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# Successful discontinuation of insulin treatment after gestational diabetes is shown to be a case of MODY due to a glucokinase mutation

**Case Report**

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**Abstract:** We describe a woman who first presented with gestational diabetes at 26 weeks gestation and was managed with insulin. Following delivery of a healthy baby she had an abnormal OGTT (oral glucose tolerance test) 6 weeks post partum and was managed with diet. In her second pregnancy she was diagnosed with gestational diabetes at 10 weeks and required insulin. Following delivery she was again managed on diet alone. Four years later, during her third pregnancy, she was managed with insulin from the outset. She remained on insulin post partum and for several years. Later her two younger children, aged 11 years and 7 years, were found to have *GCK* mutation causing MODY (Maturity Onset Diabetes Of the Young) subtype glucokinase . Following this she underwent molecular genetic testing and was also shown to have the *GCK* mutation. She was gradually taken off insulin and is now managed on diet alone with excellent glycaemic control. Her two children are under regular follow up care and on no medication for diabetes.

**Keywords:** *Gestational diabetes • Maturity onset diabetes of the young • Glycosylated haemoglobin*



## 1. Introduction

Gestational Diabetes is defined as impaired glucose tolerance with recognition during pregnancy. Previously unrecognised Type 1 or Type 2 diabetes may be diagnosed as gestational diabetes during pregnancy. Maturity Onset Diabetes of the Young or MODY [1,2,3] is an autosomal dominant disorder characterised by hyperglycaemia and relative insulinopenia and often presents before the age of 25 years. Presentation of MODY as gestational diabetes is rare. We present one such patient who was diagnosed with gestational diabetes in all three pregnancies and subsequently was found to have a *GCK* gene mutation but only after her children revealed the condition. This subtype is relatively benign in contrast with the hepatic nuclear factor mutations *(HNF 1A, HNF 1B and HNF 4A genes)*. The patient initially remained on insulin following delivery of the third child but following this diagnosis she was able to discontinue her insulin. She is currently on diet control alone with excellent glycaemic control.

## 2. Case report

A 25 year old woman presented at 26 weeks of pregnancy with gestational diabetes. She had a history of partial left salpingectomy following an ectopic pregnancy. Her grandfather had pernicious anaemia but there was no family history of diabetes at the time of her initial presentation. Her father was diagnosed with Type 2 diabetes seven years later just before his death. Her OGTT showed the following results presented in Table 1. She was commenced on Human Insulatard 4 units pre lunch and subsequently required 14 units twice daily. She delivered a healthy baby weighing 3.7 kilograms by caesarean section on

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**Table 1.** OGTT of patient presented in the study.

| | Fasting | 1 hour post glucose (75 grams) | 2 hours post glucose |
|---|---|---|---|
| Plasma glucose level (mmol/l) | 5.9 | 10.9 | 13 |

the 37th week. Her insulin was stopped post partum. She underwent another OGTT 6 weeks postpartum, which showed the results presented in Table 2.

**Table 2.** OGTT 6 weeks postpartum.

| | Fasting | 1 hour post glucose | 2 hours post glucose |
|---|---|---|---|
| Plasma glucose (mmol/l) | 7.5 | 9.7 | 9.8 |

She remained on a proper diet and was normal weight. One year later she conceived again and was diagnosed at 10 weeks with gestational diabetes on the basis of an abnormal OGTT (Table 3).

**Table 3.** OGTT at 10 weeks.

| | Fasting | 1 hour post glucose | 2 hours post glucose |
|---|---|---|---|
| Plasma glucose (mmol/l) | 6.6 | 11.1 | 10.3 |

She was managed with insulin and ultimately required Human Actrapid 4-6 units three times premeal and Insulatard 18 units daily. Following delivery her insulin was stopped. Two subsequent OGTTs undertaken at 6 weeks and 12 months post partum showed the results shown in Table 4.

**Table 4.** Two subsequent OGTTs undertaken at 6 weeks and 12 months post partum.

| | Fasting | 1 hour post glucose | 2 hours post glucose |
|---|---|---|---|
| Plasma glucose (mmol/l) | | | |
| 6 weeks post partum | 6.8 | 10.6 | 8.1 |
| 12 months post partum | 6.1 | 11.9 | 12.9 |

She was managed with diabetic diet with good glycaemic control. She became pregnant 4 years later and her initial capillary blood glucose results were between 7-9 mmol/l. She was commenced on Human Insulatard 4 units twice daily and went on to need 4 units in the morning and 8-10 units in the evening. Following delivery she was maintained on insulin: 4 units in the morning and 10-12 units in the evening. Her HbA1c (Glycosylated Haemoglobin) continued to remain between 6.2-6.4%.

Her youngest son at the age of seven years was seen in hospital with abdominal pain. A routine glucometer reading was elevated and he was then diagnosed with impaired glucose tolerance: fasting and postprandial glucose levels of 5.7 and 9.1 mmol/l respectively (HbA1c 6.3%). He was subsequently found on genetic testing to be have a heterozygous *GCK* mutation. Her second son also has the same glucokinase mutation. Genetic testing showed that she also had the same *GCK* mutation. Her other son was unaffected. She was heterozygous for frameshift mutation, D344fsdel10, in exon 9 of the *GCK* (Glucokinase) gene. The mutation was a deletion of 10 nucleotides from codon 344 (c.1030_1039delGACCGCAAGC), which resulted in premature termination at codon 349. The diagnosis was confirmed as MODY, subtype Glucokinase. This mutation has not been reported previously but is predicted to result in a loss of function. Her insulin dose was reduced and discontinued three months later. She remains on diet control alone and 1 year later: her most recent HbA1c is 6%.

## 3. Discussion

MODY is a rare hereditary form of diabetes due to dominantly inherited defects of insulin secretion. This was first described by Tatersall [1,2] and Fajans [2] in 1974. MODY is a monogenic diabetes since it is caused by a mutation in a single gene. The first MODY gene was found in 1992 [3] and so far 7 genes have been identified that account for 87% of MODY [4-8] in the UK. MODY can be caused by mutation in one of the following genes:

*HNF4A* encoding hepatic nuclear factor 4-α (previously described as MODY1)

*GCK* gene encoding glucokinase (MODY 2)

*HNF 1A* gene encoding hepatic nuclear factor 1-α (MODY 3)

*PDX1 (IPF1)* encoding insulin promoter factor-1(MODY 4)

*HNF 1B* gene encoding hepatic nuclear factor 1-β (MODY 5)

*NEUROD 1* gene encoding neurogenic differentiation 1 (MODY6)

*CEL gene encoding carboxy ester lipase or MODY 7 [9]*

**Table 5.** Showing the *GCK* mutation of the mother and her sons.

| Ages of the three sons at the time of genetic testing | OGTT (Impaired: 0 hour= 6.1-7mmol/l, 2 hr= 7.8-11.1mmo/l) | Mutations tested | Method | Genotype (N= no mutation) |
|---|---|---|---|---|
| Youngest son, tested at the age of 7 yrs | 0 hr= 5.7 mmol/l; 2 hr= 9.1 mmol/l | *GCK* Exons 1-10 | PCR/direct sequencing | D344fsdel10/N |
| Second son tested at the age of 11 years | 0 hr =8.3 mmol/; 2 hrs= 11.8 mmol/l | *GCK* D344fsdel10 | PCR/direct sequencing | D344fsdel10/N |
| Eldest son tested at the age of 13 years | Fasting plasma glucose 4.1 mmol/l | *GCK* D344fsdel10 | PCR/direct sequencing | N/N ( not inherited the condition) |
| Mother | | *GCK* D344fsdel10 | PCR/direct sequencing | D344fsdel110/N |

*MODY X: Other possible forms of MODY*

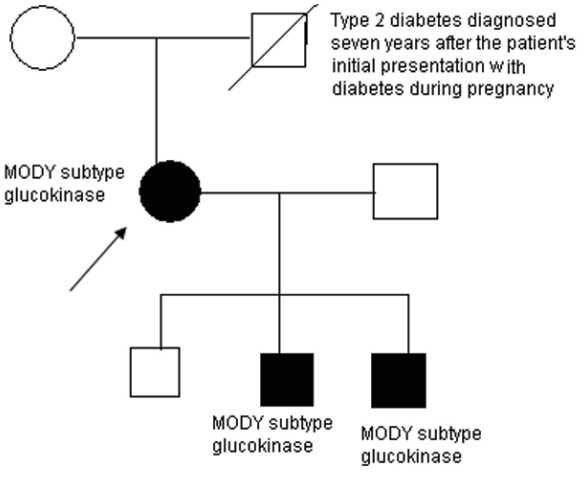
The known first six types described above account for about 85%–90% of cases identified by clinical criteria, suggesting that there are other forms and causes still to be identified.

Neonatal diabetes has always been around. One of the newest forms of monogenic diabetes is neonatal-onset diabetes due to KATP channel defects . Heterozygous activating mutations of the *KCNJ11* gene, which codes for the Kir6.2 subunit of the beta cell $K_{ATP}$ channel, cause both permanent and transient neonatal diabetes. Mutations of the other subunit of the $K_{ATP}$ channel, SUR1, which is encoded by the ABCC8 gene [10] and anomalies on the imprinted region on chromosome 6q24 result in transient neonatal diabetes [11].

MODY Type 2 is due to any of several hundred mutations in the *GCK* gene [12-14] on chromosome 7. Glucokinase catalyses the rate limiting step of glucose phosphorylation after which glucose-6 phosphate can be metabolised to ATP eventually causing insulin secretion at glucose values above 5 mmol/l. The beta cells in patients with inactivating heterozygous *GCK* mutations secrete insulin at or above a glucose threshold of 7-8 mmol/l. This produces chronic mild hyperglycaemia [6], which is usually asymptomatic. It is often detected incidentally. Rarely, mild hyperglycaemia may be detected during pregnancy screening and the patient is diagnosed as having Gestational diabetes [15] as in our case. The diagnosis of a glucokinase mutation is very important for the patient's treatment, eg in contrast to type 2 diabetes mellitus; glucokinase mutations donot deteriorate over time and in contrast to Type 1 diabetes and does not need insulin. As the glucokinase defect may be subclinical in family members the absence of family history should not exclude the diagnosis.

Our patient had no family history of diabetes when she initially presented with diabetes in pregnancy. Saker *et al* [16] and Ellard *et al* [17] confirmed the speculation that the frequency of *GCK* mutations may be high in GDM cases because they typically result in subclinical hyperglycaemia and are only detectable upon the burden of pregnancy. However, it was only when her two younger children were found to have MODY that she underwent molecular genetic testing and was shown to have the same mutation in the *GCK* gene as her children confirming a diagnosis of MODY subtype glucokinase (Table 5 and Figure 1).

**Figure 1.** Family tree including the affected mother and her two children.




In *GCK* MODY treatment with oral agents or insulin is not required and patients are better off without treatment. The exception is during pregnancy when insulin is often used. In MODY due *to HNF 1A or 4A* mutations patients may eventually require insulin treatment though small doses of sulfonylureas are recommended as the first pharmacological therapy. Our patient with MODY 2 is now on diet control alone.

There has been no previous report of the *GCK*

mutation which she and her children presented with [18].

In conclusion persistently abnormal OGTT in the post partum period should raise awareness of the possibility of MODY to explain the gestational diabetes. Clearly in this case there was a major treatment change for mother as a result of the diagnosis.

It is important to recognise MODY because of the following reasons:

(1) By diagnosing MODY and its type, the treatment can be determined.
(2) The person can be advised as to how their diabetes will progress in future.
(3) As it is a dominantly inherited type of diabetes it is important to advise other family members of their risk .

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