Information on pregnancy and HNF4A diabetes

HNF4A MODY **in either parent** can impact on pregnancy and this leaflet aims to provide information for individuals with HNF4A diabetes and their health care professionals. It may be printed and copies given to families and professionals e.g. midwives, diabetes consultants, obstetric consultants, GPs and added to the patient's hospital notes. It is important to emphasis that complications from pregnancy in patients with HNF4A MODY are unusual and this guidance aims to increase awareness of the potential issues and reduce the slight risks even further.

What is HNF4A diabetes?

HNF4A is a gene which acts as a switch which turns on and off other genes in the body. Changes in the HNF4A gene cause diabetes by reducing the amount of insulin that is produced by the pancreas but unusually has different effects on insulin secretion at different ages. People carrying the changes produce excess insulin secretion in the womb and during the first months of life, there is normal insulin secretion in early childhood and then this reduces with age resulting in diabetes due to too little insulin secretion in late childhood or early adulthood. HNF4A is a type of diabetes that runs in families, has diabetes diagnosed at a young age (often before 25 years) and may be treated with sulphonylurea tablets rather than insulin. HNF4A diabetes is one of the types of diabetes referred to as maturity onset diabetes of the young (MODY). Further information can be found at http://www.diabetesgenes.org/content/hepatic-nuclear-factor-4-alpha-hnf4a.

Changes in HNF4A can increase birth weight and put a baby at risk of low blood glucose soon after delivery

Babies with a change in the HNF4A gene produce increased amounts of insulin when in the womb, this increases the growth of the baby making them on average 800g (just under 2lbs) heavier than normal babies or their unaffected siblings. Most of these babies have macrosomia, which is defined as a birth weight of more than 4kg (9lbs). In addition some individuals with HNF4A have low blood sugar levels (hypoglycaemia) at, or shortly after birth, which may require prolonged treatment. The low blood glucose is also a result of excessive insulin secretion. When either parent is known to have HNF4A MODY there is a 50% chance that a baby will inherit the genetic change. Therefore close monitoring is required both during pregnancy and after birth to reduce any complications of having a large baby or the baby having low blood glucose after birth.

When the mother has diabetes resulting from a change in the HNF4A gene her high blood sugar in pregnancy can also increase insulin secretion of the baby resulting in an additional increase in birth weight on top of the direct effect of the HNF4A genetic change in the baby. Even if the baby does not inherit the genetic change they may still be large as a result of mother's blood sugars not being normal.

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) as soon as a pregnancy is confirmed for a couple in whom either has a diagnosis of HNF4A MODY as non-invasive testing may be possible.

Treatment of a mother with HNF4A diabetes during pregnancy

The optimum treatment for HNF4A MODY outside pregnancy is sulphonylureas but there is little evidence regarding the most appropriate treatment during pregnancy. Glibenclamide has been widely used in the treatment of gestational diabetes, but recent data have established that Glibenclamide crosses the placenta and increases risk of macrosomia and neonatal hypoglycaemia. As there is a very high risk of macrosomia in HNF4A pregnancies anyway if the fetus is affected, achieving excellent glycaemic control is essential.

There are two main treatment options for HNF4A MODY in pregnancy:
1) Stop sulphonylureas pre-pregnancy and transfer to insulin or
2) Treat with Glibenclamide pre-/early pregnancy and transfer to insulin in the second trimester. The second option should only be considered if pre-pregnancy HbA1c reaches local targets for glycaemic control.

Further details regarding diabetes management in HNF4A pregnancies can be found here: Shepherd *et al* 2017. Management of sulfonylurea-treated monogenic diabetes in pregnancy: implications of placental glibenclamide transfer. Diabet Med 34: 1332-1339.

Ultrasound scanning in pregnancy

Serial growth assessment should be undertaken from 28 weeks, at 2-weekly intervals at least, depending on growth trajectory, in addition to routine anomaly screening at earlier gestation as advised by the National Institute of Health and Care Excellence (NICE), to detect developing macrosomia in affected fetuses.

Management of pregnancies when the father has HNF4A MODY

A fetus inheriting the HNF4A mutation from the father has a similar risk of macrosomia and neonatal hypoglycaemia to that associated with maternal inheritance (see above). We therefore recommend regular ultrasonography monitoring from 28 weeks' gestation if the father has HNF4A MODY. If there is evidence of fetal macrosomia on ultrasonography, early delivery (37–38+6 weeks) should be considered. A paediatrician should review the child soon after birth and assess for hypoglycaemia

Delivery

Early delivery is needed even with excellent glucose control if the fetus is genetically affected. Induction of labour or elective caesarean section should be considered from 35 to 38 weeks, based on estimated fetal size on ultrasonography. A paediatrician should be available at delivery.

Post delivery

Post-delivery the infant should be monitored for neonatal hypoglycaemia for at least 48 hours, as this may be prolonged and need continued treatment. Intravenous glucose and tube feeding is sometimes needed and prolonged treatment with Diazoxide has also been reported. The mother can resume Glibenclamide post-delivery and during breastfeeding, with transfer to an alternative sulphonylurea, if desired, once breastfeeding is completed.

Further guidance

So we can understand more about HNF4A pregnancies we would be very grateful if patients or their doctors could contact us when there is a pregnancy where either the father or mother has HNF4A MODY. We are also very happy to be contacted for further discussion of individual pregnancies and we can be contacted on the numbers and e-mail below:
Professor Andrew Hattersley on 01392 408260 (A.T.Hattersley@exeter.ac.uk) or Maggie Shepherd on 01392 408261 (M.H.Shepherd@ex.ac.uk).

Further information available in:

Details about the evidence for this guidance can be found in:

Shepherd M, Brook AJ, Chakera AJ, Hattersley AT (2017). Management of sulfonylurea-treated monogenic diabetes in pregnancy: implications of placental Glibenclamide transfer. Diabet Med. 34: 1332-1339

Pearson ER, Boj SF, Steele AM, Barrett T, Stals K, Shield JP, Ellard S, Ferrer J, Hattersley AT (2007). Macrosomia and hyperinsulinaemic hypoglycaemia in patients with heterozygous mutations in the *HNF4A* gene. PloS Med. 4: e118
These papers are freely available and can be downloaded from the internet directly

A third reference with details about the occasional child who has prolonged low blood glucose values is:

Kapoor RR, Locke J, Colclough K, Wales J, Conn JJ, Hattersley AT, Ellard S, Hussain K (2008). Persistent hyperinsulinemic hypoglycemia and maturity-onset diabetes of the young due to heterozygous HNF4A mutations. Diabetes 57: 1659-1663.