

ENDOCRINOLOGY OF PREGNANCY

Gestational diabetes mellitus: definition, aetiological and clinical aspects

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Abstract

Gestational diabetes (GDM) is defined as a glucose intolerance resulting in hyperglycaemia of variable severity with onset during pregnancy. This review aims to revisit the pathogenesis and aetiology of GDM in order to better understand its clinical presentation and outcomes. During normal pregnancy, insulin sensitivity declines with advancing gestation. These modifications are due to placental factors, progesterone and estrogen. In a physiological situation, a compensatory increase in insulin secretion maintains a normal glucose homeostasis. GDM occurs if pancreatic β -cells are unable to face the increased insulin demand during pregnancy. GDM is most commonly a forerunner of type 2 diabetes (T2D) – the most prevalent form of diabetes. These women share similar characteristics with predisposed subjects to T2D: insulin resistance before and after pregnancy, and carry more T2D risk alleles. Auto-immune and monogenic diabetes are more rare aetiologies of GDM. Adverse pregnancy outcomes of GDM are mainly related to macrosomia caused by fetal hyperinsulinism in response to high glucose levels coming from maternal hyperglycaemia. Screening recommendations and diagnosis criteria of GDM have been recently updated. High risk patients should be screened as early as possible using fasting plasma glucose, and if normal, at 24–28 weeks of gestation using 75 g oral glucose tolerance test. The treatment of GDM is based on education with trained nurses and dieticians, and if necessary insulin therapy.

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In humans, normal glucose tolerance is maintained because of a balance between adequate insulin secretion and insulin sensitivity. The secretory response of the pancreatic β -cells to glucose (particularly in the early phase) and the sensitivity of the glucose utilizing tissues to insulin determine the ability of insulin to dispose of carbohydrates (1). In individuals with the same degree of glucose tolerance, the product of insulin sensitivity and insulin secretion is constant and the relationship between

the two variables follows an approximate hyperbola (2). This constant is termed the disposition index; it reflects the ability of the β -cell to compensate for insulin resistance. It is now well recognized that abnormal glucose tolerance occurs when the pancreatic β -cells output do not meet tissues insulin needs in response to changes in insulin resistance (3, 4).

GDM is defined as a glucose intolerance resulting in hyperglycaemia of variable severity with onset or first

Invited Author's profile

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recognition during pregnancy (5). GDM prevalence is influenced by several factors like the population studied and the diagnostic tests employed (6, 7). Prevalence in Northern Europe ranges from 0.6% in The Netherlands to 3.6% in Denmark. It is higher in Italy (6.3%) (8). In the USA, 7% of all pregnancies are complicated by GDM (9). GDM prevalence (6) was 2.4 times higher using the most recent International Association of Diabetes in Pregnancy Study Group (IADPSG) criteria compared to the World Health Organization (WHO) 1999 criteria. Using the new criteria, GDM prevalence ranged between 9 and 26% in the 15 centers that participated in the hyperglycemia and adverse pregnancy outcome (HAPO) study, a large international observational study (10).

Adverse pregnancy outcomes of GDM are mainly related to macrosomia caused by fetal hyperinsulinism in response to high glucose levels coming from maternal hyperglycaemia. In pre-gestational diabetes, which is when diabetes pre-exists to pregnancy, there is also a risk of fetal malformation due to the teratogenicity effect of glucose and/or its associated metabolic abnormalities at a crucial period for organogenesis in early gestation (11). In this article, we will describe glucose homeostasis during normal pregnancy and discuss the pathogenesis and aetiologies of GDM. We will also address the consequences in adult offspring who were exposed *in utero* to GDM. Diagnosis criteria of GDM will also be discussed in light of the recent recommendations from the IADPSG in 2010 (12), which has been endorsed by the American Diabetes Association (ADA) (13) and more recently by WHO (14).

Mechanism of glucose regulation during normal pregnancy

Fasting blood glucose decreases at early pregnancy and continuously during gestation (15). Insulin sensitivity declines with advancing gestation to reach at late gestation (34–36 weeks) 50–60% of pre-gravid state (16). As a reflection of insulin resistance occurrence, fasting insulin concentrations increase. The changes in insulin sensitivity are inversely related to changes in maternal body fat mass (17). Hepatic glucose production increases during pregnancy suggest that the defect in insulin action also targets the liver. Catalano *et al.* (18, 19) found a significant increase in basal endogenous glucose production at the end of gestation in spite of the important increase in fasting insulin concentration. Endogenous glucose production remained sensitive to insulin infusion throughout gestation.

Alterations in maternal physiology during pregnancy are mediated by placental factors, as evidenced by the significant increase in maternal insulin sensitivity that occurs within days after delivery (20). Alterations in maternal metabolism have generally been ascribed to placental hormones, such as human placental lactogen (hPL), progesterone and oestrogen (21, 22). Prolactin, progesterone and oestrogens increase during pregnancy (23). The lipolytic effect of hPL allows the re-orientation of maternal metabolism toward lipid rather than glucose utilization, favouring glucose sparing for the foetus. The consequent increase in free fatty acid levels may participate to insulin sensitivity changes occurring during pregnancy as is the case in non-pregnant subjects (24). However, a direct effect of hPL on mother insulin sensitivity has not been demonstrated. In addition, changes in inflammatory circulating factors such as tumour necrosis factor alpha (TNF α) may also be involved in pregnancy-associated insulin resistance (25). Kirwan *et al.* reported that the level of placental TNF α is the most important determinant of insulin resistance during pregnancy independently from fat mass changes (26).

Meanwhile insulin secretion increases as a consequence to the development of insulin resistance. Catalano *et al.* (27) reported in the 1990s that first and second phase insulin secretion increase by almost 300% throughout gestation. This insulin secretion adaptation is probably due to the rise of maternal hormones which coincides with the development of maternal insulin resistance.

In conclusion, the robust plasticity of β -cell function in the face of progressive insulin resistance is the hallmark of normal glucose regulation during pregnancy. Diabetes may occur if pancreatic β -cells are unable to keep up with heightened insulin demand during pregnancy.

Pathogenesis of gestational diabetes

The pathogenesis of GDM has been extensively studied by Catalano *et al.* using euglycaemic hyperinsulinemic clamp techniques and glucose infusion. The conclusion he reported is that women who develop GDM are before pregnancy insulin resistant 1 compared to women who did not develop diabetes during pregnancy (28). The significant decrease in insulin sensitivity in late gestation reflects the decreased insulin sensitivity that exists prior to pregnancy (27). In addition, defects in insulin secretion have been reported during pregnancy and related to the degree of glucose intolerance (29). After, delivery β -cell dysfunction persists and is also correlated with the severity of glucose intolerance during pregnancy (30, 31). In GDM,

circulating TNF α and interleukin 6 (IL6) has been inversely correlated with insulin sensitivity suggesting a role of inflammatory factors in the pathogenesis (25, 32). Other cytokines such as leptin have been found elevated in GDM (33). However, the main determinant of leptin during pregnancy is the pre-gravid maternal weight (34). After pregnancy, insulin sensitivity returns to pre-gravid values (26). Like all forms of hyperglycaemia, GDM is characterized by insulin secretion that is insufficient to meet insulin demands. Thus, pregnancy represents a situation in which undiagnosed diabetes, or rather unknown β -cell failure, is revealed by the physiological occurrence of insulin resistance.

Aetiologies of gestational diabetes

Type 2 diabetes

GDM is most commonly a forerunner of T2D (35). In a meta-analysis from Bellamy *et al.* (35), women with GDM have a sevenfold risk of T2D for several years compared to women with normal glucose tolerance (NGT) during pregnancy. Longitudinal studies longer than 10 years indicate that more than 25% of GDM will develop T2D (36, 37). Women with GDM display insulin resistance before and after pregnancy as in predisposed T2D subjects (38). GDM is found to carry more T2D risk alleles. Lauenborg *et al.* have shown a strong association between ten of 11 studied T2D risk alleles and a history of GDM (39). A *genome-wide association study* performed from the HAPO study shows that among the susceptibility genes, variants of glucokinase (GCK) and TCF7L2 loci are associated with higher glucose levels during oral glucose tolerance tests in pregnant women (40).

Monogenic diabetes

Monogenic form of diabetes may also be revealed during pregnancy. It has also been shown that common variants in maturity onset diabetes of the young (MODY) genes contribute to GDM, like polymorphism of the promoter of GCK and polymorphism of Hepatocyte nuclear factor 1 α (HNF1 α) (41). MODY refers to any of the several forms of hereditary diabetes caused by mutations in an autosomal dominant gene influencing insulin production. One of these forms is MODY 2, which seems to be the most frequently associated with GDM, with a prevalence of around 10% of GDM (42). It is due to mutations of the GCK gene (43). Ellard *et al.* (44), from the UK, reported 12 out of 15 GDM having MODY 2. In this study, the

extremely high prevalence of MODY 2 was due to the fact that genotyping was performed in phenotypically pre-selected women. They all had an abnormal fasting glucose outside pregnancy with a low increment between the fasting and 2-h plasma glucose concentrations on 75 g OGTT. Additionally, included women were insulin treated during at least one pregnancy and they had a history of T2D, GDM or fasting hyperglycaemia in a first-degree relative. Few MODY 3 and MODY 4 have also been reported in GDM women (45, 46).

Type 1 diabetes

Auto-immune diabetes may also be considered as aetiology of GDM. The prevalence of auto-immune markers of type 1 diabetes (T1D) is between 0.98 and 14.7% in women with GDM. It predicts later development of T1D in these women but not necessarily (47). In some studies (48, 49), positive islet cell autoantibodies were not predictive of future diabetes development. Thus GDM may reveal T1D but whether or not antibodies need to be tested in GDM deserves further studies. Autoimmunity was associated with poor pregnancy outcomes (fetal death, preterm delivery and macrosomia) (50).

Other factors

Some factors like ethnicity and race may be at the origin of GDM onset. Jenum *et al.* (6) found that ethnic minority origin, in particular South Asian, is an independent predictor for GDM whatever the criteria used. GDM may result from interaction between genetic and environmental risk factors. Old age, obesity and high fat diet represent some important non-genetic factors (51).

Maternal and fetal complications and outcomes of GDM

The most common maternal outcome of GDM is caesarean section. Another frequently found outcome is preeclampsia which combines gestational hypertension (at least 140/90 mmHg occurring for the first time after mid-pregnancy) and proteinuria (≥ 0.3 g/24 h). In comparison with gestation without metabolic abnormalities, GDM is associated with a 50% increased risk of severe preeclampsia and mild preeclampsia (52, 53, 54, 55).

GDM may lead to fetal complications including fetal hypoglycaemia immediately after delivery when glucose input from the mother is disrupted and the newborn is still hyperinsulinaemic, hypocalcaemia, respiratory

distress, stillbirth and macrosomia associated sometimes with birth trauma (56). Additionally, fetal malformation may occur when hyperglycaemia is present in early pregnancy (first trimester) particularly in unknown pre-GDM (57).

It is important to keep in mind that GDM criteria were defined first by O'sullivan (58). The aim of these criteria was to evaluate the risk of future development of T2D in the mother and not to prevent short term adverse pregnancy outcomes. By contrast, the HAPO Study was designed to assess the relationship between the level of maternal hyperglycaemia with adverse pregnancy outcomes such as caesarean section rates, vascular pregnancy complications, macrosomia and fetal hyperinsulinism (59).

As previously discussed, GDM is a situation that predicts all forms of diabetes later in life particularly T2D, the most prevalent form of diabetes. The progression to T2D in the years after delivery is driven by the worsening of insulin secretion defect (60, 61, 62). Ignell *et al.* (63) evaluated insulin sensitivity after GDM in relation to ethnicity. Women of non-European origin were more insulin resistant than European women and exhibited a higher frequency of diabetes after GDM. The effect of ethnicity on insulin resistance was more pronounced in Asian women after adjustment for BMI, but eradicated among Arab women. In addition to BMI, Asian ethnicity was associated with diabetes after GDM, whereas Arab origin was not.

GDM may predict atherogenic dyslipidemia (64, 65, 66), metabolic syndrome (67, 68, 69) and cardiovascular disease (70).

There is strong evidence that intrauterine exposure to maternal hyperglycaemia is associated with impaired glucose tolerance in 20% of offspring aged 5–9 years old (71) and 10–16 years old (72). Studies in Pima Indians have shown that fetal exposure to maternal T2D are at higher risk of obesity, IGT and T2D in adult offspring (73). In this population, non-diabetic offspring who have been exposed *in utero* to maternal T2D had a decreased insulin secretion with no modification insulin action (74).

Clausen *et al.* (75) found in a follow up study in adult offspring of women with diet-treated GDM and T1D compared to a control group, that intrauterine hyperglycaemia may contribute to the pathogenesis of overweight and the metabolic syndrome, and may be involved in the pathogenesis of T2D/pre-diabetes in adult offspring (76). Both reduced insulin sensitivity and impaired pancreatic β -cell function may explain the increased risk of glucose intolerance among adult offspring (77).

In order to circumvent the genetic confounding effect of T2D, we compared insulin sensitivity and insulin secretion in adult offspring of mothers with T1D (exposed participants) and offspring of T1D fathers (controls). We found that adult offspring of women who had T1D during pregnancy are more likely to have impaired glucose tolerance and a deficient insulin secretory response to glucose (78). We also found that fetal exposure to maternal T1D was associated with a reduced functional renal reserve in offspring at adult age (79) suggesting that fetal exposure to maternal diabetes is associated with multiorgan dysfunction at adult age.

In a cohort of MODY 2 families, Singh *et al.* (80) found that infants from MODY 2 mothers had higher birth weight and even macrosomia (81). If the offspring also carries the GCK mutation, his birth weight is lower probably because his β -cells do not secrete enough insulin as demonstrated in trials conducted in adults (82).

One of the underlying mechanisms linking fetal exposure to maternal diabetes and metabolic diseases in adult offspring may be epigenetic modification as it transmitted across generations in animal studies (83). Studying methylation levels of some imprinted genes in newborn (cord blood) from GDM, El Hajj *et al.* (84) recently found an under-methylation of the maternally imprinted MEST gene. A recent study (85) linked increased maternal-induced methylation at guanine nucleotide binding protein alpha subunit of differentially methylated regions in fetuses of GDM compared to normal pregnancy with increased risk of metabolic diseases in later life of offspring.

Diagnosis of GDM

GDM can be diagnosed by using the same criteria used to diagnose T1D and T2D: a fasting plasma glucose (FPG) concentration of >126 mg/dl on two separate occasions or a random blood glucose concentration of >200 mg/dl on two separate occasions. HbA1c is important to detect pre-gestational diabetes but is often normal in GDM particularly in the first trimester (14).

The predisposing factors for GDM include being part of a specific ethnic group (i.e. Hispanic, African, Native American, Asian); having a BMI of >27 kg/m² before pregnancy; being >25 years old; having a previous diagnosis of GDM; and having a family history of T2D. Most of these risk factors are the same as those of T2D (86, 87).

The first glucose values used to detect GDM were determined by O'Sullivan in 1964 (58) using a 100 g OGTT

Table 1 IADPSG diagnostic criteria for GDM.

	75 g OGTT (IADPSG) latest criteria	75g OGTT (WHO)	100 g OGTT (Carpenter and Coustan (89))
Number of abnormal values required for diagnosis	≥1	≥2	≥2
Fasting glucose mg/dl (mmol/l)	≥92 (5.1)	≥95 (5.3)	≥95 (5.3)
1st h mg/dl (mmol/l)	≥180 (10)	≥180 (10)	≥180 (10)
2nd h mg/dl (mmol/l)	≥153 (8.5)	≥155 (8.6)	≥155 (8.6)
3rd h mg/dl (mmol/l)	–	–	≥140 (7.8)

IADPSG, International Association of Diabetes in Pregnancy Study Group; GDM, Gestational Diabetes; OGTT, Oral Glucose Tolerance Test; WHO, World Health Organization.

in a retrospective cohort study designed to detect risk of developing T2D in the future. Until 2010, screening for GDM involved a 50 g 1 h glucose challenge test (GCT). If the result is positive, a diagnostic 75 g or 100 g OGTT was performed. For diagnosis, two values were required reaching or exceeding the set value to be positive (86).

The ADA recommends screening high risk patients (i.e. those who are obese, have a strong family history of T2D, have a previous pregnancy with GDM or macrosomia, are glucose intolerant, or have glucosuria) as soon as is feasible using a 75 g OGTT and again at 24–28 weeks of gestation if the original screening test result was negative. Low-risk patients require no screening. These are women who meet all of the following criteria: age of <25 years, normal prepregnancy weight, not a member of a high risk ethnic group, no known diabetes in first-degree relatives, no history of abnormal glucose tolerance, and no history of poor obstetric outcomes. Patients at average risk for developing GDM (those not satisfying low risk criteria and not reaching high risk) should be screened at 24–28 weeks of gestation (5, 88).

The HAPO Study (59) reported associations of maternal 'moderate' hyperglycaemia with risks of adverse pregnancy outcome in a very heterogeneous cohort of 25 505 pregnant women from 15 centres in nine countries. This helped to publish the most recent diagnostic criteria by the IADPSG (12) where the same test is used for both screening and diagnosis (Table 1).

In France, it is recommended to screen for GDM as early as possible if there is at least one of four risk factors (BMI >25 kg/m², age >35 years old, first degree family history of diabetes, previous history of GDM or macrosomia). Screening is done by testing FPG followed by a diagnostic 75 g OGTT. If FPG is normal (<0.92 g/l), the

OGTT is done at 24–28 weeks of gestation (90) with the same criteria as IADPSG (Table 1).

Cosson *et al.* (91) showed in a study performed in a large cohort of more than 18 000 deliveries that more than 30% of diagnosed GDM are at low risk for GDM. This was the direct consequence of the lowered glycaemia threshold in the diagnostic criteria. Curiously, diagnosed low risk women had more GDM-related events compared with women without GDM. In a recent study designed to evaluate retrospectively the IADPSG criteria in about 23 000 pregnancies, there was a significant 1.5% increase in GDM prevalence when using the new criteria without any significant increase in maternal or fetal outcomes except for neonatal hypoglycaemia which was significantly higher (92).

These criteria are still in debate and we need to obtain studies using them, evidence that additional patients identified have increased frequency of maternal/perinatal morbidities. It is also evident that GDM morbidities can be prevented or decreased by intervention and evidence that benefits of screening outweigh harm incurred.

Management

The treatment of GDM intends to decrease adverse pregnancy outcome. There is insufficient knowledge of clinical outcomes of both lifestyle as well as pharmacological interventions against GDM using the new criteria. Treatment is based on blood glucose targets independently from the aetiology of GDM. Diabetes phenotyping may be performed later on as it is usually done during pregnancy in routine diabetes care.

Treatment evaluation is based on blood glucose self-monitoring (pre- and 1 or 2 h post-prandial according to recommendations) and not on A1c level. Blood glucose targets (12) are shown in Table 2.

Education is the cornerstone of GDM management. Trained nurses and dieticians are the most effective in this regard. The aim of dietary therapy is to avoid large meals and simple carbohydrates rich foods. Insulin therapy is added if targets are not obtained with lifestyle

Table 2 Target blood glucose for women with GDM.

Time of day	Targets mg/dl (mmol/l)
Preprandial or fasting	95 (5.3) or lower
1 h after meal	140 (7.8) or lower
2 h after meal	120 (6.7) or lower

GDM, Gestational diabetes.

modifications alone. This strategy has been shown to reduce perinatal complications in the ACHOIS study (93). The efficacy and safety of insulin have made it the standard for treating GDM (9).

Oral antidiabetic agent metformin and glyburide have shown efficacy with no evidence of harm to the foetus, although long-term safety remains a concern. Trials have shown that glyburide does not cross the placental barrier (94, 95) or may cross it in low concentrations (96) while metformin concentration is similar in the fetal and maternal circulation. In the Metformin in Gestational Diabetes (MiG) trial, the largest study of metformin use in women with GDM compared to insulin therapy (97). There was no significant difference in the fetal outcome between the two groups and approximately half of the metformin-treated mothers also required insulin in order to achieve target glucose levels. Nevertheless, metformin seems to be favourable with regards to weight gain and amount of insulin needed during pregnancy (98).

Conclusion

Because of the physiological insulin resistance, pregnancy is a favourable period to reveal undiagnosed diabetes. GDM results from β -cell failure to cope with gestational insulin resistance. It should be considered not only as a pre-diabetic condition of T2D. T1D and MODY 2 are potential aetiologies of GDM. Further studies are needed to demonstrate that the new guidelines are useful in terms of complication reduction.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

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