 0.0001$) and lower BMI (23.9 vs. 31.2 kg/m^2, $P < 0.0001$) and were younger at the time of pregnancy (29.5 vs. 33.1 years, $P < 0.0001$) (Fig. 2). Glucose increment (P = 0.15) and family history (P = 0.62) were not different between the two groups. The demographics of the three groups normal glucose tolerance, GDM, and GCK-MODY are shown in Table 1.

ROC curves (Fig. 3) showed that only fasting glucose (AUC 0.9) and BMI (AUC 0.85) could be used to differentiate GCK-MODY from GDM. From the ROC curve data, the optimum cutoff for fasting glucose is 5.5 mmol/L, with sensitivity 98% and specificity 74%, and the optimum cutoff for BMI is 26.3 kg/m^2, with sensitivity 76% and specificity 90%.

We found three clinically useful combinations of BMI and fasting glucose to differentiate GCK-MODY from GDM at different levels of sensitivity and specificity.

1. BMI ≤21 kg/m^2 and a fasting glucose ≥5.5 mmol/L; sensitivity 20%, specificity 100%: all cases tested would be positive, but only one-fifth of cases would be identified.
2. BMI <25 kg/m^2 (i.e., normal weight) and a fasting glucose of ≥5.5 mmol/L; sensitivity 68%, specificity 99%: 2.7 women would need genetic testing to find one case of GCK-MODY, and over two-thirds of cases would be identified.

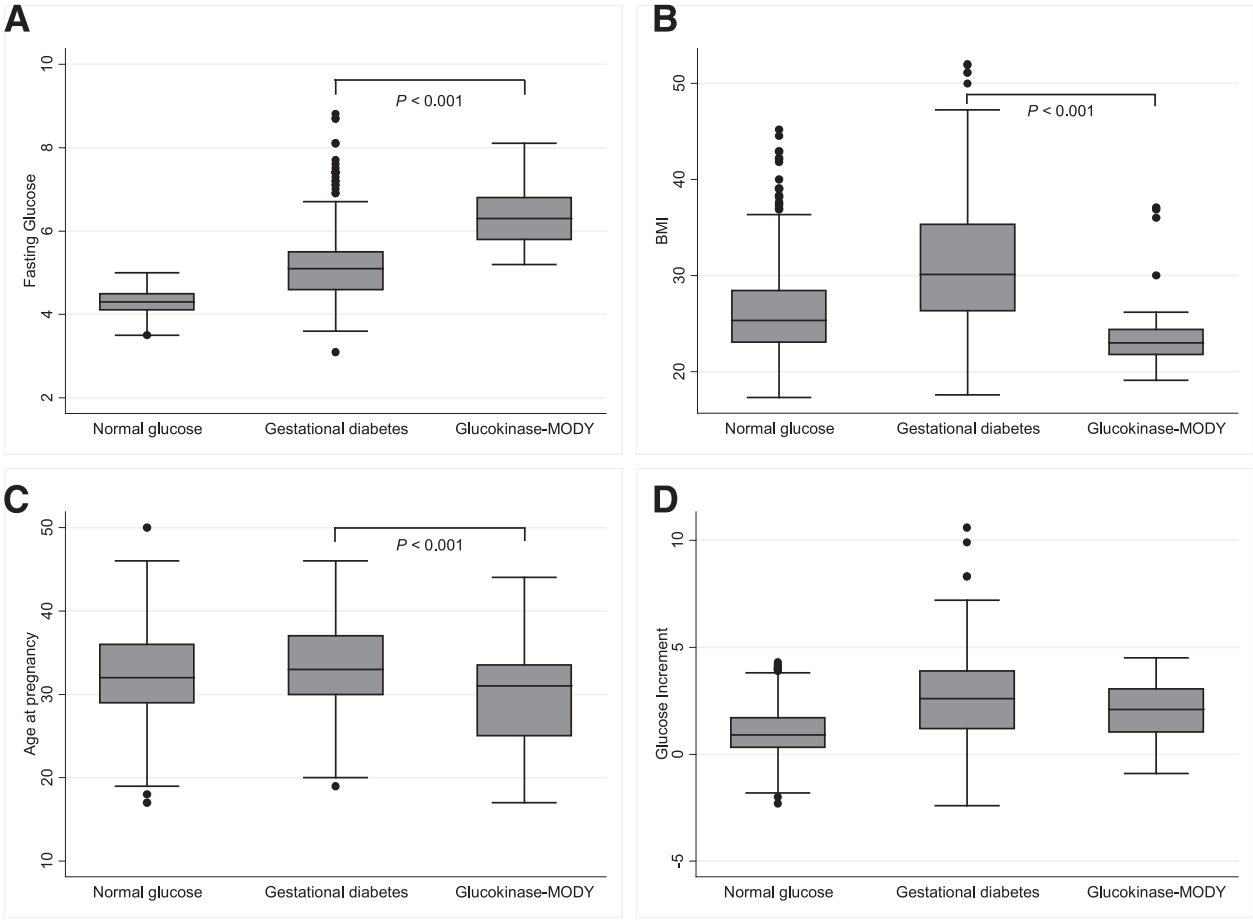

Figure 2—Box-and-whisker plots of clinical variables by diabetes types (normal glucose, *n* = 1,108; GDM, *n* = 447; GCK-MODY, *n* = 44). *A*: Fasting glucose for GCK-MODY significantly higher than for GDM ($P < 0.001$) and normal glucose ($P < 0.001$). *B*: BMI for GCK-MODY significantly lower than for GDM ($P < 0.001$) and normal glucose ($P = 0.0012$). *C*: Age at pregnancy for GCK-MODY significantly lower than for GDM ($P < 0.001$) and normal glucose ($P = 0.0055$). *D*: Glucose increment on OGTT; no significance between groups. Box, median and interquartile range; whisker, range; circles, outliers (>1.5 × interquartile range).

3. BMI <30 kg/m^2 (i.e., nonobese) and a fasting glucose ≥5.5 mmol/L; sensitivity 82%, specificity 96%: 6.5 women would need genetic testing to find one case of GCK-MODY, and more than three-quarters of cases would be identified.

CONCLUSIONS

Statement of Principal Findings

We have demonstrated that GCK-MODY affects ~1 in 1,000 of this primarily Caucasian population and defined clinical criteria that can be used to determine which women with GDM (by WHO/IADPSG criteria) should be tested for *GCK* mutations in pregnancy.

This is the first study to use a population-based sample to estimate the prevalence of GCK-MODY. The prevalence of 1 in 1,000 is similar to that estimated by Gloyn in 2003 (19) based on the prevalence of GCK mutations in GDM and the population prevalence of GDM. This is the first study to look at the prevalence of GCK mutations in GDM as defined by the WHO/IADPSG criteria. The finding that ~1% of GDM case subjects have a glucokinase mutation is similar to previous smaller studies of GDM by 1999 WHO criteria (8,12). This is because although the WHO/IADPSG lower fasting criteria mean that all women with GCK-MODY will now meet

Table 1—Clinical characteristics of pregnant women by diabetes subtype

	GCK-MODY in pregnancy (*n* = 44)		GDM in pregnancy (*n* = 447)		Normal glucose tolerance in pregnancy (*n* = 1,092)	
	Mean	Range	Mean	Range	Mean	Range
Age at pregnancy (years)	29.5	17–44	33.1	19–46	31.8	17–50
BMI (kg/m^2)	23.9	19.1–37.1	31.2	17.6–52.0	26.2	17.3–45.2
Fasting glucose (mmol/L)	6.4	5.2–8.1	5.2	3.1–8.8	4.3	3.5–5.0
2-h glucose on OGTT (mmol/L)	8.3	5.4–10.2	7.7	2.9–16.9	5.3	2.0–8.4

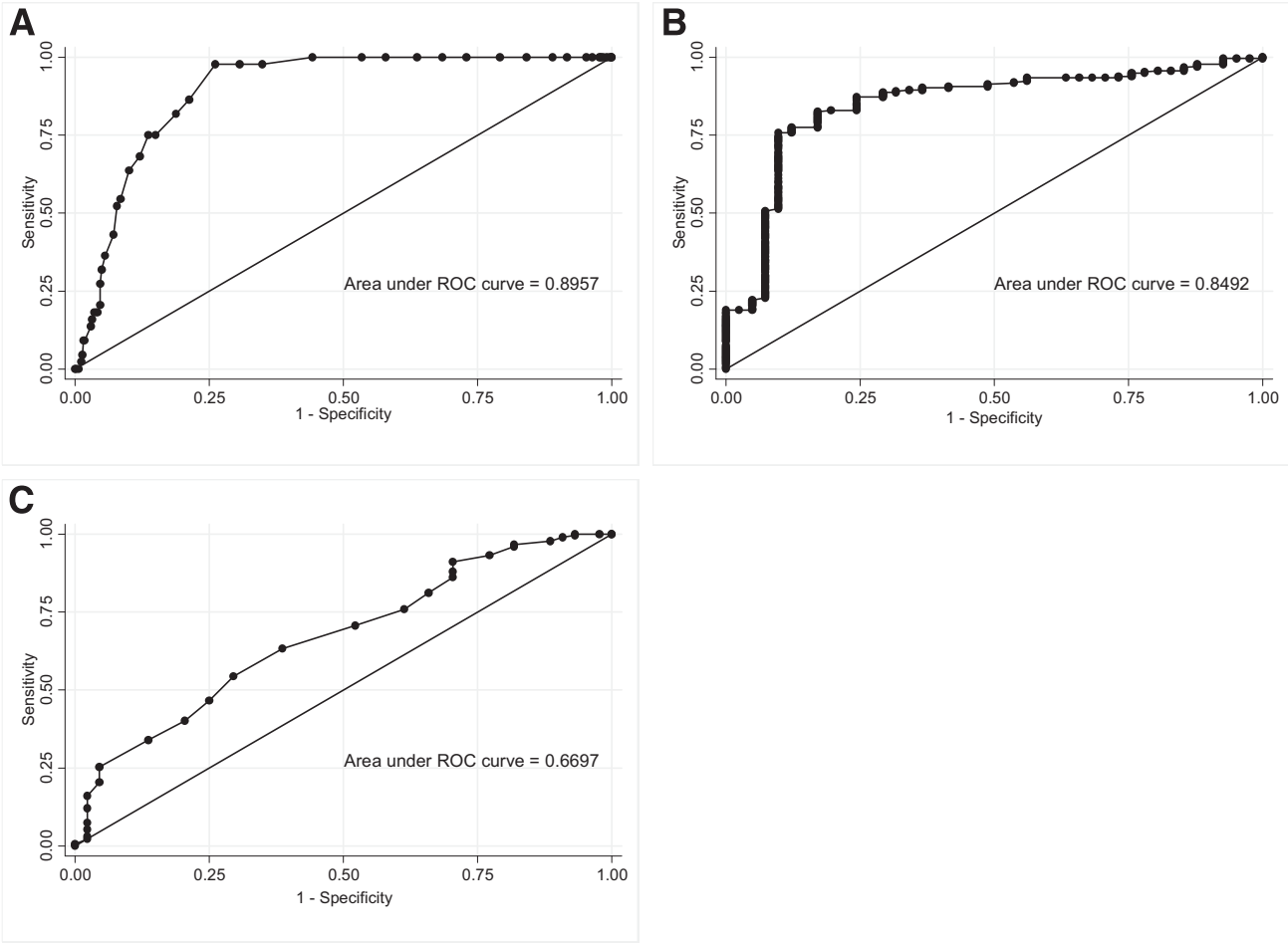

Figure 3—ROC curves of clinical variables by diabetes types. *A*: Fasting glucose. *B*: BMI. *C*: Age at pregnancy. An AUC of >0.8 is consistent with a clinically useful discriminating variable.

the criteria for GDM, the prevalence of GDM is higher using WHO/IADPSG than former 1999 WHO criteria.

This population prevalence has important implications for the diagnosis (or lack of diagnosis) of GCK-MODY. From the records of the U.K. National Molecular Genetics service for MODY, only 630 people with GCK-MODY have been diagnosed to date (i.e., a prevalence of 1 in 100,000), which means 99% of GCK-MODY cases are not diagnosed. Half of these missing cases will be women, many of whom will have been diagnosed with and potentially mistreated as having GDM. It has previously been estimated that the prevalence of MODY is 0.1 in 1,000 (20). Our prevalence for GCK-MODY alone is 10-fold higher; it is likely that many people with a *GCK* mutation are never diagnosed with diabetes and so are not identified in previous estimates.

Approximately 1% of women who fulfill the WHO/IADPSG criteria for GDM have GCK-MODY. It is important to diagnose GCK-MODY in pregnancy to optimize management for the mother. As antenatal clinics move toward the WHO/IADPSG criteria for GDM using universal screening, an increasing number of women with GCK-MODY will be misdiagnosed and potentially mistreated.

At present, screening all women with GDM and a fasting glucose ≥5.1 mmol/L for *GCK* mutations is neither practical nor economical. We have identified criteria of fasting glucose and BMI that can be used as a guide to select GDM patients for genetic testing. It is interesting that this population analysis has shown that other criteria previously used (13) to select cases such as family history are not discriminatory in this situation. The cutoff values of fasting glucose and BMI used in practice will be influenced by the cost of the test and the benefits to the patient of finding a mutation. Determining the cutoffs of fasting glucose and BMI that should be used in clinical practice is a balance between the sensitivity and specificity of the test (i.e., balancing the number of cases of GCK-MODY that you identify against the number of people that you have to test to find each case). All women with GDM with a BMI ≤21 kg/m^2 and fasting glucose ≥5.5 mmol/L will have GCK-MODY; however, this will only identify one-fifth of women with GCK-MODY (9 of 44 cases in our study). Setting a more generous cutoff of BMI <30 kg/m^2 and fasting glucose of 5.5 mmol/L will identify four-fifths of those with GCK-MODY (36 of 44 cases), but you will need to test 6.5 women to find one case. Choosing an absolute cutoff is a matter of balancing the costs of the

genetic test against the benefit of correctly treating a woman with GCK-MODY. A pragmatic, clinically simple approach is to test for *GCK* mutations in all those with a normal BMI and fasting glucose ≥5.5 mmol/L. In our study, this would detect 30 of 44 patients and require testing 2.7 patients to find one case.

Strengths and Weaknesses of the Study

We have looked at the prevalence and clinical characteristics of GCK-MODY on a population basis. As the number of cases found is small, there is error around these findings (95% CI for population prevalence 0.03–0.29%), but it is the only population study performed to date and by far the largest study of GCK-MODY in GDM. Previous studies in GDM have studied 119 cases or fewer (4,13) and used predefined pre- and postnatal selection criteria without a control group to allow an assessment of sensitivity and specificity.

Our calculations of prevalence have required assumptions that may introduce some error. In calculating the population prevalence, we assume that the cohort we have studied is representative of the entire Atlantic DIP cohort, which is likely to be true (comparisons reported in the method section). Furthermore, we assume that the Atlantic DIP cohort is representative of the population. There is evidence of a statistically significant but small clinical difference between the Atlantic DIP cohort and those in the population not recruited to the study: patients recruited were more obese (BMI 26.9 ± 5.1 vs. 25.9 ± 4.5 kg/m^2, $P < 0.0001$) and older (31.5 ± 5.5 vs. 30.5 ± 5.8 years old, $P < 0.0001$) (17). These small differences are unlikely to be a major source of bias.

The data supporting the WHO/IADPSG criteria for GDM and results from the Atlantic DIP study are based on glucose values from an OGTT at 24–28 weeks' gestation. It is likely that the clinical cutoffs that we have derived in this study would be applicable earlier in the course of the pregnancy, though we have not been able to test this. Influencing management during the third trimester would require rapid genetic testing, and some laboratories including our own can provide a result within a week of receiving a sample. Before the genetic result is available, standard treatment of hyperglycemia in pregnancy should be continued, including pharmacological treatment if deemed necessary, while awaiting the result.

The clinical variance around the four case subjects identified from the Atlantic DIP cohort would be too great to draw any conclusions. So, to determine the clinical features of GCK-MODY in pregnancy we have used all known U.K. cases that have been diagnosed in pregnancy. This means the study of the clinical features is not a population-based study, and this could introduce bias. Therefore, these criteria are not established for a specific population or ethnic group and should be considered a guide to testing for GCK-MODY in women diagnosed with GDM that needs further testing in population-based cohorts. However, given our prevalence estimate, to assess clinical criteria, with the same precision, on a population basis would require a cohort of over 40,000 women. The assumption that our cohort is representative of the population may also affect the sensitivity and specificity of the clinical cutoffs provided.

The Atlantic DIP population is predominantly white European, with 7% from another ethnic background, and so our conclusions and criteria will not apply to other populations with a higher prevalence of GDM. The prevalence of GCK-MODY may be consistent across populations; the clinical criteria used to find them may not be.

As a practical note, using an OGTT to guide genetic testing requires awareness that women may not be truly fasted prior to the test and that timed samples can get mixed up. We recommend repeating any tests where the 2-h value is less than the fasting glucose value and the difference would change whether the patient is diagnosed with GDM. In our cohort, there were 15 of 447 women diagnosed with GDM where the 2-h value was <5.1 mmol/L. None of these were diagnosed with GCK-MODY. If all 15 of these cases were false–positive GDM cases, the prevalence of GCK-MODY may be very slightly higher than we have calculated.

Implications for Clinicians

We have calculated a prevalence of GCK-MODY of 1 in 1,000, which means the vast majority of GCK-MODY cases remain undiagnosed. The cost of molecular genetic testing continues to fall, which means that using clinical cutoffs to determine whether a pregnant woman has GCK-MODY will become an increasingly cost-effective way to personalize and optimize the care of women with diabetes in pregnancy. The WHO/IADPSG criteria for GDM are based upon a 1.75 increase in the odds ratio for adverse outcome in pregnancy. This does not apply to GCK-MODY in pregnancy, as the birth weight and, hence, complications are dependent on fetal genotype (2,3). We estimate that using a normal prepregnancy BMI and fasting glucose on OGTT ≥5.5 mmol/L to determine which women should have *GCK* mutation testing is an efficient strategy for identifying GCK-MODY and has important implications for the management of these pregnancies.

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