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Clinical Management of Women with Monogenic Diabetes During Pregnancy

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Abstract

Purpose of Review—Monogenic diabetes accounts for 1-2% of all diabetes cases, but is frequently misdiagnosed as type 1, type 2, or gestational diabetes. Accurate genetic diagnosis directs management; such as no pharmacologic treatment for GCK-MODY, low dose sulfonylureas for HNF1A-MODY and HNF4A-MODY, and high dose sulfonylureas for K_{ATP} channel related diabetes. While diabetes treatment is defined for the most common causes of monogenic diabetes, pregnancy poses a challenge to management. Here we discuss the key issues in pregnancy affected by monogenic diabetes.

Recent Findings—General recommendations for pregnancy affected by GCK-MODY determine need for maternal insulin treatment based on fetal mutation status. However, a recent study suggests macrosomia and miscarriage rates may be increased with this strategy. Recent demonstration of transplacental transfer of sulfonylureas also raises questions as to when insulin should be initiated in sulfonylurea-responsive forms of monogenic diabetes.

Summary—Pregnancy represents a challenge in management of monogenic diabetes, where factors of maternal glycemic control, fetal mutation status, and transplacental transfer of medication must all be taken into consideration. Guidelines for pregnancy affected by monogenic diabetes will benefit from large, prospective studies to better define the need for and timing of initiation of insulin treatment.

Keywords

monogenic diabetes; MODY; glucokinase gene mutation; hepatocyte nuclear factor-1A; pregnancy

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Compliance with Ethical Standards

Conflict of Interest

Laura T. Dickens and Rochelle N. Naylor declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article contains unpublished data from retrospective studies with human subjects performed by Laura T. Dickens and Rochelle N. Naylor. Informed consent was obtained from all subjects.

INTRODUCTION

Monogenic diabetes refers to a heterogeneous group of inherited forms of diabetes caused by mutations in genes involved in beta cell development, function, and regulation. These mutations result in beta cell dysfunction with abnormalities in glucose sensing or insulin secretion and lead to diabetes [1]. Monogenic diabetes includes maturity-onset diabetes of the young (MODY), neonatal diabetes, and syndromic forms of diabetes. The most common form of monogenic diabetes is MODY, which is estimated to account for 1-2% of all diabetes worldwide [2]. However, MODY is frequently misdiagnosed as type 1 or type 2 diabetes and studies estimate that as many as 95% of MODY cases in the US go undiagnosed [3]. It is important to distinguish MODY from type 1 or type 2 diabetes because targeted treatments for MODY can improve glycemic control and reduce the burden of therapy. Furthermore, appropriate genetic diagnosis can identify at-risk family members for genetic testing. Therapy for the most common subtypes of monogenic diabetes are well established, however there is less data about management during pregnancy. Pregnancy introduces several important considerations for monogenic diabetes and a complex interplay between maternal glycemic control and mutation status of the fetus. Here we will review the pathophysiology of the common forms of monogenic diabetes and recent evidence and recommendations for management during pregnancy.

PATHOPHYSIOLOGY AND CLINICAL PRESENTATION OF MONOGENIC DIABETES

Four subtypes account for a majority of MODY cases with a genetic diagnosis: HNF1A, GCK, HNF4A, and HNF1B. The frequencies of these subtypes vary in different populations in part due to differences in recruitment for genetic testing. A large study in the United Kingdom of 564 probands observed HNF1A mutations to be most common (52%), followed by GCK (32%), HNF4A (10%) and HNF1B (6%) [4]. An additional class of monogenic diabetes which warrants discussion is persistent neonatal diabetes due to K_{ATP} channel mutations. We will begin by discussing the pathophysiology, clinical presentation, and recommended treatment outside of pregnancy for the most common subtypes of monogenic diabetes.

GCK-MODY

GCK-MODY is caused by mutations in the glucokinase gene, which catalyzes the conversion of glucose to glucose-6-phosphate and functions as the beta cell's glucose sensor. This results in an increase set-point for glucose stimulated insulin release which manifests clinically with mild, stable fasting hyperglycemia that is present from birth (fasting glucose 98-150 mg/dl, HbA1c 5.6–7.6%) [5]. Patients with GCK-MODY have low rates of clinically significant microvascular and macrovascular complications which are not different from control populations. One study observed higher rates of retinopathy in patients with GCK-MODY (30% compared to 14% in controls and 63% with type 2 diabetes). However, this difference was exclusively due to background retinopathy and no patients with GCK-MODY required laser therapy [6]. Treatment with oral hypoglycemic agents or insulin does not

significantly change glycemic control [7]. Therefore, treatment for GCK-MODY outside of pregnancy is not recommended.

HNFI1A-MODY

HNFI1A-MODY is caused by mutations in hepatocyte nuclear factor 1-alpha, a transcription factor that regulates the tissue-specific expression of many genes in pancreatic islet cells and the liver. Clinically, HNFI1A-MODY presents in adolescence or early adulthood with hyperglycemia, a large rise in 2 hour glucose level on oral glucose tolerance test (OGTT, >90mg/dL), and a lowered renal threshold for glucosuria due to the role of HNFI1A in SGLT2 gene expression [8, 9]. Development of diabetic complications in HNFI1A-MODY is strongly related to glycemic control. Older studies have shown complications develop at similar frequency as patients with type 1 and type 2 diabetes [10]. However, the rate of microvascular complications and cardiovascular disease was shown to be lower in a recent study of HNFI1A-MODY in a dedicated MODY clinic [11]. A distinguishing feature of HNFI1A is sensitivity to treatment with sulfonylureas, which are recommended as first line therapy. A majority of patients who have been previously treated with insulin can be transitioned off insulin to sulfonylureas with equal or improved glycemic control. Patients who are not able to successfully transition off insulin tend to have longer duration of diabetes and have experienced progressive loss of beta cell function [12]. Low doses of sulfonylureas are typically sufficient for treatment and the recommended starting dose is one-fourth of typical doses for type 2 diabetes. Though sulfonylureas can remain effective for many years, obesity and loss of beta cell function over time can cause worsening glycemic control [11]. Second line therapies such as meglitinides (nateglinide) and GLP1 receptor agonists (liraglutide) have been shown to effectively lower glucose in patients with HNFI1A-MODY with lower rates of hypoglycemia compared to sulfonylureas [13, 14].

HNFI4A-MODY

HNFI4A-MODY is caused by mutations in hepatocyte nuclear factor 4-alpha, an upstream regulator of HNFI1A transcription factor. Clinical characteristics of HNFI4A-MODY are similar to HNFI1A-MODY and include progressive defects in insulin secretion with presentation in adolescence or early adulthood. Patients with HNFI4A-MODY may have large birth weight with macrosomia in ~50% of affected babies and transient neonatal hypoglycemia due to fetal hyperinsulinism [8, 15, 16]. In contrast, occurrence of fetal hyperinsulinism in HNFI1A-MODY has only been described in rare cases [17]. Diabetic complications occur at rates similar to type 1 and type 2 diabetes and are linked to glycemic control. Treatment with low dose sulfonylureas is first line and is similarly effective as for HNFI1A-MODY.

HNFI1B-MODY

HNFI1B-MODY is caused by mutations in hepatocyte nuclear factor 1-beta, a transcription factor expressed in embryonic development of the kidney, pancreas, liver, and GU tract. In addition to diabetes, HNFI1B-MODY is associated with developmental renal disease (typically cystic and not diabetes related), genital tract malformations, abnormal liver function, hyperuricemia, and gout. Renal disease is particularly common with a 66% incidence of renal cysts and 86% incidence of renal impairment [18]. Patients with HNFI1B-

MODY have decreased insulin sensitivity compared to HNF1A-MODY patients. Only rarely are sulfonylureas successful; insulin treatment is required in the majority of cases for glycemic control [19, 20].

K_{ATP} Channel Mutation Diabetes

Permanent neonatal diabetes is most commonly caused by mutations in the ATP-sensitive potassium channel including activating mutations in the genes KCNJ11 and ABCC8. These mutations result in failure of K_{ATP} channel closure and insufficient beta cell insulin secretion [21, 22]. Sulfonylureas cause K_{ATP} channel closure through an ATP-independent mechanism and are effective treatments for a majority of patients with KCNJ11 and ABCC8 related diabetes. In contrast to HNF1A- and HNF4A-MODY, high doses of sulfonylureas are typically required to treat patients with K_{ATP} channel diabetes with average doses of 0.45 mg/kg/day [23].

MANAGEMENT OF MONOGENIC DIABETES IN PREGNANCY

Table 1 summarizes the management of each subtype of monogenic diabetes during pregnancy including the effect of fetal genotype, treatment and monitoring during pregnancy, and postpartum considerations.

GCK-MODY

I. Background

i. Prevalence of GCK-MODY in pregnancy: Several research studies have focused on identification of GCK-MODY in women with gestational diabetes (GDM). Since all pregnant women undergo glycemic screening, this is an opportunity to identify women with GCK-MODY who will require different treatment during and after pregnancy. The Atlantic Diabetes in Pregnancy Cohort estimated the prevalence of GCK-MODY to be 1% in gestational diabetes and identified body mass index (BMI) and fasting glucose to be useful clinical characteristics to distinguish GCK-MODY from GDM. In this population, the combination of BMI less than 25 and fasting glucose ≥ 100 was 68% sensitive and 99% specific for distinguishing GCK-MODY from GDM with a number needed to undergo genetic testing of 2.7 to diagnose one case of GCK-MODY [24]. These screening cutoffs have been validated in an Australian cohort with a similar sensitivity of 75% and specificity of 96.1%, however concern was raised in this study about the performance of these cutoffs in a multiethnic population [25]. Additional research is ongoing to determine the applicability of these parameters in the US multiethnic population.

ii. Influence of fetal genotype: In GCK-MODY, pregnancy outcomes depend on whether the fetus has inherited the *GCK* mutation or not. The unaffected fetus of a mother with GCK-MODY will increase insulin secretion in response to mild maternal hyperglycemia, resulting in increased birthweight and risk for macrosomia. In contrast, an affected fetus of a mother with GCK-MODY would sense mild maternal hyperglycemia to be normal and growth and birth weight will be normal. Fetuses with paternally-inherited *GCK* mutations born to unaffected mothers have lower birth weight of ~400 grams and rates of weight below the 10th percentile are increased 3-fold [26]. In the case of GCK-unaffected offspring, it has

been suggested that insulin treatment to lower glucose could reduce the risk of macrosomia and associated complications. However, aggressive insulin therapy in a women with GCK-MODY carrying an affected fetus may negatively impact fetal growth by decreasing fetal insulin secretion and thereby reducing insulin-mediated growth [26, 27].

The largest study to assess the effect of mutation status on birth weight was carried out by Spyer et al. In this study of 98 live births (genotype data was obtained in 82 offspring) in 42 women with GCK-MODY, fetal birth weight was significantly greater in unaffected offspring compared to affected offspring (3.9 versus 3.2 kg) and a higher rate of macrosomia was seen in unaffected offspring compared to affected offspring (39% versus 7%) [26]. In the aforementioned study 38% of mothers with GCK-MODY were treated with insulin which was initiated at variable times and in variable doses. There was no difference in birth weight of offspring between insulin and non-insulin treated mothers or between fetal genotypes within treatment groups [26]. The authors suggest that the lack of effect may have been due to late timing of insulin initiation and relatively low doses of insulin, since it has been shown that high doses of insulin up to 1 unit/kg/day are required to normalize glucose in GCK-MODY women during pregnancy.

II. Treatment/Management Recommendations—Based on these findings, current recommendations advise that management of GCK-MODY in pregnancy should be based on fetal mutation status. Invasive sampling for the sole purpose of determining fetal genotype is not recommended [28]. The emergence of non-invasive prenatal genetic testing through cell free circulating DNA (cfDNA) extracted from maternal plasma presents an intriguing option for determining fetal genotype. However, to date there have been no recommendations about the use of cfDNA in this setting. Thus, second trimester fetal growth scans are used to infer fetal genotype. The recommendations state that insulin should not be used preconception or in early pregnancy. Starting at 26 weeks gestation, fetal ultrasound should be performed every two weeks to identify accelerated fetal growth as indicated by abdominal circumference >75th percentile. If accelerated fetal growth is detected, this suggests that the fetus does not carry a *GCK* mutation. Insulin therapy is recommended to reduce the risk of macrosomia and delivery should be induced at 38 weeks. If no accelerated fetal growth is seen, the fetus can be inferred to have inherited the *GCK* mutation and would not be at risk for macrosomia, so no treatment is indicated [5]. In two cases where invasive sampling was indicated for other reasons, inheritance of a *GCK* mutation was confirmed in the fetuses and neither mother received treatment for their hyperglycemia. Birth weight was normal and there were no peripartum complications in the offspring [29]. Unfortunately, data to support these recommendations are limited and at least one study raises questions regarding this approach.

A retrospective study by Bacon et al in 2015 examined 56 pregnancies in 12 women with GCK-MODY. In this cohort insulin was used in 26.6% of pregnancies and initiated at an average of 14 weeks gestation. The GCK-unaffected offspring whose mothers were treated with insulin had a lower rate of macrosomia of 33.3% compared with 62.5% in the non-insulin treated GCK-unaffected group, though this difference was not statistically significant. There was no SGA observed in insulin treated, GCK-affected offspring (n=3) and no significant adverse effects of insulin therapy were observed including no severe

hypoglycemia [30]. The authors concluded that “the lack of available clinical studies... necessitates the use of guidelines designed for the management of GDM”. They suggest that all women with GCK-MODY should be treated with insulin early during pregnancy since it is not clear if fetal genotype can be accurately predicted or if insulin initiated late in gestation can prevent macrosomia. No prospective studies about use of ultrasound to predict fetal genotype have been done, nor have studies specifically addressed the efficacy of insulin in reducing macrosomia when initiated in the late second/early third trimester according to current recommendations. The major limitations of this study are the retrospective nature and small sample size. Anecdotal experience and unpublished data from the University of Chicago Monogenic Diabetes Registry based on 130 pregnancies in 55 women with GCK-MODY suggests that hypoglycemia, including severe hypoglycemia, may occur commonly during pregnancy in women with GCK-MODY treated with insulin and requires consideration.

Currently, more data exist to support use of fetal *GCK* mutation status (confirmed from genetic testing or inferred from fetal ultrasound) to direct management of maternal hyperglycemia. Studies from GDM also offer support of this approach [31]. However, findings by Bacon et al., show the need for additional studies.

III. Other Considerations

i. Miscarriage rates in GCK-MODY: Concerns have also been raised about the effects of maternal hyperglycemia on miscarriage rate and long-term glycemic control in offspring. The same retrospective study by Bacon et al discussed above observed a higher rate of miscarriages in women with GCK-MODY of 33%, compared to 14% in women with HNF1A-MODY and a background population rate of 15%. Miscarriages in women with GCK-MODY tended to occur early in gestation at an average of 7.5 weeks [30]. This study is the first to raise the concern about increased miscarriage with GCK-MODY and confirmation of these findings is needed. Unpublished data from the University of Chicago Monogenic Diabetes Registry observed a miscarriage rate of 18% in a total of 130 pregnancies in women with GCK-MODY, which is not significantly different from background population miscarriage rates.

ii. Long-term outcomes in offspring: Data show that despite increase in birth weight of children born to mothers with GCK-MODY, there appear to be no long-term effects of exposure to mild maternal hyperglycemia in utero. A study in 2007 showed no evidence of impaired glucose tolerance on OGTT or reduced beta cell function in unaffected offspring of GCK-MODY mothers compared to the control group of offspring of GCK-MODY fathers [32].

HNF1A-MODY

I. Background—In pregnancies affected by HNF1A-MODY, maternal glycemic control is the major determinant of fetal outcomes. In the majority of cases, fetal inheritance of *HNF1A* mutations does not result in increased birth weight or incidence of hypoglycemia [15]. However, there are case reports of congenital hyperinsulinism due to *HNF1A* mutations associated with MODY [17] Though optimal treatment of HNF1A-MODY

outside of pregnancy is with sulfonylureas, there is limited data about best management during pregnancy. The sulfonylurea glyburide (glibenclamide) has been commonly used to treat gestational diabetes and previous publications suggested this would be reasonable treatment for HNF1A-MODY during pregnancy [28]. However, recent studies have shown that glyburide crosses the placenta and can be measured in fetal umbilical venous samples. In one study a majority (79%) of umbilical vein glyburide levels were below the typical limit of detection of 10 ng/mL, though in 37% of cases the fetal glyburide levels were higher than maternal levels [33]. Another study using an LC/MS assay found umbilical cord plasma glyburide concentrations to average 70% of maternal blood concentrations [34]. In addition to these findings that transplacental glyburide transfer does occur, evidence has also shown that glyburide may negatively impact fetal and neonatal outcomes. A meta-analysis in 2014 found significant increase in the risk of macrosomia (RR 3.07) and neonatal hypoglycemia (RR 2.30) in pregnant women with gestational diabetes treated with glyburide compared with insulin treatment [35]. These findings have led some to suggest that sulfonylureas should be avoided in pregnancies with monogenic diabetes, particularly in the third trimester when risk for fetal hyperinsulinism and macrosomia is greatest. In light of these recent data, insulin therapy appears to be the most conservative approach.

II. Treatment and Monitoring Recommendations—Recent recommendations for management of HNF1A-MODY pregnancies attempt to balance the risk of uncontrolled hyperglycemia during the first trimester at the time of organogenesis with the risk for macrosomia and neonatal hypoglycemia with sulfonylurea therapy in the third trimester. These recommendations present two potential management options: stop sulfonylurea before pregnancy and switch to insulin or continue sulfonylurea treatment pre-conception and in early pregnancy and switch to insulin in the second trimester. The second option is suggested only for patients with excellent pre-pregnancy glycemic control on sulfonylureas. If a woman on a sulfonylurea presents during early pregnancy, the risk of deteriorating glycemic control during organogenesis should be considered when determining treatment strategy. If glycemic control is excellent on sulfonylurea therapy it may be reasonable to continue sulfonylureas until the end of the first trimester and then switch to insulin [36].

Glyburide is specifically recommended as the sulfonylurea of choice if this class of medication is used because it has been most extensively studied in pregnancy. Patients on alternative sulfonylureas who are continuing on sulfonylureas in pregnancy should be switched to equivalent doses of glyburide. To transition from glyburide to insulin, first basal insulin should be initiated and then bolus insulin added and glyburide discontinued. This transition should be completed prior to 26 weeks gestation. In exceptional circumstances where glyburide is continued in the third trimester, the lowest dose that provides adequate glycemic control should be used. Fetal monitoring in pregnancies with HNF1A-MODY should be the same as pregnancies with pre-existing diabetes [36]. After delivery, glyburide can be resumed and continued during breastfeeding. Studies have shown that low dose glyburide is not excreted in breast milk nor is it associated with neonatal hypoglycemia [37].

HN4A-MODY

I. Background—In contrast to HN1A-MODY, fetal outcomes in HN4A-MODY pregnancies are highly dependent upon fetal genotype. Offspring who inherit *HN4A* mutations demonstrate median increases in birthweight of 790g compared to wild type family members. Incidence of macrosomia is significantly increased in *HN4A* mutation carriers at 56% compared to 13% in wild type family members and neonatal hyperinsulinemic hypoglycemia has been seen in 15% of *HN4A* mutation carriers [15]. There is an additive effect of maternal hyperglycemia on rates of macrosomia whereby *HN4A* mutation carriers born to HN4A-affected mothers have increased birth weight compared to *HN4A* mutation carriers who inherited the mutation from their father.

II. Treatment and Monitoring Recommendations—In light of these significant risks of fetal and neonatal morbidity related to macrosomia and hypoglycemia, tight maternal glycemic control is critical. No treatments have been shown to improve fetal outcomes or macrosomia in HN4A-MODY pregnancies. The therapeutic strategies are the same as previously described for HN1A-MODY pregnancies: stop sulfonylurea before pregnancy and switch to insulin or continue sulfonylurea treatment before and in early pregnancy and switch to insulin in the second trimester [36]. Fetal monitoring during pregnancy with HN4A-affected mothers should include ultrasounds for growth assessment at least every 2 weeks starting at 28 weeks. If macrosomia is detected, induction of labor or elective cesarean section should be considered at 35 to 38 weeks. After delivery the baby should be monitored for at least 48 hours for hypoglycemia. Postpartum and during breastfeeding, glyburide can be resumed. Recommendations are similar for pregnancies with HN4A-affected fathers and include ultrasound monitoring beginning at 28 weeks with consideration of early delivery at 37 weeks based on fetal size and close monitoring for neonatal hypoglycemia [36].

HN1B-MODY

There is very limited data published about pregnancies affected by HN1B-MODY. Patients with HN1B-MODY will typically require insulin for glycemic control and should continue this during pregnancy. The effects of maternal treatment on fetal outcomes have not been studied, though one small cohort study did demonstrate a significant impact of maternal/fetal genotype on birth weight. Babies with HN1B-MODY born to unaffected mothers had significantly reduced birthweight and 69% incidence of SGA while birth weight was increased in babies with HN1B-MODY born to mothers with HN1B-MODY and diabetes [38]. Offspring of affected parents should undergo genetic testing to identify carriers of the *HN1B* mutation for close follow up and screening for renal abnormalities.

K_{ATP} Channel Mutation Diabetes

I. Background—In pregnancies affected by K_{ATP} channel mutation diabetes, fetal birth weight also depends on fetal genotype. Offspring who inherit these mutations from either their mother or father will have reduced fetal insulin secretion resulting in low birth weight [39]. Outside of pregnancy, treatment with high dose sulfonylureas is standard of care; however, during pregnancy the benefit of sulfonylurea treatment depends on fetal genotype.

If the fetus has inherited the K_{ATP} channel mutation, case reports indicate that sulfonylurea treatment will restore fetal insulin secretion and result in normal birth weight [40]. If the fetus has not inherited the mutation, sulfonylurea treatment can result in excess fetal insulin secretion, macrosomia, and neonatal hypoglycemia [41]. Fetal genotyping can be performed using chorionic villous sampling or amniocentesis, though these invasive procedures carry a risk of miscarriage. Non-invasive cfDNA is a promising option for prenatal genetic testing. One case report described effective use of cfDNA for prenatal genetic testing for a fetus at risk of inheriting a KCNJ11 mutation causing permanent neonatal diabetes [42]. Further study is needed before this new technology can be routinely used in this setting. Current recommendations advise that fetal genotype be inferred from serial ultrasound growth monitoring starting at 28 weeks. Reduced growth indicates the fetus has inherited the K_{ATP} channel mutation while normal growth suggests the fetus is wild type.

II. Treatment and Monitoring Recommendations—Maternal treatment should again take into consideration the risk of adverse effects from deteriorating glycemic control during critical times in fetal development and the risk of macrosomia and neonatal hypoglycemia in an unaffected offspring exposed to high dose sulfonylurea treatment. Recommendations advise that it is reasonable to switch to insulin prior to conception or to continue sulfonylurea treatment through the first trimester at the lowest dose possible to maintain good glycemic control with $A1c < 6.5$. If ultrasound scans show reduced fetal growth, suggesting the fetus has inherited the K_{ATP} channel mutation, then glyburide is the treatment of choice and should be continued or reintroduced if the patient was switched to insulin previously. If ultrasound scans show normal fetal growth, transfer from glyburide to insulin is advised to avoid excessive fetal growth, macrosomia, and neonatal hypoglycemia [36]. After delivery, fetal genetic testing should be completed if it was not done during pregnancy. If the offspring has inherited the K_{ATP} channel mutation, neonatal diabetes will typically present before 6 months of age and close follow up with a pediatrician is recommended. Maternal glyburide treatment can be resumed after delivery and is generally considered to be safe during breastfeeding, though at high maternal doses there may be excretion of glyburide to breast milk [41].

CONCLUSIONS

This review summarizes available evidence and recommendations for management of monogenic diabetes in pregnancy. These recommendations are based on limited data due to multiple challenges for controlled studies in this field. These diagnoses are relatively rare and many women do not have a genetic diagnosis at the time of pregnancy and are treated as type 1, type 2, or gestational diabetes. Thus, data about pregnancy monitoring, effects of therapy, and outcomes are primarily retrospective. The available evidence does highlight the importance of understanding the impact of fetal genotype on in utero growth and the effect of maternal glycemic control. Prospective studies in pregnancies affected by GCK-MODY can help to determine if ultrasound monitoring is indeed an effective tool for inferring fetal genotype and making treatment decisions. Furthermore, the effects of maternal hyperglycemia on miscarriage rates require further study to confirm and better understand this observation. The recent data on transplacental transfer of sulfonylurea represents a

paradigm shift from prior thinking about management of HNF1A/HNF4A and K_{ATP} channel diabetes during pregnancy, suggesting insulin therapy may be the preferred therapy. Theoretically the use of non-invasive cell free DNA for prenatal genotyping could help to clarify management strategies moving forward for many forms of monogenic diabetes.

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Table 1

Clinical Features and Management During Pregnancy of Monogenic Diabetes

	Clinical Features	Treatment Outside of Pregnancy	Effect of Fetal Genotype on Pregnancy	Treatment During Pregnancy	Monitoring During Pregnancy	Postpartum Considerations
GCK-MODY	Mild, stable fasting hyperglycemia with fasting glucose 98-150 mg/dL. HbA1c 5.6-7.6%	None	<i>GCK fetus</i> : Normal growth and birth weight <i>WT fetus</i> : Increased birth weight, risk of macrosomia <i>GCK fetus/WT mother</i> : reduced birthweight	No treatment preconception and early pregnancy. If accelerated fetal growth is seen on ultrasound, insulin should be started and delivery should be at 38 weeks	Fetal ultrasound every 2 weeks starting at 26 weeks to monitor for accelerated growth	Treatment can be discontinued postpartum
HNF1A-MODY	Hyperglycemia, a large rise in 2 hour glucose level on OGTT (>90mg/dL), lowered renal threshold for glucosuria	Low dose SU	Limited or no effect (case reports of neonatal hyperinsulinemic hypoglycemia)	Two options: 1. Stop SU before conception and start insulin 2. Continue SU* in early pregnancy and switch to insulin in the second trimester	Fetal monitoring should be the same as for pregnancies with pre-existing diabetes**	SU can be resumed postpartum including during breastfeeding
HNF4A-MODY	Hyperglycemia, macrosomia and hypoglycemia in the neonatal period	Low dose SU	<i>HNF4A fetus</i> : Increased birth weight, risk of macrosomia, neonatal hyperinsulinemic hypoglycemia <i>WT fetus</i> : Normal birth weight, no hypoglycemia	Two options: 1. Stop SU before conception and start insulin 2. Continue SU* in early pregnancy and switch to insulin in the second trimester If macrosomia consider delivery at 35-38 weeks	Fetal ultrasound every 2 weeks starting at 28 weeks to monitor for accelerated growth	Monitor baby for at least 48 hours for hypoglycemia. SU can be resumed postpartum including during breastfeeding
HNF1B-MODY	Hyperglycemia, developmental renal disease, genital tract malformations, abnormal liver function, hyperuricemia, and gout	Typically requires insulin	<i>HNF1B fetus/WT mother</i> : reduced birthweight, risk of SGA <i>HNF1B fetus/HNF1B mother</i> : increased birth weight	Continue pre-pregnancy insulin treatment	No specific recommendations. Fetal monitoring should be the same as for pregnancies with pre-existing diabetes**	Offspring should undergo genetic testing, carriers of <i>HNF1B</i> require screening for renal abnormalities
K _{ATP} Channel Mutation Diabetes	Permanent neonatal diabetes, typically presents before 6 months of age	High dose SU	<i>K_{ATP} channel mutation fetus</i> : low birth weight <i>WT fetus</i> : macrosomia,	Either switch to insulin or continue SU at lowest effective dose pre-conception and early pregnancy. If ultrasound shows reduced fetal growth on insulin, switch to SU.	Fetal ultrasound starting at 28 weeks to monitor growth	Offspring should undergo genetic testing, carriers of <i>K_{ATP}</i> channel mutation require close follow up for development of neonatal diabetes.

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	Clinical Features	Treatment Outside of Pregnancy	Effect of Fetal Genotype on Pregnancy	Treatment During Pregnancy	Monitoring During Pregnancy	Postpartum Considerations
			neonatal hypoglycemia (if mother treated with SU)	If ultrasound shows normal growth on SU, switch to insulin		SU can be resumed postpartum, though at high doses may have transfer to breast milk

SU= sulfonylurea

* Glibenclamide/glyburide is the preferred sulfonylurea

** Recommended monitoring in pregnancies with pre-existing diabetes includes ultrasound early in gestation for detection of fetal anomalies followed by periodic ultrasound examinations to confirm appropriate growth. Additional monitoring can include assessment of fetal wellbeing with fetal movement counting, nonstress testing, biophysical profile, and/or contraction stress testing [43].