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Management and pregnancy outcomes of women with GCK-MODY enrolled in the US Monogenic Diabetes Registry

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Abstract

Aims—GCK-MODY is characterized by mild hyperglycemia. Treatment is not required outside of pregnancy. During pregnancy, insulin treatment is recommended if second trimester fetal ultrasound monitoring shows macrosomia, suggesting the fetus has not inherited the GCK gene. There are limited data about GCK-MODY management in pregnancy. The aim of this study was to examine clinical management and pregnancy outcomes amongst women with a known diagnosis of GCK-MODY.

Methods—In this observational, cross-sectional study, a survey was distributed via Redcap to women 18 years enrolled in the University of Chicago Monogenic Diabetes Registry ($n = 94$). All or part of the survey was completed by 54 women (128 pregnancies).

Results—There were 78 term births (61%), 15 pre-term births (12%), and 24 miscarriages (19%). Of the 39 pregnancies where insulin was given, 22 (56%) had occasional or frequent hypoglycemia including 9 with severe hypoglycemia. Average birth weight for full-term GCK-affected infants was significantly less in cases of maternal insulin treatment versus no treatment (2967 and 3725 g, $p = 0.005$). For GCK-affected infants, conclusions are limited by small sample size but large for gestational age (LGA) was common with maternal insulin treatment (56%) and no treatment (33%), $p = 0.590$.

Conclusions—The observed miscarriage rate was comparable to the background US population rate (15–20%). Patients treated with insulin experienced a 23% incidence of severe hypoglycemia and lower birth weights were observed in the insulin-treated, GCK-affected neonates. These data support published guidelines of no treatment if the fetus is suspected to have inherited GCK-MODY and highlight the importance of additional studies to determine optimal pregnancy management for GCK-MODY, particularly among unaffected fetuses.

Keywords

Glucokinase; MODY; Pregnancy

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Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval This study was approved by the University of Chicago Institutional Review Board and was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Introduction

GCK-MODY is an autosomal dominant form of diabetes caused by heterozygous mutations in the glucokinase gene (*GCK*). It is characterized by altered thresholds for blood glucose regulation leading to mild increases in blood glucose and hemoglobin A1c [1]. Both microvascular and macrovascular complications are rare in GCK-MODY compared to type 1 or type 2 diabetes mellitus. A cross-sectional study in the United Kingdom evaluated complications in 99 patients with GCK-MODY compared to 91 controls (nondiabetic, familial, mutation negative) and 83 subjects with type 2 diabetes diagnosed at age 45 or younger. Clinically significant microvascular complications occurred in 1% of patients with GCK-MODY compared to 2% of controls and 36% of patients with type 2 diabetes. Similarly, clinically significant macrovascular complications occurred in 4% of patients with GCK-MODY compared to 11% of controls and 30% of patients with type 2 diabetes [2].

Treatment for hyperglycemia in GCK-MODY is almost always unnecessary and ineffective outside of pregnancy [3]. There are published recommendations for treatment of women with GCK-MODY during pregnancy. Management depends on the fetal genotype which determines how the fetus senses and responds to maternal hyperglycemia. Fetal genotype is rarely known but can be inferred by the assessment of fetal growth on second trimester ultrasound; accelerated fetal growth with abdominal circumference > 75% suggests that the fetus does not carry the *GCK* mutation. If the fetus carries the *GCK* mutation, it will have the same increased glucose set point and will sense maternal hyperglycemia to be normal and thus growth will be normal. Glucose-lowering therapies for the mother are not indicated in this scenario and could increase risk for small for gestational age (SGA). If the fetus does not carry the *GCK* mutation, it will sense the maternal glucose to be high and increase insulin secretion. Insulin therapy is recommended in these pregnancies with an unaffected fetus to attempt to normalize maternal blood sugar to prevent development of macrosomia. In these cases, consideration of delivery at 38 weeks is also recommended [4].

Data supporting these recommendations are limited. A case report in 2001 documented low birth weight < 1st percentile in a *GCK*-mutation carrier infant with maternal insulin treatment, compared to normal birth weight with maternal insulin treatment in an unaffected sibling of the same mother [5]. Two cases have reported GCK-affected infants (diagnosed prenatally by chorionic villus sampling for other indications) who had normal birth weight and no complications without treatment for maternal hyperglycemia [6]. A retrospective study of 82 infants born to 42 women with GCK-MODY found that fetal genotype was the major determinant of birth weight with a 700-g difference in birth weight between GCK-affected and unaffected infants. Birth weight percentile was lower in GCK-affected infants with maternal insulin treatment compared to diet alone (39.3 versus 51.0 percentile) though the difference was not statistically significant. In this study, birth weight in unaffected infants was not reduced by insulin treatment [7].

A retrospective study in 2015 examined clinical management and outcomes for 12 women with GCK-MODY who had a total of 56 pregnancies. In this study, GCK-unaffected infants whose mothers were not treated with insulin had an increased rate of macrosomia (62.5%) and complications (37.5%). Additionally, insulin treatment for mothers of GCK-affected

infants did not result in any cases of SGA. It was also observed that patients with GCK-MODY had an increased miscarriage rate of 33% compared to background population rate of 15% [8]. Based on these findings, the authors suggested early insulin treatment for all pregnant women with GCK-MODY.

The aim of this study was to assess management of high blood sugar and pregnancy outcomes in women with GCK-MODY enrolled in the US Monogenic Diabetes Registry through a structured, online survey. The University of Chicago Monogenic Diabetes Registry is an online registry that was started in 2008 at the University of Chicago to learn more about monogenic diabetes [9, 10]. As of 4/25/18, the Registry included 3074 participants and 205 women with a known diagnosis of GCK-MODY, which provides a unique opportunity to analyze pregnancy management and outcomes in this population.

Methods

This was an observational, cross-sectional study which used a survey designed through an iterative process to collect details about pregnancy management and complications. Cognitive interviews were used to increase reliability and validity. The survey was distributed electronically via REDCap to women in the US Monogenic Diabetes Registry age 18 and older with a known genetic diagnosis of GCK-MODY [11].

Data collected included:

- Demographic information.
- Number of pregnancies and result of each (term birth after 37 weeks, pre-term birth before 37 weeks, miscarriage, elective termination, currently pregnant).
- Pre-pregnancy diagnosis of hyperglycemia, glycemic monitoring, and treatment.
- Management of high blood sugar during pregnancy including dietary recommendations, glycemic monitoring, and medications (oral, insulin)
- Blood sugar control during pregnancy (fasting and post-prandial glucose values, hypoglycemia frequency and severity, and hemoglobin A1c).
- Delivery information, birth weight and length, neonatal complications.
- Genetic testing of children.

For partially completed surveys, all available data were included in the analysis. Descriptive statistics were used to describe the examined cohort. Linear and logistic regression models were fit with robust standard errors to account for the correlation among multiple births from the same mother. *p* values are reported as comparing birth weight, birth weight percentiles, LGA rates, and gestational age based on maternal treatment (insulin versus no treatment) for infants with each genotype (GCK+ or GCK-). We used a two-tailed *p* value with an alpha level for significance set at 0.05.

Results

Survey responses

94 women were invited to complete the survey. Of these, 69 were known to have had a pregnancy based on existing data collected in the US Monogenic Diabetes Registry. 54 women completed all or part of the survey. The response rate for women known to have had a pregnancy was 78.2% and the overall response rate was 57%. The 54 respondents reported a total of 128 pregnancies. The delivery dates ranged from 1964 to 2017. Table 1 outlines background information about the 54 survey respondents and 128 pregnancies.

Pre-pregnancy diagnoses and treatment

In 40% of the 128 total pregnancies (51/128), women had been diagnosed with hyperglycemia prior to pregnancy and some had been given more than one diagnosis. The most common diagnosis was type 2 diabetes or pre-diabetes. 18 cases had a known diagnosis of GCK-MODY prior to pregnancy and two additional cases had a suspected MODY diagnosis.

Of the 51 pregnancies with a prior diagnosis of hyperglycemia, in 22 cases (43%) women were checking blood sugar prior to pregnancy an average of 2.2 times per day (range 1–4). In 39 cases, women were on no treatment. Of the 12 cases where women were treated with glucose-lowering medications before pregnancy, treatments included metformin ($n = 4$), metformin and sulfonylurea ($n = 2$), metformin and rapid-acting insulin ($n = 1$), basal insulin ($n = 1$), basal and rapid-acting insulin ($n = 1$), and insulin pump ($n = 3$).

Treatment during pregnancy

Details about treatment during pregnancy were collected for the 93 pregnancies that resulted in term or pre-term births (see pregnancy outcomes below). In 56 cases (60%) women were told to make dietary changes. The most common recommendations were to follow a ‘diabetic diet’ or to reduce carbohydrate intake.

In 49 pregnancies, women were on no treatment. In five pregnancies, women were treated with oral medications only and all received the sulfonylurea glyburide. A majority of the pregnancies treated with glyburide occurred prior to 2015 and before sulfonylureas were associated with adverse neonatal outcomes [12]. In 39 pregnancies, women were treated with insulin of which 8 cases were on insulin prior to pregnancy and continued treatment, and 31 were newly started on insulin. The time of insulin initiation was known in 30 pregnancies. The average timing of insulin initiation was 16.2 weeks (median 14 weeks) with a range of 2–32 weeks.

Pregnancy management in known GCK-MODY

Table 2 describes the management of pregnancies with a known diagnosis of GCK-MODY ($n = 18$). In 12/18 cases with a prior diagnosis of GCK-MODY, women were on no treatment before pregnancy. Glucose-lowering therapy in the six cases where medication was used before pregnancy included combinations of metformin, sulfonylureas, basal and rapid-acting insulin. In 9 cases, women felt they were treated differently than other women with

gestational diabetes because of their GCK-MODY diagnosis. Differences in treatment included more frequent ultrasounds ($n = 3$), higher blood sugar targets ($n = 2$), and expert consultation ($n = 2$).

During pregnancy, for seven cases (39%) no medication was given. For ten cases (65%) women were treated with insulin during pregnancy; this included seven cases where insulin was started during pregnancy and three cases where insulin was given before pregnancy and continued. For one pregnancy the respondent was started on oral medication (glyburide). Insulin initiation occurred at an average of 16.4 weeks (range 5–32 weeks). In four of seven cases, the respondent reported that the baby was measuring normal size for gestational age at the time insulin was initiated. For seven of ten pregnancies treated with insulin (70%), occasional or frequent hypoglycemia was reported.

Insulin doses and glycemic control

A wide range of insulin doses was reported from 0 to 90 units of basal insulin and 0–33 units of rapid-acting meal-time insulin. Women treated with insulin reported fasting blood sugars ranging from 65 to 168 mg/dl ($n = 26$ reported), 1–2-h post-prandial blood sugars of 57–218 mg/dl ($n = 26$), and hemoglobin A1c from 4.9 to 7.7% ($n = 18$). Women on no treatment reported fasting blood sugars from 90 to 172 mg/dl ($n = 16$), 1–2-h post-prandial blood sugars of 115–178 mg/dl ($n = 6$), and hemoglobin A1c from 5.8 to 6.4% ($n = 3$).

Adverse effects of insulin

For women treated with insulin, hypoglycemia was common. 56% reported occasional or frequent hypoglycemia and 23% reported severe hypoglycemia requiring assistance from another person. In two cases, glucagon was required and in one case the respondent had to stop working due to frequent hypoglycemia. Only 4 of 17 women with no or rare hypoglycemia reported insulin doses. In those pregnancies insulin doses tended to be lower (basal 3–6 units, bolus 8–10 units).

Pregnancy outcomes

A majority of outcomes were term births (61%). Other outcomes included 12% pre-term births, 19% miscarriages, and 7% elective abortions. Average gestational age of miscarriage was 8.7 weeks. For 6 of the 24 miscarriages, women reported a presumed cause of miscarriage: tubal pregnancy ($n = 2$), “heart did not form properly” ($n = 1$), hyperglycemia ($n = 1$), trisomy 8 ($n = 1$), and uterine septum ($n = 1$). For two of the nine elective terminations, women reported that a fetal anomaly was present before termination.

Neonatal birth weight

Genetic testing of children was done for 35 cases. Average birth weight for full-term *GCK*-mutation-positive children was significantly less in cases of maternal insulin treatment versus no treatment at 2967 and 3725 g, respectively ($p = 0.005$). Birth weights for full-term infants and birth weight percentiles for all gestational ages are shown in Table 3. Birth weight percentile and gestational age by fetal genotype/maternal treatment are displayed in Fig. 1.

For children who did not inherit the *GCK* mutation, conclusions about differences in birth weight based on maternal treatment are limited based on small sample size. LGA was common in cases of maternal insulin treatment (56%) and no treatment (33%, $p = 0.590$).

Gestational age at delivery

For *GCK*-mutation-positive infants, gestational age at delivery was significantly earlier in cases of maternal insulin treatment versus no treatment at 38.0 weeks and 40.4 weeks, respectively ($p = 0.003$). There was no significant difference in gestational age at delivery for *GCK*-mutation-negative infants based on treatment (37 weeks with insulin, 36 weeks with no treatment, $p = 0.459$).

Neonatal complications

Complications were observed in three of eight *GCK*-mutation-positive, insulin-treated neonates and included mild respiratory issues ($n = 2$) and hypoglycemia ($n = 1$). For *GCK*-positive, untreated neonate complications were seen in 4/15 cases and included prolonged labor due to large baby size ($n = 2$), failed vaginal delivery or need for emergency C-section due to large baby size ($n = 1$), planned C-section due to large baby size ($n = 1$), birth injury ($n = 1$, broken collarbone), and meconium aspiration ($n = 1$). For insulin-treated, *GCK*-negative neonates, 3/9 reported complications including failed vaginal delivery or need for emergency C-section due to large baby size ($n = 1$), planned C-section due to large baby size ($n = 1$), and mild respiratory issues ($n = 1$). For untreated, *GCK*-negative neonates, 1/3 reported a complication (plan for C-section due to large baby size).

Discussion

This is the largest study to our knowledge investigating pregnancy management and outcomes in women with *GCK*-MODY, and there are several important findings. First, in our study the miscarriage rate for women with *GCK* was 19%. In the general population, the miscarriage rate is 15–20% and most early pregnancy loss is attributable to fetal anomalies with approximately 50% of all miscarriages attributed to chromosomal abnormalities [14–16]. In our *GCK*-MODY cohort, the rate of miscarriages and reports of anomalies are similar to the general population. Some have suggested that the mild hyperglycemia associated with *GCK*-MODY during early pregnancy may increase the risk of miscarriage, in which case pre-conception glucose-lowering therapy could theoretically have a benefit for reducing miscarriage risk [8]. Our observation that the miscarriage rate for women with *GCK*-MODY was similar to the general population would support the current recommendation for no treatment of high blood sugars prior to conception and is useful for pre-conception counseling for women with *GCK*-MODY.

Significantly lower birth weights were observed in full-term insulin-treated, *GCK*-positive neonates. This finding is consistent with the current theory that insulin therapy for pregnancies with a *GCK*-positive fetus will lower blood sugars below the fetus's glucose set point and restrict growth. SGA infants are at risk for adverse outcomes including perinatal asphyxia, hypothermia, hypoglycemia, and polycythemia [17]. Additionally, pregnancies with *GCK*-positive infants treated with insulin delivered earlier than pregnancies with *GCK*-

positive infants and no treatment. This finding has previously been reported by Spyer et al. and was proposed to be due to more obstetric intervention in the insulin-treated pregnancies [7]. Overall, our findings support not treating hyperglycemia in pregnancies where the fetus is suspected to have inherited the GCK mutation.

Interestingly, though the average birth weight for GCK-positive infants with no maternal treatment was average (58th percentile) there was a subset of five infants born to four women who were large for gestational age (LGA, birth weight percentile > 90) or had complications related to large size. These four women had a total of 16 pregnancies which were reviewed to determine if there were other potential factors contributing to large size. One woman had three other pregnancies with GCK-unaaffected infants and two of these were LGA (97 and 99th percentiles) despite insulin treatment in one case. Another woman had three other pregnancies where the infants' genotype was unknown, but two were LGA (95 and 97th percentiles). The other two women had two pregnancies each with GCK-positive infants and all cases had large birth weights. One of these women was reported to be "mildly overweight" and had a maximum lifetime hemoglobin A1c of 7.5%, at the high end of the typical GCK-MODY range. The large size observed in these *GCK*-mutation-positive infants with no maternal treatment could be related to confounding factors such as other genetic factors, maternal obesity, or co-existing insulin resistance, and warrants further investigation.

GCK-unaaffected infants had higher average birth weight percentiles in cases of maternal insulin treatment and no treatment, though conclusions about differences between the two groups are limited by small sample size. There was no clear pattern of reduced birth weight percentile based on timing and dose of insulin therapy, though the adequacy of glycemic control was difficult to assess by patient reported glucose ranges. Further study and ideally prospective data could help determine the efficacy of insulin initiated in the second trimester to reduce risk for macrosomia. A potential challenge for this treatment strategy is the high doses of insulin that are often required to overcome the increased glucose set point in GCK-MODY. Without aggressive titration to higher insulin doses, sub-optimal glycemic control could allow macrosomia to develop even in cases of insulin therapy.

In pregnancies where hyperglycemia was treated with insulin, there was a 23% incidence of severe hypoglycemia and in two cases glucagon was needed to treat hypoglycemia. This rate of severe hypoglycemia is similar to rates observed during pregnancy for patients with type 1 diabetes (up to 45%) and significantly higher than gestational diabetes, where hypoglycemia is rarely observed [18, 19]. One potential explanation for the high rate of hypoglycemia is the supraphysiologic doses of insulin which are required in GCK-MODY to overcome the increased glucose set point and lower blood sugar [3]. Of note, insufficient diabetes education and rapid/inappropriate insulin dose titration are both factors which could contribute to hypoglycemia and were not assessed in this survey. Nevertheless, this hypoglycemia rate is of particular concern for cases where the fetus has inherited the GCK mutation and insulin therapy may have the additional adverse effect of lower birth weight.

Overall, the findings of this study support the current recommendation that insulin should be used in cases where it is strongly suspected that the fetus has not inherited the GCK mutation based on ultrasound monitoring of fetal growth. The risks of maternal

hypoglycemia and reduced fetal birthweight are significant concerns with the alternative strategy of insulin treatment in all cases. This study has important limitations, primarily related to the retrospective and observational survey-based design. For GCK-MODY in pregnancy, a randomized controlled trial is not ethical nor is it feasible because a majority of women do not have a genetic diagnosis [20]. Retrospective studies are currently the best methodology to assess management practices and have yielded important findings in prior publications [7, 8]. Self-reported treatment and complication information is inherently less reliable than medical record documentation and can omit important clinical factors. Furthermore, there is substantial clinical variability in these patients as illustrated by the wide range of blood sugars and insulin doses reported in this survey. Individual patient factors such as co-existing insulin resistance (as evident by blood sugars and A1c above typical GCK range) are important to assess and could impact the best treatment strategy during pregnancy. Despite these limitations, this study adds to the building knowledge about GCK-MODY in pregnancy and highlights the risks of adverse effects from insulin treatment, particularly in pregnancies with unaffected fetuses.

Several challenges remain for the care of these patients. The best method to infer fetal genotype during pregnancy is not known and it is unknown whether second trimester ultrasound is sensitive or specific enough to infer fetal genotype. It is also not clear if current insulin strategies are effective in reducing risk for macrosomia when a fetus is suspected to be GCK negative. Finally, the problem remains that many women with GCK-MODY do not have a genetic diagnosis at the time of pregnancy to direct management. Current ongoing research is investigating the use of BMI and glycemic parameters to identify women with GDM who should be screened for GCK-MODY, a strategy which has been effective in European and Australian cohorts [21, 22]. Ultimately, these data highlight the importance of additional studies to determine optimal management of GCK-MODY in pregnancy to minimize maternal morbidity (particularly hypoglycemia) and to optimize fetal outcomes.

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Fig. 1.
Birth weight percentiles by fetal genotype/maternal treatment

Table 1

Background information about survey respondents and pregnancies

Respondents	54
Pregnancies	128
Average age at pregnancy	29.9 years (range 17–41 years)
Average number of pregnancies	2.7 (range 1–6)
Hyperglycemia diagnosed before pregnancy	51 (40%)
GCK	18 (+ 2 suspected MODY)
Gestational diabetes	10
Type 1 diabetes	4
Type 2 diabetes or pre-diabetes	26
Caucasian race by self-report	48 (89%)

Table 2**Management of known GCK-MODY**

GCK diagnosis known before pregnancy	18/128 (14%)
Glucose-lowering medication prior to pregnancy	6 (33%)
Healthcare provider during pregnancy (respondents could select more than 1)	
Family physician	2 (11%)
General obstetrician	13 (72%)
High-risk obstetrician	11 (61%)
Endocrinologist	13 (72%)
Midwife	3 (17%)
Dietary changes recommended	10 (56%)
Treatment during pregnancy	
No medication	7 (39%)
Oral (glyburide)	1 (6%)
Insulin ^a	10 (56%)
Average timing of insulin initiation when started during pregnancy (weeks)	16.4 (range 5–32)
Pregnancy outcome	
Term birth	13 (72%)
Pre-term birth	3 (17%)
Currently pregnant	2 (11%)

^aIncludes seven cases where insulin was initiated during pregnancy and three cases where insulin was given before pregnancy and continued

Table 3

Fetal birth weight by genotype and maternal treatment

Infant genotype	Maternal treatment	Number of infants (full term)	Average birth weight (SD) for term infants (g)	<i>p</i> value	Average birth weight percentile (SD) ^a for all infants	<i>p</i> value
GCK +	Insulin	8 (7)	2967 (9330)		34 (27)	
	No treatment	15 (14)	3725 (568)	0.005	58 (33)	0.110
GCK –	Insulin	9 (5)	3757 (532)		84 (22)	
	No treatment	3 (2)	4023 (284)	0.489	90 (8)	0.530

p values are reported comparing birth weight and birth weight percentiles based on maternal treatment (insulin versus no treatment) for infants with each genotype (GCK + or GCK –). Linear regression models were fit with robust standard errors to account for the correlation among multiple births from the same mother *SD* standard deviation

^aBirth weight percentiles were calculated using 2013 Fenton growth charts to report percentiles and *Z* scores [13]