

Management of pregnancy in patients with hyperglycaemia due to disease-causing variants in the glucokinase (*GCK*) gene

INTRODUCTION

Glucokinase is an enzyme present in the beta cells of the pancreas. It has a vital role in enabling the pancreatic beta cells to accurately detect circulating blood glucose levels and adjust insulin secretion accordingly to keep blood sugar levels at a homeostatic set point of approximately 5mmol/L. A disease-causing variant in the gene encoding the enzyme impairs its function and causes an inability of the pancreas to “sense” the circulating blood glucose. This means that insulin secretion is delayed causing a rise in the homeostatic set point of blood glucose typically with a fasting plasma glucose (FPG) between 5.5 and 8mmol/L.

CLINICAL CHARACTERISTICS

Patients with glucokinase (*GCK*) gene variants generally have a mildly raised fasting blood glucose (typically 5.5 - 8mmol/L) and a small increment at 2 hours (< 4.5mmol/L) on a 75g OGTT (1). Raised FPG is detectable from birth and deteriorates only slightly with age. Because the blood glucose is generally only mildly raised patients with this condition are usually asymptomatic and are not at risk from the usual complications of diabetes. Treatment is not usually necessary. In addition unless they have Type 2 diabetes as well treatment is very difficult as the glucose is regulated at this higher level. This means that counter regulatory hormones will be secreted when the glucose is reduced to even normal levels (e.g. 3.5 - 4.0mmol/L). There is a 50% chance that offspring of an affected individual will have inherited the condition.

GCK IN PREGNANCY

Many patients with *GCK* variants are probably identified initially when they present to an antenatal clinic where women are screened for abnormal glucose tolerance. By conventional diagnostic criteria they would have GDM as they have glucose intolerance diagnosed for the first time in pregnancy. However there are several important differences between *GCK* and the more conventional and common type of gestational diabetes;

- Gestational diabetes is detected first during pregnancy (usually at the beginning of the 3rd trimester) and has usually not been present for a long time before diagnosis and usually is not present on repeat OGTT after delivery of the baby. *GCK* hyperglycaemia is always present from birth, and hence before conception (but is often unrecognised) and persists after delivery of the baby.
- *GCK* hyperglycaemia is typified by a raised FPG and a small 2-hour increment on OGTT. In GDM FPG is often normal with a larger increment at 2 hours on OGTT. This means some criteria for hyperglycaemia in pregnancy, which put main emphasis on the 2-hour glucose value rather than fasting, may not detect *GCK* as abnormal.
- GDM mothers are at very high risk of developing Type 2 diabetes in the 10 years following diagnosis while *GCK* patients are likely to have stable glucose intolerance deteriorating only slightly with time (1)
- In GDM, offspring will almost certainly have normal glucose tolerance. In *GCK* hyperglycaemia 50% of offspring will have inherited the abnormal gene and will therefore have abnormal glucose tolerance from birth.

DIAGNOSING WOMEN WITH PROBABLE GCK HYPERGLYCAEMIA

The differences outlined above for prognosis and below for treatment make it important to consider making a diagnosis of GCK hyperglycaemia. The only way to make a diagnosis of GCK hyperglycaemia is to perform a diagnostic molecular genetic test. This is labour intensive, as the whole gene needs to be sequenced and hence expensive. If the patient is known to have a relative with a *GCK* variant it is possible to test just for this variant, which is considerably easier and cheaper. The details of the testing, costs, patient information sheet and a request form are on the www.diabetesgenes.org website under the “Maturity-onset diabetes of the young section”.

WHAT FEATURES ARE SUGGESTIVE OF GCK IN THE ANTENATAL CLINIC

Using clinical features to guide the patients who are sequenced may increase the detection rate to as high as 75% (2)

1. Persisting fasting hyperglycaemia both inside and outside pregnancy (5.5-8mmol/L).
2. Small 2 hour increment (<4.6mmol/L) in an OGTT in or outside pregnancy
3. Fasting glucose intolerance diagnosed in the first trimester
4. Slim rather than overweight or obese although obesity does not exclude the diagnosis.
5. Insulin treatment used during pregnancy (usually in attempt to lower fasting glucose) but post-delivery controlled on diet.
6. History of GDM or fasting hyperglycaemia (>5.5mmol/L) or “type 2 diabetes”, in a first-degree relative.

RISKS OF PREGNANCY IN PATIENTS WITH A GCK VARIANT

This is a relatively rare condition (3% Caucasian women with GDM) and hence there are many unanswered questions. This means all clinical decisions need to be made by the clinicians looking after the patient. This information sheet is aimed to share experience but not to take the place of local clinical decisions based on knowledge of the individual patient.

We have collected data on 42 women with *GCK* variants and collected information on 82 pregnancies (8). A key point is that the fetal size and hence complications related to fetal size are entirely dependent on whether the baby inherits the *GCK* variant. Babies who inherit the variant will on average be normal size even if mother’s hyperglycaemia is untreated. If the baby does not inherit the variant they will be on average 600g heavier than normal. The *GCK* variant status of the baby therefore has much more impact on fetal outcome than the treatment of the mother (3).

The main risks we are aware of during pregnancy therefore relate to those pregnancies where the fetus has not inherited the maternal variant and include an increased risk of fetal macrosomia (birth weight > 4kg at term) (40%) and related obstetric complications such as obstructed labour and shoulder dystocia. There is a high risk of instrumental delivery and Caesarean section (26 %). Unaffected offspring but not affected offspring are also at risk of hypoglycaemia immediately post-delivery.

NON-INVASIVE PRENATAL TESTING

The rationale for non-invasive prenatal diagnosis in pregnancies at risk of monogenic diabetes is to influence the management of the pregnancy according to fetal genotype. This is because in many types of monogenic diabetes fetal growth is considerably altered according to genotype. When a woman is pregnant, there is a small amount of her baby's DNA circulating in her bloodstream. This is called cell free fetal DNA (cffDNA) and by testing a maternal blood sample we can analyse the baby's DNA. Please contact Maggie Shepherd on 01392 408261 (M.H.Shepherd@ex.ac.uk) or Jayne Houghton on 01392 408244 ([jaynehoughton@nhs.net](mailto:jaynehougton@nhs.net)) as soon as a pregnancy is confirmed in a mother with GCK MODY hyperglycaemia as non-invasive testing may be possible.

MANAGEMENT DURING PREGNANCY

1. *Pre-pregnancy.* There is no large series of data available regarding risk of congenital malformation or early miscarriage in this group. However in our own studies of 98 GCK pregnancies the rate of congenital anomalies did not differ from the background population. In a large series of 245 patients outside pregnancy median age 26.7 years (range 2-79), only 38% of patients reached clinical criteria for the diagnosis of diabetes (the remainder having IFG or IGT and a few with normal glucose tolerance) (1). In addition treatment with insulin due to increased counter-regulation and reduction in endogenous insulin to compensate is unlikely to reduce blood glucose values unless used in a full replacement dose. It is therefore unlikely that preconception treatment with insulin will make a significant improvement on this level of glycaemia and we have not performed this in our clinical practice.
2. *Antenatal.* Risk of fetal macrosomia and postnatal hypoglycaemia is dependent on whether the fetus has inherited the maternal variant. Treatment of maternal blood glucose with insulin (despite being difficult) carries a potential advantage particularly when the fetus is unaffected but maternal insulin treatment in pregnancies where the fetus also carries the maternal *GCK* variant may result in reduced birth weight (4) Antenatal testing of the fetus for the *GCK* variant carries a significant risk and is not advised unless CVS or amniocentesis is being performed for another reason in which case it would be appropriate. In most pregnancies it will be necessary to make a decision on the treatment of maternal blood glucose without knowing whether the fetus is affected or not.

Our current practise is based on studies of women with gestational diabetes (5,6,7). In such pregnancies it is accepted that insulin treatment is beneficial in those where FPG \geq 6.7mmol/L. In women with lesser degrees of fasting hyperglycaemia (5.8-6.6mmol/L) it may be possible to select those at high risk of fetal macrosomia (a surrogate indication of fetal *GCK* status) by measurement of fetal abdominal circumference (AC) early in the third trimester and reserve insulin treatment targeted at the group where fetal AC $>$ 70th centile. If insulin is given, large doses (at least 0.6-

1U/kg) will be needed in order to sufficiently lower maternal blood glucose enough to influence fetal growth.

3. *During labour.* A continuous infusion of intravenous insulin is unnecessary during labour for mothers with a *GCK* variant and should be avoided. Subcutaneous insulin treatment may be discontinued once labour starts. Fetal blood glucose should be measured after delivery.
4. *Postnatal.* Most women will require no further treatment once the baby has been delivered and do not need regular monitoring. A postnatal GTT is not necessary as decisions on future management can be made on the basis of a yearly HbA1c. Should a further pregnancy be planned then women should be advised to seek an early appointment with obstetrician/diabetologist once pregnancy has been confirmed.

For information either on diagnosing a *GCK* pregnancy or on management during pregnancy please contact Prof. Andrew Hattersley - a.t.hattersley@exeter.ac.uk tel 01392 408260.

References

1. Stride A, Vaxillaire M, Tuomi E, Barbetti F, Njolstad PR, Hansen T, Costa A, Conget I, Pedersen, O, Sovik O, Lorini R, Froguel P, Hattersley AT; The genetic abnormality in the beta cell determines the response to an oral glucose load. *Diabetologia* (2002) 45: 427-435.
2. Ellard S, Beards F, Allen L, Shepherd M, Ballantyne E, Harvey R, Hattersley AT. A high prevalence of glucokinase mutations in gestational diabetic subjects by clinical criteria. *Diabetologia* (2000) 43(2): 250-253.
3. Hattersley AT, Beards F, Ballantyne E, Appleton M, Harvey R, Ellard S. Mutations in the glucokinase gene of the fetus result in reduced birth weight. *Nature Genetics* (1998) 19(3): 268-270.
4. Spyer G, Hattersley AT, Sykes JE, Sturley RH, MacLeod KM. Influence of maternal and fetal glucokinase mutations in gestational diabetes. *Am J Obstet Gynecol* (2001) 185(1): 240-241
5. Buchanan TA, Kjos SL, Montoro MN, Wu PYK, Madrilejo NG, Gonzalez M, Nunez V, Pantoja PM, Xiang A. Use of fetal ultrasound to select metabolic therapy for pregnancies complicated by mild gestational diabetes. *Diabetes Care* (1994) 17(4): 275-285.

6. Kjos et al. Kjos SL, Schaefer-Graf U, Sardesi S, Peters RK, Buley A, Xiang AH, Bryne JD, Sutherland C, Montoro MN, Buchanan TA. A randomized controlled trial using glycemic plus fetal ultrasound parameters versus glycemic parameters to determine insulin therapy in gestational diabetes with fasting hyperglycemia. *Diabetes Care* (2001) 24(11): 1910.
7. Schaefer-Graf UM, Kjos SL, Fauzan OH, Buhling KJ, Siebert G, Buhner C, Ladendorf B, Dudenhausen JW, Vetter K. A randomized trial evaluating a predominantly fetal growth-based strategy to guide management of gestational diabetes in Caucasian women. *Diabetes Care* (2004) 27(2): 297-302.
8. Spyer G, Macleod KM, Shepherd M, Ellard S, Hattersley AT. Pregnancy outcome in patients with raised blood glucose due to a heterozygous glucokinase gene mutation *Diabetic Medicine* (2009) 26(1): 14-18
9. Chakera AJ, Steele AM, Gloyn AL, Shepherd MH, Ellard S, Hattersley AT. Recognition and Management of Individuals with Hyperglycemia Because of a Heterozygous Glucokinase Mutation. *Diabetes Care* (2015) 38(7): 1383-1392.