Gestational diabetes mellitus: risks and management during and after pregnancy

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Abstract | Gestational diabetes mellitus (GDM) carries a small but potentially important risk of adverse perinatal outcomes and a long-term risk of obesity and glucose intolerance in offspring. Mothers with GDM have an excess of hypertensive disorders during pregnancy and a high risk of developing diabetes mellitus thereafter. Diagnosing and treating GDM can reduce perinatal complications, but only a small fraction of pregnancies benefit. Nutritional management is the cornerstone of treatment; insulin, glyburide and metformin can be used to intensify treatment. Fetal measurements complement maternal glucose monitoring in the identification of pregnancies that require such intensification. Glucose testing shortly after delivery can stratify the short-term diabetes risk in mothers. Thereafter, annual glucose and HbA_{1c} testing can detect deteriorating glycaemic control, a harbinger of future diabetes mellitus, usually type 2 diabetes mellitus. Interventions that mitigate obesity or its metabolic effects are most potent in preventing or delaying diabetes mellitus. Lifestyle modification is the primary approach; use of medications for diabetes prevention after GDM remains controversial. Family planning enables optimization of health in subsequent pregnancies. Breastfeeding may reduce obesity in children and is recommended. Families should be encouraged to help children adopt lifestyles that reduce the risk of obesity.

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Introduction

Gestational diabetes mellitus (GDM) is one of the most common medical complications of pregnancy. The disease has important health implications for mother and child. This Review discusses current evidence for the importance of GDM, opportunities to reduce risk to mother and child and recommendations for clinical care.

What is gestational diabetes mellitus?

Definition

GDM is defined as glucose intolerance with onset or first recognition during pregnancy.[1] The definition does not require any return to normal glucose levels following delivery. Thus, GDM simply represents elevated glucose levels at one point (specifically during pregnancy) in the life of a young woman.

Detection

Outside of pregnancy, screening for clinically important hyperglycaemia is generally recommended only for individuals with specific risk profiles.[1] By contrast, screening for abnormal glucose levels is generally recommended as a routine component of care for pregnant women.[1] Traditionally, screening during pregnancy has involved two steps. The first is a simple 1 h glucose challenge test to identify the large number of women at very low risk of clinically important hyperglycaemia. The second step is a more complex 2 h or 3 h oral glucose tolerance test (OGTT) applied to women classified as 'at risk' on the basis of the results of the 1 h glucose challenge test; this second step defines the subset of women who have GDM. Specific cut-off points used in this detection process have varied widely. The use of cut-off points towards the lower limit of this range will result in proportionately increased incidence rates of GDM, and include many women with only mild hyperglycaemia. The use of cut-off points at the top end of the range results in fewer cases with greater hyperglycaemia.

For the purposes of this discussion, the specific cut-off points are less important than the general concept that GDM is diagnosed following a form of population screening for hyperglycaemia in young women.[2] That screening occurs at a time when the women are generally quite insulin-resistant, although, as discussed below, the acquired insulin resistance of late pregnancy might not be a dominant feature of the pathogenesis of GDM. As explained below, the hyperglycaemia of GDM seems to have a small but demonstrable effect on perinatal outcomes, and is also associated with important long-term health problems in affected mothers and their children.

The aim of the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study was to define uniform diagnostic criteria for GDM.[3] Unlike prior efforts, the HAPO study focused on perinatal outcomes rather than the risk of future diabetes mellitus in the mother. Approximately 25,500 women from nine countries underwent OGTTs

Competing interests
T. A. Buchanan declares associations with the following companies: Allergan, Bristol-Myers Squibb, Novo Nordisk, Takeda, Tethys Bioscience. See the article online for full details of the relationships. The other authors declare no competing interests.

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Key points

- Gestational diabetes mellitus (GDM) is caused by reduced pancreatic β-cell function, which results from the full spectrum of causes of β-cell dysfunction in young women
- GDM is associated with a modest increase in adverse perinatal outcomes, an increased risk of obesity in offspring and a high risk of subsequent development of diabetes mellitus in mothers
- GDM is treated nutritionally; insulin or oral antidiabetic agents can be added if maternal glucose levels and/or fetal growth parameters indicate a sufficiently high risk of perinatal complications
- Long-term management of mothers includes assessment of the level and type of diabetes risk, and lifestyle and/or pharmacological approaches for women at risk of type 2 diabetes mellitus
- Long-term management of offspring should focus on detection and mitigation of the development of obesity and its complications
- A great need exists for high-quality clinical evidence to determine optimal approaches for the management of GDM during and after pregnancy

Table 1 | Criteria for hyperglycaemia in pregnancy*

Diagnostic criteria	Level
***Gestational diabetes mellitus*‡**	
Fasting plasma glucose	≥5.1 mmol/l
1 h post-OGTT plasma glucose	≥10.0 mmol/l
2 h post-OGTT plasma glucose	≥8.5 mmol/l
***Overt diabetes*§**	
Fasting plasma glucose	≥7.0 mmol/l
Random plasma glucose‖	≥11.1 mmol/l
HbA_{1c}	≥6.5%

*As proposed by the International Association for Diabetes and Pregnancy Study Groups.[4] ‡One or more values must be met or exceeded for diagnosis of gestational diabetes mellitus. §One value must be met or exceeded for diagnosis of overt diabetes in pregnancy. ‖Should be confirmed by fasting plasma glucose or HbA_{1c} level. Abbreviation: OGTT, oral glucose tolerance test.

with 75 g glucose in the third trimester of pregnancy. Unless glucose levels were dangerously high, the women's providers were blinded to the OGTT results so that patients received standard antenatal care. Rates of perinatal complications were examined in relation to the OGTT results to determine whether there was a threshold for maternal glucose levels above which perinatal risks rose abruptly. No such threshold was found. Instead, risks of adverse perinatal outcomes increased gradually and smoothly in association with rising maternal glucose levels, as measured by the OGTT.

In the absence of a biological threshold for diagnosis of GDM based on perinatal risks, the International Association of Diabetes and Pregnancy Study Groups (IADPSG) convened a consensus panel that selected the diagnostic criteria for GDM presented in Table 1.[4] The individual glucose cut-off points are only modestly different from those that were already in use in many countries. However, the new criteria require only one abnormal value on a 75 g OGTT to make the diagnosis of GDM, compared with the two abnormal values commonly required in the past. As a result, many more women than before will meet the criteria for GDM if the IADPSG criteria are used. For example, when the new criteria were applied retrospectively to data from the HAPO cohort, approximately 18% of women met the criteria for GDM.[4] This incidence rate is approximately twice that reported with old diagnostic approaches.

One advantage of the new approach is that a large majority of patients can be identified by assessing fasting blood glucose levels and 1 h values on the OGTT.[4] This finding suggests that a one-step approach employing a 75 g OGTT can be used to simplify the detection of GDM in many settings. However, the 2 h value on the OGTT could be particularly important in some regions or ethnic groups.[5] Controversies surrounding the widespread adoption of the IADPSG approach for the diagnosis of GDM have been summarized in several articles.[6–8] Some professional organizations have adopted the new criteria for GDM, whilst others are waiting for evidence of the beneficial effects of treatment in this expanded population of patients before recommending any change in criteria to clinicians.

One additional recommendation of the IADPSG consensus panel was to create a category of overt diabetes in pregnancy. Women are given this diagnosis if their glucose levels meet the criteria for diabetes mellitus outside of pregnancy (Table 1). This distinction is not artificial. The offspring of women with this level of hyperglycaemia are at an increased risk of birth defects, whereas offspring of women with GDM do not have any increase in this risk.[9] Also, women with overt diabetes mellitus could have chronic diabetic complications that increase their risks of hypertensive disorders and visual deterioration during pregnancy. Thus, these women should be managed as if they had pre-existing diabetes mellitus, a topic beyond the scope of this Review.

Frequency of GDM

Diagnostic criteria for GDM have varied widely by geography and over time. As a result, it has been difficult to compare the incidence of GDM among ethnic groups or to determine whether GDM rates have changed over time. Two studies from the Kaiser Permanente health systems in the USA[10,11] assessed the incidence of GDM in pregnant women of various ethnic groups after a standardized diagnostic approach for GDM had been applied over 9–10 year periods between 1991 and 2002. In both studies, the incidence of GDM rose over time, from slightly less than 4% to more than 6%. GDM was most common among people of Asian ancestry or Hispanic ethnicity and least common in people of European ancestry; GDM had an intermediate incidence in African American women. GDM rates rose in parallel in all ethnic groups, which indicated a true increase in the incidence of GDM over time. A report from Kaiser Permanente Southern California health system published in 2011 suggests that the rise in GDM rates is continuing.[12] In this study, which spanned the period 1995–2009, the overall incidence of GDM was 10%, with higher rates in Asian (17%) and Hispanic (11%) women and lower rates in non-Hispanic white (7%) and black (7%) women.[12] As noted above, adoption of the IADPSG criteria would approximately double these figures.

Mechanisms underlying GDM

Similarly to other causes of hyperglycaemia, GDM is a disease of the pancreatic β cells, which do not produce sufficient insulin to meet the increased requirements of late pregnancy. The simplicity of this description belies a more complex set of aetiologies for GDM. Mechanistic studies of GDM reveal at least three separate underlying causes of β-cell dysfunction. First, some women have circulating immune markers (for example, anti-islet cell antibodies or antibodies to glutamate decarboxylase 65) that are diagnostic of evolving type 1 diabetes mellitus (T1DM). The frequency of these autoantibodies is generally <10% of all women with GDM and tends to parallel the background prevalence of T1DM in the population.[13–16]

Second, some women have genetic variants that are diagnostic of monogenic forms of diabetes. These women could have subtypes of maturity-onset diabetes of the young and maternally inherited diabetes.[17–19] Systematic data on the frequency of these monogenic forms of diabetes in GDM are limited, but they seem to be rare, accounting for 1–5% of cases. The third general setting in which the β-cell defects that underlie GDM occur is that of obesity and chronic insulin resistance. This group represents the majority of cases of GDM, leading many clinicians to view GDM as a form of evolving type 2 diabetes mellitus (T2DM). This view could be accurate for the majority of cases, but the full spectrum of GDM includes other causes of inadequate β-cell function in relatively young women. Appropriate care for mothers, especially after pregnancy, requires an understanding of this fact, as will be discussed below.

Knowledge of the role that acquired insulin resistance of pregnancy has in the pathogenesis of the hyperglycaemia that defines GDM has evolved over time. Traditionally, it has been thought and taught that GDM develops when β cells fail to keep pace with the increasing insulin resistance that occurs during the second half of pregnancy. The resultant increasing imbalance between insulin demand and supply manifests itself as rising glucose levels, especially during the second half of pregnancy when insulin resistance is its greatest. In this scenario, glucose regulation returns to normal postpartum, only to resurface years later as hyperglycaemia and diabetes mellitus, usually T2DM.

Serial studies of insulin resistance and β-cell function in women who develop GDM provide quite a different picture. A large majority of the insulin secretory defect that is present in the third trimester of pregnancy is present before[20,21] and soon after[2,22] pregnancy. In fact, insulin secretion during pregnancy increases in parallel in women with and without GDM (Figure 1), but from a lower starting point in women with the condition. Clinical characteristics of the women in these studies suggest that they fall into the subtype of GDM that is related to T2DM. Thus, many (perhaps most) women with GDM seem to have a β-cell defect that is chronic rather than acquired during pregnancy. This concept is consistent with the fact that GDM tends to occur in women over 30 years old who have had multiple pregnancies and who are obese. Obesity and pregnancy

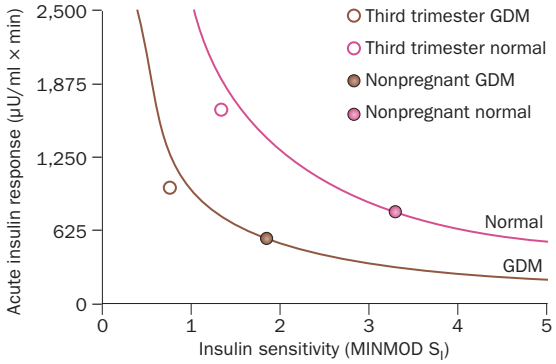

Figure 1 | Insulin sensitivity–secretion relationships during the third trimester and after pregnancy in Hispanic women with GDM ($n = 99$) and age-matched and BMI-matched Hispanic women with normal glucose tolerance ($n = 7$). Measurements were obtained using frequently sampled intravenous glucose tolerance tests. Curved lines depict β-cell compensation for insulin resistance, defined as the product of insulin sensitivity and acute insulin response, in nonpregnant women each group. Both groups increased insulin secretion in response to pregnancy-induced insulin resistance, but secretion did not fully compensate for the acquired insulin resistance of pregnancy in either group (open circles are below lines). Increases in secretion were parallel in normal and GDM groups, consistent with a chronic rather than acute defect in insulin secretion in the women with GDM. Permission obtained from the American Diabetes Association © Buchanan, T. A. *et al*. *Diabetes Care* **30** (Suppl. 2), S105–S111 (2007).

are conditions that promote chronic β-cell dysfunction, which is only detected during pregnancy, when glucose tolerance is tested for the first time in many women's lives.

In summary, GDM is a generally mild form of hyperglycaemia that reflects inadequate β-cell compensation for the body's insulin needs. In some cases, the acquired insulin resistance of pregnancy could create insulin demands that exceed the capacity of β-cells to supply insulin for the limited time frame of pregnancy alone. However, most cases probably represent chronic β-cell dysfunction that is only detected during pregnancy, when glucose tolerance is measured as part of routine care and often for the first time in a young woman's life. As discussed below, β-cell function is not just deficient during pregnancy in women with GDM, it deteriorates over time, which results in women who have had GDM being at a high risk of developing diabetes mellitus in the years following the index pregnancy.

Why is GDM important?

Antepartum and perinatal considerations

Overt maternal diabetes mellitus can adversely influence intrauterine fetal development. Spontaneous abortions and major congenital anomalies may be induced in the first trimester. Excessive fetal growth, neonatal hypoglycaemia, jaundice, polycythaemia and stillbirth may occur during the second and third trimesters. As noted above, excess birth defects are generally limited to women with gestationally diagnosed hyperglycaemia

Table 2 | Perinatal outcomes in the HAPO cohort*

Outcome	Frequency in pregnancies affected by GDM (%)	Frequency in pregnancies not affected by GDM (%)	Frequency difference (%)
Pre-eclampsia	9.1	4.5	4.6
Delivery at <37 weeks	9.4	6.4	3.0
Primary caesarean delivery	24.4	16.8	7.6
Shoulder dystocia or birth injury	1.8	1.3	0.5
Intensive neonatal care	9.1	7.8	1.3
Clinical neonatal hypoglycaemia	2.7	1.9	0.8
Neonatal hyperbilirubinaemia	10.0	8.0	2.0
Birthweight >90th percentile	16.2	8.3	7.9
Cord C-peptide levels >90th percentile	17.5	6.7	10.8
Percent body fat >90th percentile	16.6	8.5	8.1

*GDM diagnosed according to IADPSG criteria (Table 1). Abbreviations: GDM, gestational diabetes mellitus; HAPO, Hyperglycemia and Adverse Pregnancy Outcomes; IADPSG, International Association for Diabetes and Pregnancy Study Groups. Permission obtained from the American Diabetes Association © Metzger, B. E. *et al*. *Diabetes Care* **33**, 676–682 (2010).[4]

that meets the criteria for overt diabetes mellitus. The frequency of adverse fetal outcomes across the full range of maternal hyperglycaemia that defines true GDM is difficult to determine. The reason is simple —women in the upper part of that range almost always receive some form of treatment.

Results from the HAPO study provide useful insight into the frequency of perinatal complications in women with mild to moderate GDM in the absence of treatment. In the HAPO study, women with fasting plasma glucose levels of >5.8 mmol/l or a 2 h glucose level of >11.1 mmol/l on the 75 g OGTT were referred for treatment of GDM. Women with glucose levels below these thresholds received no diagnosis or interventions targeted to their glycaemic control. Retrospective application of the new IADPSG criteria for GDM to these untreated women revealed statistically significant increases in 10 different adverse perinatal outcomes in women who met these criteria compared with those who did not (Table 2). Although the increase in relative risk ranged from 1.70 to 2.02 across the 10 complications, the absolute risk (the difference in complication rates between the GDM and control groups) was not more than 11% for any complication. Similar patterns have been observed in many smaller studies; for example, a 10% absolute risk of caesarean delivery and a 14% absolute risk of macrosomia in women with untreated, borderline GDM in the Toronto Tri-Hospital GDM project.[23]

The main message is that the diagnosis of GDM imparts some excess risk of perinatal complications. However, only a minority of pregnancies have an adverse outcome that could be attributed to GDM. This fact will become important when approaches to antepartum management are discussed below.

Long-term health of the mother

Women who are diagnosed with GDM are at high risk of developing diabetes mellitus later in life. An estimated ~10% of women with GDM have diabetes mellitus soon after delivery. The rest develop diabetes mellitus at rates of 20–60% within 5–10 years after the index pregnancy in the absence of specific interventions to reduce their risk of diabetes mellitus. Limited long-term data suggest that not all women with GDM will get diabetes mellitus,[24] but certainly the majority will. Thus, as is true for perinatal complications, GDM is a risk factor for diabetes mellitus after pregnancy. However, the risk of diabetes mellitus in the mother after GDM is much higher than the risk of perinatal complications associated with GDM. Thus, GDM can be reasonably considered to be a form of prediabetes, similar to impaired glucose tolerance in nonpregnant individuals.

As discussed above, diabetes mellitus after GDM can take several forms, but the majority of patients fit the phenotype of prediabetes leading to T2DM. Longitudinal studies of glucose regulation after GDM reveal falling β-cell compensation for chronic insulin resistance, which might also worsen over time.[25] Risk factors for the early development of diabetes mellitus after pregnancy include markers suggestive of profound decompensation, which include high glucose levels, marked insulin resistance and poor β-cell function. Women with these characteristics do not have to deteriorate much to cross the line to glucose levels that define diabetes mellitus. Risk factors for acceleration of the deterioration in β-cell function that causes diabetes mellitus include weight gain, insulin resistance, rising levels of C-reactive protein and falling levels of adiponectin.[26] These findings suggest that the metabolic effects of obesity are important determinants of the β-cell deterioration that leads to diabetes mellitus. Indeed, as discussed below, amelioration of the adverse metabolic effects of obesity—through weight loss or the use of medications that improve adipose tissue biology—provide the strongest protection against the development of T2DM following GDM.

The background upon which T2DM develops is one of obesity and related conditions that are often referred to as the metabolic syndrome. As might be expected, women who have had GDM manifest components of the metabolic syndrome more often than do women without GDM.[27] A history of GDM is also associated with increases in cardiovascular risk factors[28] and cardiovascular event rates.[29]

Long-term health of the offspring

Several[30–33] but not all[34,35] studies of growth and development in the offspring of mothers with diabetes mellitus indicate an increased risk of obesity during childhood and adolescence. Some of this effect could represent simple heredity or shared environment between mothers and children; however, several observations suggest an independent effect of exposure to diabetes mellitus *in utero*. First, offspring of mothers with diabetes mellitus have a higher risk of developing obesity than the offspring of fathers with diabetes mellitus.[36] Second,

offspring of mothers with T1DM (who are generally not obese) have higher BMI by age 14–17 years and more often have impaired glucose tolerance than offspring of nondiabetic mothers.[37] Third, and most convincingly, in sibling pairs discordant for exposure to maternal diabetes mellitus, offspring born after the mother developed diabetes mellitus had a higher BMI and a higher risk of developing diabetes mellitus than offspring born before their mother developed diabetes mellitus.[36]

In Pima Indians, glucose levels in the range diagnostic for GDM were associated with an increased risk of obesity in offspring. These findings suggest that fetal exposure to maternal diabetes mellitus, including GDM, influences important aspects of the regulation of appetite and/or energy expenditure in favour of a positive caloric balance. Interestingly, the effect of maternal diabetes mellitus on offspring does not become manifest as increased BMI until after ~2 years of age,[37,38] and effects on other components of the metabolic syndrome, including hyperglycaemia, have been observed.[37] All these findings suggest that exposure to maternal diabetes mellitus *in utero* could be an important contributor to the rising rates of obesity and diabetes mellitus that are occurring in developed countries throughout the world.[31]

Can the risks of GDM be reduced?

Antenatal and perinatal complications

Traditionally, most evidence about the antenatal and perinatal benefits of diagnosing and treating GDM has come from a mix of clinical observations and nonrandomized treatment trials. As a result, expert bodies have made a wide range of recommendations about the importance of diagnosing and treating GDM. At one end of the spectrum are organizations that recommend widespread or universal screening for GDM and implementation of stepped care protocols for women with the disease.[1,39] At the other end of the spectrum are groups that have questioned the cost-effectiveness of detecting GDM at all.[40–42]

Two randomized clinical trials have provided evidence that diagnosing and treating GDM can have statistically significant beneficial effects, albeit in a relatively small fraction of patients. In the Australian Carbohydrate Intolerance Study (ACHOIS),[43] participants underwent a 75 g OGTT between 16 and 30 weeks of gestation, and fasting plasma glucose levels of <7.8 mmol/l or 2 h post-OGTT glucose levels 7.8–11.0 mmol/l were used as the criteria for the diagnosis of GDM. Women with GDM were randomly allocated to usual care (patients and providers blinded to the OGTT results) or intervention. In the intervention group, patients and providers were aware of the OGTT results. Treatment included individualized nutritional advice and glucose self-monitoring. Exogenous insulin was given when glucose levels exceeded prespecified targets. The intervention group had a lower rate of serious perinatal complications (1% versus 4%; mostly shoulder dystocia) but a higher rate of admissions to the neonatal intensive care unit (71% versus 61%).

The Maternal–Fetal Units Network study in the USA used a 100 g OGTT, administered between 24 and 30 weeks gestation, and GDM was diagnosed when at least two glucose values met or exceeded the following levels: fasting 5.3 mmol/l, 1 h 10.0 mmol/l, 2 h 8.6 mmol/l, 3 h 7.8 mmol/l.[44] Patients were randomly allocated to usual care (blinded to the diagnosis) or intervention, as in the ACHOIS study. A composite of clinically significant perinatal outcomes (death, trauma, jaundice, hypoglycaemia or elevated C-peptide levels) occurred in the offspring at similar frequencies in the two groups. Rates of shoulder dystocia were reduced in the intervention group (1.5% versus 4%), similar to the results of the ACHOIS study. In both randomized clinical trials, intervention was associated with significant reductions in mean birth weights (~100–150 g), in rates of infants that were born large for gestational age or that weighed >4,000 g at birth, and in rates of maternal hypertensive disorders. For these last three adverse outcomes, the absolute differences in rates between groups were ~6–10%.

Taken together, these two studies and a meta-analysis that included them both and three smaller studies[45] reveal a consistent pattern. Diagnosing GDM and treating it using nutritional advice, glucose self-monitoring and, if required, exogenous insulin, lowers the relative risk of fetal overgrowth, shoulder dystocia and maternal hypertensive disorders. However, only a small fraction of pregnancies benefit from these interventions, since most pregnancies affected by GDM do not incur any adverse perinatal outcomes in the absence of treatment and some pregnancies incur them despite treatment.

A much larger body of evidence exists regarding the effect of intensifying treatment beyond nutritional therapy once GDM has been diagnosed. In a meta-analysis of 13 studies,[45] the methods of intensification varied considerably across the thirteen studies and included insulin treatment versus diet alone, different intensities of insulin therapy, insulin versus aerobic exercise, glucose monitoring at clinic visits versus glucose self-monitoring by patients, more-frequent versus less-frequent glucose self-monitoring, glucose self-monitoring versus continuous glucose monitoring, therapy adjustments at visits versus adjustments using telemedicine, caloric restriction versus unrestricted diets with insulin treatment, and the use of ultrasonography to guide decisions on insulin treatment.

The studies were generally small (41–342 individuals each). As might be expected, it was difficult to identify uniform or consistent findings across this heterogeneous group of studies in the meta-analysis. Rates of shoulder dystocia, which were reported in five of the 13 studies, were significantly reduced in the intensification groups (~3% absolute risk reduction). There was a trend towards a reduction in the rate of large for gestational age babies in the intensification groups that did not reach statistical significance and represented only a 4% absolute risk reduction overall. No important differences in rates of caesarean delivery, birth trauma, macrosomia or perinatal mortality were found. Thus, as is true for diagnosing and treating GDM, intensifying treatment can benefit

a numerically small but potentially important subset of patients.

The information presented above highlights a major weakness in the current approach to GDM. Intensive monitoring and, to a lesser extent, pharmacological treatments are applied to a large number of patients to improve outcomes in a few. Even if this approach proves cost-effective,[46] it is almost certainly inefficient. In truth, when it comes to perinatal complications, GDM is more of a risk factor than a disease. A very great need exists for precise methods to identify the subset of pregnant women with GDM who are at the highest risk of perinatal complications so that the most intensive monitoring and treatment efforts can be directed at them. Maternal blood glucose measurements are a very crude tool in this regard. This issue is discussed below in relation to approaches to treatment during pregnancy.

Protecting long-term maternal health

A reasonably robust and growing body of clinical trial evidence supports reducing the risk of diabetes mellitus in high-risk individuals. For individuals at high risk of developing T1DM, the evidence is that we do not have any interventions that work well in humans. For individuals at high risk of developing T2DM, the story is very different. Lifestyle interventions, metformin, acarbose and thiazolidinediones reduce the risk of T2DM by 25–72% in adults with impaired glucose levels.[47–52] The best evidence for risk reduction and disease mitigation comes from approaches that either change body adipose tissue content (lifestyle changes can produce ~58% risk reductions) or adipose tissue biology (thiazolidinediones can produce 55–72% risk reductions).[53] Evidence is less strong for approaches that primarily reduce rates of glucose appearance in the circulation (acarbose and metformin can produce 25–31% risk reductions).[53]

Two trials provide information for the specific group of women with a high risk of T2DM owing to a history of GDM. The Troglitazone in the Prevention of Diabetes study was conducted solely in Hispanic women with prior GDM.[48] The study demonstrated a 55% reduction in the incidence of T2DM over a 30-month period. Protection from T2DM was associated with reduced secretory demands on β cells and with significant slowing of the decline in β-cell function. Preservation of β-cell function persisted when patients were switched to pioglitazone, after troglitazone was withdrawn from clinical use.[54]

The US Diabetes Prevention Program included women with a history of GDM as one risk factor for diabetes mellitus. A post-hoc comparison of the effects of lifestyle modification or metformin treatment versus placebo revealed that lifestyle modification was equally effective in reducing the risk of diabetes mellitus in women with and without a history of GDM (50% versus 49% risk reductions, respectively).[55] By contrast, metformin was more effective in women with than without a history of GDM (50% versus 14%, respectively). Thus, metformin may be particularly effective in reducing the risk of diabetes mellitus in women with a history of GDM, for reasons that are not clear at present. The limited available evidence suggests that assessment and reduction of cardiovascular risk should be an additional component of care for women with prior GDM.[28,29]

Improving long-term health of offspring

Little high-quality evidence exists to guide clinicians aiming to reduce the risks of obesity and diabetes mellitus in the offspring of mothers with diabetes mellitus. Breastfeeding has been associated with a reduced long-term risk of obesity and diabetes mellitus compared with bottle feeding in several observational studies, some of which included mothers with diabetes mellitus.[56,57] The hope that aggressive control of maternal glucose levels in pregnancy might also mitigate the development of obesity in their children remains to be realized. Follow-up of participants in the ACHOIS study, in which diagnosis and treatment of GDM led to a reduction in birth weights and macrosomia rates in offspring, did not reveal any intergroup difference in BMI Z-scores of the offspring by ages 4–5 years.[58]

The Metformin in Gestational Diabetes trial[59] compared metformin with insulin in women with GDM who required intensification of treatment beyond dietary therapy. The two treatments provided similar perinatal outcomes, including birth weights and skin-fold measurements in newborn babies. At age 2 years, offspring of the two treatment groups had similar body adipose tissue content, but the offspring in the metformin group had small (3–16%) but statistically significant increases in skin-fold thicknesses.[60] The authors suggested that this finding might reflect increased subcutaneous and reduced visceral adipose tissue in the metformin group, but that suggestion remains to be proven. Thus, other than breastfeeding, no interventions have been proven to reduce obesity and its complications in offspring exposed *in utero* to GDM or any other form of diabetes mellitus. However, excess rates of obesity in offspring from mothers with GDM may take years to develop; long-term studies will, therefore, be required to provide definitive information on this issue.

Recommendations for clinical care

Antepartum care

Nutritional therapy is widely recommended as an integral part of the treatment of women with GDM. Unfortunately, little information from controlled trials exists to guide nutritional recommendations for this condition. In general, nutritional requirements are the same for pregnant women with and without GDM. However, several dietary modifications can lower glucose levels more effectively than a standard diet for pregnant women. These include reducing caloric intake for overweight and obese women (for example, to ~25 kcal/kg of body weight),[61] limiting carbohydrate content to 35–40% of total calories[62,63] and focusing on complex rather than simple carbohydrates. The second of these modifications improves perinatal outcomes compared with diets including higher carbohydrate levels.[64] These principles can be applied in practice by individualizing

dietary advice under the guidance of a nutritionist who is expert in the dietary management of women with diabetes mellitus in pregnancy.

The next step after initiating nutritional therapy is the identification of women who need additional treatment to minimize the risk of perinatal complications. Two general approaches have been applied, the most common of which is regular glucose self-monitoring by patients. The optimal timing and frequency of monitoring has not been determined. One study that is often cited as proof that post-meal glucose targets are more important than pre-meal targets in the management of GDM[65] actually compared rather low post-meal targets to fairly high pre-meal targets. Thus, the design was biased in favour of post-meal monitoring. Other studies have found that perinatal complications are more closely related to fasting glucose levels than to post-challenge glucose levels measured at the time of diagnosis of GDM.[66,67] In the absence of definitive evidence, it has become common practice to ask patients to measure capillary glucose levels before breakfast and 1–2 h after breakfast, lunch and dinner. Treatment targets have varied among studies that have demonstrated improved perinatal outcomes. Some commonly recommended targets are fasting plasma glucose levels ≤5.3 mmol/l, 1 h post-meal glucose levels ≤7.8 mmol/l and 2 h post-meal glucose levels 6.7 mmol/l.

The other general approach to identifying pregnancies that can benefit from intensified metabolic management employs a combination of maternal plasma glucose measurements and fetal morphological measurements. This approach is based on two principles. The first is that fasting plasma glucose concentrations above a given threshold, measured at routine clinic visits, are high enough to warrant intensified treatment because they impart a high risk of preventable perinatal complications. Studies by the authors' group suggest that a fasting plasma glucose level ≥5.8 mmol/l is useful in this regard.[68,69] The second principle is that, among women with fasting glucose levels below this value, fetal measurements can identify the substantial fraction of pregnancies that will not incur a perinatal complication in the absence of intensified treatment.

The authors' group has used fetal abdominal circumference measurements obtained by ultrasonography to identify such pregnancies. In pregnant women with a fasting plasma glucose level <5.8 mmol/l, a fetal abdominal circumference below the 70th percentile for gestational age between 29–33 weeks of gestation was associated with no excess risk of large for gestational age infants or caesarean deliveries compared with that in nondiabetic pregnant women.[69] Moreover, the findings showed that intensified insulin treatment in pregnancies with fetal abdominal circumference above the 70th percentile could eliminate the excess of large for gestational age infants.[69] The peripheral blood glucose targets employed in this last subgroup were fasting levels <4.4 mmol/l and 2 h postprandial levels <6.1 mmol/l. These low targets can be used because there is virtually no risk of the offspring becoming small for gestational age[70] when this treatment is directed at women carrying fetuses with evidence of increased growth. Note that only women who were placed on insulin require glucose self-monitoring with this approach, providing considerable savings to offset the cost of the fetal ultrasonography.

Several options are available for intensifying therapy beyond nutritional management once the decision is made to do so. Traditionally, exogenous insulin was the primary mode of pharmacological treatment. Insulin remains an important option and regimens should be tailored to meet glycaemic targets. No convincing evidence exists to exclude any available insulin from use during pregnancy. Small studies have suggested that regular aerobic exercise can reduce glucose levels as effectively as insulin does.[71,72] However, the intensity of exercise employed in these studies was high (for example, 60% of maximal oxygen uptake for 45 min 3 days a week) and not easy for pregnant women to achieve. Regular exercise of lower intensity, such as walking after meals, is often recommended for women with GDM, although data are lacking on the effect of this level of exercise on pregnancy outcomes.

Two randomized trials have expanded the pharmacological options for GDM to include oral antidiabetic agents. One study compared glyburide with insulin in women who were deemed in need of intensified treatment on the basis of maternal self-monitored glucose level results.[73] Equivalent perinatal outcomes were observed in the two groups. Only 4% of women assigned to glyburide also received insulin to meet prespecified glycaemic targets. A similar study compared metformin with insulin.[59] Perinatal outcomes were again similar in the two treatment groups; however, 46% of women assigned to metformin received supplemental insulin to achieve glycaemic targets. Patients reported a preference for metformin over insulin.

At least two oral agents can, therefore, be used to intensify treatment and achieve good perinatal outcomes. Moreover, information on offspring outcomes in early childhood is available from the metformin versus insulin trial[59] which found similar body fat content at age 2 years in offspring of the two treatment groups.[60] As noted above, the offspring of mothers assigned to receive metformin had skin-fold evidence of increased subcutaneous fat, which raises the untested possibility that adipose tissue in other locations could be reduced. Information regarding the effects of these agents, which can cross the human placenta, on truly long-term health of offspring are lacking at the present time.

In summary, medical nutritional therapy is recommended for all patients based on reduced caloric intake for overweight and obese women, limited carbohydrate intake and a focus on complex carbohydrates—principles that are supported by a small amount of good-quality evidence. Maternal glucose self-monitoring or a combination of fetal abdominal circumference measurements with fasting plasma glucose measurements in the clinic can be used to identify women who might benefit from intensified treatment (or conversely, those who do not need intensification). Insulin, glyburide and metformin

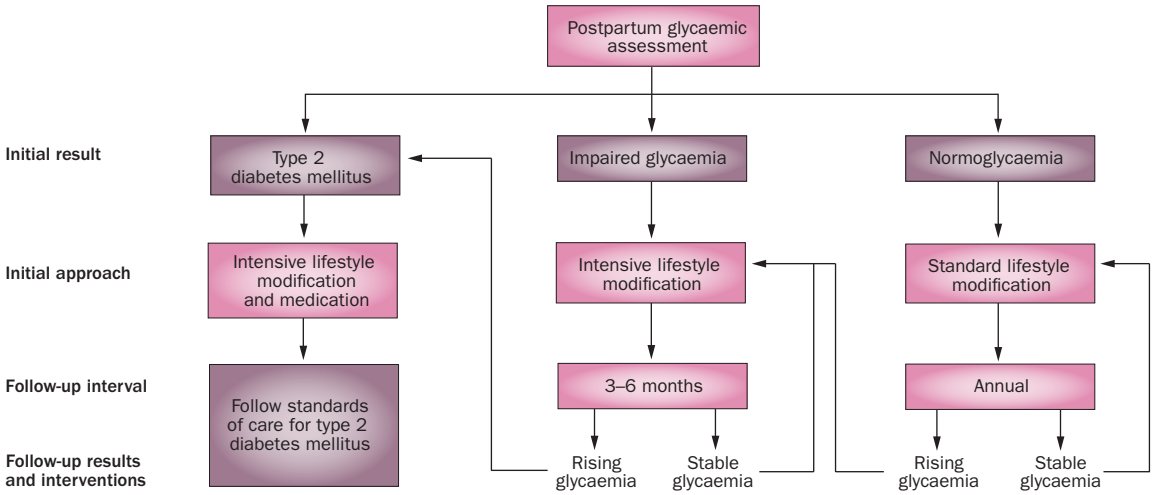

Figure 2 | Suggested management of women with prior gestational diabetes mellitus when risk appears to be for T2DM. Assessment with oral glucose tolerance test and measurement of HbA_{1c} levels is recommended at 1–4 months postpartum to stratify risk. Women whose initial result is T2DM should begin treatment for that disease. Women whose initial result is impaired glycaemia are at high risk of developing T2DM. They should participate in intensive lifestyle modification programmes[47,49] to reduce weight and they should have HbA_{1c} levels checked every 3–6 months to assess their response to this approach. Rising HbA_{1c} levels indicate an inadequate response. Women whose initial postpartum result is normoglycaemia are still at an increased risk of T2DM. They should receive dietary and exercise advice to promote weight loss and be monitored at least annually by measurement of fasting plasma glucose and HbA_{1c} levels. The onset of hyperglycaemia, whether assessed by an oral glucose tolerance test or HbA_{1c} level, is an indication of deterioration and a need for intensification of treatment. Abbreviation: T2DM, type 2 diabetes mellitus.

are viable options for intensification of treatment in the high-risk groups. Regular exercise is often recommended, but its benefits in terms of pregnancy outcomes are largely unknown.

Postpartum care for mothers

The main emphasis of postpartum care for women affected by GDM should be assessment of the future risk of diabetes mellitus and mitigation of that risk. The basic steps are outlined in Figure 2. In regard to monitoring, no systematic studies of optimal methods or timing are available. In general, these women should have a fasting plasma glucose measurement before hospital discharge to identify the rare patients who have blood glucose levels in the diabetic range at that time. These women should be treated for diabetes mellitus, whilst other women can be discharged with plans to re-assess glucose levels in the outpatient setting. Glucose tolerance testing 1–4 months postpartum is useful for the identification of additional women with diabetes mellitus and in stratifying the 1–5 year risk of diabetes mellitus.[74] The utility of HbA_{1c} testing at this time point is uncertain, owing to the potential influence of blood loss during delivery and in the early postpartum period.

In the women who do not have diabetes mellitus at postpartum testing, the risk increases linearly for at least the first 5–10 years, during which 30–50% will develop diabetes mellitus.[75] This risk is high enough to warrant testing these women for diabetes mellitus at least annually. The recommendation for using HbA_{1c} levels to diagnose diabetes mellitus,[1] made by the American Diabetes Association in 2011, makes this annual monitoring relatively simple. Levels of 6.5% or greater indicate diabetes mellitus. Levels of 5.8–6.4% indicate impaired glucose levels and a high risk of diabetes mellitus. Serial HbA_{1c} measurements can also be useful to identify the women who are progressing most rapidly toward diabetes mellitus and to assess responses to interventions designed to slow or stop that progression. In this context, the changes in HbA_{1c} are more important than any individual value.

In regard to mitigation of the risk of diabetes mellitus, the first step is to decide what type of GDM the patient had. A small fraction of patients will have β-cell dysfunction related to islet autoimmunity or monogenic diabetes, but no well-validated approach is available to identify these women. If a patient does not seem to be insulin-resistant (for example, if she is lean) one of these conditions should be considered. Measurement of glutamate decarboxylase 65 autoantibodies can identify women who may have evolving T1DM. Although no specific interventions can reduce the risk of T1DM, glycaemic control in these patients can deteriorate rapidly.[16] These patients warrant particularly close monitoring of blood glucose and/or HbA_{1c} levels. Women who have monogenic forms of diabetes that present as GDM generally have a strong family history of diabetes mellitus, consistent with autosomal-dominant or maternal inheritance patterns. The diagnosis is complex and consultation with an expert in the genetics of these forms of diabetes is advisable. Some forms respond well to specific therapies.[76] Genetic counselling is also important for these women.

The large majority of patients with GDM have other risk factors for the development of T2DM, such as obesity or non-European ancestry. Results from diabetes prevention trials[47–52] and observational studies of the development of T2DM after GDM[26] suggest that

mitigating the metabolic adverse effects of excess body adipose tissue, especially insulin resistance, is an important approach to reducing the risk of diabetes mellitus.[53] The most logical first step is to reduce body adipose tissue through lifestyle modification. The main principles are to reduce caloric intake through dietary changes and increase caloric output through exercise. This approach has been proven to reduce the risk of T2DM by ~50–60% in people with impaired glucose tolerance,[47,49] including women with a history of GDM.[55]

Given the high rate of progression to diabetes mellitus after GDM, it is advisable to implement some degree of lifestyle modification in all such patients whose risk for diabetes appears to be for T2DM. The intensity of the approach can be modified according to the perceived risk. For example, women with prediabetic HbA_{1c} levels (5.8–6.4%) are at a sufficiently high risk of diabetes mellitus that they are candidates for the type of intensive lifestyle programmes utilized in the US Diabetes Prevention Program[49] and the Finnish Diabetes Prevention Study.[47] Monitoring changes in HbA_{1c} levels over time can identify women whose response to these interventions is appropriate (stable or falling HbA_{1c} levels) and women whose response is inadequate (rising HbA_{1c} levels). Women whose HbA_{1c} levels are normal after pregnancy are still likely to be at an increased risk of diabetes mellitus compared with women who have never had GDM. Controlled trials of diabetes prevention have not been conducted in this group of women, but it makes sense to advise lifestyle changes to reduce body adipose tissue and to intensify lifestyle changes if HbA_{1c} levels rise over time.

At present, no compelling evidence suggests that use of medications to prevent diabetes mellitus after GDM provides better long-term outcomes than using medications once diabetes mellitus develops. In addition, no medications have regulatory approval for treating prediabetes. Only one medication, metformin, was suggested for 'consideration' by an expert panel of the American Diabetes Association.[77] Our suggestion is to focus on lifestyle changes and monitoring of HbA_{1c} levels in patients who do not have diabetes mellitus. Rising HbA_{1c} levels are indicative of an inadequate response to treatment and suggest a need for intensification of lifestyle changes. An HbA_{1c} level ≥6.5% indicates onset of diabetes mellitus and a need for pharmacological treatment, a topic that is beyond the scope of this Review.

Several aspects of post-pregnancy care are particularly important for women with prior GDM. One is breastfeeding, which can help women reduce weight after pregnancy, although the effects on the risk of diabetes mellitus are not proven. Breastfeeding has also been associated with reduced obesity in offspring as they grow up (see Improving long-term health of offspring), so it is recommended. Another important issue is family planning. The need is great because additional pregnancies can further increase the risk of diabetes mellitus,[25,78] and pregnancies after the development of diabetes mellitus carry an increased risk of major birth defects,[9] which could be prevented by appropriate glycaemic control before conception. Family planning provides an opportunity for prevention of GDM, in particular through weight reduction.[79]

Although data from randomized controlled trials of contraception after GDM are lacking, observational studies do not suggest contraindications to specific forms of contraception based on a history of GDM, with one exception. At least two studies have demonstrated an association between an increased risk of diabetes mellitus and use of unopposed systemic progestin contraception. Such an effect was demonstrated for norethisterone in breastfeeding women[80] and for depot medroxyprogesterone acetate (DMPA) in women not breastfeeding.[81] At least for DMPA, the detrimental effects were associated with weight gain. Thus, we do not recommend using unopposed progestin contraception in women with prior GDM. If this type of contraception is otherwise the best choice, it should be used with careful monitoring for deterioration of glucose or HbA_{1c} levels.

Postpartum care of offspring

The potential importance of breastfeeding has been mentioned above. On the basis of the increased risk of obesity and diabetes mellitus during childhood and adolescence, it seems prudent to promote healthy eating and regular exercise and to monitor offspring for development of obesity and related complications.

Conclusions

The Review highlights many of the controversies and knowledge gaps in the clinical care of women with GDM and their offspring. A great need exists for high-quality clinical evidence to support many aspects of care. Two areas deserve special attention. First, adoption of the recommendations of the IADPSG for diagnosis of GDM will result in a large increase, perhaps a doubling, of the incidence of the condition.[4] Justification for this approach is based on perinatal outcomes from the HAPO study. Indeed, because the relationship between maternal glucose levels and perinatal complications is not steep, the additional women identified by the new criteria could have perinatal complication rates that are only slightly lower than those of the women diagnosed as having GDM in the past. The real problem is that, even in the past, only about one-third of women with GDM incurred a perinatal complication of any sort that could be directly attributed to the effects of the condition. A much smaller fraction (<10%) incurred clinically important complications, such as birth trauma or neonatal jaundice. Doubling the number of women with a diagnosis of GDM will at least double the number of women whose pregnancies do not actually have increased perinatal risk. Approaches based on fetal measurements hold great promise to help clinicians further stratify the antenatal and perinatal risks associated with GDM so that intensive treatment can be directed at the women with truly high-risk pregnancies. Such approaches are deserving of expanded evaluation in clinical trials.

The second area deserving special attention is the heterogeneity of GDM. The Review has already alluded to the existence of subtypes of GDM based on known

causes of β-cell dysfunction. Even among the large majority of women who do not have autoimmune or monogenic forms of diabetes, considerable heterogeneity exists. Asian women tend to be leaner than many other ethnic groups, and yet they have high rates of GDM. Women of African ancestry have lower GDM rates than other ethnic groups, but higher rates of diabetes mellitus after GDM.[12] Understanding the genetic and pathophysiological underpinnings of these differences may be useful in developing targeted approaches to preventing both GDM and diabetes mellitus after GDM in mothers and their offspring.

Review criteria

The manuscript was built on principles of biology and clinical management that our group have developed in >20 years of research in gestational diabetes mellitus. This knowledge was complemented by examination of published literature in the areas of antepartum management, diabetes prevention and the effects of maternal diabetes on offspring. To this end, PubMed was searched for full-text articles in the English language covering the time period up to September 2011 using the search term "gestational diabetes mellitus".

1. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* **35** (Suppl. 1), S64–S71 (2012).
2. Buchanan, T. A., Xiang, A., Kjos, S. L. & Watanabe, R. M. What is gestational diabetes? *Diabetes Care* **30** (Suppl. 2), S105–S111 (2007).
3. Metzger, B. E. *et al.* Hyperglycemia and adverse pregnancy outcomes. *N. Engl. J. Med.* **358**, 1991–2002 (2008).
4. Metzger, B. E. *et al.* International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care* **33**, 676–682 (2010).
5. Sacks, D. A. *et al.* Frequency of gestational diabetes mellitus at collaborating centers based on IADPSG consensus panel-recommended criteria: the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study. *Diabetes Care* **35**, 526–528 (2012).
6. Ryan, E. A. Diagnosing gestational diabetes. *Diabetologia* **54**, 480–486 (2011).
7. Long, H. Diagnosing gestational diabetes: can expert opinions replace scientific evidence. *Diabetologia* **54**, 2211–2213 (2011).
8. Paglia, M. J. & Coustan, D. R. Gestational diabetes: evolving diagnostic criteria. *Curr. Opin. Obstet. Gynecol.* **23**, 72–75 (2011).
9. Schafer, U. M. *et al.* Congenital malformations in offspring of women with hyperglycemia first detected during pregnancy. *Am. J. Obstet. Gynecol.* **177**, 1165–1171 (1997).
10. Dabelea, D. *et al.* Increasing prevalence of gestational diabetes mellitus (GDM) over time and by birth cohort: Kaiser Permanente of Colorado GDM Screening Program. *Diabetes Care* **28**, 579–584 (2005).
11. Ferrara, A., Kahn, H. S., Quesenberry, C. P., Riley, C. & Hedderson, M. M. An increase in the incidence of gestational diabetes mellitus: Northern California, 1991–2000. *Obstet. Gynecol.* **103**, 526–533 (2004).
12. Xiang, A. H. *et al.* Racial and ethnic disparities in diabetes risk after gestational diabetes. *Diabetologia* **54**, 3016–3021 (2011).
13. Xiang, A. H. *et al.* Multiple metabolic defects during late pregnancy in women at high risk for type 2 diabetes mellitus. *Diabetes* **48**, 848–854 (1999).
14. Petersen, J. S. *et al.* GAD65 autoantibodies in women with gestational or insulin dependent diabetes mellitus diagnosed during pregnancy. *Diabetologia* **39**, 1329–1333 (1996).
15. Catalano, P. M., Tyzbir, E. D. & Sims, E. A. Incidence and significance of islet cell antibodies in women with previous gestational diabetes. *Diabetes Care* **13**, 478–482 (1990).
16. Mauricio, D. *et al.* Islet cell antibodies identify a subset of gestational diabetic women with higher risk of developing diabetes shortly after pregnancy. *Diabetes Nutr. Metab.* **5**, 237–241 (1992).
17. Kousta, E. *et al.* Glucokinase mutations in a phenotypically selected multiethnic group of women with a history of gestational diabetes. *Diabet. Med.* **18**, 683–684 (2001).
18. Weng, J. *et al.* Screening for MODY mutations, GAD antibodies, and type 1 diabetes–associated HLA genotypes in women with gestational diabetes mellitus. *Diabetes Care* **25**, 68–71 (2002).
19. Chen, Y., Liao, W. X., Roy, A. C., Loganath, A. & Ng, S. C. Mitochondrial gene mutations in gestational diabetes mellitus. *Diabetes Res. Clin. Pract.* **48**, 29–35 (2000).
20. Catalano, P. M. *et al.* Carbohydrate metabolism during pregnancy in control subjects and women with gestational diabetes. *Am. J. Physiol.* **264**, E60–E67 (1993).
21. Catalano, P. M., Huston, L., Amini, S. B. & Kalhan, S. C. Longitudinal changes in glucose metabolism during pregnancy in obese women with normal glucose tolerance and gestational diabetes. *Am. J. Obstet. Gynecol.* **180**, 903–916 (1999).
22. Homko, C., Sivan, E., Chen, X., Reece, E. A. & Boden, G. Insulin secretion during and after pregnancy in patients with gestational diabetes mellitus. *J. Clin. Endocrinol. Metab.* **86**, 568–573 (2001).
23. Naylor, C. D., Sermer, M., Chen, E. & Sykora, K. Cesarean delivery in relation to birth weight and gestational glucose tolerance: pathophysiology or practice style? *JAMA* **275**, 1165–1170 (1996).
24. O'Sullivan, J. B. Diabetes after GDM. *Diabetes* **40** (Suppl. 2), 131–135 (1991).
25. Xiang, A. H., Kjos, S. L., Takayanagi, M., Trigo, E. & Buchanan, T. A. Detailed physiological characterization of the development of type 2 diabetes in Hispanic women with prior gestational diabetes mellitus. *Diabetes* **59**, 2625–2630 (2010).
26. Xiang, A. H., Kawakubo, M., Trigo, E., Kjos, S. L. & Buchanan, T. A. Declining beta-cell compensation for insulin resistance in Hispanic women with recent gestational diabetes mellitus: association with changes in weight, adiponectin, and C-reactive protein. *Diabetes Care* **33**, 396–401 (2010).
27. Retnakaran, R. *et al.* Glucose intolerance in pregnancy and postpartum risk of metabolic syndrome in young women. *J. Clin. Endocrinol. Metab.* **95**, 670–677 (2010).
28. Sullivan, S. D., Umans, J. G. & Ratner, R. Gestational diabetes; implications for cardiovascular health. *Curr. Diab. Rep.* **12**, 43–52 (2012).
29. Retnakaran, R. & Shah, B. R. Mild glucose intolerance in pregnancy and risk of cardiovascular disease: a population-based cohort study. *CMAJ* **181**, 371–376 (2009).
30. Silverman, B. L. *et al.* Long-term prospective evaluation of offspring of diabetic mothers. *Diabetes* **40** (Suppl. 2), S121–S125 (1991).
31. Hillier, T. A. *et al.* Childhood obesity and metabolic imprinting: the ongoing effects of maternal hyperglycemia. *Diabetes Care* **30**, 2287–2292 (2007).
32. Dabelea, D. *et al.* Association of intrauterine exposure to maternal diabetes and obesity with type 2 diabetes in youth: the SEARCH Case–Control Study. *Diabetes Care* **31**, 1422–1426 (2008).
33. Krishnaveni, G. V. *et al.* Intrauterine exposure to maternal diabetes is associated with higher adiposity and insulin resistance and clustering of cardiovascular risk markers in Indian children. *Diabetes Care* **33**, 402–404 (2010).
34. Whitaker, R. C., Pepe, M. S., Seidel, K. D., Wright, J. A. & Knopp, R. H. Gestational diabetes and the risk of offspring obesity. *Pediatrics* **101**, E9 (1998).
35. Catalano, P. M. *et al.* Perinatal risk factors for childhood obesity and metabolic dysregulation. *Am. J. Clin. Nutr.* **90**, 1303–1313 (2009).
36. Dabelea, D. *et al.* Intrauterine exposure to diabetes conveys risks for type 2 diabetes and obesity: a study of discordant sibships. *Diabetes* **49**, 2208–2211 (2000).
37. Silverman, B. L., Rizzo, T. A., Cho, N. H. & Metzger, B. E. Long-term effects of the intrauterine environment. The Northwestern University Diabetes in Pregnancy Center. *Diabetes Care* **21** (Suppl. 2), B142–B149 (1998).
38. Crume, T. L. *et al.* The impact of *in utero* exposure to diabetes on childhood body mass index growth trajectories: the EPOCH study. *J. Pediatr.* **158**, 941–946 (2011).
39. Nathan, D. M. *et al.* Medical management of hyperglycaemia in type 2 diabetes mellitus: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* **32**, 193–203 (2009).
40. [No authors listed] Screening for gestational diabetes mellitus: U. S. Preventive Services Task Force recommendation statement. *Ann. Intern. Med.* **148**, 759–765 (2008).
41. Scott, D. A., Loveman, E., McIntyre, I. & Waugh, N. Screening for gestational diabetes: a systematic review and economic evaluation. *Health Technol. Assess.* **6**, 1–161 (2002).
42. Canadian Task Force on the Periodic Health Examination. *The Canadian Guide to Clinical Preventive Health Care*, 15–23 (Health Canada, Ottawa, 1994).
43. Crowther, C. A. *et al.* Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. *N. Engl. J. Med.* **352**, 2477–2486 (2005).

44. Landon, M. B. *et al.* A multicenter, randomized trial of treatment for mild gestational diabetes. *N. Engl. J. Med.* **361**, 1339–1348 (2009).
45. Horvath, K. *et al.* Effects of treatment in women with gestational diabetes mellitus: systematic review and meta-analysis. *BMJ* **340**, c1395 (2010).
46. Ohno, M. S., Sparks, T. N., Cheng, Y. W. & Caughey, A. B. Treating mild gestational diabetes: a cost-effectiveness analysis. *Am. J. Obstet. Gynecol.* **205**, 282.e1–282.e7 (2011).
47. Tuomilehto, J. *et al.* Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N. Engl. J. Med.* **344**, 1343–1350 (2001).
48. Buchanan, T. A. *et al.* Preservation of pancreatic beta-cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk Hispanic women. *Diabetes* **51**, 2796–2803 (2002).
49. Knowler, W. C. *et al.* Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N. Engl. J. Med.* **346**, 393–403 (2002).
50. Chaisson, J. L. *et al.* Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. *Lancet* **359**, 2072–2077 (2002).
51. Gerstein, H. C. *et al.* Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: randomised controlled trial. *Lancet* **368**, 1096–1105 (2006).
52. DeFronzo, R. A. *et al.* Pioglitazone for diabetes prevention in impaired glucose tolerance. *N. Engl. J. Med.* **364**, 1104–1115 (2011).
53. Buchanan, T. A. (How) can we prevent type 2 diabetes? *Diabetes* **56**, 1502–1507 (2007).
54. Xiang, A. H. *et al.* Effect of pioglitazone on pancreatic beta-cell function and diabetes risk in Hispanic women with prior gestational diabetes. *Diabetes* **55**, 517–522 (2006).
55. Ratner, R. E. *et al.* Prevention of diabetes in women with a history of gestational diabetes: effects of metformin and lifestyle intervention. *J. Clin. Endocrinol. Metab.* **93**, 4774–4779 (2008).
56. Pettitt, D. J. & Knowler, W. C. Long-term effects of the intrauterine environment, birth weight, and breast-feeding on Pima Indians. *Diabetes Care* **21** (Suppl. 2), B138–B141 (1998).
57. Mayer-Davis, E. J. *et al.* Breast-feeding and type 2 diabetes in the youth of three ethnic groups: the SEARCh for diabetes in youth case–control study. *Diabetes Care* **31**, 470–475 (2008).
58. Gillman, M. W. *et al.* Effect of treatment of gestational diabetes on obesity in the next generation. *Diabetes Care* **33**, 964–968 (2010).
59. Rowan, J. A., Hague, W. M., Gao, W., Battin, M. R. & Moore, P. M. Metformin versus insulin for treatment of gestational diabetes. *N. Engl. J. Med.* **358**, 2003–2015 (2008).
60. Rowan, J. A. *et al.* Metformin in gestational diabetes: the offspring follow-up (MiG TOFU): body composition at 2 years of age. *Diabetes Care* **34**, 2279–2284 (2011).
61. Knopp, R. H., Magee, M. S., Raisys, V. & Benedetti, T. Metabolic effects of hypocaloric diets in management of gestational diabetes. *Diabetes* **40** (Suppl. 2), 165–171 (1991).
62. Peterson, C. M. & Jovanovic-Peterson, L. Percentage of carbohydrate and glycemic response to breakfast, lunch, and dinner in women with gestational diabetes. *Diabetes* **40** (Suppl. 2), 172–174 (1991).
63. Clapp, J. F. 3rd. Effect of dietary carbohydrate on the glucose and insulin response to mixed caloric intake and exercise in both nonpregnant and pregnant women. *Diabetes Care* **21** (Suppl. 2), B107–B112 (1998).
64. Major, C. A., Henry, M. J., De Veciana, M. & Morgat, M. A. The effects of carbohydrate restriction in patients with diet-controlled gestational diabetes. *Obstet. Gynecol.* **91**, 600–604 (1998).
65. de Veciana, M. *et al.* Postprandial versus preprandial blood glucose monitoring in women with gestational diabetes mellitus requiring insulin therapy. *N. Engl. J. Med.* **333**, 1237–1241 (1995).
66. Naylor, C. D., Sermer, M., Chen, E. & Sykora, K. Cesarean delivery in relation to birth weight and gestational glucose tolerance: pathophysiology or practice style? *JAMA* **275**, 1165–1170 (1996).
67. [No authors listed] Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study: associations with neonatal anthropometrics. *Diabetes* **58**, 453–459 (2009).
68. Kjos, S. L. *et al.* A randomized controlled trial utilizing glycemic plus fetal ultrasound parameters versus glycemic parameters to determine insulin therapy in gestational diabetes with fasting hyperglycemia. *Diabetes Care* **24**, 1904–1910 (2001).
69. Buchanan, T. A. *et al.* Use of fetal ultrasound to select metabolic therapy for pregnancies complicated by mild gestational diabetes. *Diabetes Care* **17**, 275–283 (1994).
70. Langer, O. *et al.* Glycemic control in gestational diabetes mellitus—how tight is tight enough: small for gestational age versus large for gestational age? *Am. J. Obstet. Gynecol.* **161**, 646–653 (1989).
71. Bung, P., Artal, R., Khodiguian, N. & Kjos, S. Exercise in gestational diabetes. An optional therapeutic approach? *Diabetes* **40** (Suppl. 2), 182–185 (1991).
72. Jovanovic-Peterson, L. & Peterson, C. M. Is exercise safe or useful for gestational diabetic women? *Diabetes* **40** (Suppl. 2), 179–181 (1991).
73. Langer, O., Conway, D. L., Berkus, M. D., Xenakis, E. M. & Gonzales, O. A comparison of glyburide and insulin in women with gestational diabetes mellitus. *N. Engl. J. Med.* **343**, 1134–1138 (2000).
74. Kjos, S. L. *et al.* Predicting future diabetes in Latino women with gestational diabetes. Utility of early postpartum glucose tolerance testing. *Diabetes* **44**, 586–591 (1995).
75. Kim, C., Newton, K. M. & Knopp, R. H. Gestational diabetes and the incidence of type 2 diabetes: a systematic review. *Diabetes Care* **25**, 1862–1868 (2002).
76. Hattersley, A. T. & Pearson, E. R. Minireview: pharmacogenetics and beyond: the interaction of therapeutic response, beta-cell physiology, and genetics in diabetes. *Endocrinology* **147**, 2657–2663 (2006).
77. Nathan, D. M. *et al.* Impaired fasting glucose and impaired glucose tolerance: implications for care. *Diabetes Care* **30**, 753–759 (2007).
78. Peters, R. K., Kjos, S. L., Xiang, A. & Buchanan T. A. Long-term diabetogenic effect of a single pregnancy in women with previous gestational diabetes mellitus. *Lancet* **347**, 227–230 (1996).
79. Ehrlich, S. F. *et al.* Change in body mass index between pregnancies and the risk of gestational diabetes in a second pregnancy. *Obstet. Gynecol.* **117**, 1323–1330 (2011).
80. Kjos, S. L. *et al.* Oral contraception and the risk of type 2 diabetes mellitus in Latina women with prior gestational diabetes. *JAMA* **280**, 533–538 (1998).
81. Xiang, A. H., Kawakubo, M., Kjos, S. L. & Buchanan, T. A. Long-acting injectable progestin contraception and risk of type 2 diabetes in Latino women with prior gestational diabetes mellitus. *Diabetes Care* **29**, 613–617 (2006).

Author contributions

T. A. Buchanan researched data, wrote and reviewed and/or edited the article before submission. A. H. Xiang and K. A. Page provided a substantial contribution to discussions of the content, wrote and reviewed and/or edited the manuscript before submission.