HHS Public Access

Author manuscript

Am J Perinatol. Author manuscript; available in PMC 2017 July 12.

Published in final edited form as:

Am J Perinatol. 2016 November ; 33(13): 1319–1326. doi:10.1055/s-0036-1592078.

The Genetic Architecture of Diabetes in Pregnancy: Implications for Clinical Practice

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Abstract

The genetic architecture of diabetes mellitus in general and in pregnancy is complex, owing to the multiple types of diabetes that comprise both complex/polygenic forms and monogenic (largely caused by a mutation in a single gene) forms such as maturity onset diabetes of the young (MODY). Types 1 and 2 (T1D and T2D) have complex genetic etiologies, with over 40 and 90 genes/loci respectively implicated that interact with environmental/lifestyle factors. The genetic etiology of gestational diabetes mellitus (GDM) has largely been found to overlap that of T2D. Genetic testing for complex forms of diabetes is not currently useful clinically, but genetic testing for monogenic forms, particularly MODY, has important utility for determining treatment, managing risk in family members and pregnancy management. In particular, diagnosing MODY2, caused by *GCK* mutations, indicates that insulin should not be used including during pregnancy, with the possible exception of an unaffected pregnancy during the third trimester to prevent macrosomia. A relatively simple method for identifying women with MODY2 has been piloted. MODY1, caused by *HNF4A* mutations, can paradoxically cause neonatal hyperinsulinemic hypoglycemia and macrosomia, indicating that detecting these cases is also clinically important. Diagnosing all MODY types provides opportunities for diagnosing other family members.

Introduction

Nearly all forms of diabetes have a genetic component. The American Diabetes Association classifies diabetes into four categories. The first two categories are type 1 diabetes (T1D) and type 2 diabetes (T2D) and typically have a multifactorial etiology, meaning they are caused by a complex interaction of genetic and environmental/lifestyle factors. The third category is gestational diabetes, and the fourth category is “specific types of diabetes due to other causes,” such as those secondary to diseases of the exocrine pancreas, drug or chemical exposure, or, most relevant here, those, caused by a mutation in a single gene, called monogenic diabetes [1]. Nearly all forms of diabetes can be diagnosed before pregnancy and affect some women and their pregnancies as pre-gestational diabetes, whereas other women are only diagnosed with gestational diabetes mellitus (GDM) during pregnancy. Great strides in elucidating the genetic factors in all types of diabetes have been made in recent decades. While our increasing knowledge of the genetics of complex forms

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of diabetes is improving the understanding of diabetes etiology and potential treatments, our current knowledge of monogenic diabetes presents underutilized opportunities for personalized management of diabetes in pregnancy. Here we provide an overview of the genetics of both pre-gestational and gestational diabetes, followed by a review of monogenic diabetes and associated pregnancy-specific implications.

Genetics of Complex Diabetes: An Overview

Genetics of type 1 diabetes

Type 1 diabetes (T1D) is an early onset form of hyperglycemia caused by destruction of insulin-producing pancreatic beta cells. It accounts for approximately 5% of all diabetes cases [2]. T1D is strongly but incompletely genetic, as evidenced by moderate concordance (30–50%) within genetically identical twin pairs [3]. Genetic association studies have revealed a strong association between T1D and haplotypes in the *HLA* genes of major histocompatibility complex (MHC), which is associated with many autoimmune diseases and some non-autoimmune diseases. T1D is strongly associated with HLA-DR3 (DRB1*03-DQB1*0201) and HLA-DR4 (DRB1*04-DQB1*0302), in addition to complex network of weaker associations with many other HLA genotypes that comprise MHC class II molecules integral in humoral immunity [4]. These haplotypes result in vulnerability to autoimmune destruction of pancreatic beta cells, which causes most T1D and may be triggered by a number of different environmental factors, some not yet understood. Genotyping for these haplotypes is not currently considered clinically useful, but research using HLA haplotypes to identify genetically vulnerable individuals and track the non-genetic triggers as well as understand the comprehension[5] and psychological impact of testing [6] is underway through the PANDA (Prospective Assessment in Newborns of Diabetes Autoimmunity) study in the U.S. [5] and the MIDIA (Environmental Trigger of Type 1 Diabetes) study in Norway [7]. Variability in seasonal incidence of T1D may indicate that viral attack can trigger pancreatic beta cell autoimmunity, but other environmental factors, such as dietary factors, other microbial elements, or psychosocial factors, may also play a role [8]. In addition to the HLA association of T1D, specific non-MHC related genes such as *PTPN22*, *CTLA4*, and *INS* are also associated with T1D [9–11], with over 40 loci discovered through genome-wide association studies [12], including some involved in beta cell development and function. Monogenic forms of T1D are present in two rare syndromes: APECED (autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome) and IPEX (immunodysregulation, polyendocrinopathy and enteropathy, x-linked), caused by genetic variants in *AIRE* and *FOXP3*, respectively [13]. IPEX is an extremely rare, X-linked autoimmune disorder due to a deficit in regulatory T-cell function causing multi-organ effects, including T1D (in over 60% of reported subjects), dermatitis, diarrhea, and failure to thrive [14]. APECED is a rare, autosomal recessive disorder characterized by the autoimmune destruction of several, mostly endocrine, tissues, leading to a classic triad of chronic mucocutaneous candidiasis, hypoparathyroidism, and adrenal insufficiency, as well as diabetes [15].

Genetics of type 2 diabetes

T2Dis a complex group of polygenic multifactorial diseases characterized by hyperglycemia resulting from a combination of insulin resistance and relative insulin insufficiency that generally begins during or after the fourth decade of life. The heritability of T2D is estimated to be between 30–70% [16, 17]; however, only approximately 15% of T2D heritability has been explained by genetic associations [18]. More than 90 common variants with small effect sizes (generally 1.05–1.6 odds ratios) have been discovered [18]. These variants have been found through multiple study formats, including family- linkage studies, candidate gene analyses, genome-wide association studies (GWAS), and GWAS meta-analyses. Associations with T2D have been found in genes known to cause monogenic forms of diabetes (e.g. *HNF4A*, *KCNJ11*, *PPARG*) and in genes/loci involved in beta cell function(e.g., *TCF7L2*, *KCNQ1*, *SLC30A8, CDKAL1, IGF2BP2*). Genes/loci (e.g., *G6PC2*, *MTNR1B*, *GCKR*) have also been found to be associated with T2D-related quantitative traits, such as fasting plasma glucose level or oral glucose tolerance test response. Other genes/loci have been found to be associated with T2D only in specific family history (*HCCA2* variant is strongly associated with T2D only when paternally inherited [19]) or metabolic (association between T2D and *FTO* locus is mediated by increased BMI [20]) contexts. The majority of all associated genes relate to beta cell function, and the genetics of insulin resistance is less well-understood. Additionally, the role of rare variants, epigenetics, and other genomic structural or copy-number variants are future areas in need of study as genomic sequencing techniques increase in capacity and decrease in cost. The many environmental and lifestyle factors of T2D also emphasize the importance of accounting for gene-environment interactions, and a small number of studies have provided evidence that the effects of certain variants associated with T2D appear to be mitigated through lifestyle intervention [21, 22]. For example, in the Diabetes Prevention Program, the robustly replicated *TCF7L2* rs7903146 T2D risk allele was associated with increased risk of progression to T2D in the placebo group and to a lesser extent in the metformin group, but not in the group undergoing intensive lifestyle intervention [21].

Genetics of gestational diabetes

GDM is characterized by hyperglycemia during pregnancy resulting from insufficient increase in insulin secretion in response to the physiological increase in insulin resistance of pregnancy. This is a similar pathologic mechanism to the process whereby patients with T2D progress from a state of impaired fasting glucose or impaired glucose tolerance to frank diabetes. As expected, the genetic architecture that underlies GDM and T2D has considerable overlap. The high prevalence of T2D in the general population has provided the opportunity to study the genetics of T2D on a large scale, with some studies including tens of thousands of participants [23–25]. GDM does not have the same opportunities for study scale due to a lower prevalence than T2D (4–10% of pregnancies vs. 8–10% of the entire population in the United States for T2D [26]) and its temporary nature. Consequently, many genetic GDM studies have utilized a candidate gene approach, prioritizing targets based on T2D-associated variants. Building from that data, two meta-analyses have successfully confirmed that many susceptibility genes related to beta cell function are conserved between GDM and T2D, including single-nucleotide variants in *TCF7L2*, *MTNR1B*, *KCNJ11*, *IGF2BP2*, *CDKAL1*, *GCK*, and *KCNQ1* [27]. Additionally, a single insulin sensitivity gene

variant in *IRS1* is associated with GDM [27]. The overlap between the genetic architecture of GDM and T2D was further confirmed by studies in Finnish, Mexican, African-American, and Caucasian populations that reported *TCF7L2*, *MTNR1B*, *KCNQ1*, and *GCKR* associations with GDM [28–30]. These studies also discovered that genetic variants associated with T2D had genetic associations with specific maternal metabolic quantitative traits, such as fasting glucose and insulin sensitivity, providing more evidence of the overlap between the genetic architecture of GDM and T2D.

To test for genetic associations with GDM in an unbiased, hypothesis- free manner, a limited number of GWAS have been performed. A study in 1,399 Korean women with GDM and 2,025 nondiabetic controls confirmed associations with polymorphisms near *CDKAL1* and *MTNR1B* [31]. These variants were also associated with specific maternal metabolic traits in the study. Another GWAS based on maternal metabolic traits in 4,437 pregnant women of mixed ancestries confirmed associations with previously implicated T2D-susceptibility genes (*GCKR*, *G6PC2*, *PCSK1*, *PPP1R3B*, and *MTNR1B*) and two other genes (*HKDC1* and *BACE2*) [32]. HKDC1 rs4746822 was strongly associated with elevated plasma glucose 2 hours post-glucose load. This gene had been nominally associated with T2D previously in a large meta-analysis, but functional studies have determined that rs4746822 reduces the expression of *HKDC1* and also the activity of the HKDC1 protein [33, 34]. The *BACE2* variant rs6517656 was associated with higher fasting c-peptide levels, and had not been previously associated with T2D characteristics. These findings suggest that while there is significant overlap between the genetics of T2D and GDM, there are likely to be genetic associations specific to GDM that will be borne out through larger GWAS studies or studies on cohorts with different ancestral characteristics. However, as with T2D, genetic testing is not yet clinically useful in polygenic GDM due to the relatively small amount of risk explained by known genetic variants.

Identifying Individuals with Monogenic Diabetes Before and During Pregnancy Creates Opportunities for Personalized Diabetes Management

As summarized above, great strides have been made in elucidating the genetic architecture of T1D, T2D, and to a lesser extent GDM. The limited data from GDM genetic studies suggests largely shared genetic susceptibility with T2D. These findings are expected to improve our understanding of the diverse and complex etiology of diabetes, but current evidence is not sufficient to lend to opportunities for clinical usage of genetic testing. In contrast, diagnosing certain types of monogenic diabetes has implications for management (treatment with oral medications or no treatment vs. insulin), counseling of family members (usually autosomal dominant inheritance, and in some cases pregnancy management. There are several forms of monogenic diabetes, in which a mutation in a single gene is largely responsible for the diabetes, where genetic testing can be very useful [1]. The mutation may cause isolated hyperglycemia, as is the case in most types of MODY (the most common subcategory of monogenic diabetes) and neonatal diabetes, or it may cause a genetic syndrome in which hyperglycemia is one of a constellation of symptoms, such as Wolfram syndrome [35]. To date there are 14 different types of MODY, caused by defects in different genes that control beta cell function [36] with three types (MODY1–3) accounting for an estimated 85% of cases and impacting pregnancy. The majority of MODY subtypes are

inherited in an autosomal dominant manner, which means that first-degree relatives of affected individuals have up to a 50% chance of developing diabetes [37]. Diabetes diagnosed in the first 6–12 months is known as neonatal diabetes and is usually monogenic. It can be transient or permanent and is most often caused by mutations in genes also implicated in rarer forms of MODY--*KCNJ11* (MODY13), *ABCC8* (MODY12), or *INS* (MODY10)--with several other genes involved less commonly[38]. Discussion of genetic testing and its strong importance for properly managing neonatal diabetes is beyond the scope of this review and can be found elsewhere [35, 39].

Less than 5% of diabetes has a monogenic etiology, and due to its rarity and overlap of symptoms with both T1D and T2D, is often misdiagnosed as such [40–42]. Misdiagnosis of monogenic diabetes as T1D occurs due to the fact that both are found in young individuals who are often (but not always) non-obese [43]. Unlike T1D however, individuals with monogenic diabetes do not typically have islet autoantibodies, and often do have some endogenous insulin production (measured by C-peptide) three years after diagnosis. Diabetes diagnosed in the first 6–12 months as noted above is known as neonatal diabetes and is now known to be much more likely to be monogenic than type 1 [35]. Finally, whereas only about 5% of individuals with T1D have an affected parent, the majority of individuals with most monogenic diabetes subtypes have a strong family history of diabetes [37]. Although monogenic diabetes is often misdiagnosed as T1D, attention to these differentiating factors can help guide clinical suspicion for monogenic diabetes.

Individuals diagnosed with T2D and monogenic diabetes are both often non-insulin dependent, have a family history of diabetes, and in the context of increasing prevalence of early-onset obesity, can be diagnosed young. However, there is usually no evidence of insulin resistance or presence of acanthosis nigricans in individuals with monogenic forms of diabetes. Additionally, individuals with monogenic diabetes and their diabetic family members *often* have a normal body weight because obesity is not required for penetrance, whereas those affected with T2D are typically overweight or obese [1, 35]. However, with the increasing prevalence of overweight and obesity, particularly in youth, weight is expected to be less effective as a discriminating characteristic and MODY can certainly be found in overweight individuals [42]. Although challenging, it is both possible and important to identify individuals with monogenic diabetes because of treatment and familial risk implications [37].

While genetic testing is necessary for a definitive diagnosis, we [44] and others [45, 46] (also see MODY Calculator developed by the University of Exeter group, which yields a probability of testing positive for a MODY mutation based on patient clinical characteristics and their resemblance to previously diagnosed individuals, at http://www.diabetesgenes.org/content/mody-probability-calculator) are working to develop methods of identifying candidates for genetic testing and diagnosis of monogenic diabetes. The broad application of these algorithms is currently limited given that the full spectrum of the MODY phenotype, particularly in non-European populations, is not yet known[43]. Continued epidemiological studies [43], improvement and validation of these screening methods and decreasing cost of testing have the potential to improve access to testing by making the yield higher and testing more cost effective. When available, genetic counselors, who can be found at many medical centers and in a directory on the National Society of Genetic Counselors website

www.nsgc.org, and other medical genetics professionals can be a valuable resource when considering genetic testing for monogenic diabetes. They are knowledgeable about the advantages and disadvantages of certain testing methodologies, have experience working with insurance to ensure coverage for genetic testing, and can effectively communicate the benefits, limitations, and results and their implications to patients and their families [35].

Herein we will provide an update on the pregnancy and neonatal implications for the three most common forms of MODY. Pregnancy management and outcomes differ depending on MODY subtype. A correct diagnosis of these types of monogenic diabetes is critical for proper etiology-based treatment, which may lead to better glucose control and reduced pregnancy complications from uncontrolled or over-controlled preexisting diabetes.

Transcription factor MODY: MODY1 (HNF4A) and MODY3 (HNF1A)

Mutations in transcription factors that affect expression of molecules in the glucose-dependent insulin secretory pathway are among the most common causes of monogenic diabetes. MODY3, which accounts for about 50% of all cases of MODY in the Caucasian population, arises from defects in the hepatocyte nuclear factor-1α (*HNF1A*, formerly called *TCF1*) gene [47, 48]. MODY1 accounts for approximately 10% of MODY cases and is caused by defects in the *HNF4A* (hepatocyte nuclear factor-4α) gene [49, 50]. Loss of function of either transcription factor causes impaired glucose-stimulated insulin secretion from beta cells in the pancreas [51]. A mutation in either gene was observed to be highly penetrant in family studies, with 60% of *HNF1A* (MODY3) mutation carriers exhibiting diabetes by age 25, 80% by age 35, and 95% by age 55 [52] and about 50% of *HNF4A* (MODY1) mutation carriers exhibiting diabetes by age 30, with age-dependent penetrance varying by mutation location [53]. It is important to note, however, that penetrance estimates were much lower in a population-based study [54] and thus predictive testing in asymptomatic individuals outside of affected families is unlikely to be useful at this time.

Since *HNF4A* regulates *HNF1A*, MODY1 and MODY3 have a great deal of clinical overlap [55]. Both disorders are characterized by the dominant inheritance of non-ketosis-prone diabetes in adolescents and young adults who are typically (but not always) non-obese [35]. Individuals with MODY1 and MODY3 have better glucose control when treated with low doses of sulfonylureas, a class of oral medications that bypasses the metabolic defect caused by mutations in *HNF4A* and *HNF1A* [56]. Beta cell function becomes progressively worse over time however, and treatment with insulin is often eventually necessary [57].

Despite their clinical overlap, the implications for MODY1 and MODY3 in pregnancy differ. In 2007, a study by Pearson and colleagues on 15 European families with mutations in *HNF4A* established that infants with MODY1 have significantly increased birthweight, with 56% of mutation carriers having macrosomia (birthweight >4000 g) compared to 13% of unaffected family members. Macrosomia risk was increased whether the mutation came from the mother (64%) or father (46%), albeit more when maternal, presumably due to exacerbation by the hyperglycemic intrauterine environment (Table 1). Transient neonatal hyperinsulinemic hypoglycemia was also found in approximately 15% of affected infants and not found in any unaffected infants [58]. These findings indicate that paradoxically and

unexpectedly, in the fetal and neonatal stage, *HNF4A* mutations increase rather than decrease insulin secretion as they do in later childhood. These findings have been confirmed in multiple other multi-generational families with a molecular diagnosis of MODY1, and it has also been shown that these infants respond well to treatment with diazoxide [59–62]. Unlike the hyperinsulinemia resulting purely from maternal hyperglycemia, MODY1-related hyperinsulinemic hypoglycemia has in several cases persisted and required treatment with diazoxide for several months or even years after birth [62]. This has led to the recommendation that *HNF4A* (MODY1) mutations should be considered in cases of unexplained macrosomia, especially when there is neonatal hyperinsulinemic hypoglycemia and family history of young onset diabetes [60].

Similar retrospective analyses have not found increases in fetal birthweight and incidence of hyperinsulinemic hypoglycemia in infants with MODY3 [58, 63]. Unlike MODY1, where no parent-of-origin effect with respect to diabetes onset has been found, individuals who inherit *HNF1A* (MODY3) mutations from their mothers were shown in one study to develop diabetes at an earlier age than those with a paternally- inherited mutation. This discrepancy appeared to result from exposure to hyperglycemia in utero, as individuals who inherited *HNF1A* mutations from mothers who had developed diabetes prior to the pregnancy were more likely to develop diabetes before age 15 or 25 than those inheriting mutations from mothers who developed diabetes after the pregnancy [52]. Another study showed no overall difference in age of onset between those with maternally vs. paternally inherited mutations, but similarly, those inheriting mutations from mothers with diabetes during the pregnancy had an earlier age of onset (15 ± 5 years) than those inheriting mutations from mothers who developed diabetes after the pregnancy (27 ± 13 years) or those inheriting mutations from fathers (23 ± 11 years) [64], again providing evidence for the ability of exposure to intrauterine hyperglycemia to hasten age of onset of MODY3.

The above evidence demonstrates the importance of recognizing symptoms of these two disorders due to possible changes in pregnancy management. When there is a known mutation in *HNF4A* (MODY1) in either the mother or father, it has been recommended that fetal size should be monitored closely via ultrasound and alternative route of delivery or potential shoulder dystocia counseling should be considered in the presence of macrosomia. Additionally, the infant should be tested for hypoglycemia at birth and 24 hours later [58]. A molecular diagnosis of either MODY1 or MODY3 can lead to change in therapy (insulin to sulfonylurea), and thus overall lifestyle and quality of life, for patients and their families [56] and improved glucose control in pregnancies affected by both maternal and fetal MODY3 could delay age of onset in offspring.

MODY2 (GCK-MODY)

MODY2/GCK-MODY, caused by mutations in the glucokinase (*GCK*) gene, is a common type of monogenic diabetes, with an estimated prevalence of approximately 1 in 1000 in Caucasians [65]. The function of glucokinase is the rate-limiting step in the glycolytic pathway to produce ATP, which stimulates insulin release in pancreatic beta cells. Defects in glucokinase result in a higher threshold for insulin release [66]. Consequently, starting at birth individuals with MODY2 have mild fasting hyperglycemia (5.4–8.3 mmol/L [98 – 150 mg/

dl], HbA1c 5.8–7.6% [40–60 mmol/mol]) which may or may not reach into the diabetic range and normal postprandial insulin release [67, 68].

Hyperglycemia does not progress over time beyond the slow lifetime increase seen in euglycemic individuals [69]. Individuals with MODY2 do not require or even respond to treatment with insulin or oral medications [70] unless they develop T1D or T2D, for which they are at population risk [67]. They may be of normal weight and they rarely experience symptoms of diabetes such as increased thirst and frequent urination [67]. Unlike patients with other forms of diabetes (other MODYs and multifactorial forms), those with MODY2 are not at increased risk for complications of diabetes including nephropathy, peripheral neuropathy, microvascular disease, cardiovascular disease, or clinically significant retinopathy, though they do have statistically more background retinopathy compared to controls [67, 69, 70].

Given that individuals with MODY2 are asymptomatic and that pregnancy increases insulin resistance, hyperglycemia in affected women is often initially discovered during routine screening for GDM in the third trimester. The prevalence of MODY2 in the gestational diabetic population has been estimated to be approximately 2% [67]. Identifying these women is important because it alters clinical management during pregnancy and beyond in several ways [67, 71]. First, while GDM is generally treated with insulin when dietary control of glucose levels cannot be achieved, insulin treatment is not indicated for women with MODY2 with the possible exception of the third trimester of pregnancy with a fetus who has not inherited the mutation [71]. While all fetuses in GDM-affected pregnancies will be exposed to maternal hyperglycemia, a fetus that has inherited a *GCK* mutation from its mother has the same glucose threshold and thereby senses higher glucose levels as normal. These babies are expected to have a normal birth weight. In this situation, maternal treatment with insulin is not recommended, as doing so may result in abnormally low birth weight [72, 73]. In contrast, treatment with insulin may be indicated when a fetus has not inherited the *GCK* mutation, since the fetus will produce more insulin in response to the maternal hyperglycemia [63, 71]. Insulin acts as a growth factor in pregnancy and these babies are at increased risk of macrosomia [71]. Given the risk of miscarriage with amniocentesis and chorionic villus sampling (CVS), an accepted alternative to prenatal genetic diagnosis is serial monitoring of fetal size in the third trimester, and induction of labor at term if necessary [67, 71, 73].

Fetuses who have inherited a paternal *GCK* mutation are at risk for low birth weight [72] (Table 2). A maternal diagnosis of MODY2 is also an indication that the inevitable persistent post-partum hyperglycemia should in most cases not be diagnosed as T1D, T2D or pre-diabetes but left untreated [67]. Finally, awareness that first degree relatives, including offspring, have a 50% chance of having a GCK mutation is important for properly classifying hyperglycemia in family members when it is discovered. It is also important for providers to be aware that there is a higher risk of miscarriage in women with MODY2 compared to the general population, and that placentas of fetuses with *GCK* mutations have reduced size (studies of parent of origin effect sizes on the placenta have not been performed) [63, 74].

To identify an efficient way to identify pregnant women likely to have MODY2 rather than GDM or pre-existing T2D, Chakera and colleagues analyzed the clinical characteristics of a cohort of pregnant Anglo-Celtic women with and without a molecular diagnosis of MODY2 [65]. They determined that a combined criteria of BMI <25 kg/m^2 and fasting glucose ≥5.5 mmol/L has a sensitivity of 68% and specificity of 96% for MODY2 in the pregnant population. Rudland, et al. subsequently tested these new criteria in a population of Anglo-Celtic, Southeast Asian, and Indian pregnant women and found that while they correctly identified all Anglo-Celtic women, one Indian woman was missed due to her overweight range BMI [75].

Summary of Clinical Implications

In summary, pre-gestational diabetes can be T1D, T2D or monogenic. True GDM generally appears to have a shared polygenic genetic etiology with T2D. Testing for genes implicated in polygenic forms of diabetes does not appear to be clinically useful at this time. Monogenic diabetes, particularly MODY, accounts for at least 1%, or over 300,000 cases of diabetes in the United States alone. Correct MODY genetic diagnosis leads to more optimal therapy, improved glycemic control, decreased health care costs, and possible diagnosis of family members. Because of clinical overlap, it may be misdiagnosed as T1D, T2D, or GDM. MODY2 in particular, is susceptible to first manifesting as GDM because of its associated mild hyperglycemia and lack of symptoms. In pregnancy, diagnosing MODY2 is important to avoid unnecessary use of insulin, particularly when a fetus inherits a *GCK* mutation from the mother. Testing women with pre-pregnancy BMI < 25 and pregnancy fasting glucose ≥ 100 mg/dl for MODY2 is a relatively simple, sensitive and specific way to diagnose patients with MODY2. It is important to be aware that this approach may be less effective in non-Caucasian women, and the optimal algorithm may evolve over time.

Diagnosing MODY1 and MODY3 is also important for clinical care during pregnancy. Knowing that diabetes in a family is due to MODY1 is important in order to anticipate the risk of macrosomia-related delivery complications and neonatal hyperinsulinemic hypoglycemia, which may persist for several months and require treatment. Thus, considering *HNF4A* (MODY1) genetic testing in families with a high prevalence of both diabetes and neonatal macrosomia/hyperinsulinemic hypoglycemia would also be expected to be useful. A diagnosis of MODY3 in a pregnant woman could prompt tighter glycemic control during the pregnancy and potentially delay onset of diabetic complications in a child inheriting the same *HNF1A* (MODY3) variant. Genetic testing is expensive and complex, but the cost is decreasing and there is emerging guidance on selecting appropriate individuals for testing. When monogenic diabetes is suspected, early collaboration with clinical genetics teams, including medical geneticists and genetic counselors, can help ensure that opportunities for personalized medicine in patients with diabetes are not missed.

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Table 1

Effects of parental/fetal *HNF4A* (MODY1) mutation status on macrosomia risk

Fetal MODY1 (*HNF4A* mutation) status →	Yes	No
Maternal MODY1 (*HNF4A* mutation)	64% macrosomic	25% macrosomic
Paternal MODY1 (*HNF4A* mutation)	46% macrosomic	6% macrosomic

Table 2

Effects of parental/fetal GCK (MODY2) mutation status on birthweight

Fetal MODY2 (*GCK* mutation) status →	Yes	No
Maternal MODY2 (*GCK* mutation)	Normal birthweight	Increased birthweight
Paternal MODY2 (*GCK* mutation)	Decreased birthweight	Normal birthweight