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Review Article

# Management of sulfonylurea-treated monogenic diabetes in pregnancy: implications of placental glibenclamide transfer

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## Abstract

The optimum treatment for HNF1A/HNF4A maturity-onset diabetes of the young and ATP-sensitive potassium ($K_{ATP}$) channel neonatal diabetes, outside pregnancy, is sulfonylureas, 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. This raises questions about its use in pregnancy. We review the available evidence and make recommendations for the management of monogenic diabetes in pregnancy. Due to the risk of stimulating increased insulin secretion *in utero*, we recommend that in women with *HNF1A/ HNF4A* maturity-onset diabetes of the young, those with good glycaemic control who are on a sulfonylurea per conception either transfer to insulin before conception (at the risk of a short-term deterioration of glycaemic control) or continue with sulfonylurea (glibenclamide) treatment in the first trimester and transfer to insulin in the second trimester. Early delivery is needed if the fetus inherits an *HNF4A* mutation from either parent because increased insulin secretion results in ~800-g weight gain *in utero*, and prolonged severe neonatal hypoglycaemia can occur post-delivery. If the fetus inherits a $K_{ATP}$ neonatal diabetes mutation from their mother they have greatly reduced insulin secretion *in utero* that reduces fetal growth by ~900 g. Treating the mother with glibenclamide in the third trimester treats the affected fetus *in utero*, normalising fetal growth, but is not desirable, especially in the high doses used in this condition, if the fetus is unaffected. Prospective studies of pregnancy in monogenic diabetes are needed.

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## Introduction

The recognition of monogenic diabetes is important as therapy can be improved accordingly. For several subtypes of monogenic diabetes, insulin treatment or other glucose-lowering medication can be replaced by sulfonylureas. The common subtypes of maturity-onset diabetes of the young (MODY) resulting from mutations in *HNF1A* and *HNF4A* are optimally treated with low-dose sulfonylureas [1,2] and, in the most common subtypes of permanent neonatal diabetes resulting from *KCNJ11* or *ABCC8* mutations, excellent glycaemic control can be achieved with high-dose sulfonylureas [3–5].

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It remains unclear, however, how sulfonylurea-treated monogenic diabetes should be managed in pregnancy. The sulfonylurea most widely use in pregnancy is glibenclamide. Until recently it was believed that transfer across the placenta was minimal; however, evidence from its use in gestational diabetes mellitus (GDM) now clearly shows that glibenclamide crosses the placenta [6,7] and stimulates fetal insulin secretion, resulting in increased fetal growth and increased rates of neonatal hypoglycaemia [8–10].

In monogenic diabetes the situation is more complex, as there are specific considerations in addition to concern about maternal glycaemia; these include the sulfonylurea doses required, the fetal mutation status and the desirability of exposure to sulfonylureas that differs across the specific genetic subtypes.

In the present review we discuss first the evidence for use of glibenclamide in pregnancies in mothers who do not have monogenic diabetes. We then consider the three common subtypes of sulfonylurea-treated monogenic diabetes, HNF1A

**What's new?**

- Recent data show that glibenclamide crosses the placenta and its use in pregnancy is associated with increased birth weight and neonatal hypoglycaemia. This has implications for the treatment of pregnant women with monogenic diabetes whose diabetes is usually well controlled with sulfonylureas.
- Optimum management of HNF1A/HNF4A maturity-onset diabetes of the young (MODY) in pregnancy requires excellent glycaemic control in the first trimester to minimize the risk of fetal malformations, whilst avoiding the negative impact of glibenclamide on fetal weight gain in the third trimester.
- In mothers with ATP-sensitive potassium channel ($K_{ATP}$) neonatal diabetes, glibenclamide treatment in pregnancy can be beneficial if the fetus is affected because restoration of fetal $K_{ATP}$ function will result in improved fetal growth.
- If the genotype of the fetus is unknown, when a parent has $K_{ATP}$ neonatal diabetes or *HNF4A* MODY, serial antenatal ultrasound assessment of fetal growth may be used as a proxy to aid management decisions.
- Management of monogenic diabetes during pregnancy could be revolutionized in future by testing cell-free fetal DNA in the mother.

and HNF4A MODY and KCNJ11/ABCC8 permanent neonatal diabetes. We outline sulfonylurea treatment outside pregnancy in these conditions and review the evidence for treatment and outcome in pregnancy. We also suggest a practical approach given the paucity of evidence available.

## Literature search

A systematic literature review was undertaken using PubMed, Embase and OVID. Keywords included: monogenic diabetes, MODY, *HNF1A, HNF4A*, ATP-sensitive potassium channel ($K_{ATP}$) neonatal diabetes mellitus (*KCNJ11* and *ABCC8*), pregnancy, glibenclamide or glyburide, and gestational diabetes.

## Sulfonylurea treatment in pregnancy in Type 2 diabetes and gestational diabetes: a changing landscape

Data on the use of glibenclamide in pregnancy consist of more than 9500 exposures, mainly in late pregnancy in women with GDM [11]. Glibenclamide has until recently been considered a safe drug to use in pregnancy. *In vitro* studies suggested that transfer across the placenta was minimal [12–14] and glibenclamide was undetectable in cord blood [15]. Early clinical studies suggested there was no significant increase in macrosomia or neonatal hypoglycaemia with the use of glibenclamide compared to insulin use [15–20], but these studies were limited in their power to demonstrate differences [21]. In a meta-analysis (10 studies on 471 women exposed to sulfonylureas and biguanides in the first trimester), no significant difference was found in the rate of major malformations or neonatal death in the offspring of women with exposure to oral antidiabetic agents in the first trimester compared with non-exposed women, but the meta-analysis was limited by study heterogeneity [22]. In one study of 379 pregnancies there was a significant increase in perinatal mortality (125/1000 births vs 33/1000 births) and stillbirth with oral glucose-lowering agents vs those treated with insulin (91/1000 births v 33/1000 births; $P<0.05$), but the authors of that study concluded that early exposure to these agents was unlikely to be deleterious [23].

Subsequent studies, using more sensitive assays, have confirmed that glibenclamide does cross the placenta, with umbilical cord plasma concentrations averaging 70% of maternal values [24]. More recent publications have demonstrated an increased risk of obstetric and neonatal complications with sulfonylurea use. Even though good glycaemic control may be maintained, pregnant women with GDM treated with glibenclamide had larger babies than insulin-treated mothers, further increasing the risk of obstetric and neonatal complications from macrosomia [25,26]. In a meta-analysis of randomized controlled trials, glibenclamide use resulted in greater birth weight (mean difference 109 g; 95% CI 36–181), and higher risks of macrosomia [risk ratio (RR) 2.62, 95% CI 1.35–5.08) and fetal hypoglycaemia (RR 2.04, 95% CI 1.30–3.20) [10]. In a large cohort study from the USA in 110 000 women with GDM, newborns of women treated with glibenclamide (glyburide) were at higher risk of neonatal intensive care unit admission (RR 1.41; 95% CI 1.23–1.62), respiratory distress (RR 1.63; 95% CI 1.23–2.15), hypoglycaemia (RR 1.40; 95% CI 1.00–1.95), birth injury (RR 1.35; 95% CI 1.00–1.82), and large for gestational age (RR 1.43, 95% CI 1.16–1.76) compared with those treated with insulin [26]. An additional study in 2073 women also found higher odds of neonatal intensive care admission (adjusted odds ratio 1.46, 95%CI 1.07–2.00) and birth weight >4000 g (adjusted odds ratio 1.29, 95% CI 1.03–1.64) amongst infants born to mothers receiving glibenclamide during pregnancy [27]. The evidence now indicates that glibenclamide treatment in the third trimester exacerbates fetal hyperinsulinism *in utero* and has an additive effect on birth weight [10,26,28]. These studies have raised concern regarding the use of glibenclamide in pregnancy [25].

There is limited experience of sulfonylurea use in the first trimester; the data that exist suggest sulfonylureas are not teratogenic when used at conception or in the first trimester [22,23,29], although maternal $HbA_{1c}$ was independently associated with congenital anomalies [30]. Many studies group women who are on different oral agents together, however, so data for specific sulfonylureas, and in particular

glibenclamide, are not available. As there are extremely limited data on other sulfonylureas, and these are not recommended in pregnancy, we do not consider these in the present review.

Current recommendations for the use of glibenclamide in pregnancy now reflect the concerns that have arisen from the recent studies. Glibenclamide is not recommended in GDM if insulin or metformin is available [10,31]. In women with Type 2 diabetes it is recommended that oral antidiabetic agents (other than metformin) are discontinued before pregnancy, and insulin substituted [31]. The UK Teratology Information Service (UKTIS) advises, in the absence of evidence for teratogenicity, that glibenclamide may be considered in pregnancy where clinically indicated [11]; this could include $K_{ATP}$ neonatal diabetes and *HNF1A/HNF4A* MODY, where excellent glycaemic control can be achieved with sulfonylurea treatment. Glibenclamide can be resumed post-delivery and during breastfeeding for those with pre-existing diabetes [32].

Current opinion suggests that glibenclamide is not teratogenic, and that it is probably safe in the first trimester. Its use in later pregnancy is a cause for concern, with an increase in adverse fetal outcomes reported, in particular excess fetal growth and neonatal hypoglycaemia.

## What are the specific issues for sulfonylurea-treated monogenic diabetes in pregnancy ?

Individuals with HNF1A MODY, HNF4A MODY and KCNJ11/ABCC8 permanent neonatal diabetes can achieve excellent control on sulfonylureas outside pregnancy, and glycaemic control may be better on sulfonylureas than insulin [1–5]; however, given that glibenclamide treatment increases the risk of macrosomia and neonatal hypoglycaemia, its use in pregnancy in women with monogenic diabetes needs to be reconsidered.

These conditions are dominantly inherited, so there is a 50% chance of each fetus inheriting the mutation from their affected parent. Sulfonylureas crossing the placenta may be beneficial or detrimental depending on fetal genotype, but in the majority of cases, the fetal genetic status will be unknown, making management more complicated.

Treatment decisions need to consider many factors, including monogenic subtype, pre-pregnancy glycaemic control and treatment, gestation, patient preference, fetal growth and fetal inheritance status (if known). Optimum glycaemic control is essential during organogenesis, and fetal growth is an important consideration with advancing gestation (Fig. 1). Decisions regarding pregnancy management are, of course, individual and should be made with multidisciplinary input involving the patient, diabetologists and obstetricians.

As there are different issues to consider within the three subtypes we will discuss each separately.

## Monogenic diabetes pregnancy

### HNF1A maturity-onset diabetes of the young

*Optimum therapy outside pregnancy*

HNF1A MODY is optimally managed using low doses of sulfonylureas [1,2,33]. The mechanism for the increased glycaemic response to sulfonylureas observed in HNF1A MODY, compared with Type 2 diabetes, is thought to be attributable to increased pancreatic insulin secretory response to sulfonylureas and increased sensitivity to the insulin released [1].

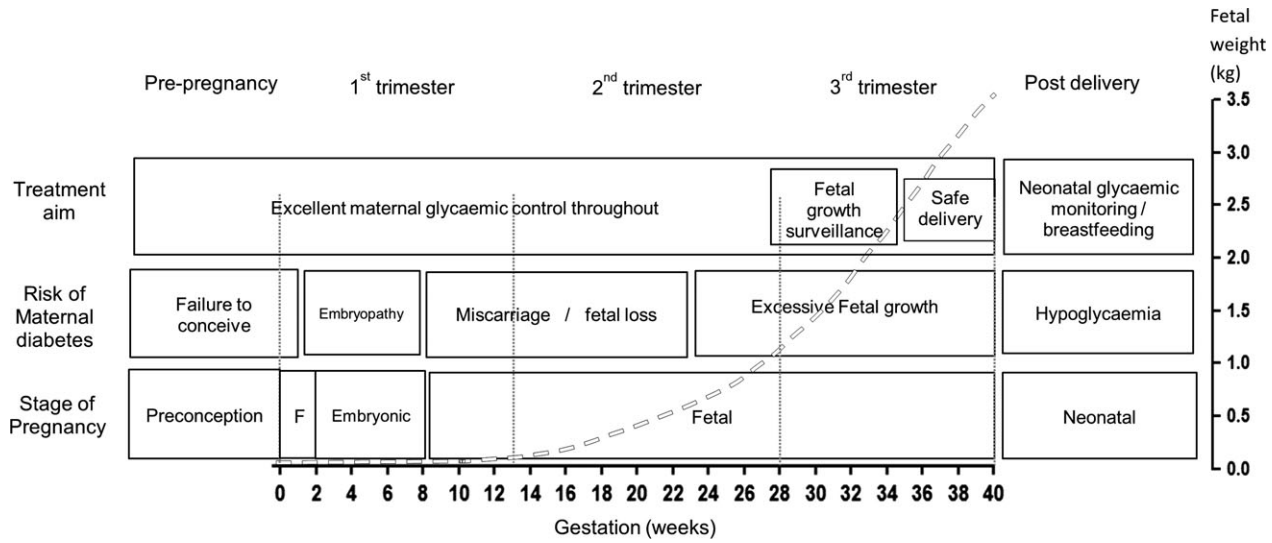


FIGURE 1 Risks associated with different stages of pregnancy in a mother with diabetes. Dashed line indicates fetal weight gain across advancing gestation and is population-derived, representing the 50th percentile of fetal growth as the trajectory for normal fetal growth. F, fertilisation.

*Reports on pregnancy*

*Impact of fetal genotype.* The largest study of neonatal outcomes associated with monogenic diabetes found no difference in birth weight or rate of macrosomia in 134 infants inheriting HNF1A MODY mutations compared with their unaffected siblings (median birth weight 3490 g) [34]. Mutations in *HNF1A* were not associated with a greater birth weight, with a median difference of 10 g and a mean difference in the analysis of 24 discordant sibling pairs of 3 g. Neither the birth weight nor the incidence of hypoglycaemia in heterozygous *HNF1A* mutation carriers differed from their unaffected sibling, suggesting that fetal insulin secretion was not increased in *HNF1A* mutation carriers [34]. If the mother carried the mutation, the birth weight was increased as a result of maternal hyperglycaemia, but the increase was similar if the fetus was affected or unaffected. Similar findings were identified in other cohorts [35]. A single reported case of neonatal hypoglycaemia in a *HNF1A* mutation carrier resolved within 48 h [34]. Consequently, inheritance of an *HNF1A* mutation is not considered to be associated with adverse birth outcomes or obstetric morbidity.

*Impact of maternal therapy in pregnancy.* There are no reports on the outcomes of sulfonylurea treatment in HNF1A MODY pregnancies, so the neonatal effects of sulfonylureas are not known.

*Recommendations*

There are two main treatment options for HNF1A MODY in pregnancy (Fig. 2): stop sulfonylureas pre-pregnancy and transfer to insulin or treat with glibenclamide pre-/early pregnancy and transfer to insulin in the second trimester. The second option should only be considered if pre-pregnancy $HbA_{1c}$ reaches local targets for glycaemic control. The advantage of excellent glycaemic control at conception and in the first trimester needs to be balanced against the lack of sufficient safety data on glibenclamide in the first trimester and the need to transfer from glibenclamide before the third trimester. Using insulin prior to conception has the advantage that this treatment can be continued throughout pregnancy and has a proven safety record at all stages of pregnancy; however, optimum glycaemic control at the time of conception and in the first trimester may be harder to achieve with insulin therapy.

If a woman taking sulfonylureas presents already pregnant, the benefit of transferring to insulin in early pregnancy needs to be weighed up against the potential deterioration in glycaemic control during organogenesis. In women with good glycaemic control [$HbA_{1c} < 48$ mmol/mol (6.5%)] on a sulfonylurea, the deterioration in control on discontinuing a sulfonylurea can be marked, and there is a case for continuing with a sulfonylurea until the end of the first trimester. Those on an alternate sulfonylurea should be transferred to an equivalent dose of glibenclamide.

If used before pregnancy and in the first trimester, glibenclamide should be discontinued before the third trimester, to avoid its trans-placental transfer. If this option is chosen, we suggest introducing a basal insulin in the second trimester and then replacing glibenclamide with bolus insulin as a second phase, aiming to achieve excellent glycaemic control well before week 26 of gestation. If glibenclamide is continued into the final trimester, doses should be as low as possible (≤5 mg/day) as the impact on the fetus is likely to be dose-related.

We recommend that women with HNF1A MODY have the same fetal checks/scans as recommended for other pre-

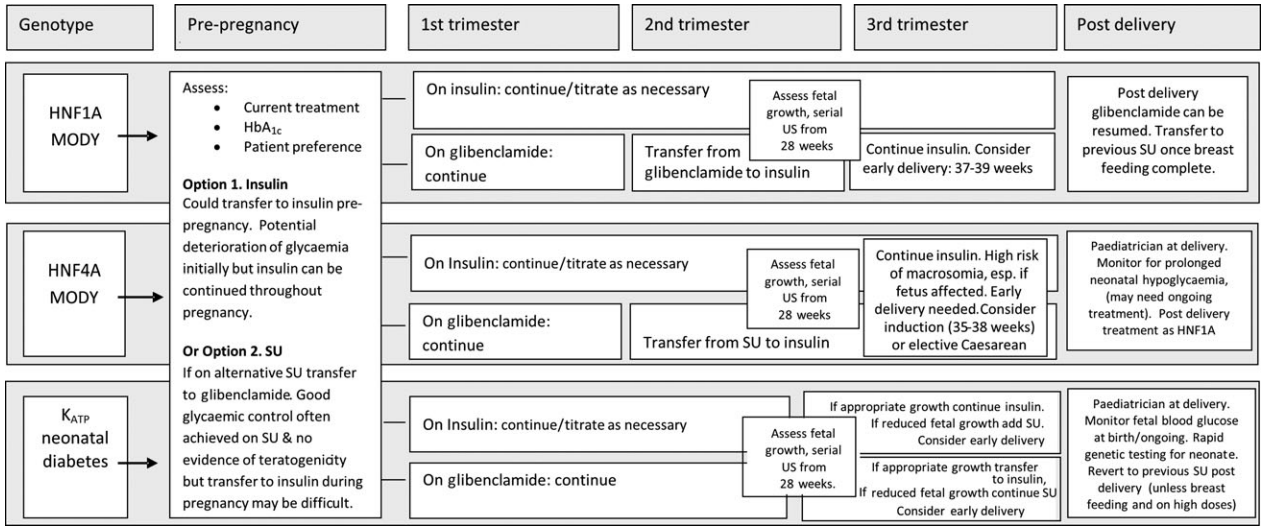


**FIGURE 2** Options for pregnancy management in HNF1A/HNF4A maturity-onset diabetes of the young (MODY) and ATP-sensitive potassium ($K_{ATP}$) channel neonatal diabetes. SU, sulfonylurea; US, ultrasonography.

existing diabetes in pregnancy [31]. Delivery should be considered between 37 and $38^{+6}$ weeks, in line with management of other pregnancies involving pre-existing diabetes [31]. Glibenclamide can be resumed post-delivery and during breastfeeding, with transfer, if desired, to an alternative sulfonylurea after weaning.

### HNF4A maturity-onset diabetes of the young

#### *Optimum therapy outside pregnancy*

Low-dose sulfonylureas are the optimum therapy in HNF4A MODY outside pregnancy [2].

#### *Reports on pregnancy*

*Impact of fetal genotype.* Inheritance of an *HNF4A* mutation results in a dramatic increase in birth weight. In a study of 108 individuals from families with HNF4A MODY, babies inheriting an *HNF4A* mutation had a median birth weight 790 g greater than their unaffected siblings ($97^{th}$ v $58^{th}$ centile) [34]. There was an additional effect of maternal glycaemia; hence affected *HNF4A* infants born to mothers with HNF4A MODY had a median corrected birth weight of 4840 g compared with 4170 g when the father was affected [34]. The prevalence of macrosomia was 64% if the *HNF4A* mutation was inherited from the mother and 46% if it was inherited from the father. Extreme macrosomia (birth weight >5000 g) was seen in 15% of cases with an affected mother and 7% of cases with an affected father [34]. The increase in birth weight when the mother is affected is likely to be attributable to the effects of maternal hyperglycaemia.

The increased fetal growth associated with inheriting a fetal *HNF4A* mutation results in marked morbidity including neonatal hypoglycaemia, shoulder dystocia, brachial plexus birth injury, assisted delivery and emergency caesarean section [34,36–39]. Infants born to a parent with HNF4A MODY require glucose monitoring after delivery as at least 10% of affected neonates have hypoglycaemia (blood glucose <2.5 mmol/l) [34,40]. Severe hyperinsulinaemic hypoglycaemia (blood glucose 0.8–2.5mmol/l for >24 h) may require prolonged treatment (intravenous glucose infusion, glucagon and diazoxide/chlorthiazide) as the hypoglycaemia can persist for months or years [37,40,41]. The increased birth weight and neonatal hypoglycaemia are a result of hyperinsulinism before and after birth [34]. The only exception is found in individuals with the p.R114W mutation, which is atypical of HNF4A MODY in that it has no effect on birth weight [42].

*Impact of maternal therapy in pregnancy.* Reports of maternal treatment during pregnancy in HNF4A MODY are scarce. In one case, insulin treatment did not prevent macrosomia or hypoglycaemia [38]. The published data are inadequate to determine if there is an effect of sulfonylurea use.

#### *Recommendations*

As there is a very high risk of macrosomia in *HNF4A* pregnancies if the fetus is affected, achieving excellent glycaemic control is essential. The two main treatment options (Fig. 2) are the same as those for HNF1A pregnancies, as discussed above. Additional information specific to *HNF4A* pregnancies is detailed below.

In women with *HNF4A* MODY, 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. 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 the infant should be monitored for neonatal hypoglycaemia for at least 48 h, as this may be prolonged and need continued treatment. The mother can resume glibenclamide post-delivery and during breastfeeding, with transfer to an alternative sulfonylurea, if desired, once breastfeeding is completed.

#### *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 its complications (shoulder dystocia, obstructed birth, etc) to that associated with maternal inheritance (median corrected birth weight 4200 g) [34]. In addition, there is a high risk of fetal hypoglycaemia that may be severe and profound (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 (see recommendations above).

### $K_{ATP}$ neonatal diabetes

#### *Optimum therapy outside pregnancy*

The vast majority of individuals with KCNJ11 or ABCC8 permanent neonatal diabetes are successfully managed with glibenclamide, with improvements in HbA1c and no increase in hypoglycaemia [3,4,43]. The key difference in sulfonylurea treatment in neonatal diabetes is the high dose of glibenclamide required (0.45 mg/kg/day) [3] compared with the low doses in HNF1A/HNF4A MODY (<0.01 mg/kg/day) [1, 2] or typical doses in Type 2 diabetes (0.06–0.2 mg/kg/day) [32].

### Reports on pregnancy

*Impact of fetal genotype.* In $K_{ATP}$ neonatal diabetes pregnancies neonatal birth weight is dependent on fetal genotype. If the fetus has inherited the genetic mutation from either the mother or father, reduced fetal insulin secretion results in low birth weight (median 2580 g at median 39 weeks' gestation) [44–46].

*Impact of maternal therapy in pregnancy.* Glibenclamide treatment may be beneficial or detrimental, depending on whether or not the fetus is affected. Three women with *KCNJ11* mutations who were treated with a sulfonylurea during four pregnancies have been described. The glibenclamide doses ranged from 2.8 to 90 mg/day [47–49]. If the fetus is unaffected, then maternal use of high-dose glibenclamide leads to high fetal doses, excess fetal insulin secretion, excess insulin-mediated growth and neonatal hypoglycaemia [47–49]. In contrast when the fetus is affected, trans-placental transfer of sulfonylurea restores fetal $K_{ATP}$ function and improves fetal growth, resulting in normal birth weight (median 3010 g at 38 weeks) [47]. Interestingly, one of the children described has not presented with neonatal diabetes in the first 18 months of life [47]. Whether this is a legacy effect of the high-dose glibenclamide or a mutation effect (the E229K mutation causes transient neonatal diabetes) [47] is not clear.

Offspring ($n$=6) who inherited a *KCNJ11* mutation from their affected insulin-treated mothers had a normal birth weight. In contrast, if the baby was born to a non-diabetic mother, birth weight was reduced (−1.81 v −0.12 median Standard Deviation Score for birth weight) [45]. This suggests that maternal hyperglycaemia can lead to increased fetal growth, even when there is a fetal mutation greatly reducing fetal insulin secretion.

*Breastfeeding.* In one mother with *KCNJ11* neonatal diabetes taking very high doses of glibenclamide (90 mg a day), persistent postnatal exposure led to hypoglycaemia in her unaffected neonate through transfer of the drug in breast milk [48]; however, the doses of glibenclamide typically used in Type 2 diabetes are considered safe for breastfeeding [32].

### Recommendations

The majority of women with $K_{ATP}$ neonatal diabetes will already be treated with glibenclamide pre-pregnancy and excellent glycaemic control can usually be achieved [typically $HbA_{1c}$ <48 mmol/mol (6.5%)]. If it is decided to continue sulfonylureas pre-conception and in the first trimester to aid glycaemic control then it is appropriate to reduce the glibenclamide dose to the lowest that maintains $HbA_{1c}$ concentration at ≤48 mmol/mol (6.5%).

If pregnancy is planned, transfer to insulin may be considered pre-conception but this will usually result in deterioration of glycaemic control with potential consequences with regard to fetal outcome.

The fetal genotype has a crucial role in determining whether glibenclamide therapy is recommended in $K_{ATP}$ neonatal diabetes. To determine if the fetus is affected, fetal genotyping should be offered if amniocentesis or chorionic villus sampling are being performed for another reason. Some authors have suggested that fetal genetic testing should be performed in all affected mothers, despite the risk (~1%) of miscarriage associated with invasive testing, as it would directly alter management [48,49]. If the fetal genotype is not tested directly, it may be possible to infer whether a fetus is likely to be affected by detecting reduced fetal growth by serial ultrasonography from 28 weeks' gestation.

If the fetus is affected, maternal glibenclamide treatment is appropriate when the mother has $K_{ATP}$ neonatal diabetes, as it will cross the placenta and provide *in utero* treatment of an affected fetus. This improves both fetal growth and, potentially, brain development. If the fetus is thought to be affected, glibenclamide should be continued at the lowest dose required for optimum glycaemic control. If the mother had been transferred to insulin pre-conception then glibenclamide should be reintroduced at the pre-pregnancy dose. If the mutation has been inherited from an affected father, treatment with sulfonylurea during pregnancy is not possible.

If the fetus is unaffected, or there is no ultrasound evidence that it is affected, glibenclamide in the last trimester will exacerbate excessive fetal growth and neonatal hypoglycaemia, therefore, insulin is advised; however, transfer to insulin will risk deterioration in glycaemic control at this time. Transfer from glibenclamide to insulin should be rapid (<3 days), a basal-bolus regimen should be introduced as the glibenclamide is stopped and rapidly titrated to achieve good glycaemic control.

Timing of delivery should take into account the risk of continuing pregnancy in a suboptimum intrauterine growth environment vs that of prematurity from early intervention. Usually this will be between 37 and $38^{+6}$ weeks.

A fetus inheriting a $K_{ATP}$ mutation from its mother or father will usually present with diabetes before the age of 6 months and will have elevated glucose levels before presenting with ketoacidosis. Prompt diagnosis and treatment is essential. A paediatrician should be available at delivery and the neonate's blood glucose should be checked at birth and at least 8-hourly for a minimum of 48 h. If the fetal genotype was not determined in pregnancy, rapid genetic testing of the fetus should be offered, as 50% of cases will be affected.

Cord blood samples can be sent to the molecular genetics laboratory at the Royal Devon and Exeter NHS Foundation Trust (www.diabetesgenes.org) and will be tested as a priority, without charge. Genetic test results in these cases should be available within 1 week of the arrival of the sample. The initial treatment of neonatal diabetes should usually be insulin, but sulfonylurea can be started as soon as the diagnosis of KATP neonatal diabetes is confirmed.

After delivery, women with $K_{ATP}$ neonatal diabetes can restart glibenclamide at pre-pregnancy doses. The exception

to this is when doses >0.2 mg/kg/day are used and breast-feeding is planned. The transfer of the drug in breast milk may be significant at higher doses [48].

## Antenatal testing for fetal genetic diagnosis

Awareness of fetal genotype allows individualized obstetric care, but fetal genotype is usually unknown, as at present it requires invasive testing. Due to the risks involved in chorionic villus sampling or amniocentesis, genetic testing is only usually considered antenatally if these tests are performed for another reason. Fetal growth on ultrasonography may provide a surrogate of fetal inheritance in HNF4A MODY and $K_{ATP}$ neonatal diabetes in the absence of a confirmatory antenatal genetic test, and may be useful in guiding the most appropriate management. Non-invasive genetic testing of cell-free fetal DNA in maternal blood is likely to revolutionize the management of monogenic diabetes pregnancies in the future [50].

## Conclusions

Glibenclamide is now known to cross the placenta and its use in pregnancy can result in increased risk of large-for-gestational-age infants, macrosomia and neonatal hypoglycaemia. The management of monogenic diabetes pregnancies that are treated with sulfonylureas outside pregnancy aims to achieve optimum glycaemic control during the first trimester, whilst limiting the adverse effects of glibenclamide on fetal birth weight.

We recommend avoiding glibenclamide use during the third trimester in women with HNF1A/HNF4A MODY. In $K_{ATP}$ neonatal diabetes glibenclamide can be continued throughout pregnancy if the fetus has reduced or low/normal fetal growth or is known to have inherited a $K_{ATP}$ channel mutation.

In the future, non-invasive pre-natal genetic testing will enable personalized management of HNF4A MODY and $K_{ATP}$ neonatal diabetes pregnancies. As data are currently lacking, we advocate an international system of reporting all pregnancy management/outcomes in monogenic diabetes pregnancies to enable an evidence-based approach. The monogenic diabetes team at the Royal Devon and Exeter NHS Foundation Trust would offer to act as a repository collating this information.

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### Competing interests

None declared.

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