



Raised Blood Glucose Due to Heterogeneous Glucokinase Gene Mutation (MODY 2) Diagnosed for the First Time in Pregnancy: The Dilemmas and Successful Management- Case Report and Review of Literature

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Abstract

Hexokinase mutation (MODY-2) is frequently misdiagnosed as either type I or type II diabetes mellitus especially if presented for the first time during pregnancy. Generally MODY affects 1% to 2% of diabetes. The defect in glucose sensing mechanism in MODY-2 results in higher set point for maintenance of glucose homeostasis. Treatment is not recommended outside the pregnancy however in pregnancy fetal abdominal circumference helps to decide about the insulin requirement. We are presenting a case in which MODY 2 was diagnosed for the first time after her first pregnancy, there were controversies around the first pregnancy and the second one was uneventful. Genetic testing is mandatory to establish the diagnosis. In addition to it, implications of MODY and its subtypes along with pattern of inheritance and management aspects have been discussed in detail.

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Introduction

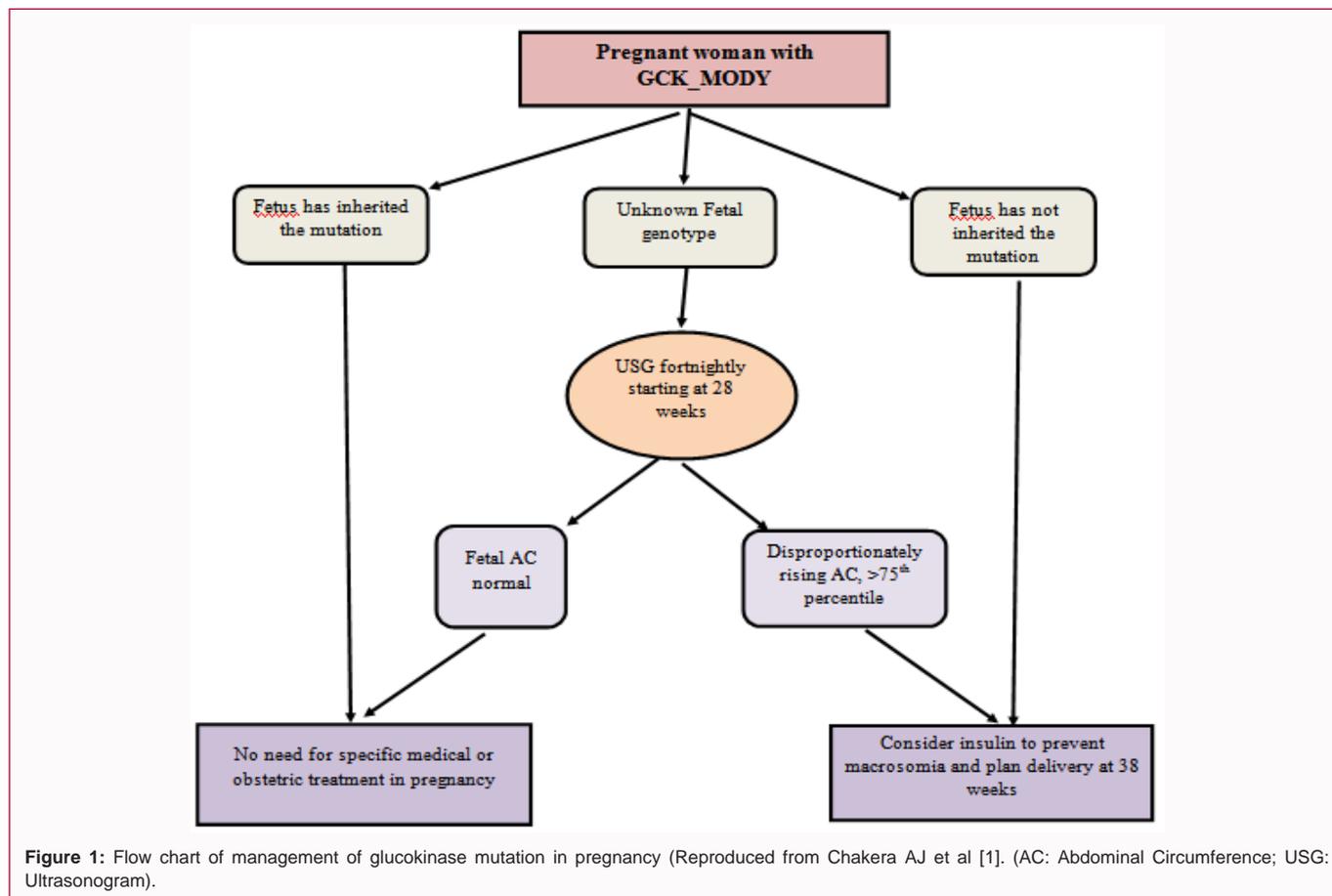
Gestational diabetes is the one of the most common medical disorder in pregnancy apart from anemia and hypertensive disorders of pregnancy. It's defined as glucose intolerance of varying severity either with its first onset or recognition during pregnancy. It is not uncommon for type II or even type I diabetes recognised for the first time in pregnancy. Rarely, Glucokinase gene mutation related hyperglycaemia-Maturity Onset Diabetes of the Young (GCK-MODY) may get detected for the first time in pregnancy [1] (Figure 1). If the diagnosis is known the management is straight forward. However during pregnancy it is not uncommon to misdiagnose it as Gestational Diabetes Mellitus (GDM) and they may not respond to usual treatment modalities of gestational diabetes. We are presenting a case of pregnant woman with glucokinase mutation with the clinical dilemma in management during her first pregnancy before its recognition and successful management of the same once the genetic mutation is identified.

Case Presentation

The pregnant lady presented to us at 24 weeks with known case of genetic mutation. She was G2L1 with previous caesarean section that had high fasting blood sugar values at the time of presentation. Her previous pregnancy was managed at different hospital. She was diagnosed to have GDM at 28 weeks in her previous pregnancy and which required treatment with insulin apart from Medical Nutrition Therapy (MNT). In spite of 80 units of insulin per day (Figure 2) it was difficult to achieve optimal control of blood sugar throughout the pregnancy. Since there was a lag in the growth of the fetus pregnancy was terminated at 36 completed weeks. An elective caesarean section was done in view of Fetal Growth Restriction (FGR) and the neonatal outcome was good. Her blood sugar level did not come down as in cases of GDM and hence she was evaluated for MODY. It was found to be that the mutation in hexokinase enzyme which was responsible for the marginal fasting hyperglycaemia and her medications were stopped. She was on follow up. After 4 years, the present pregnancy was after the diagnosis of hexokinase mutation. Even though she had high fasting blood sugar values and mild post prandial hyperglycaemia she was not on any medications. In discussion with endocrinologist, it was decided to start insulin only if post prandial blood sugar is more than 200 mg % and the abdominal circumference of the growing fetus was also used as a guide to decide

Table 1: Diagnostic criteria for glucokinase gene mutation related hyperglycaemia in pregnancy [1,12].

Persistent fasting hyperglycaemia before, during and after pregnancy, in the range of 5.5-8.1 mmol/L
An increment of <4.6 mmol/L on at least 1 OGTT (either during or after pregnancy)
A parent may have mild type II DM but often it has not been detected. A negative family history does not exclude the condition
BMI <25 kg/m ²



about the initiation of insulin treatment. With minimal physical activity and diet her blood sugar levels were always between 140 to 160 mmHg. She did not develop any other complications and the target ultrasound was normal. Fetal biometry at appropriate intervals did not show any evidence of macrosomia. It was decided to allow her for Trial of Labour after Caesarean Section (TOLAC) after assessing the risks and explaining the pros and cons of it. Epidural analgesia was offered as labour analgesia in discussion with anaesthesiologist. She came with Rupture of Membranes (PROM) at 37th week and the labour was induced with oxytocin and had successful Vaginal Birth after Caesarean Section (VBAC). The baby weighed 3.2 kg and had shoulder dystocia which required Mc Robert’s manoeuvre. Baby had mild Erb’s palsy and recovered completely over the period of 6 weeks.

Discussion

Glucokinase is the key regulatory enzyme in regulation of insulin secretion from pancreatic cells [2,3]. Mutation in this enzyme can lead to either hypoglycaemia or hyperglycaemia. There are about 195 mutations have been detected. Heterogeneous mutation in this enzyme usually presents as MODY and it is detected in later part of life and is called as MODY-2. Since there is a defect in glucose sensing mechanism the glucose homeostasis is maintained at a higher set point

resulting in mild, asymptomatic fasting hyperglycaemia. They don’t develop microvascular complications usually and the prevalence of macro vascular complications is similar to general population.

This monogenic diabetes, caused by single gene mutation was first described by Tatersall et al. [4]. There is paucity on specific data about monogenic diabetes in pregnancy. The GCK-MODY is unique and it differs from others sub groups. GCK-MODY usually presents with mild hyperglycaemia and has distinct pathology unlike other subtypes. Other types of MODY are usually born normoglycaemic and they develop diabetes in adolescents or in young adults and it progresses over the period of time. Such individuals require treatment outside the pregnancy too as there is increased risk of diabetic related complications.

It affects 1% to 3% of all GDM population. The prevalence of HCK-MODY may not be different in different population unlike type II DM which is more prevalent in black and south Indian population [1]. The universal screening gives an opportunity to pick up the condition in pregnancy and the diagnostic criteria is similar to non-pregnant population. Lachance et al. [5] had reviewed a total 11 cases in a cohort study in which 4 were diagnosed in pregnancy and 7 were diagnosed after the pregnancy. It was found that fasting blood sugar

Table 2: Pregnancy implications in different type of MODY Wheeler BJ et al. [11].

Gene and MODY subtype in the mother	Gene Function + Phenotype	Pregnancy implication	Prognosis
Glucokinase (GCK) gene (MODY 2)	Catalyses conversion of glucose to glucose-6-phosphate Reduced glucose sensing by β cells-Mild diabetes	Unaffected fetus-Excess fetal growth if no GCK mutation Affected fetus-maternal hyperglycemia will be sensed as normal and result in normal growth	Generally non or slowly Progressive Complications rare
HNF1-alpha gene (MODY 3)	Regulates insulin gene Transcription Reduced insulin secretion/diabetes and marked sensitivity to sulfonylurea	Not associated with increased birth weight	Progressive May require insulin May develop secondary complications
HNF4-alpha gene (MODY 1)	Nuclear transcription factor that regulates hepatic and pancreatic β cell gene expression Reduced insulin secretion/diabetes and marked sensitivity to sulfonylurea	Associated with increased birth weight (50% of babies) Can cause neonatal Hyperinsulinaemic hypoglycaemia	Progressive May require insulin May develop secondary complications
HNF1-beta gene (MODY 5)	Regulates HNF4 α gene Transcription Insulin resistance + wide clinical spectrum +/- Urogenital/pancreatic Anomalies & Pancreatic exocrine Failure +/- Developmental delay/Learning difficulties	In affected mother-possible pregnancy complications associated with genital and uterine malformations, such as recurrent miscarriages or preterm labour For affected fetus-Urogenital malformations may be visible on prenatal ultrasound	Progressive beta-cell failure with diabetes onset around Puberty Insulin resistance without Obesity Insulin dependence

level was ≥ 5.5 mmol/L in 98% of cases (Table 1). However most of the time they were erroneously diagnosed as either GDM or type II DM which can lead to unnecessary interventions. Generally any treatment with an intent to normalize the blood sugar is ineffective outside the pregnancy in women with GCK-MODY as there is lack of evidence of any long term complications [1,6].

Fetal growth depends on whether the fetus inherits the GCK gene mutation from the mother or not. On routine USG if there is evidence of increased abdominal growth, it suggests that the fetus is unaffected and insulin treatment is required in such situations only [7,8]. If fetus is inherited with GCK mutation and insulin treatment is initiated in such women, it will result in fetal growth restriction which happened in her first pregnancy (inappropriate high dose of insulin to optimize glucose homeostasis resulted in baby weight of 2.25 kg). Generally the treatment is not initiated before 32 weeks. There is 50% chance that the offspring is affected [9]. Knowledge of fetal genotyping is not usually not mandatory to determine the need for initiation of insulin treatment and regular monitoring of abdominal circumference would suffice. Whenever the fetus is unaffected, the AC usually goes beyond 75th percentile. In such situations, an intensive insulin treatment is required and large doses of insulin may be required which may be difficult sometimes to reduce the blood sugar values to near normal range of pregnancy.

The birth weight was more than 90th percentile in 55% of babies who were not inherited with hexokinase enzyme compared to only 9% when the inheritance was present [7]. It was also found that there was reduction in birth weight of around 400 gm in those babies who were inherited and the mother was not. There is no increased risk of congenital anomalies reported so far in women with hexokinase

mutation. In spite of having an impact on fetal growth in GCK mutation, the evidence is lacking for the development of any long term complications in the off spring [10].

There is a data of metformin outside the pregnancy and it shows that there is no effect on lowering blood glucose in women with hexokinase mutation. There is no place for OHA in women with hexokinase mutation in pregnancy.

If the fetal growth is unaffected, pregnancy can be continued till term and the pregnancy is terminated at 38 weeks if there is any evidence of macrosomia. The pregnancy implication in different types of common forms of MODY is described in Table 2 [11].

Postpartum evaluation of the mother and genetic screening is needed if the condition is not diagnosed earlier. There is no need for routine follow up of women with glucokinase mutation. Medical nutrition therapy has little impact on blood glucose level in women with hexokinase mutation. At present there is no evidence to initiate treatment outside the pregnancy as these individuals are not at risk of developing any vascular complications. If the women is already on treatment and if subsequently diagnosed as glucokinase mutation the treatment can be stopped. There was a longitudinal study in which there were about 799 GCK-MODY patients were compared. The HbA1C levels of those who received treatment was not different from those who were not on treatment (6.5% vs. 6.4%) [6]. The risk of developing type I and type II DM in future is similar to general population.

Conclusion

The heterozygous mutation of hexokinase enzyme results in mild fasting hyperglycaemia. They don't require treatment outside the

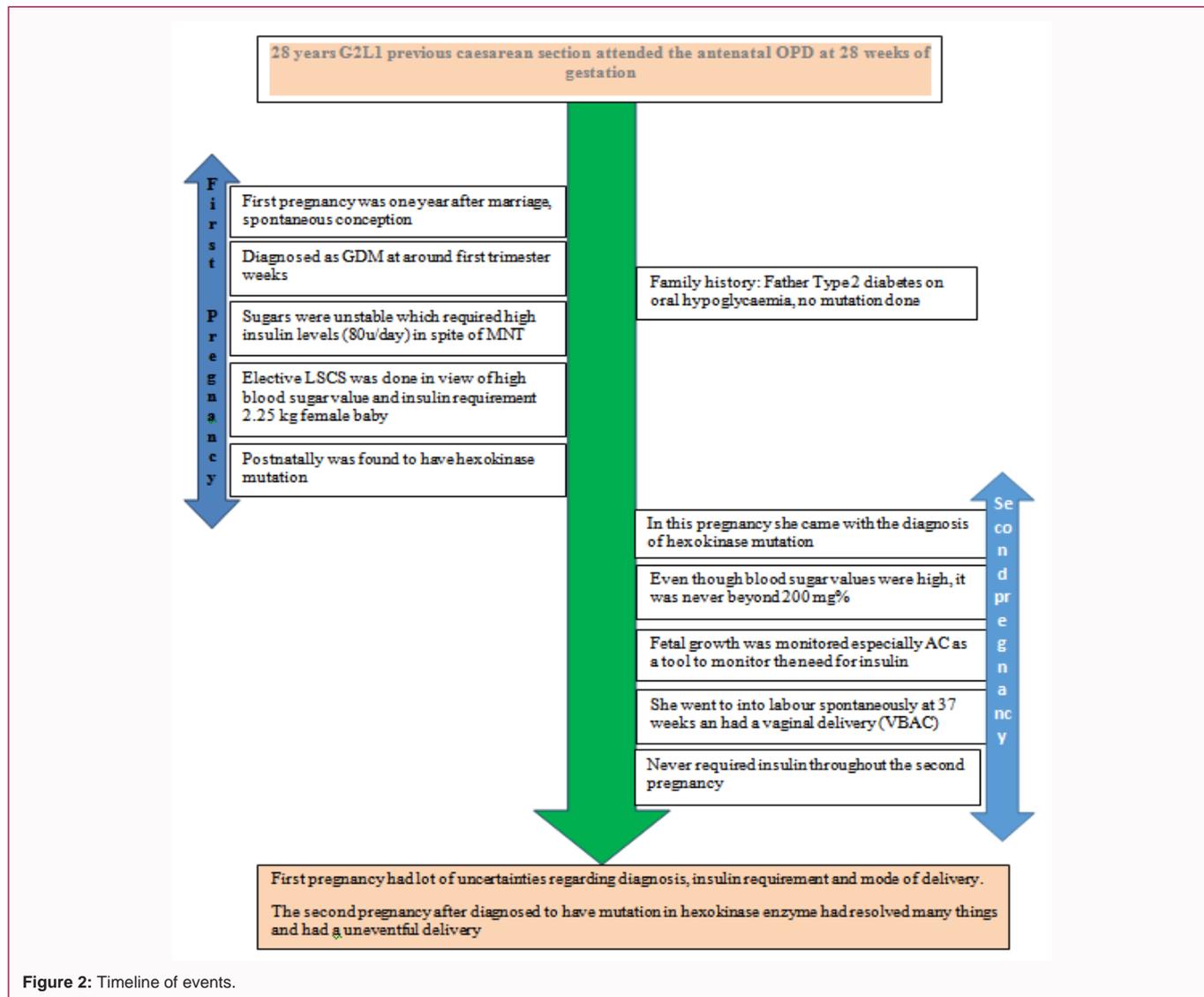


Figure 2: Timeline of events.

pregnancy. They are not at risk of developing long term complications and they don't respond to oral hypoglycaemic agents. If the baby does not inherit the enzyme and there is an evidence of macrosomia insulin treatment is required. Uncontrolled fasting hyperglycaemia in spite of high doses of insulin during pregnancy should always raise the suspicion of this simple condition. However other subtypes of MODY requires multidisciplinary management which involve other specialities like endocrinologist, geneticist and neonatologist.

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