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HIGH-RISK GESTATION AND PRENATAL MEDICINE (T CHAN, SECTION EDITOR)

Gestational Diabetes: Seeing Both the Forest and the Trees

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Abstract Gestational diabetes is a heterogeneous disorder. Various metabolic etiologies underpin the diagnosis and influence perinatal outcomes as well as an individual's propensity for the subsequent development of diabetes. Recent landmark studies have driven a review of the diagnostic criteria for gestational diabetes, with an emergent category, "overt diabetes during pregnancy," recognizing the increased surveillance required for some women. As we strive for consensus in diagnosis at a global level, consideration for its application to local populations, with different ethnicities, genetics, and immunological make-up, is essential to optimize obstetric care and neonatal outcomes. An individualized approach must remain the mainstay of management.

Keywords Gestational diabetes · Pregnancy · Heterogeneity · Diagnosis · Autoimmunity · GAD antibodies · IA-2 antibodies · ICA antibodies · Insulin antibodies · Genetics · Glucokinase · Maturity-onset diabetes of the young · Monogenic diabetes · High-risk gestation

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Introduction

Gestational diabetes (GDM) is classically defined as any degree of hyperglycemia or glucose intolerance with onset or first recognition during pregnancy [1]. This definition stems from O'Sullivan and Mahan's proposed concept for GDM in 1964, whereby women with glucose levels on an oral glucose tolerance test (OGTT) above the proposed pregnancy thresholds were at increased risk for subsequent diabetes [2]. However, identification and treatment of GDM also are essential to reduce adverse perinatal outcomes and to improve maternal morbidity.

It is increasingly recognized that GDM is a heterogeneous disorder, embracing women with varying degrees of hyperglycemia and different patterns of glucose intolerance. The metabolic abnormalities underpinning the diagnosis are varied, as is the associated pregnancy risk. Some women will have type 1 diabetes or type 2 diabetes, which either develops or is first recognized during pregnancy. These women require increased surveillance during pregnancy and tailored postnatal advice. Other women will have positive diabetes-related autoantibodies, the significance of which is unclear for the individual patient, despite several small studies that investigated prevalence and the subsequent risk of developing type 1 diabetes.

A heterozygous mutation in the glucokinase (*GCK*) gene causes a mild, asymptomatic form of monogenic diabetes, known as Maturity Onset Diabetes of the Young (*GCK*-MODY or MODY2) [3]. Women with *GCK* mutations often are first identified during pregnancy and are, therefore, almost invariably diagnosed with GDM. However, the standard management of GDM, particularly the implementation of intensive glycemic control, can affect the fetus of a woman with a *GCK* mutation adversely [4•]. Identification of *GCK* mutations in the GDM population is therefore extremely important.

As individual diabetes and obstetric organizations around the world continue to debate the International Association of

Diabetes and Pregnancy Study Groups' (IADPSG) proposed diagnostic criteria for GDM, an individualized approach to diagnosis and management of GDM must prevail to deliver appropriate obstetric care and optimize maternal and neonatal outcomes.

This review focuses on the scope and implications of the IADPSG' proposed GDM diagnostic criteria, recent advances in GDM management and the heterogeneity of GDM, with particular reference to ethnicity, islet autoimmunity, and *GCK*-MODY.

Background to Consensus Guidelines for GDM

Whilst GDM has long been recognized to increase the risk of subsequent maternal diabetes, the relative risk of adverse neonatal outcomes associated with glucose levels during an OGTT in pregnancy has only recently been investigated. The Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study, a multicenter, international study, was designed to assess the level of hyperglycemia on an OGTT associated with adverse neonatal outcomes [5]. More than 25,000 pregnant women at 15 centers across 9 countries were studied using a 75-g, 2-hour, OGTT performed between 24 and 32 weeks gestation. Primary outcomes were birth weight >90th percentile, primary cesarean section delivery, neonatal hypoglycemia, and cord C-peptide >90th percentile. The study demonstrated a continuous and linear relationship between maternal glucose levels on the OGTT and increasing frequency of all primary outcomes, even at glucose levels below those that are currently diagnostic of GDM.

The outcomes of the HAPO study are supported by two major treatment trials in GDM. The Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) was the first large, randomized clinical trial to demonstrate that treatment of GDM reduces serious perinatal complications [6]. In this trial, 1,000 women with a fasting glucose level less than 7.8 mmol/L were assigned to receive treatment or routine care. Infants of treated women had lower rates of macrosomia, perinatal complications, and preeclampsia. Landon et al., through a multicenter, randomized trial of 958 women with even "milder" GDM, defined by a fasting plasma glucose less than 5.3 mmol/L, demonstrated that treatment of "mild" GDM reduced the rates of macrosomia, cesarean section, and gestational hypertension [7].

These landmark studies, which demonstrated both a continuum of perinatal risk across a range of maternal glucose levels, as well as clear benefits of treating even mild GDM, formed the basis of the IADPSG proposed diagnostic criteria.

Scope and Implications of Proposed Diagnostic Criteria for GDM

The IADPSG recommended universal testing with a 75-g, 2-hour OGTT at 24–28 weeks' gestation. In addition, given the rising background rates of maternal diabetes and obesity as well as increasing maternal age, an assessment of glucose tolerance at the first antenatal visit in all women or only those women classified as high risk according to locally defined criteria was proposed [8••]. A new category, "overt diabetes in pregnancy" emerged, recognizing the need for increased surveillance, more rapid treatment, and closer follow-up of patients with possible (but not previously diagnosed) pre-pregnancy glucose intolerance.[8•] The consensus criteria are summarized in Fig. 1.

The IADPSG recommendations have widespread implications. If the proposed screening criteria are adopted, the prevalence of GDM, currently reported at approximately 7 % in the United States, is expected to exponentially increase [9]. When the IADPSG diagnostic criteria were applied to the HAPO cohort, the overall frequency of GDM was 17.8 % (range 9.3–25.5 %) at the different centers [10•]. In a high-risk Australian population, this anticipated increase in prevalence could increase workload by >30 %, which would significantly increase health care costs [11]. To cope with this workload, the structure of GDM services may need to change.

Indeed, a universal OGTT may not be practicable in all parts of the world, particularly in countries with limited resources. It has been suggested that some women could be excluded from having an OGTT on the basis of their fasting blood glucose level between 24 and 28 weeks. According to HAPO data, a fasting blood glucose level <80 mg/dL (4.4 mmol/L) is associated with a low risk of adverse perinatal outcomes. Excluding women with a fasting blood glucose in this range may avoid an OGTT in nearly half of the pregnant population [12]. The OGTT would continue to be highly sensitive, with a sensitivity >95 % [12]. Of course, women with a fasting blood glucose ≥92 mg/dL (5.1 mmol/L) already fulfill criteria for a diagnosis of GDM, so these women also could possibly be excluded from undergoing a full OGTT. This strategy of using a fasting blood glucose level as the initial diagnostic test would reduce the number of women who need to undergo a full OGTT, which may be a reasonable alternative in areas where local resources are limited.

Current Controversies with IADPSG Diagnostic Criteria

A contentious issue with the IADPSG recommendations is the threshold at which GDM would be diagnosed in early

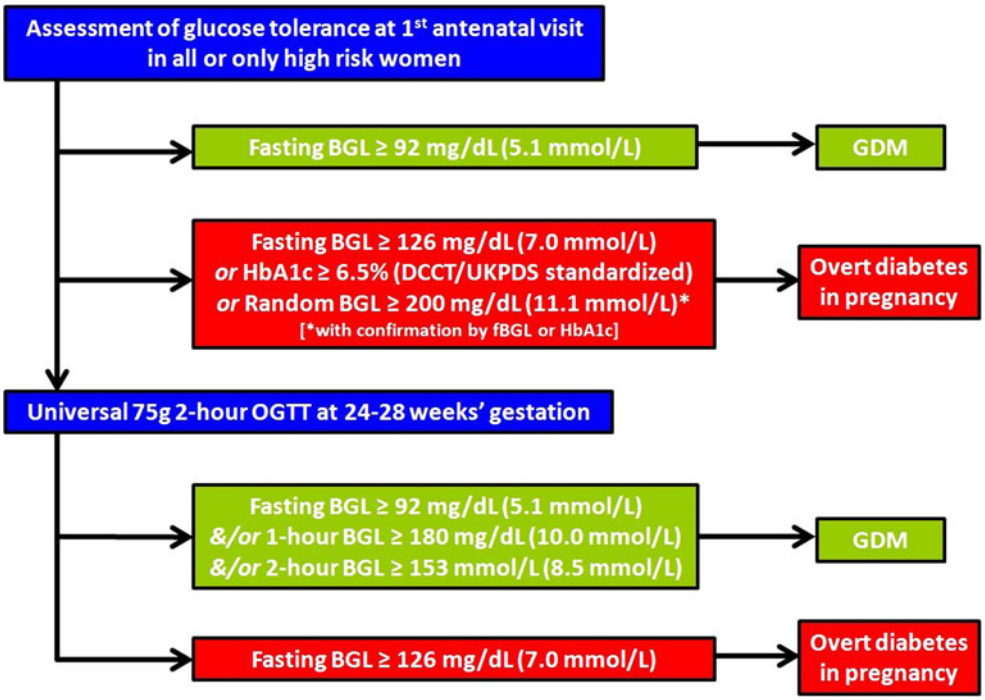

Fig. 1 IADPSG consensus criteria for the diagnosis of GDM and "overt diabetes in pregnancy"

pregnancy. Fasting blood glucose levels decline during pregnancy but the profile of this is uncertain [13]. Consequently, a fasting blood glucose level ≥92 mg/dL (5.1 mmol/L) in early pregnancy may risk overdiagnosis of GDM.

It should be emphasized that a diagnosis of "overt diabetes in pregnancy" is, by definition, an antenatal diagnosis and is not synonymous with type 2 diabetes. The presence of diabetes must therefore be confirmed postpartum.[8•] A recent review of local Australian data revealed that when patients with overt diabetes in pregnancy were retested 6-8 weeks postpartum, 21 % had type 2 diabetes, 38 % had prediabetes (impaired fasting glucose or impaired glucose tolerance), and 41 % had returned to normal glucose tolerance [14].

It is important to note that pregnancy outcomes using the IADPSG criteria cannot be directly inferred from the aforementioned large treatment studies, because the diagnostic criteria for GDM in these treatment studies was different to those proposed by IADPSG. So, whilst the recent IADPSG criteria have being endorsed, for the most part, by the American Diabetes Association (ADA), they have not yet been endorsed by the American College of Obstetricians and Gynecologists who cite "no evidence that diagnosis using these criteria leads to clinically significant improvements in maternal or newborn outcomes and it would lead to a significant increase in health care costs." [15]

Medical Management of GDM

The mainstay of treatment for GDM remains dietary intervention, targeted at reducing postprandial glucose levels, while providing adequate nutrients to sustain the pregnancy. The general principle is an even distribution of carbohydrate intake across three meals and three snacks, with carbohydrates accounting for 33–40 % of caloric intake [16]. A recent, randomized, controlled trial comparing a low-glycemic index diet with a conventional high-fiber, moderate-glycemic index diet did not demonstrate any difference in pregnancy outcomes [17]. Caloric restriction (<1,500 kcal/d) is associated with maternal ketonuria and increases the risk of small-for-gestational-age infants, so should be avoided [18].

Higher levels of physical activity before pregnancy or in early pregnancy are associated with a reduced risk of GDM [19]. Women participating in the highest levels of pre-pregnancy physical activity demonstrated a 55 % risk reduction compared with women participating in the lowest levels. In early pregnancy, the results were similar but less striking, with women who undertake high levels of physical activity experiencing a 25 % risk reduction. Physical activity should be promoted among women of childbearing age.

Women with GDM should perform self-monitoring of blood glucose—fasting and postprandially. Our preference for postprandial testing is with 1-hour levels, because this has been demonstrated to represent peak glucose excursion in pregnancy [20]. Current target thresholds are for a fasting capillary glucose level <95 mg/dL (5.3 mmol/L), 1-hour level <140 mg/dL (7.8 mmol/L), and 2-hour level <120 mg/dL (6.7 mmol/L) [21]. These targets are currently being reviewed in light of emerging data regarding normal glucose levels during pregnancy. Lowering the fasting glucose treatment target would appear appropriate given the

proposed lowering of the diagnostic threshold for GDM. HbA1c also may be a useful adjunct in assessing glycemic control [22]. The upper limit of normal for HbA1c in pregnancy is 5.4 % [23].

Medical therapy, preferably with insulin, is required if blood glucose levels remain elevated despite appropriate diet and exercise. Most commonly, a tailored multiple daily injection regimen is used, with rapid-acting insulin at mealtimes and intermediate-acting insulin at bedtime. In our experience, approximately 50 % of women with GDM require insulin treatment [24]. In an era of rising prevalence of GDM, prediction of insulin treatment based on clinical or biochemical characteristics would enable stratification of GDM women into high-risk or low-risk groups. However, we recently assessed a risk-prediction tool that included ethnicity, gestation at diagnosis, HbA1c, glucose levels on an oral glucose tolerance test, body mass index, and diabetes family history; whereas these factors were all significant independent determinants of insulin treatment, only 9 % of the attributable risk for insulin therapy could be explained by the clinical and biochemical factors studied [24]. We hypothesize that dietary compliance may have the greatest impact on need for insulin treatment but did not assess this in that study. Unmeasured fetal or placental factors that promote insulin resistance may play a role.

The use of metformin in the treatment of GDM remains controversial and is not universally recommended. A recent Australasian study of 751 women with GDM, randomized to receive either metformin or insulin, demonstrated less hypoglycemia but an increase in preterm birth in the group treated with metformin [25]. Although there was no statistical difference in other maternal and neonatal outcomes between the groups, the insulin-treated group had worse glycemic indices at the commencement of treatment compared with the metformin-treated group, which may have biased the results [25]. Metformin crosses the placenta, so the long-term safety of metformin use in pregnancy for the offspring must be assessed before recommendations during pregnancy can be made confidently. Results of the 2-year offspring follow-up study of children exposed to metformin in utero have been published, demonstrating that these children had larger measures of subcutaneous fat, but the same overall body fat, as children whose mothers were treated with insulin alone [26]. Longer-term follow-up is ongoing.

Recent Advances in Obstetric Management of GDM

Women with GDM require increased obstetric monitoring. Ultrasonography between 28 and 32 weeks gestation is a useful tool for predicting large for gestational age (LGA) birth weights in women with GDM. Neonates whose early third-trimester ultrasound estimated fetal weight $\geq 75^{th}$ percentile were ten times more likely to be LGA at birth compared with neonates whose early third-trimester ultrasound estimated fetal weight $<75^{th}$ percentile [27]. Serial ultrasonography appears to predict fetal growth more accurately and also may help to determine the intensity of medical management and appropriateness of glycemic targets for individual patients [28–30].

The optimal mode and timing of delivery for women with GDM remains controversial. The risk of late stillbirth must be weighed against the risk of neonatal morbidity and mortality. In a retrospective cohort study of more than 193,000 deliveries to women with GDM, the risk of expectant management had a higher risk of mortality than the risk of delivery at 39 and 40 weeks gestation [31•]. In addition, women with GDM who were induced at 39 weeks gestation and who delivered an LGA neonate (birthweight 4,000± 125 g) were less likely to require cesarean delivery than women who delivered at a later gestational age [32]. These studies support 39 weeks as the most appropriate gestational age at which to plan delivery for a woman with GDM.

Postpartum Testing and Prevention of Future Diabetes

Women with GDM have a sevenfold increased risk of developing subsequent type 2 diabetes [33]. Up to one-third of women with GDM will already have diabetes or prediabetes on postpartum testing [34•]. Despite this, postpartum testing rates remain low, ranging from 23 % to 58 % [34•]. This represents a missed opportunity to diagnose and treat early diabetes. For women with GDM, the ADA and the American College of Obstetricians and Gynecologists recommend universal OGTT testing 6 to 12 weeks postpartum and 3-yearly thereafter [1, 35].

A past history of GDM should prompt the promotion of healthy lifestyle measures that target modifiable risk factors for macrovascular disease. Women in the Nurses' Health Study II with a past history of GDM had a 26 % increased risk of hypertension compared with those without this history [19]. Fifty to seventy-five percent of obese women with previous GDM develop type 2 diabetes compared with <25 % of women with GDM who achieve a normal body mass index (BMI) after delivery [36]. For women with GDM and pre-pregnancy overweight or obesity, a reduction in BMI of ≥ 2.0 kg/m^2 between pregnancies can reduce the risk of subsequent GDM by 74 % [37•]. We recommend postnatal advice that is individualized, specific, and goal-driven.

Primary Prevention of GDM: A Paradigm Shift?

From a public health perspective, more emphasis should be placed on prevention of GDM. There is ever-expanding

literature regarding the importance of pre-pregnancy BMI, gestational weight gain, and interpregnancy weight gain on GDM risk. Yet, the focus of patient care remains on medical and obstetric management subsequent to a diagnosis of GDM. Perhaps a paradigm shift to focus on dietary advice and BMI-appropriate pregnancy weight targets, provided before, or early in, pregnancy is required.

Heterogeneity of GDM: Remember the "Trees"

The GDM population is ethnically, genetically, and immunologically diverse, which impacts the underlying pathophysiology, clinical characteristics, and pregnancy outcomes. As we take steps toward consensus guidelines for GDM, an individualised approach to diagnosis and management must always be considered.

Ethnicity: Impact on Prevalence, Clinical Characteristics, and Pregnancy Outcomes

Several ethnic groups have an increased prevalence of GDM [38]. Local Australian data demonstrated that Indian (16.7 %), Chinese (15 %), and Aboriginal women (10.1 %) had the highest prevalence of GDM [39]. Maternal indices and neonatal outcomes also are influenced by ethnicity [40]. In our own multiethnic GDM population, compared with Anglo-Celtic women, women from Chinese and Indian backgrounds had a lower pre-pregnancy BMI, earlier diagnosis of GDM, higher 1-hour glucose level on their antenatal OGTT, lower rate of LGA (birth weight >90th percentile) and an increased likelihood of abnormal glucose tolerance postpartum (significant paired tests, $p<0.0001$; unpublished data; Table 1). Chinese women had significantly lower insulin requirements than Anglo-Celtic women. The opposite was true for Indian women. Aboriginal women with GDM were younger, had a higher pre-pregnancy BMI, and were more likely to have a cesarean section and abnormal glucose tolerance postpartum than their Anglo-Celtic counterparts (unpublished data; Table 1). An understanding of the demographic profile according to ethnicity is invaluable in highlighting patients with an increased risk for adverse pregnancy outcomes who therefore require more intensive medical and obstetric management.

Islet Autoimmunity in GDM: Prevalence, Trajectory and Clinical Significance

GDM could be considered a "stress test" for the pancreatic beta cell. The presence of positive diabetes-associated autoantibodies in women with GDM may indicate less beta cell reserve and preclinical type 1 diabetes. Identifying these women may avoid incorrect diagnoses of type 2 diabetes and prevent delays with instituting insulin treatment to avoid ketoacidosis, which can be life-threatening.

The prevalence of autoantibodies in GDM has been assessed in several small studies. The prevalence of glutamic acid decarboxylase (GAD) varies from 0–11 %, tyrosine-phosphatase-like islet antigen (IA-2) from 0–6 %, islet cell antibodies (ICA) from 1–15 %, and anti-insulin autoantibodies (IAA) from 0–6 % [41–44]. Antibodies to a zinc transporter (ZnT8) have not yet been reported in GDM. Additionally, IAA may develop in up to 44 % of women treated with insulin during pregnancy and can persist for 2 years postpartum [45].

Few studies have assessed diabetes-related autoantibody titers in both the antenatal and postpartum periods. Given that pregnancy is a relative state of immunosuppression, antibody titers could be expected to decline throughout pregnancy. Thus, the reported prevalence of antibody positivity during pregnancy may not necessarily reflect an individual's nonpregnant antibody status. The trajectory from antenatal to postnatal titer may itself influence an individual's propensity to develop type 1 diabetes.

Preliminary data from our multiethnic GDM population demonstrated an overall prevalence for antibody positivity of 5.6 % during pregnancy and 10.7 % postpartum (unpublished data). GAD antibody and IAA titers in insulin-naïve patients remained stable from diagnosis of GDM to the early postpartum period. However, IA2 antibody trended upwards postpartum (significant paired test). These results may reflect hemodilution or immunomodulation during pregnancy.

There is a paucity of data regarding the clinical characteristics and pregnancy outcomes of women with positive diabetes-related autoantibodies and GDM. Antibody positivity has been inconsistently associated with a normal pre-pregnancy BMI, lower weight gain during pregnancy, lower fasting insulin, human leukocyte antigen alleles DR3 and DR4, and insulin treatment during pregnancy [46–48]. Studies that have investigated obstetric and neonatal outcomes have conflicting results; one study reported no significant difference in pregnancy outcomes [48] and another reported an increase in stillbirth and macrosomia rates [47]. However, the latter study included women with more severe hyperglycemia during pregnancy, i.e., women who were likely to have had first presentation of type 1 diabetes during pregnancy and women for whom commencement of appropriate insulin therapy was delayed, which is likely to have negatively biased the results. Clinical correlates and pregnancy outcomes in women with antibody-positive GDM need to be further investigated in larger, multiethnic studies.

With regard to future diabetes risk, the presence and number of positive diabetes-related autoantibodies in GDM have been associated with an increased risk of type

Table 1 Demographic profile for GDM by ethnicity

N=4,881	Anglo-Celtic (n=1,262) 25.8 %	Mediterranean (n=414) 8.4 %	Arabic (n=281) 5.8 %	Chinese (n=1,282) 26.2 %	SE Asian (n=843) 17.1 %	Indian (n=556) 11.4 %	Aboriginal (n=73) 1.5 %	Islander (n=170) 3.5 %	Test statistics and p value
Age (yr)	34.3±5.2	33.7±5.2	32.0±5.8*	34.8±4.5	33.9±5.1	31.2±4.7*	30.6±5.8*	33.2±6.2	F=38.7; $p<0.0001$
BMI (kg/m^2)	26.3±6.3	27.4±6.5*	27.1±5.8*	21.7±3.1*	22.5±4.0*	24.8±4.3*	32.0±7.2*	32.5±7.3*	F=186; $p<0.0001$
Family history (%)	54.6	60.7	58.1	31.2	39.9	58.5	87.5	59.9	X2=303; $p<0.0001$
Gestation at GDM diagnosis (weeks)	26.9±5.8	26.6±5.9	26.5±5.8	25.5±6.2*	25.8±6.3*	24.8±6.2*	27.6±6.6	27.3±6.8	F=10.3; $p<0.0001$
Antenatal OGTT (mmol/L)									
Fasting BGL	4.9±0.9	4.9±0.9	5.0±0.8	4.7±0.7*	4.8±0.9	5.0±0.8*	5.2±1.5	5.5±1.2*	F=21.9; $p<0.0001$
1-hour BGL	9.7±1.7	10.1±1.5*	10.2±1.5*	10.0±1.6*	10.2±1.8*	10.3±1.8*	10.2±1.3	10.4±2.1*	F=10.5; $p<0.0001$
2-hour BGL	8.5±1.2	8.7±1.4	8.6±1.6	8.8±1.2*	8.8±1.5*	8.7±1.7	8.9±2.1	8.4±1.9	F=4.5; $p<0.0001$
Insulin Treatment (%)	54.2	53.1	47.3	39.8	44.1	61.4	52.1	48.5	X2=101; $p<0.0001$
Gestation at insulin initiation (weeks)	29.6±6.8	29.9±6.5	29.3±7.5	30.4±6.1	29.9±6.5	27.6±6.2*	26.7±8.5	30.0±7.1	F=6.3; $p<0.0001$
Maximum dose insulin (units)	26 [12-50]	22 [12-48]	36* [18-32]	20* [11-36]	24* [12-50]	30* [14-58]	42 [26-114]	52* [20-78]	X2=79; $p<0.0001$
Gestation at confinement (weeks)	38.6±1.9	38.5±2.0	38.6±1.9	38.6±1.6*	38.5±1.9	38.3±2.2*	38.1±2.5	38.8±1.7	F=6.8; $p<0.0001$
Cesarean section (%)	32.3	36.4	27.6	26.8	26.9	35.6	53.0	28.4	X2=45.2; $p<0.0001$
LGA^ (%)	14.2	9.5	16.7	6.9	7.2	3.0	26.5	29.4	X2=171; $p<0.0001$
Neonatal hypoglycemia (%)	17.3	19.7	17.8	16.7	17.8	17.8	35.8	29.5	X2=30.7; $p<0.0001$
Postpartum OGTT (%)									
No diabetes	88	85	87	71	77	78	80	74	X2=75; $p<0.0001$ (excluding diabetes)
Prediabetes [IFG/IGT]	10	13	8	26	21	18	20	24	
Diabetes	2	2	5	3	2	4	0	2	

*Different to Anglo-Celtic

^Large for gestational age

1 diabetes in populations with a high background risk, such as Finland and Sardinia [43, 49]. A study of 385 Swedish women with GDM found that 24 women (6 %) had one antibody positive [42]. Of those, 12 women (50 %) developed type 1 diabetes by 8 years postpartum and another 5 women (20.8 %) developed prediabetes. Half of the women who developed type 1 diabetes had been GAD-positive during pregnancy. IA-2 was less consistent and not necessarily predictive of future type 1 diabetes [49, 50].

There are currently no recommendations regarding testing for diabetes-related autoantibodies during pregnancy. With the increasing prevalence of GDM, universal antibody testing is probably not feasible. Better documentation of clinical and biochemical characteristics of women with antibody-positive GDM may help to guide clinical recommendations for antibody testing in the future, which would help to guide appropriate follow-up of these "high-risk" women.

GCK-MODY: Obstetric Implications and Diagnostic Challenges

Women with heterozygous *GCK* mutations have mild, asymptomatic, fasting hyperglycemia that is present at birth and persists lifelong. These women often are first identified during pregnancy and, therefore, are almost invariably diagnosed with GDM. However, the standard management of GDM, particularly the implementation of intensive glycemic control, can affect adversely the fetus of a woman with a *GCK* mutation [4•]. Previous studies have suggested that the prevalence of *GCK* mutations in pregnancy is 2–5 % [51]. A strong case can therefore be made for the antenatal molecular screening for *GCK* gene mutations in women with GDM.

In pregnancy, treatment of maternal hyperglycemia due to a *GCK* mutation is primarily influenced by fetal genotype (Table 2). An affected fetus, in the setting of untreated maternal hyperglycaemia, will have a normal birth weight. However, birth weight is increased by 550–700 g if the fetus is unaffected [4•, 52]. Insulin is indicated if the fetus is unaffected; otherwise macrosomia can ensue. However, if the fetus has inherited a *GCK* mutation, fetal growth will potentially be reduced if maternal euglycemia is achieved, so insulin is not recommended [4•, 53]. *GCK* mutations have an autosomal dominant pattern of inheritance, so the fetus has a 50 % chance of inheriting the mutation. Recently, we described the first two cases of pregnancy outcomes of *GCK*-MODY where a *GCK* gene mutation was identified in both the mother and fetus during the antenatal period [54]. Our clinical experience has highlighted the need to distinguish hyperglycemia due to a *GCK* gene mutation from classical GDM during pregnancy.

Diagnosis of a *GCK* mutation has important lifelong implications for the mother and affected offspring. Unlike type 1 or type 2 diabetes, *GCK*-MODY is not usually associated with micro- or macrovascular complications and does not require specific pharmacological treatment outside of pregnancy [55]. Correct diagnosis of a *GCK* mutation is therefore important to prevent unnecessary investigations and treatments.

Universal screening for *GCK* mutations during pregnancy is not currently practicable. However, pregnancy-specific screening criteria have not been developed. *GCK*-MODY results in a higher homeostatic set-point for glucose, so that for any given glucose level, the insulin secretion response is lower [3]. Genetic testing for *GCK* mutations in the general population is recommended if the fasting blood glucose level is 100-145 mg/dL (5.5–8.0 mmol/L) and the 2-hour increment on a 75-g OGTT is <83 mg/dL (4.6 mmo/L) [56]. The applicability of these criteria in pregnancy has not been assessed.

We postulate that the current nonpregnant screening criteria may underdiagnose *GCK*-MODY in pregnancy. If current criteria are applied to our local OGTT data from 3,466 women with GDM, 12.6 % would fulfill criteria for genetic *GCK* testing (unpublished data). However, blood glucose levels fall by approximately 20 % during pregnancy [57]. An equivalent fasting threshold for *GCK* screening early in the third trimester therefore would be approximately 80 mg/dL (4.4 mmol/L). If

Table 2 Management plan for pregnant women with *GCK* mutations, depending on maternal-fetal genotype interactions

		MATERNAL GENOTYPE *GCK* mutation	Appropriate management of maternal hyperglycemia in pregnancy
FETAL GENOTYPE	*GCK* mutation	Fetus relies on maternal hyperglycemia to stimulate insulin secretion.	*Don't treat maternal hyperglycemia.* Usual GDM management and insulin treatment potentially harmful, due to risk of intrauterine growth restriction.
	No *GCK* mutation	Risk of macrosomia due to excess nutrient availability.	*Intensive insulin treatment required.* Larger insulin doses required to overcome counter-regulatory mechanisms.
	Genotype unknown		Initially withhold pharmacotherapy; regular monitoring of fetal growth from 24 weeks gestation indicated; treat with insulin if acceleration of fetal growth in third trimester.

this lower threshold were used in a screening algorithm, 53 % of women with GDM would be eligible for *GCK* testing (unpublished data). Clearly, this is not feasible in the setting of the increasing prevalence of GDM.

It would be very valuable if readily obtainable screening criteria could be established to identify women in the antenatal period with a high probability of having a *GCK* mutation to enable selective molecular genetic testing.

Conclusions

The concept of heterogeneity in GDM is not new. Freinkel et al. wrote in 1987 that GDM entails phenotypic and genotypic heterogeneity [58]. As international organizations consider whether to adopt the new IADPSG diagnostic criteria for GDM, it is increasingly important to remember that an individualized approach to the diagnosis and management of GDM is crucial to optimize maternal and neonatal outcomes. Consideration for the underlying genetic and pathophysiological contributions to an individual's GDM will serve better than a "one size fits all" approach.

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- •• Of major importance

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