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Review

Management and Outcomes of Maturity-Onset Diabetes of the Young in Pregnancy

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Key Messages

- Maturity-onset diabetes of the young (MODY) is often underdiagnosed and clinical experience during pregnancy is lacking.
- Outcomes of pregnancies affected by MODY depend on both maternal and fetal mutation status as well as the glycemic environment in utero.
- When fetal mutation status is unknown, fetal growth should guide management and glycemic targets should be individualized.

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ABSTRACT

Maturity-onset diabetes of the young (MODY) is a group of monogenic disorders that accounts for 1% to 5% of diabetes. The most common mutations are those in the hepatocyte nuclear factor-1-alpha (HNF-1-alpha) and in the glucokinase (GCK) genes. Although management of MODY is well established, no guidelines currently exist for management during pregnancy. Both maternal glycemic control and fetal mutation status are factors that may influence outcomes during pregnancy. The primary aim of this project was to describe cases of MODY during pregnancy to highlight the clinical implications of management of this disorder during pregnancy. The Ottawa Hospital is the primary referral centre for high-risk obstetrical patients, including those with diabetes in pregnancy, in Ottawa, Canada. Referrals between 2008 and 2018 were reviewed and a case series of three women and five pregnancies is described. Together with the illustrative cases, a literature review of MODY in pregnancy is used to highlight clinical considerations unique to MODY in pregnancy. We describe 5 pregnancies with MODY-2 (GCK mutation) and MODY 3 (HNF-1-alpha mutation). Important issues identified included monitoring of fetal growth and individualization of maternal glycemic control, particularly in cases where fetal mutation status is unknown. Management of MODY in pregnancy is challenging and there is little evidence to guide recommendations. Fetal growth can be used to guide management of maternal glycemic targets when fetal mutation status is unknown.

Mots clés:
poids foetal
MODY
diabète monogénique
grossesse

RÉSUMÉ

Le diabète de la maturité apparaissant chez le jeune (MODY) constitue un groupe d'anomalies monogéniques qui représente de 1 % à 5 % des types de diabète. Les mutations les plus fréquentes sont celles des gènes codant pour le hépatocyte nucléaire facteur 1-alpha (HNF-1-alpha) et pour la glucokinase (GCK). Bien que la prise en charge du MODY soit bien établie, il n'existe actuellement aucune ligne directrice sur sa prise en charge durant la grossesse. La régulation de la glycémie maternelle et le statut mutationnel du fœtus sont des facteurs qui peuvent influencer les issues de la grossesse. L'objectif principal de la présente étude était de décrire les cas de MODY durant la grossesse pour démontrer les conséquences cliniques de la prise en charge de cette anomalie durant la grossesse. L'Hôpital d'Ottawa

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est le principal centre, à Ottawa, au Canada, qui offre des services de consultation en obstétrique aux patientes exposées à un risque élevé, y compris aux patientes diabétiques durant leur grossesse. Nous avons passé en revue les consultations entre 2008 et 2018, et nous avons décrit des séries de cas de 3 femmes et de 5 grossesses. Conjointement aux cas cités en exemple, une revue de littérature du MODY durant la grossesse est utilisée pour faire valoir les considérations cliniques propres au MODY durant la grossesse. Nous décrivons 5 grossesses de femmes ayant le MODY-2 (mutation codant pour la GCK) et le MODY-3 (mutation codant pour le HNF-1-alpha). Les points importants sont la surveillance de la croissance fœtale et l'individualisation de la régulation de la glycémie maternelle, notamment dans les cas où l'on ignore le statut mutationnel du fœtus. La prise en charge du MODY durant la grossesse est difficile. Il existe peu de données probantes pour mener à des recommandations. La croissance fœtale peut être utilisée pour orienter la prise en charge des valeurs cibles de la glycémie maternelle lorsqu'on ignore l'état mutationnel du fœtus.

Introduction

Maturity-onset diabetes of the young (MODY) is a monogenic subcategory of diabetes that can have major impacts on pregnancy outcomes. It is rare, accounting for ~1% to 5% of all patients with diabetes (1,2) and may often be misdiagnosed as type 1, type 2 or gestational diabetes. It is caused by a single gene mutation that results in a beta-cell defect. There are at least 14 known types of MODY, with MODY 1 to 3 accounting for ~85% of cases (3–5). The mutation is often autosomal dominant; thus, a fetus with an affected parent has a 50% chance of being affected (2,3). In each MODY type, fetal and maternal genotype and maternal glycemic control have major effects on pregnancy outcomes.

In this study we describe 5 pregnancies with MODY 2 (*glucokinase [GCK]*-MODY mutation) and MODY 3 (*hepatocyte nuclear factor HNF-alpha1* [*HFN1A*]-MODY mutation), to: 1) highlight challenges and clinical considerations in management of MODY during pregnancy, 2) review the literature concerning MODY in pregnancy and 3) propose a practical approach to management.

Case Reports

Table 1 presents a summary of the clinical characteristics and outcomes of each of the 5 pregnancies.

Patient 1

Pregnancy 1: A 27-year-old female gravida (G)1, at 29 weeks gestational age (GA), was referred to the Obstetrical Medicine Clinic for an abnormal oral glucose tolerance test (OGTT). A 50-g glucose challenge test performed at 24 weeks was abnormal at 8 mmol/L, and subsequent 75-g OGTT at 26 weeks had an abnormal fasting blood glucose (FBG) only (5.8 mmol/L; 1 h, 8.5 mmol/L; 2 h, 6.9 mmol/L). Her past medical history was significant for prediabetes diagnosed 5 years earlier, with FBG of 6.7 mmol/L and 75-g 2-h OGTT of 8.4 mmol/L. Her mother and maternal grandmother both had a diagnosis of type 2 diabetes managed with oral agents, and her brother had a diagnosis of *GCK*-MODY, managed with diet alone. A diagnosis of *GCK*-MODY was considered in our patient, but genetic testing was not performed at the time of presentation. Her prepregnancy body mass index (BMI) was 21.

Basal insulin was initiated at 29 weeks GA due to FBG being above target for pregnancy (>5.3 mmol/L). At 33 weeks GA, bolus insulin was added for postprandial hyperglycemia. By 36 weeks GA, she was on a multiple daily injection regimen with a total daily dose of about 0.55 U/kg. Estimated fetal weight was in the 20th percentile at 39+4 weeks GA. She was induced at 40+2 weeks GA and her blood glucose remained within the normal range during labour, without therapy. Weight gain during pregnancy was 12 kg. Birthweight was 3,125 g and in the ~20th percentile. The baby required initial resuscitation, with Apgar scores of 3 and 9, but did not have hypoglycemia. Placental weight was in the <10th percentile for GA (394 g).

Six months postpartum, a 2-h OGTT was positive at 16.7 mmol/L, confirming a new diagnosis of diabetes. At the time of the OGTT, the patient's weight was less than her prepregnancy weight. She had no risk factors for insulin resistance. She was referred to Endocrinology and Genetics for diagnosis and a mutation in the *GCK* gene was found, confirming *GCK*-MODY. Due to persistent impaired fasting glucose (FBG 6.1 to 6.9 mmol/L) and prediabetes (glycated hemoglobin [A1C] 6%), metformin 500 mg twice daily was prescribed. The decision to start metformin was made by her treating endocrinologist over a sulfonylurea to avoid hypoglycemia.

Pregnancy 2: The patient was referred to the Obstetric Medicine Clinic in week 11 of her second pregnancy. Preconception A1C was 6%. Metformin was continued during the pregnancy, but, due to elevated FBG (6.3 to 8.3 mmol/L), basal insulin (NPH at each night at bedtime) was added at 11 weeks GA. Insulin was titrated to pregnancy targets and she was receiving approximately 0.6 U/kg by 35 weeks GA.

Fetal growth was monitored with serial ultrasound. Ultrasound in the third trimester revealed an estimated fetal weight in the 20th to 25th percentile, provoking concern for overtreatment of maternal hyperglycemia in the context of an unknown fetal mutation status. A postprandial glucose of <10 mmol/L was then targeted and this less-tight glycemic control was successful in maintaining normal fetal growth.

At 38 weeks GA, she was induced and had an uncomplicated delivery (Apgar scores were 9/9). Birthweight was 2,924 g (20th percentile). Placental weight was not documented. Fetal genotypes for the patient's first and second babies are unknown.

Patient 2

Pregnancy 3: A 26-year-old woman, G2 T0 P0 A1 L0, diagnosed with *HNF1A*-MODY (MODY 3) by genetic testing at 13 years of age, was referred to the Obstetric Medicine Clinic at 28+4 weeks GA. She was initially managed with metformin and gliclazide, but, 3 years prior to the index pregnancy, she was able to able to stop all oral hypoglycemic agents and maintain glycemic control with diet alone. Her prepregnancy BMI was 22.1 kg/m^2 and she had no microvascular or macrovascular complications. The patient's mother was diagnosed with type 1 diabetes in her teens and both maternal grandparents had a diagnosis of type 2 diabetes, but no genetic testing was done to confirm these diagnoses.

At the time of referral to the Obstetric Medicine Clinic, the patient's preconception A1C was 5.7% and blood glucose was

Table 1
Clinical characteristics and pregnancy outcomes

	Patient 1		Patient 2		Patient 3
	Pregnancy 1	Pregnancy 2	Pregnancy 3	Pregnancy 4	Pregnancy 5
MODY type	*GCK*-MODY	*GCK*-MODY	*HNF1A*-MODY	*HNF1A*-MODY	*HNF1A*-MODY
Maternal age	27	29	26	28	28
Prepregnancy BMI	21	24	22	22	24
Family history of diabetes	Brother with *GCK*-MODY	Brother with *GCK*-MODY	Mother with diabetes	Mother with diabetes	Father and brother with diabetes
Preconception A1C	NA	6.0%	5.7%	6.0%	7.1%
Prior miscarriages	0	0	1	1	0
Prior live births	0	1	0	1	0
Treatment before pregnancy	None	Metformin	Diet	Sulfonylurea	Insulin
Treatment during pregnancy	Insulin	Insulin + metformin	Diet	Insulin	Insulin
GA insulin initiated	29 weeks	11 weeks	NA	22 weeks	Pre-existing
Insulin dose in third trimester	0.55 U/kg	0.6 U/kg	NA	0.2 U/kg	1.9 U/kg
GA of delivery	40+2 weeks	38+2 weeks	36 weeks	37+4 weeks	35+5 weeks
Mode of delivery	Induction, vaginal delivery	Induction, vaginal delivery	SVD	SVD	Unplanned C section
Maternal complications					Preeclampsia C section
Neonatal complications	Baby required resuscitation	None	Late preterm Jaundice Transient neonatal hypoglycemia	None	Late preterm
Fetal birthweight	3,125 g (~20th percentile)	2,924 g (~20th percentile)	3,430 g (~95th percentile)	2,995 g (40th percentile)	3,000 g (~90th percentile)

A1C, glycated hemoglobin; *BMI*, body mass index; C, caesarean; *GA*, gestational age; *GCK*, glucokinase; *HNF1A*, hepatocyte nuclear factor-alpha1; *MODY*, maturity-onset diabetes of the young; *NA*, nonapplicable; *SVD*, spontaneous vaginal delivery.

mainly within pregnancy targets (FBG <5.3 mmol/L, 1 h postprandial <7.8 mmol/L). She maintained glycemic control on diet alone throughout her pregnancy. The patient was discharged from clinic at 35+5 weeks GA with stable blood glucose and she delivered spontaneously preterm at 36 weeks GA at a community hospital. Fetal weight was 3,430 g (~95th percentile), and the baby had transient neonatal hypoglycemia and jaundice.

Four months postpartum, her A1C was 7.2% and home blood glucose monitoring revealed glucose in the 8- to 10-mmol/L range. She started on gliclazide MR 30 mg/day, which successfully managed her diabetes.

Pregnancy 4: The patient became pregnant after 1 year and she immediately stopped gliclazide. Her preconception A1C this time was 6%. She was able to maintain glycemic control during the first half of her pregnancy with diet and exercise. At 22 weeks GA, basal insulin was initiated for FBG above target (>5.3 mmol/L). Bolus insulin was later added to control her postprandial blood glucose. Fetal weight was estimated to be in the 42nd percentile at 30 weeks GA. She had an uncomplicated spontaneous vaginal delivery at 37+4 weeks GA. The baby's weight at birth was 2,995 g (~40th percentile). Insulin was stopped immediately postpartum, but blood glucose later became difficult to control, ranging between 9 and 10 mmol/L throughout the day. The patient was advised to restart on gliclazide but she opted to restart insulin therapy due to previous frequent hypoglycemia.

Patient 3

Pregnancy 5: A 28-year-old female G1 was diagnosed with diabetes at 11 years of age. She was started on insulin therapy 18 months after diagnosis. Her family history is positive for diabetes (father, brother and paternal grandfather had a diagnosis of type 1 diabetes). At age 20, she had genetic testing that confirmed an *HNF1A* mutation. Insulin was discontinued and she was managed with gliclazide with excellent glycemic control and no known diabetes-related complications. She was transitioned back to multiple daily injection of insulin due to plans for pregnancy.

The patient's A1C at the time of conception was 7.1% on 33 U/day (0.5 U/kg) of insulin. Insulin was titrated to pregnancy targets and, by the third trimester, she required up to 168 U/day (1.9 U/kg) of insulin. Gestational weight gain was 16 kg. During pregnancy, she developed mild–moderate diabetic retinopathy, which did not require treatment, and remained stable.

At 34 weeks GA, the patient experienced persistent hypoglycemia and her insulin requirements dropped by at least 25%. An ultrasound to rule out placental insufficiency was normal. Concurrently, she developed hypertension and proteinuria consistent with preeclampsia. She was admitted to hospital at 35 weeks GA for induction and required an emergency caesarean section due to abnormal fetal heart rate. Apgar scores were 7 and 9 and birthweight was 3,000 g (90th percentile for GA). Postpartum course was unremarkable.

Discussion

A MODY diagnosis may have significant impacts on pregnancy outcomes, and the recommended therapy may differ depending on the genetic status of both the mother and the fetus. It is, however, frequently misdiagnosed as type 1, type 2 or gestational diabetes (GDM), which may result in inappropriate glycemic targets and management during pregnancy. Table 2 presents key characteristics of the most common types of MODY and the impact on pregnancy. Next, we highlight the 3 most common forms of MODY (*GCK*-MODY, *HNF1A*-MODY and *HNF4A*-MODY) and their impact on pregnancy.

GCK-MODY (MODY 2)

Prevalence, pathophysiology and clinical characteristics: MODY 2, or *GCK*-MODY, is caused by a mutation in the *GCK* gene. *GCK*-MODY is one of the most common types of MODY, with prevalence estimated to be 1 in 1,000 Caucasians (3). Among women with GDM, the prevalence of *GCK* mutation has been reported to be 0.93%. Criteria for identifying women with *GCK*-MODY in pregnancy has been proposed and validated (6,7). Women with both fasting hyperglycemia >5.5 mmol/L and BMI <25 kg/m^2 had a 67% sensitivity and 99% specificity for screening positive for *GCK*-MODY (3,7,8).

Table 2
Effects of MODY in pregnancy and recommended management

MODY type	Clinical presentation	Treatment outside of pregnancy	Fetal implications in pregnancy	Management in pregnancy
GCK-MODY (MODY 2)	• Mild fasting hyperglycemia, low increments in glucose rise with OGTT • Lack of typical features for T2DM or insulin resistance • No microvascular complications of diabetes • Often diagnosed in pregnancy as GDM	Diet + lifestyle	• Higher miscarriage rate seen in some studies • Fetal growth is affected by fetal mutation status: 1. Unaffected fetus: High BW is expected if maternal hyperglycemia is untreated 2. Affected fetus: Normal BW is expected without treatment *If treated with insulin, there is a theoretical risk of reduced fetal growth.* 3. Affected fetus in an *unaffected* mother: Reduced BW	• If treatment is required, insulin is first line • When fetal genotype is known: 1. Unaffected fetus: Tighter glycemic control is preferred 2. Affected fetus: Less-tight glycemic targets—pharmacologic treatment not necessary • When unknown fetal genotype, treat with insulin only if ultrasounds show the development of macrosomia or accelerated growth (abdominal circumference >75th percentile) • Monitoring with serial ultrasound starting at 26 weeks at 2-week intervals
HNF1A-MODY (MODY 3)	• Early-onset diabetes in at least 1 family member • Large glucose increments on OGTT • Lack of typical features for T2DM or insulin resistance • Microvascular complications are similar to those in T1DM • Low threshold for glycosuria	• Low-dose SU • Can consider meglitidines and GLP-1 agonists • Insulin therapy may eventually be required as disease progresses	• No association between fetal genotype and BW or neonatal hypoglycaemia. • Fetal growth is affected by maternal glycemic control: similar to pre-existing diabetes (regardless of if fetus is affected or unaffected) • Case reports exist of neonatal hypoglycemia in the affected fetus	• Management is similar to pre-existing diabetes. • Insulin is preferred over SU: 1. For patients managed with SU prepregnancy, options include switching to insulin preconception or before the third trimester 2. Glyburide is an option during pregnancy, although, when used in the third trimester (in the case of GDM), it has been associated with macrosomia and neonatal hypoglycemia • Monitoring with serial ultrasounds starting at 28 weeks, at 2-week intervals • Early delivery should be considered based on fetal growth on ultrasound assessment
HNF4A-MODY (MODY 1)	• Similar characteristics as MODY 3 but no glycosuria • Diagnosis suspected in the presence of strong family history, macrosomia or neonatal hypoglycemia	Low-dose SU	• Fetal growth is affected by fetal mutation status: 1. Affected fetus: Larger BW and higher rates of macrosomia have been observed. 2. Unaffected fetus: Normal BW is expected, no hypoglycemia 3. Affected fetus in unaffected mother: Larger BW and higher rates of macrosomia • Maternal hyperglycemia may have an additive effect on fetal BW • Risk of transient or persistent neonatal hypoglycemia; duration and severity are variable	• Insulin is preferred over SU with similar considerations to *HNF1A*-MODY • Monitoring with serial ultrasound assessment starting at 28 weeks, at 2-week intervals • Early delivery should be considered based on fetal growth on ultrasound • Postpartum, monitor for prolonged neonatal hypoglycemia for ≥48 h; in extreme cases of prolonged hypoglycemia, diazoxide may be required

BW, birthweight; *GCK*, glucokinase; *GDM*, gestational diabetes mellitus; *GLP-1*, glucagon-like peptide 1; *HNF1A*, hepatocyte nuclear factor-alpha1; *MODY*, maturity-onset diabetes of the young; *OGTT*, oral glucose tolerance test; *T1DM*, type 1 diabetes mellitus; *T2DM*, type 2 diabetes mellitus; *SU*, sulfonylurea.

GCK is the rate-limiting step in the glycolysis pathway and acts as the beta cell's glucose sensor stimulating insulin release (5,9,10). As a consequence, individuals with a *GCK* mutation have mild fasting hyperglycemia. Other key clinical characteristics are described in Table 2. Given that women with *GCK*-MODY are generally asymptomatic, they are often only identified during GDM screening. Outside of pregnancy, these individuals typically do not respond well to pharmacologic management, and treatment is often not required. Management with diet alone is usually sufficient. *GCK*-MODY is usually not associated with vascular complications.

Pregnancy implications: GCK-MODY is unique as the impact on the fetus is dependent on both maternal and fetal mutation status. However, prenatal testing is not commonly performed to screen for MODY and the mutation status of the fetus is often unknown.

Three possible scenarios should therefore be considered:

1. *Unaffected fetus of an affected mother:* In response to hyperglycemia in the mother, the fetus will be hyperinsulinemic in utero. As insulin is a growth factor in pregnancy, hyperinsulinemia leads to increased birthweight and risk of macrosomia (11). One of the largest observational studies to date, which included 82 offspring with known genotypes among 42 women with *GCK*-MODY demonstrated that offspring born without the mutation were larger than those with the mutation (4.1 kg vs 3.4 kg; $p<0.001$) (12). There was also a significantly higher rate of macrosomia among offspring without the mutation as compared to those with the mutation (39% vs 7%).

2. *Affected fetus of an affected mother:* When a *GCK* mutation is present, the fetus shares the mother's higher setpoint to hyperglycemia and, therefore, will not oversecrete insulin as in the case of an unaffected fetus. Hyperglycemia is sensed as "normal," and birthweight should not be affected. Observational studies confirmed significantly lower birthweight among offspring who inherited the mutation from at least 1 parent compared with offspring who were not affected by the mutation (mean 46.8th vs 85th percentile, $p<0.001$) (1,12). In the case of a *GCK* mutation, insulin therapy would cause a reduction in blood glucose levels seen in the fetus, which can theoretically result in reduced fetal growth (13). This may explain the low birthweight in pregnancy 1 (Table 1), in which the mother was treated with insulin but the fetal mutation status was unknown.
3. *Affected fetus of an unaffected mother:* Similarly, when a fetus inherits the mutation paternally and the mother is unaffected, fetal weight was found to be lower by ~400 g as compared with unaffected offspring (12). The mechanism is similar: A fetus with a nonfunctioning GCK enzyme has a higher threshold for insulin secretion, and normoglycemia may lead to a reduction in growth. In a retrospective chart review of 28 cases of *GCK*-MODY–affected offspring, birthweights were significantly lower in the group that inherited the mutation from the father than those who inherited it from the mother (14). In addition, there were more cases of small for gestational age (SGA; 43% vs 10%), which was defined as birthweight in <10th percentile. This suggests that maternal hyperglycemia in a mother with *GCK*-MODY can balance the effect of a *GCK* mutation in a fetus. In a normoglycemic environment in utero, a *GCK*-mutated fetus would be hypoinsulinemic, which may lead to a reduced growth (14).

Effect on placenta size: In pregnancy 1 (Table 1), with a *GCK* mutation treated with insulin, placental weight was found to be in <10th percentile, with fetal weight in the 20th percentile. In a study that examined placental weight in *GCK*-MODY, offspring that carried the mutation were found to have a lighter placenta when compared with their siblings. In normal pregnancies, placental weight was found to correlate with birthweight and with cord insulin levels (15). In the third trimester, most of the insulin receptors are on the fetal side of the placenta. Therefore, fetal insulin likely regulates placental growth, which affects fetal growth (10,15). Data have shown that fetal insulin secretion decreases by ~70% in the presence of a *GCK* mutation. In *GCK*-affected fetuses, the reduced insulin secretion leads to reduced placental and fetal growth. Although the mutation status of the fetus remains unknown in pregnancy 1, the low birthweight, together with the reduced placental weight in the setting of maternal insulin therapy, suggests that the fetus likely inherited the *GCK* mutation.

Management: Prenatal counselling. Making a genetic diagnosis of *GCK*-MODY is essential so that family members can undergo genetic testing, ideally before pregnancy.

Prenatal counselling in women with *GCK*-MODY is particularly important for prevention of fetal complications. In addition to the risk of macrosomia, hyperglycemia in the first trimester is known to be teratogenic and can lead to congenital anomalies or miscarriage in uncontrolled type 1 and 2 diabetes. However, the effect of mild hyperglycemia in *GCK*-MODY in early pregnancy is unknown. One observational study showed higher miscarriage rates among women with *GCK*-MODY (33% vs 15% the regular population) (16). However, these results were not replicated in other studies.

Overall, prenatal counselling regarding good glycemic control prior to pregnancy is similar for type 1 and type 2 diabetes (Figure 1). Given that pharmacologic therapy is not indicated in nonpregnant individuals with *GCK*-MODY, we propose close glucose monitoring and management with diet alone. The difference lies in the management of diabetes during pregnancy. Women with *GCK*-MODY can be advised that glycemic targets may differ from others depending on the suspected fetal genetic state.

Glycemic management: Given the effects of fetal mutation status on fetal growth and birthweight, near-normal glycemic control is not

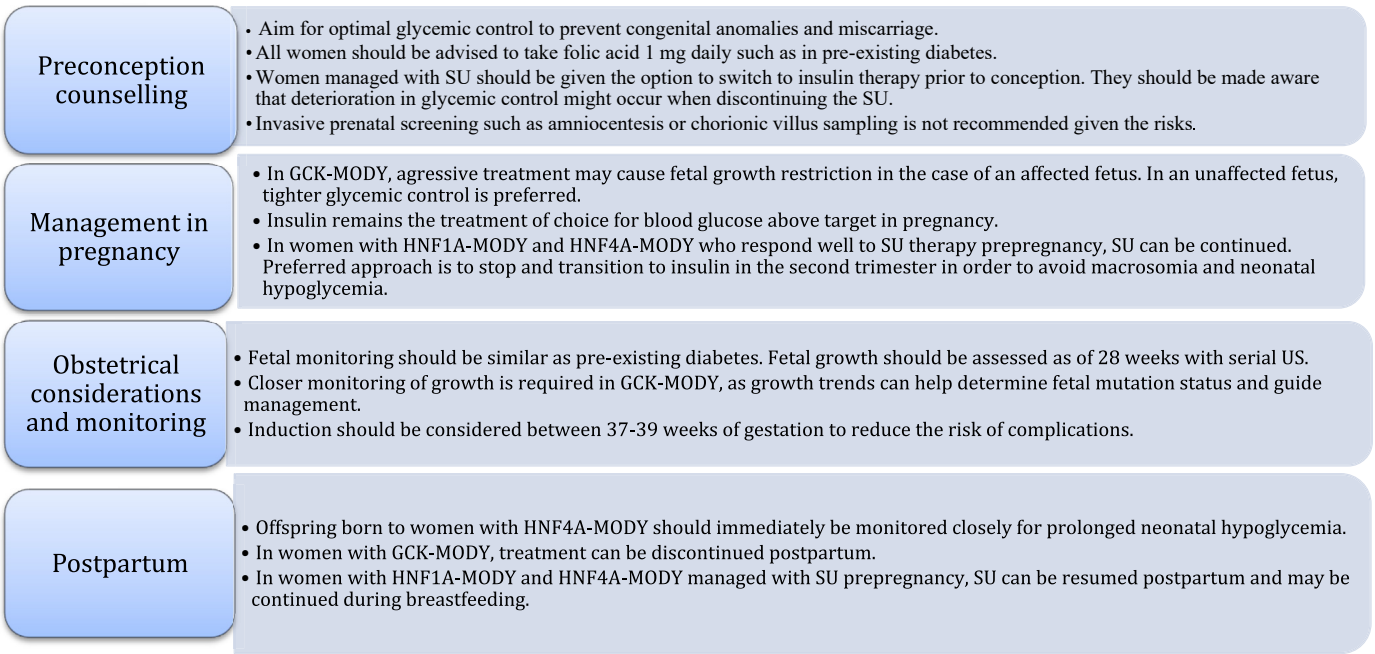

Figure 1. A practical approach to MODY in pregnancy. *GCK*, glucokinase; *HNF1A*, hepatocyte nuclear factor-alpha 1; *HNF4A*, hepatocyte nuclear factor-4-alpha; *MODY*, maturity-onset diabetes of the young; *SU*, sulfonylurea; *US*, ultrasound.

the gold standard for management of women with *GCK*-MODY. In an affected fetus, insulin therapy may not be necessary.

With an unknown mutation status of the fetus, treating physicians must depend on other approaches to decide on management. Invasive testing, such a chorionic villus sampling or amniocentesis, is not recommended due to the risk of miscarriage. In one report, 2 women with *GCK*-MODY who had had chorionic villus sampling for high-risk aneuploidy screen, also had the fetuses tested for MODY, because DNA was available for other reasons. The fetuses were tested and confirmed positive for the *GCK* mutation. Hyperglycemia was not treated during pregnancy and resulted in good outcomes with normal birthweights (17). Noninvasive prenatal testing with cell-free circulating DNA is not yet available for *GCK*-MODY, but it may be used in the future to help guide both antenatal and postnatal management. Although there is 1 published case of cell-free circulating DNA used for suspected neonatal diabetes, there have not been any published cases of its use in *GCK*-MODY (17,18).

The suggested optimal way to monitor and guide glycemic management of *GCK*-MODY is with frequent fetal ultrasound for growth. Ultrasound every 2 weeks starting at 26 weeks has been recommended (9). When accelerated fetal growth is detected or abdominal circumference is disproportionately above the 75th percentile, this implies that the fetus does not have the mutation and insulin should be used (9,10). In a number of randomized, controlled studies of women with GDM, strict or relaxed glycemic control was used according to serial fetal abdominal circumferences on ultrasound, with good results (19). To date, no study has been done in women with MODY. In pregnancy 2 (Table 1), relaxed glucose targets were successfully used toward the end of pregnancy given the reduced fetal growth seen on serial ultrasound assessment.

Insulin therapy: In management of women with hyperglycemia secondary to GDM, insulin is first line when diet control alone fails. Among women with *GCK*-MODY, there is little evidence to show that insulin impacts pregnancy outcomes. In the study by Spyer et al, 38% of women with *GCK*-MODY were treated with insulin. When comparing each group, there was no statistically significant difference in fetal birthweights among diet-controlled vs insulin-treated women. However, women treated with insulin delivered at an earlier GA and had higher rates of induction and labor assistance. The authors concluded that these results may have been related to late timing of insulin initiation (9,12).

Similarly, another retrospective analysis did not show any statistically significant difference in birthweight in insulin-treated and noninsulin-treated women. Rates of macrosomia in the study were higher in the noninsulin-treated vs insulin-treated groups (62.5% vs 33.3%), but not statistically significant. Complication rates were also higher in the noninsulin-treated group compared with the insulin-treated group (37.5% vs 0%). These complications included neural tube defects, shoulder dystocia and prolonged neonatal hypoglycemia (16).

There is 1 case report in which insulin was used and resulted in SGA in the case of an affected fetus. However, larger observational studies did not show any SGA among affected offspring from insulin-treated mothers (12,16). Although not clearly associated, there is potential harm for insulin treatment in the case of a known *GCK* mutation, and therefore unnecessary treatment with insulin should be avoided.

With regard to maternal risks, hypoglycemia is a possible complication of insulin therapy. With a higher glucose setpoint in *GCK*-MODY, higher insulin doses are often required.

Insulin therapy can be discontinued postpartum and patients are generally managed with diet alone.

In summary, *GCK*-MODY is a rare genetic disorder that may have implications for both mothers and offspring. Current data suggest that treatment in pregnancy should be individualized and tailored to fetal growth. With a normal-growing fetus or evidence of reduced growth, higher blood glucose can be targeted and insulin or pharmacotherapy may be able to be avoided. For fetuses with evidence of increased growth, lower blood glucose levels should be targeted and appropriate insulin management initiated as required.

HNF1A-MODY (MODY 3)

Prevalence, pathophysiology and clinical characteristics: HNF1A-MODY is the most common type of MODY, accounting for up to 65% of cases. In pregnancy, the reported prevalence is 1% (10). It is caused by a defect in hepatocyte nuclear factor *HNF1A*, which regulates the expression of key enzymes in the glucose metabolism pathway. A mutation in *HNF1A* decreases beta-cell proliferation and increases apoptosis, leading to a progressive decline in beta-cell function and failure of insulin secretion (3).

Patients with *HNF1A*-MODY usually present early in adolescence and are generally nonobese (Table 2). Unlike with *GCK*-MODY, they can have normal fasting glucose but tend to have an abnormal response to an OGTT (9).

Individuals with *HNF1A*-MODY have an increased sensitivity to sulfonylureas, which represent the first-line treatment outside of pregnancy (10,13,20). Meglitinides and glucagon-like peptide 1 agonists have also been shown to reduce postprandial glucose excursions (21,22). Due to the progressive decline in beta-cell function, these patients may eventually require insulin therapy. Patients with *HNF1A*-MODY are at risk of vascular complications of diabetes.

Pregnancy implications: In *HNF1A*-MODY, it is the maternal glycemic control rather than fetal mutation status that primarily determines fetal outcome. Although case reports of macrosomia and neonatal hyperinsulinemic hypoglycemia exist, retrospective studies have not shown a significant increase in fetal birthweight or incidence of hypoglycemia among carriers of the *HNF1A* mutation compared with unaffected offspring (4,16,23,24). Among mothers with the mutation, birthweights of offspring were found to be increased as a result of hyperglycemia, but this was independent of fetal mutation status (23).

In a retrospective chart review that included 25 women with *HNF1A*-MODY and a total of 76 pregnancies, there was no significant difference in birthweight between offspring who were and were not affected by the mutation (3.8 kg vs 3.4 kg, p=0.8) (16). Miscarriage rate was found to be comparable with that of the general population at ~15%.

Pregnancy 5 (Table 1) demonstrates the similarities with nonmonogenic forms of diabetes during pregnancy. The patient developed diabetic retinopathy during pregnancy as well as preeclampsia—both of which are known risks of pre-existing diabetes in pregnancy.

Management in pregnancy: Prenatal counselling. The approach to prenatal counselling is similar to that in women with type 1 or type 2 diabetes and involves targeting good glycemic control prepregnancy (25). Similarly, women should be screened for diabetes-related complications. Counselling on sulfonylurea use during pregnancy should be addressed preconception, as discussed in what follows.

Glycemic management: Outside of pregnancy, sulfonylureas are the recommended therapy for *HNF1A*-MODY, but there is no consensus for use of sulfonylureas in pregnancy. There are no

reported cases of women with *HNF1A*-MODY treated with sulfonylureas during pregnancy, so the effects of sulfonylurea use in this population is based on extrapolation from other populations. Glyburide is the most widely used sulfonylurea in pregnancy and there are >9,500 exposures documented in the literature, mostly among women with GDM (23). There is evidence that glyburide crosses the placenta and is measurable in fetal umbilical vein samples (9). Diabetes Canada guidelines (2018) suggest that glyburide should be avoided in pregnancy, but can be used as a third-line treatment in GDM if insulin and metformin are not available (25).

Glycemic control is important in the first trimester to avoid fetal malformations. In women with *HNF1A*-MODY who respond well to sulfonylureas, it is unclear whether sulfonylureas should be discontinued in early pregnancy. In a meta-analysis of 471 women with type 2 diabetes who were exposed to sulfonylureas in the first trimester, there was no significant difference in malformations or neonatal death (23). Thus, glyburide could be considered in the first trimester of pregnancy in certain cases if glucose is well controlled and there is concern about potential hyperglycemia with changing therapy. Evidence for use of glyburide in late pregnancy is primarily derived from the GDM population. In a 2014 meta-analysis of 2,151 women with GDM, glyburide was associated with increased birthweight, macrosomia and neonatal hypoglycemia when compared with insulin, raising concerns about management with glyburide in the third trimester (26).

Overall, the decision on sulfonylurea use in pregnancy in *HNF1A*-MODY involves balancing the risks and benefits in the first trimester compared with those in the third trimester. Options include switching to insulin preconception to avoid disruptions in glucose control in early pregnancy or continuing glyburide throughout the first trimester and switching to insulin before the third trimester to avoid the risk of macrosomia and neonatal hypoglycemia that may be associated with third trimester use of glyburide (23).

In pregnancy 5, the decision was made to switch from a sulfonylurea to insulin prepregnancy to optimize glycemic control preconception.

Insulin therapy: In a 2015 study, Bacon et al demonstrated there was no difference in mean birthweight between women treated with insulin vs those not treated with insulin (3.2 kg vs 3.6 kg, p=0.5), but the rate of macrosomia was higher among the *HNF1A* offspring who were not treated with insulin (25%). The rate of complications, specifically prolonged neonatal hypoglycemia, was higher in unaffected offspring who were not treated with insulin (16).

In patient 2, outcomes differed when she was treated with diet alone (pregnancy 3) compared with when she was treated with insulin (pregnancy 4). When no insulin was used, outcome was complicated by preterm labour, macrosomia and hypoglycemia, which contrasted to positive outcomes during her second pregnancy when insulin was used. This example highlights the benefits of treatment with insulin in *HNF1A*-MODY in pregnancy.

Fetal monitoring during pregnancy in *HNF1A*-MODY is similar to that for pre-existing diabetes. Early ultrasound to screen for fetal anomalies is typically done followed by periodic ultrasound assessment later in pregnancy to monitor for fetal growth (9).

Postpartum, women can resume sulfonylurea therapy, as it is safe in breastfeeding (27).

HNF4A-MODY (MODY 1)

Prevalence, pathophysiology and clinical characteristics: HNF4A-MODY is less common than *HNF1A*-MODY and accounts for approximately 10% of MODY (28). The disorder is caused by a defect in *HNF4A* transcription factor, which is an upstream regulator of *HNF1A*. For this reason, clinical presentation is very similar to *HNF1A*-MODY (9,13). Like *HNF1A*-MODY, patients are typically nonobese and lack signs of insulin resistance. A strong family history of diabetes is usually present. Diagnosis is suspected with a history of fetal macrosomia or prolonged neonatal hypoglycemia. Similar to *HNF1A* mutation, it shares the same sensitivity to sulfonylureas, which are the treatment of choice outside of pregnancy.

Pregnancy implications: In contrast to *HNF1A*-MODY, fetal genotype does have significant implications on outcomes in pregnancy. A fetus that inherits the mutation will have increased insulin secretion in utero, which in turn leads to increased birthweight and risk of macrosomia. In addition to increased fetal growth, fetal hyperinsulinemia may also result in prolonged neonatal hypoglycemia postpartum. In contrast, a young adult with an *HNF4A* mutation has reduced insulin secretion over time, due to progressive decline in beta-cell function. This is described as a "dual phenotype" (3).

Observational studies have shown larger birthweights in offspring with the mutation as compared to those without the mutation. In a study that looked at birthweights of 15 families with an *HNF4A* mutation, infants who had the mutation also had significantly higher birthweights than those without (difference in corrected mean birthweight of 790 g, p<0.001). Macrosomia was higher among family members with the mutations compared to those without (56% vs 13%, p<0.001). When the fetus inherited the mutation from the mother, the incidence of macrosomia was higher (64%) than if it was paternally inherited (46%). This is likely explained by the additional effect of maternal hyperglycemia on fetal growth. In addition, hyperinsulinemic hypoglycemia was seen in 15% of neonates with the mutation and was not seen among any of those without the mutation (p=0.003) (3,5,23,24).

Management in pregnancy: Data about the effects of therapy in these patients are lacking. One report did not show a decrease in macrosomia or hypoglycemia in women treated with insulin (23). Recommendations about sulfonylurea use in pregnancy, as described for *HNF1A*-MODY, apply to *HNF4A*-MODY and should be determined on an individual basis. Insulin therapy remains the gold standard in diabetes therapy during pregnancy. Monitoring is similar to that in other types of diabetes, including *GCK*-MODY and *HNF1A*-MODY. Serial ultrasound assessments for fetal growth, starting at 28 weeks, are recommended.

Due to the high risk of developing neonatal hyperinsulinemic hypoglycemia, postpartum monitoring for 24 to 48 h is essential. The duration and severity of hypoglycemia is variable. Neonates may require therapy, such as glucose infusions, glucagon or diazoxide, depending on the severity. In some cases, diazoxide use is required for several years (13,23).

Long-term effects: An *HNF4A* mutation should be strongly suspected in a neonate with macrosomia, prolonged neonatal hypoglycemia and positive family history for MODY. Genetic testing and early diagnosis is important for long-term follow up of these individuals. In a child with a known *HNF4A* mutation, screening for diabetes is recommended annually starting at 10 years of age.

Conclusions

Management of MODY in pregnancy is associated with many challenges. We have reported 5 cases of women with *GCK*-MODY and *HNF1A*-MODY, and major issues from each case were identified. A practical approach to MODY is presented in Figure 1.

Due to the rarity of the disease, evidence-based recommendations are lacking, and our understanding of the condition is based on observational studies alone. Outcomes depend on both maternal and fetal mutation status as well as the glycemic environment in utero. Therefore, preconception counselling and close surveillance during pregnancy are necessary to ensure good outcomes. Less-intensive treatment targets based on suspected fetal genotype are unique to *GCK*-MODY. When fetal mutation status is unknown, particularly in *GCK*-MODY, fetal growth should guide management and glycemic targets should be individualized.

Author Disclosures

Conflicts of interest: None.

Author Contributions

SM and JM conceived of the study and designed the analysis; SM collected the data; SM, JM, AK, TS, HC, PO contributed and analyzed the data; SM and JM, wrote the initial draft of the paper; SM, JM, AK, TS, HC, PO reviewed, edited and approved the final manuscript.

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