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MINIREVIEWS

Gestational diabetes: A clinical update

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Abstract

Gestational diabetes mellitus (GDM) is increasing in prevalence in tandem with the dramatic increase in the prevalence of overweight and obesity in women of childbearing age. Much controversy surrounds the diagnosis and management of gestational diabetes, emphasizing the importance and relevance of clarity and consensus. If newly proposed criteria are adopted universally a significantly growing number of women will be diagnosed as having GDM, implying new therapeutic challenges to avoid foetal and maternal complications related to the hyperglycemia of gestational diabetes. This review provides an overview of clinical issues related to GDM, including the challenges of screening and diagnosis, the pathophysiology behind GDM, the treatment and prevention of GDM and the long and short term consequences of gestational diabetes for both mother and offspring.

Key words: Gestational diabetes; Diagnostic criteria; Treatment; Complications

Core tip: Gestational diabetes is increasing in prevalence coincidently with the dramatic increase in the prevalence of overweight and obesity in women of childbearing age. Much controversy surrounds the diagnosis and management of gestational diabetes, making it an important subject to discuss as the risk of foetal and maternal complications are increased in gestational diabetes. This review provides an overview of issues related to gestational diabetes, including the challenges of screening and diagnosis, the pathophysiology behind gestational diabetes, the treatment and prevention of gestational diabetes and the long and short term consequences of gestational diabetes for both mother and offspring.

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INTRODUCTION

Gestational diabetes mellitus (GDM) occurs in about 5% of pregnancies but figures vary considerably depending upon the criteria used and demographic characteristics of the population. The prevalence is expected to increase as the epidemic of obesity continues[1]. Pregnancies affected by GDM impose a risk for both mother and child as the risk of cesarean and operative vaginal delivery, macrosomia, shoulder dystocia, neonatal hypoglycemia and hyperbilirubinemia is increased[2]. Women with a history of GDM are also at an increased risk of developing type 2 diabetes mellitus (T2DM) in the years following their pregnancy and their children have a higher risk of developing obesity and T2DM early in life[3].

For those reasons it is important to pay rigorous attention to GDM and the purpose of this review is therefore to cover a wide range of clinical issues related to GDM, including the challenges of epidemiology, diagnostic criteria and screening, the pathophysiology of GDM, the treatment and prevention of GDM and the long and short term consequences of GDM for both mother and child.

EPIDEMIOLOGY

It is problematic to determine the true prevalence of GDM. The prevalence varies worldwide and even within a country's population, depending on the racial and ethical composition of the residents. Accordingly, in the United States the prevalence is higher amongst African American, Hispanic American, Native American, Pacific Islander, and South or East Asian women than in Caucasian women[4]. Furthermore the prevalence of GDM differs depending on the variety of screening strategies (universal or selective), diagnostic criteria and the prevalence of T2DM in any specific country. While data from western countries are frequently reported, data from developing countries are sparse. Recently Jiwani *et al*[5] and Macaulay *et al*[6] tried to determine the prevalence of GDM worldwide, including developing countries. The prevalence was found to be ranging from < 5% in countries such as Pakistan, Belgium, Denmark, Estonia, Ireland, South Korea, South Africa and United Kingdom, to < 10% in Italy, Turkey, Brazil, United States, Morocco and Australia, to a prevalence as high as 20% in Bermuda and Nepal. A recent report from the International Diabetes Federation estimated that worldwide 16% of live births in 2013 were complicated by hyperglycemia during pregnancy[7] and it is most likely that the prevalence of GDM will increase due to the increase in risk factors like obesity and physical inactivity.

SCREENING AND DIAGNOSIS

Recently the American Diabetes Association (ADA) defined GDM as "diabetes diagnosed during pregnancy that is not clearly overt diabetes"[8]. Screening and diagnostic testing for GDM is however important in order to identify the women at risk for developing GDM and thereby reduce or prevent the risk of adverse events for both mother and child associated with GDM.

In most countries a selective screening is carried out, using parameters such as previous GDM, previous large for gestational age babies, diabetes (of any kind) in first degree relatives, pre-pregnancy adipositas, belonging to a particular ethnic group associated with a high prevalence of GDM, glucosuria, and high maternal age. By using selective screening there is a risk of missing GDM cases. On the other hand, selective screening could help to concentrate medical resources on subjects with the highest risk of complications.

Also, screening for preexisting diabetes in the very early weeks of pregnancy by the measurement of a fasting glucose is warranted. This is important because of the rising prevalence of T2DM at younger ages. Accordingly there is an increasing number of young women in their twenties and thirties presenting with undiagnosed preexisting T2DM.

Pregnant women have a higher physiological turnover of erythrocytes, rendering glycosylated hemoglobin (HbA1c) inadequate as a diagnostic tool, because of underestimation of the average glucose level. In fact a reduction of HbA1c is seen in normal pregnancy[9] Instead, a variety of oral glucose tolerance tests (OGTT) have been applied, but a consensus regarding screening for and classification of GDM is yet to be achieved globally[10]. However, a 2-h 75 g OGTT at 24-28 wk of gestation is now being recommended both by the European Association for the Study of Diabetes, International Association of Diabetes and Pregnancy Study Group (IADPSG), ADA and World Health Organization (WHO)[6].

The HAPO study recently demonstrated that no specific threshold for the risk of adverse events for both mother and child associated with GDM can be set as the risk increase is continuous[11]. Other studies[12-14] have supported the idea of lowering the diagnostic threshold in the diagnostic criteria for GDM, taking the maternal and foetal risks of hyperglycemia into consideration. In 2010 the IADPSG outlined new diagnostic criteria for GDM[15] based on the knowledge achieved in the HAPO study. This new guideline from IADPSG was adopted by the WHO in 2013[16] and ADA in 2014[8] and is based on the risk of adverse pregnancy outcomes As shown in Table 1 the threshold for a positive test is exceedance of one of the following three plasma glucoses; fasting plasma glucose ⩾ 5.1 mmol/L (⩾ 92 mg/dL), 1 h ⩾ 10.0 mmol/L (180 mg/dL), or 2 h ⩾ 8.5 mmol/L (153 mg/dL)[15]. In comparison the WHO recommended threshold in 1999 was fasting plasma glucose ⩾ 7.0 mmol/L (126 mg/dL) and in 1985 fasting plasma glucose ⩾ 7.8 mmol/L (140 mg/dL)[6].

It has been estimated that with this new diagnostic criteria the prevalence of GDM will increase to nearly 18%[11], which will have a major impact on the costs, the capacity of the health care systems, and the pathologization of pregnancies that were earlier categorized as normal. The vast majority of the women diagnosed with

Table 1 New (2013) World Health Organization recommendations for the diagnosis of gestational diabetes based on the general principles behind how the IADPSG criteria were derived

Gestational diabetes mellitus should be diagnosed at any time in pregnancy if one or more of the following criteria are met	
Fasting plasma glucose	5.1-6.9 mmol/L (92-125 mg/dL)
1-h plasma glucose following a 75 g oral glucose load	≥ 10.0 mmol/L (180 mg/dL)
2-h plasma glucose following a 75 g oral glucose load	8.5-11.0 mmol/L (153-199 mg/dL)

If fasting plasma glucose ≥ 7.0 mmol/L (126 mg/dL), and/or 2-h plasma glucose ≥ 11.1 mol/L (200 mg/dL) and/or random plasma glucose ≥ 11.1 mol/L (200 mg/dL) in the presence of diabetes symptoms overt diabetes is diagnosed.

GDM will however have mild hyperglycemia, requiring non-pharmaceutical treatment, including lifestyle modifications.

PATHOPHYSIOLOGY

In normal pregnancy, maternal tissues become progressively insensitive to insulin. This is believed to be caused partly by hormones from the placenta and partly by other obesity and pregnancy related factors that are not fully understood.

Skeletal muscle and adipose tissue are the main whole-body glucose disposable sites. In normal pregnancy, insulin-mediated whole-body glucose disposal decreases by 50% and in order to maintain a euglycemic state, the woman must increase her insulin secretion by 200%-250%[17].

GDM develops when the pregnant woman is not able to produce an adequate insulin response to compensate for this normal insulin resistance.

GDM is observed in obese as well as in lean women. However, the pathophysiology behind the disease is believed to differ between these groups. In obese women, the pathophysiology is primarily characterized by the pregnancy-induced insulin resistance being amplified by the already elevated pre-pregnant insulin resistance level. The elevated insulin resistance level is a known factor in the metabolic syndrome. In lean women, the same factors seem to play a role but a defect in the first-phase insulin response contributes to a larger extend[18].

These defects culminate in a disruption of the action of insulin in maintaining glucose levels, resulting in maternal hyperglycaemia. Glucose is transferred *via* the placenta to the fetus. Maternal hyperglycaemia therefore stimulates a foetal hyperinsulinaemia to counter the excess placental glucose transfer. The high insulin level in the fetus stimulates growth which results in foetal macrosomia (birth weight over 4000 g)[19].

RISK FACTORS FOR DEVELOPING GDM

There is a range of established risk factors for GDM, chief amongst which are the following. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study reported that a higher pre-pregnant BMI and the BMI at 28 wk are strongly correlated to increased insulin resistance at 28 wk[11]. Adipose tissue is, like the placenta, believed to produce a large amount of diabetogenic adipokines. Especially the adipokine TNF-α, which the placenta likewise produces, is suspected to play an important role in insulin resistance pathways. This could be one explanation to the elevated pre-pregnant insulin resistance level seen in obese women[20].

As mentioned previously, ethnicity seems to play an important role as well. Berkowitz *et al*[21] reported that the United States Native Americans, Asians, Hispanics, and African-American women have a higher risk of GDM compared to non-Hispanic white women. In addition studies have shown that women from Asia are at very high risk of developing GDM and the increased insulin resistance is observed at much lower BMI levels when compared to European women. Retnakaran *et al*[22]. reported that Asian women's pre-pregnancy BMI has a greater influence on the pregnancy related insulin resistance than that of Caucasian women.

Cypryk *et al*[23] reported that maternal age over 25 years and previous GDM are strongly correlated to development of GDM. These findings are in agreement with other authors[23-25]. In addition Polycystic Ovary Syndrome, multiparity, twin pregnancy and a family history of diabetes are well known risk factors[26].

COMPLICATIONS DURING PREGNANCY AND BIRTH

Women with GDM are at higher risk of hypertensive disorders including gestational hypertension, preeclampsia, and eclampsia. In the HAPO study, 5.9% had gestational hypertension and 4.8% had preeclampsia. The study showed that the glucose level at the first glucose tolerance test was positively correlated with the risk of preeclampsia[27]. Likewise, Rowan *et al*[28] reported that 5% had gestational hypertension and 6.3% had preeclampsia.

The HAPO study, found a direct correlation between Cesarean section rate and maternal glycemia with an overall frequency of 23.7%[27]. Gorgal *et al*[28] reported a non-elective cesarean section rate for women with GDM of 19.5% compared to 13.5% for non-diabetic women.

Macrosomia in newborns of diabetic mothers is characterized by increased body fat[16]. The IADPSG study found that percentage of body fat in newborns, maternal glycemia and foetal insulin levels estimated by cord C-peptide level were strongly positively correlated[15]. Thus maternal glycemia is directly related to neonatal adiposity. Although rare, shoulder dystocia is a serious complication of childbirth. A clear association between increased foetal size and the risk of shoulder dystocia has been shown once the birth weight exceeds 4 kg[29].

In older studies, the risk of stillbirth was increased fourfold[30]. In more recent studies, this risk is found to

be lower; probably due to the initiation of monitoring and treatment of GDM. In the HAPO study, there was no increased risk of prenatal death with increased maternal glucose levels[11]. In comparison, Crowther *et al*[31] observed five deaths in the Routine Care Group and none in the Treatment Group.

MATERNAL LONG-TERM CONSEQUENCES OF GDM

GDM is not only associated with adverse pregnancy outcomes, such as macrosomia, increased caesarian section rates, hypertensive disorders and foetal hyperinsulinaemia[32,33], but also significantly increases the risk for long-term problems for both mothers and their offspring.

T2DM

Women who have had GDM have a substantially increased risk for development of T2DM, even though most women return to a euglycaemic state shortly after delivery[34-36]. The evidence of this association is massive, but the magnitude of the risk varies among studies, primarily explained by differences in length of follow-up, number of women participating in follow-up, diagnostic criteria and in the selection of the population[37]. A Danish study found that 40% of women with diet-treated GDM had developed diabetes 10 years after the index pregnancy. Compared to the 30-60-year-old females in the background population, the incidence of diabetes was increased 10 fold[36]. A systematic review of 20 studies found an at least 7 fold increase in the risk of developing T2DM, when comparing women with a pregnancy complicated by GDM to women with a normoglycaemic pregnancy[34]. In conclusion, GDM is one of the most predictive factors for the development of T2DM later in life. These women should be followed up with an OGTT 2-3 mo after delivery and then a yearly follow-up, ideally with an OGTT. Furthermore, a yearly fasting glucose test will allow detection of the development of T2DM early in these women.

The specific biological link between GDM and T2DM remains unclear. Both disorders are characterized by insulin resistance and/or abnormal insulin secretion. In addition studies provide evidence that several of the known T2DM risk genes are more frequent in women with previous GDM[38], and many of the risk factors are the same, such as a raised body-mass index, high age, family history of diabetes and Asian and black ethnicity[37,39]. It thus appears plausible that the pathogenesis is overlapping, and GDM may serve to identify women at high risk of future T2DM[34,36].

Metabolic syndrome and cardiovascular disease

GDM may also increase a woman's risk of the metabolic syndrome and cardiovascular disease (CVD) postpartum. The metabolic syndrome is characterized by several risk factors, including central obesity, hypertension, insulin resistance and dyslipidemia. These risk factors are also associated with the development of CVD and T2DM, and the metabolic syndrome has been demonstrated to increase the risk of both outcomes[40]. The abnormalities of the metabolic syndrome and a high risk health profile are more frequent among women with previous GDM. The prevalence of the metabolic syndrome is found to be 3 times as frequent in Danish women with previous diet-treated GDM compared to population-based and age-matched control women[41]. Another study has demonstrated that the 3 mo postpartum prevalence of the metabolic syndrome increases progressively from 10% in women with normoglycaemic pregnancies to 17.6% in women with gestational impaired glucose tolerance and to 20% in women with previous GDM[42]. These results suggest that dysglycemia in pregnancy may provide an opportunity to detect otherwise unrecognized risk conditions, such as the metabolic syndrome and consequently allow targeted intervention to prevent diabetes and CVD.

The risk of CVD is found to be approximately 70% higher in women with previous GDM compared with women having normoglycaemic pregnancies when followed for 11.5 years after the index pregnancy[43]. The increased risk may also extend to women with only mild glucose intolerance during pregnancy[44]. When adjusting for the incidence of T2DM, the association was attenuated in both studies.

The increased risk of CVD in women with prior GDM is attributable to several interacting factors, primarily including the development of overt T2DM and the increased risk of the metabolic syndrome and vascular dysfunction[44]. Therapeutic interventions to prevent the development of T2DM may therefore reduce the risk of CVD, and a potential modification of cardiovascular risk factors may also help to prevent development of CVD in women with a history of GDM.

LONG TERM EFFECTS IN OFFSPRING OF WOMEN WITH GDM

Offspring of women with a history of GDM are also at increased long-term risk of developing metabolic diseases such as obesity, T2DM and the metabolic syndrome. This long-term risk depends on genetic susceptibility and is further modulated by the postnatal environment. In recent years focus has been on the phenomenon of epigenetic transmission of acquired characteristics from mother to child due to perinatal programming of the fetus[45]. Maternal glucose easily crosses the placenta and as a consequence maternal hyperglycemia leads to intrauterine hyperglycemia, which induces foetal hyperinsulinemia and possible modification of growth and future metabolism of the fetus (fuel-mediated teratogenesis)[46,47]. Also worth noticing, is the finding that the relation between birth weight and risk of T2DM is U-shaped and therefore both infants with decreased and those with increased birth weight are at increased

risk of developing T2DM as compared to persons being born with a normal birth weight[48].

Animal studies have convincingly shown that intrauterine exposure to maternal diabetes is associated with an increased risk of abnormal glucose tolerance, diabetes and obesity in offspring[49]. Although it is difficult to study the effect of intrauterine hyperglycemia separately from a genetic effect in humans observational studies among the Pima Indians have added evidence for an epigenetic mode of diabetes transmission. Thus children of diabetic mothers had a 6 fold increased risk of developing T2DM compared to children born to non-diabetic mothers[50]. Another study conducted in the Pima Indian population strengthened this association by showing a higher incidence of diabetes in siblings born after a maternal diagnosis of diabetes compared to a sibling born before the maternal diagnosis of diabetes (OR: 3.0, $P < 0.01$), which partly eliminates the genetic disposition. A greater frequency of diabetes is also seen in offspring of mothers with T2DM than offspring of T2DM fathers[51]. These results are not directly applicable to other populations, as Pima Indians have a remarkably high incidence of T2DM, but they clarify the importance of intrauterine exposure to hyperglycemia, even within a population with a strong genetic inheritance of T2DM[51].

A Danish long-term follow-up study based primarily on a Caucasian population found a high prevalence of T2DM and pre-diabetes in adult offspring of mothers with diet-treated GDM and in offspring of mothers with type 1 diabetes compared with the background population [Adjusted OR: 7.76 (95%CI: 2.58-23.39) *vs* 4.02 (95%CI: 1.31-12.33)]. These findings support the hypothesis that a hyperglycemic intrauterine environment plays a role in the pathogenesis of T2DM[52] and are in accordance with earlier studies on children with a mixed ethnic composition, finding a similar prevalence of impaired glucose tolerance in offspring born to mothers with GDM[53,54]. T2DM is characterized by both reduced insulin sensitivity and impaired B-cell function, but little is known about how these precursors are changed in the offspring after an exposure to maternal hyperglycemia in pregnancy. A recent study found that offspring exposed to intrauterine hyperglycemia due to GDM, primarily have reduced insulin sensitivity, but also a significantly lower relative insulin release taking insulin sensitivity into account (disposition index) when compared with the background population. The absolute insulin release did not differ significantly between the groups[55].

Two other possible long-term consequences of pregnancies complicated by GDM is the development of the metabolic syndrome and obesity in the offspring. Development of obesity in offspring exposed to maternal diabetes in utero is found in the Pima Indian population, where the mean BMI was 2.6 kg/m^2 higher in offspring born to diabetic mothers compared to offspring born to non-diabetic mothers[51]. This association is also seen in the multi-ethnic EPOCH study, where children of mothers with primarily GDM had a higher increase in BMI growth velocity than unexposed controls, with the increase starting at the age of 10 to 13[56]. According to a recent study, offspring of Caucasian women with GDM had a 2-fold increased risk of developing obesity and a 4-fold increased risk of the metabolic syndrome compared to the background population. This study also concludes that genetics play a major role in the development of the metabolic syndrome and obesity together with an effect of intrauterine hyperglycemia[57]. The prevalence of obesity increases worldwide among all age groups and some of the predisposition to obesity in children may be due to epigenetic foetal programming. Randomized trials are needed to clarify the possible causal relationship between maternal hyperglycemia in pregnancy and the mentioned cardiovascular risk factors in human offspring.

TREATMENT OF GDM

Recently two large randomized controlled trials have been carried out to prove that identification and treatment of GDM and even mild carbohydrate intolerance during pregnancy confer a benefit. Thus the Australian Carbohydrate Intolerance Study in Pregnant Women, a large, randomized trial of treatment for gestational diabetes mellitus, concluded that treatment reduces serious perinatal complications and may also improve health-related quality of life using treatment of gestational diabetes in the form of dietary advice, blood glucose monitoring, and insulin therapy as required for glycemic control[31]. The American Maternal-Fetal Medicine Units Network study provided further compelling evidence that among women who have GDM and normal fasting glucose levels, treatment that includes dietary intervention and insulin therapy, as necessary, reduces rates of foetal overgrowth, cesarean delivery, and preeclampsia[58].

Accordingly, the primary intervention recommended to women diagnosed with GDM is dietary counseling in combination with physical activity and self-monitoring of blood glucose[59,60]. If these measures are insufficient in terms of achieving optimal glycemic control subcutaneous insulin therapy is the therapy of choice as insulin does not cross the placenta and is therefore considered harmless to the foetus. However insulin is relatively expensive and difficult to administer. It requires education to ensure a safe administration and it is associated with an increased risk of hypoglycemia and weight gain. The use of safe and effective oral agents may therefore offer advantages over insulin but has not yet been formally approved for GDM therapy in all countries[61]. A large randomized controlled trial was performed by Rowan *et al*[62] in which 751 women with GDM at 20 to 33 wk of gestation were assigned to open treatment with metformin or insulin if lifestyle intervention had failed to achieve glycemic control. Three hundred and sixty-three women were assigned to metformin. 92.6% continued to receive Metformin until delivery and 46.3% in the Metformin group received supplemental insulin. The authors concluded that metformin, alone or with supplemental insulin, was not associated with increased

perinatal complications as compared with insulin. Thus the treatment with Metformin was considered safe and effective and moreover, the women preferred metformin to insulin treatment. Further follow-up data are however necessary to establish long-term safety.

Another randomized controlled trial included 404 women between 11 and 33 wk of gestation with singleton pregnancies and GDM that required treatment and assigned them to either glyburide or insulin. All the women received dietary advice and eight women in the glyburide group required additional insulin therapy. There were no significant differences between the glyburide and insulin groups regarding macrosomia, neonatal hypoglycemia, lung complications or foetal abnormalities and it was concluded that glyburide is a clinically effective alternative to insulin therapy[63].

Other studies show that both metformin and sulfonylurea have been increasingly and safely used in the treatment of GDM[64]. However, both glyburide and metformin cross the placenta and given the growing evidence of epigenetic foetal programming in utero, administration of drugs potentially affecting foetal metabolism is of major concern and as long term follow-up data on both mother and offspring are lacking oral antihyperglycemic agents should be used with caution.

Vitamin D and GDM

A growing body of epidemiological evidence suggests a possible association between vitamin D deficiency/insufficiency and GDM, maternal obesity and adverse maternal, neonatal and infant outcome[65]. The molecular and cellular mechanisms with respect to the interaction between vitamin D and GDM are only partly understood. However, it appears that vitamin D acts directly on pancreatic beta cells through expression of the vitamin D receptors as well as through the enzyme 25(OH)D-1-alfa-hydroxylase by regulating intracellular calcium to increase insulin secretion and by attenuating systemic inflammation associated with insulin resistance[66,67]. The association between vitamin D and glucose metabolism in GDM has been investigated in several observational studies[65] but large randomized controlled trials are lacking and it remains to be determined whether vitamin D supplementation can reduce the risk of developing GDM and/or improve glycemic control in diabetic pregnant women with vitamin D deficiency/insufficiency.

As stated above lifestyle counseling concerning diet and exercise is one of the cornerstones in the treatment of GDM, but recently it was also reported that a healthful diet was associated with a lower risk of T2DM among women with a history of GDM[68]. Additionally, newly published results from a large prospective study indicate that increasing physical activity may help lower the risk of progression from GDM to T2DM[69].

CONCLUSION

Worldwide there has been a dramatic increase in the prevalence of overweight and obesity in women of childbearing age. Overweight and obese women have an increased risk of developing GDM leading to complications during pregnancy, birth and neonatally. The clinical management of obese pregnant women and women with GDM is a challenge and puts additional stress on the healthcare system. In addition it seems more and more clear that maternal metabolic characteristics are crucial determinants of insulin resistance during pregnancy and in offspring and interventions, especially in the form of exercise, weight loss and a healthy diet before, during and after pregnancy might be a key to prevent the vicious circle that contributes to the epidemic of obesity, insulin resistance and T2DM.

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