ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Review Article on Gestational Diabetes

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ABSTRACT

Diabetes is metabolic disorder characterized by hyperglycemia glycosuria,hyperlipidemia, and ketone urea negative nitrogen balance. In its chronic forms, diabetes is associated with long-term vascular complications, including retinopathy, nephropathy, neuropathy and vascular disease. Gestational (jes-stay-shuh-nal) diabetes is diabetes that a woman can develop during pregnancy.When you have diabetes, your body cannot use the sugars and starches (carbohydrates) it takes in as food to make energy. As a result, your body collects extra sugar in your blood. Gestational diabetes is associated with an increased risk of complications in pregnancy and birth, as well as a greater likelihood of mother and child developing type 2 diabetes later in life. The good news is that with good management of gestational diabetes, these risks are significantly reduced. There are several identifiable predisposing factors for GDM, and in the absence of risk factors, the incidence of GDM is low. Importantly, women with an early diagnosis of GDM, in the first half of pregnancy, represent a high-risk subgroup, with an increased incidence of obstetric complications, recurrent GDM in subsequent pregnancies, and future development of Type 2 diabetes.

Keywords: Gestational diabetes mellitus, epidemiology, risk factors, Type 2 diabetes, insulin resistance

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ISSN: 0975-8585

INTRODUCTION

Although pregnancy is a carbohydrate-intolerant state, gestational diabetes mellitus (GDM) develops in only a small proportion of pregnant women (3–5%). As pregnancy advances, the increasing tissue resistance to insulin creates a demand for more insulin. In the great majority of pregnancies, the demand is readily met, so the balance between insulin resistance and insulin supply is maintained. However, if resistance becomes dominant the women become hyperglycemic. This usually occurs in the last half of pregnancy, with insulin resistance increasing progressively until delivery, when, in most cases, it rapidly disappears.

As in Type II diabetes, GDM is associated with both insulin resistance and impaired insulin secretion [1–3]. The two disorders also share the same risk factors, have a corresponding prevalence within a given population, and have the same genetic susceptibility. Therefore, they are assumed to be aetiologicallyindistinct, with one preceding the other.

Screening and diagnosis of GDM In two recent comprehensive reviews, Hanna and Peters [6], and Kjos and Buchanan [7] evaluated the screening and diagnosis protocol for GDM. Accordingly, all pregnant women should be assessed for clinical characteristics to determine the risk of GDM and a 50-g oral glucose-challenge test (GCT), unless they have a low-risk clinical profile, usually between 24 and 28 weeks of gestation, followed by an oral glucose tolerance test (OGTT) if the serum glucose concentration at screening is high. The GCT is positive in 14–18% of women using a glucose cut-off value of ≥ 140 mg/ dl (7.8 mol/ l), and in 20– 25% using a cut-off level of ≥ 130 mg/dl (7.2 mmol/ l), with respective sensitivity rates of approximately 80% and 90% for the diagnosis of GDM. The lower cut-off value also lowers the specificity by 25% [6].

Risk factors for GDM Being:

- 35 years of age or older
- from a high-risk group(Aboriginal, Hispanic, South Asian,Asian and African)
- obese (BMI of 30 kg/m2 or higher)
- Maternal factors, Older age, High parity, Pregnancy weight gain
- α-Thalassaemia trait, High intake of saturated fat , Family history of diabetes
- Congenital malformation, Stillbirth, Macrosomia, Caesarean section
- High blood pressure in pregnancy, Multiple pregnancy, Increased iron stores
- Protective factors, Young age, Alcohol use.

Having:

- GDM in a previous pregnancy
- given birth to a baby that weighed more than 4 kg (9 lbs.)
- a parent, brother or sister withtype 2 diabetes
- polycystic ovary syndrome(PCOS) or acanthosis nigricans(darkened patches of skin)

All pregnant women should be screenedfor GDM between 24 and 28 weeks of pregnancy. If you are pregnant, talk toyour healthcare provider about beingtested for GDM.

Having GDM puts you at increased risk of developing type II diabetes.It is important to be tested for type 2 diabetes on a regular and timely basis. Early diagnosis and proper management will help you:

- **Have healthy future pregnancies.**

Undiagnosed diabetes in a pregnant woman increases the risk of miscarrying or having a baby born with a malformation.

- **Stay healthy and avoid diabetescomplications:**

Such as heart attack,stroke and damage to your eyes,kidneys and nerves.

Remember: You need to be tested (screened) for type II diabetes:

- within six weeks to six months ofgiving birth
- when planning another pregnancy
- every three years (or more oftendepending on your risk factors)

Gestational diabetes can affect your baby.

- Grow very large (weigh more than 9 pounds), which in turn can lead to problems with the delivery of your baby. A large baby born through the birth canal can injure nerves in his shoulder; break her collarbone; or, rarely, have brain damage from lack of oxygen.
- Have quickly changing blood sugar after delivery. Your baby's doctor will watch for low blood sugar after birth and treat it if needed.
- Be more likely to become overweight or obese during childhood or adolescence. Obesity can lead to type IIdiabetes.

Gestational diabetes can affect you.

- Have problems during delivery.
- Have a very large baby and need to have a cesarean section (C-section) (an operation to get your baby out through your abdomen).
- Take longer to recover from childbirth if your baby is delivered by C-section. Other problems that sometimes happen with gestational diabetes
- Women with gestational diabetes also can develop preeclampsia* (pree-e-klamp-see-uh).
- Sometimes, diabetes does not go away after delivery or comes back later after pregnancy. When this happens, the diabetes then is called type 2 diabetes.

The American College of Obstetricians and Gynecologists [4] concluded that although universal glucose challenge screening for GDM is the most sensitive approach, there may be pregnant women at low risk who are less likely to benefit from testing. These women should have all of the following characteristics: age < 25 years, not a member of an ethnic group with a high prevalence of diabetes (Hispanic, Black, Native Americans, South-east Asian, Pacific Islander or indigenous Australian), body mass index (BMI) ≤ 25, no history of abnormal glucose tolerance, no history of adverse pregnancy outcomes usually associated with GDM, and no known diabetes in a first-degree relative.

In its recent Update and Guidelines on Diabetes and Pregnancy, the WorkingGroup on Diabetes and Pregnancy of the European Associationof Perinatal Medicine (EAPM)

recommended that all women should be considered at average or high risk of developing GDM, as few will meet all the criteria for low risk [8]. Nahum and Huffaker [9] have demonstrated that the predictive value of the GCT varies significantly with ethnicity; 27% of white women had a positive 50-g screening test and 17% had a positive 100-g test, whereas corresponding values for blacks were 18% and 43%. However, the implementation of different cut-off values in various ethnic groups is impractical [6].

The final diagnosis of GDM is based on the results of the OGTT. There is no agreement on the performance or interpretation of the OGTT in pregnant women, but two or more pathological glucose values are required for a diagnosis of GDM. In 1979, the National Diabetes Data Group [10] recommended a 3-h, 100-g test using predefined criteria to quantify the risk of subsequent diabetes in the mother [11]. Carpenter and Coustan [12] derived their criteria from previously established data, incorporating lower glucose concentrations to identify additional women with an increased risk of fetal macrosomia and caesarean delivery in the absence of specific treatment [13–15]. However, most of these women and their infants are not at risk of glucose-related morbidity [15].

The Fourth International Workshop-Conference on Gestational Diabetes Mellitus [16], the World Health Organization (WHO) [17], and the European Diabetic Pregnancy Study Group [18] proposed different criteria for interpreting the results of the 100-g 3-h OGTT or 75-g 2-h OGTT. According to the American College of Obstetricians and Gynecologists [4], there is insufficient evidence to determine the optimal antepartum testing regimen for women with GDM with relatively normal glucose levels on diet therapy and no other risk factors, and either the plasma or serum glucose level established by Carpenter and Coustan [12] or the plasma level designated by the National Diabetes Data Group [10] conversions are appropriate for use in the diagnosis of GDM. Although the American Diabetes Association (ADA) still recommends a 3-h 100-g OGTT for the diagnosis of GDM, it has recently included in its recommendations the use of a 2-h 75-g OGTT. The same fasting (= 5.3 mmol/l), 1-h (= 10 mmol/l), and 2-h (7.8 mmol/l) diagnostic cut-off points are used in both tests. However, two of three abnormal values are required for diagnosis instead of the two of four required for the 3-h test [19].

Ethnic distribution of GDM

The prevalence of GDM varies in direct proportion to the prevalence of Type 2 diabetes in a given population or ethnic group [4]. The reported prevalence of GDM in the USA ranges from 1% to 14%, with 2–5% being the most common rate [24]. The WHO Ad Hoc Diabetes Reporting Group [25] noted markedly different rates of diabetes and IGT in different populations, from as low as < 1% to > 10%. In some of the populations, more than half the cases of diabetes were undiagnosed prior to the survey. IGT was mostly overlooked in routine clinical practice. Thus, a substantial proportion of abnormal glucose tolerance in pregnancy goes undetected without screening. King [5] summarized the work of severalresearch groups that collected data on the prevalence of diabetes in pregnancy. An especially high prevalence was detected in Zuni Indian women (14.3%), Chinese women, Indian-born women in Melbourne, Australia (13.9% and 15%, respectively), andAsian women in Illawara, Australia (11.9%). Their findings,together with the

WHO study [25], show that for a givenpopulation and ethnicity, the risk of diabetes in pregnancy reflects the underlying frequency of Type II diabetes.

It remains unclear, however, if this marked ethnic and geographical variation represents true differences in the prevalence of GDM, because of the remarkably variable approaches used across different studies, with differences in methods of screening, oral and intravenous glucose loads, and diagnostic criteria. For example Dooley et al . [26] demonstrated that ethnicity as well as maternal age and degree of obesity must be taken into account in comparing the prevalence of GDM in different populations. Their adjusted relative risk for GDM was higher in black [1.81, 95% confidence interval (CI) 1.13, 2.89], and Hispanic (2.45, 95% CI 1.48, 4.04) women than in white women. Furthermore, ethnicity had a significant independent effect on birth weight, with maternal percentage ideal body weight as a significant covariate.

These findings were supported by a more recent study showing that Asian woman were more likely to have GDM than white woman (31.7% and 14%, respectively, P= 0.02), despite their lower BMI [27]. Risk factors for GDM The traditional and most often reported risk factors for GDM are high maternal age, weight and parity, previous delivery of a macrosomic infant, and family history of diabetes. These and other reported risk factors are summarized in Table 1. Some, like thalassemia or increased iron stores, are without a clear pathogenic association. It is of great importance that clinicians understand and incorporate these characteristics,

Polycystic ovary syndrome and GDM

Polycystic ovary syndrome (PCOS) is a heterogeneous disorder affecting 5–10% of women of reproductive age. It is characterized by chronic anovulation with oligo/amenorrhea, infertility, typical sonographic appearance of the ovaries, and clinical or biochemical hyperandrogenism; insulin resistance is present in 40–50% of patients, especially in obese women [28]. Holte et al . [29] reported a higher rate of ultrasonographic, clinical and endocrine signs of PCOS in 34 women who had had GDM 3–5 years before, compared with 36 matched controls with uncomplicated pregnancies. They concluded that women with previous GDM and PCOS may form a subgroup distinct from women with normal ovaries and previous GDM characterized by a stronger tendency to develop features of insulin resistance syndrome. Many other researchers reported similar results [30–33]. Some suggested a screening programme for GDM for these patients. PCOS is considered as a prediabetic state, associated with a 31–35% prevalence of IGT and a 7.5–10% prevalence of Type 2 diabetes [34]. The conversion rate from IGT to overt Type 2 diabetes is increased five- to 10-fold in women with PCOS [35].

Multiple pregnancy and GDM

The number of fetuses in multifetal pregnancies may influencethe incidence of GDM owing to the increased placental mass and, thereby, the increase in diabetogenic hormones. However, reports are somewhat conflicting, probably because of the heterogeneous populations studied. In an interesting study of the prevalence of GDM in dizygotic (DZ) twin pregnancies with two placentas compared with monozygotic (MZ) twin pregnancies with one

placenta, Hoskins et al [36] found that a higher proportion of differentsex rather than same-sex twin pregnancies was complicated by GDM (3.5% vs. 1.6%). The impact of fetal reduction (selective feticide of one or more fetuses in high-order multiple pregnancies) on the incidence of GDM may also support this theory. Sivan et al . [37] found that the rate of GDM was significantly higher in the triplet group than in the reduction group (22.3% vs. 5.8%). Similar results were reported by Schwartz et al . [38], who showed that GDM was significantly more frequent in twin deliveries (7.7% vs. 4.1%, $P < 0.05$). However, insulin requirements were not different, suggesting a minor clinical impact.

By contrast, using data derived from the Medical Birth Registry of Norway, England and Irgens [39], controlling for other risk factors such as advanced age, parity, maternal history of diabetes, and woman's own birth weight, found no elevated risk of GDM among 9271 multifetal pregnancies. Others have also failed to demonstrate a higher prevalence of GDM in multiple pregnancies [40,41].

Recurrence of GDM

MacNeill et al [42] found a 35.6% recurrence rate of GDM. Multivariate regression models showed that infant birth weight in the index pregnancy and maternal weight before the subsequent pregnancy were predictive of recurrent GDM. Higher recurrence rates (69% of 78 patients) were reported by Major et al [43]. Recurrence was more common when the following variables were present in the index pregnancy: parity ≥ 1 [odds ratio (OR) = 3.0], BMI ≥ 30 kg/m 2 (OR = 3.6), GDM diagnosis at ≤ 24 gestational weeks (OR = 20.4), and insulin requirement (OR = 2.3). A weight gain of ≥ 7 kg (OR = 2.9) and an interval between pregnancies of ≤ 24 months (OR = 1.6) were also associated with a recurrence of GDM. Spong et al [44] found a similarly high recurrence rate of 68% in 164 women with GDM. Risk factors for recurrence in this study were earlier diagnosis of GDM, insulin requirement, and hospital admissions in the index pregnancy. IGT as a risk factor of adverse outcome the cut-off level of glycaemia beyond which the risk of an adverse outcome of pregnancy is increased is of major clinical importance in the management and initiation of therapy.

Nasrat et al [45] (Saudi Arabia) examined pregnancy outcome in 212 women with IGT and 212 women with normal glucose tolerance, and concluded that IGT does not lead to any adverse outcome. Similar findings were reported by Ramtoola et al .[46] (Mauritius), who failed to find an excess perinatal mortality in 267 pregnant women with IGT compared with a background population. By contrast, Moses and Calvert [47] (Australia) suggested that the clinically optimal level for glycaemia during pregnancy should be as near to normal as possible. They studied the proportion of assisted deliveries and the proportion of infants admitted to special care in relation to the range ofglucose tolerance, and found an association between glycaemiaand both outcomes.Conflicting results were also reported by others.

Al-Shawafet al[48] (Saudi Arabia) found that women with gestational IGT were older and more obese, and had higher parity, and heavier babies than pregnant women with normal screening plasma glucose, and Roberts et al [49] (UK) found no significant difference in the

incidence of antenatal complications between mothers with normal and impaired glucose tolerance (n = 135 each). Although the IGT group had a higher rate of induced labour and caesarean section, there was no betweengroup difference in fetal outcome or neonatal morbidity. Tan and Yeo [50] (Singapore), in a retrospective analysis of 944 women with IGT in pregnancy (8.6%) and 10 065 women with normal pregnancy, noted that even when maternal age and obesity were excluded, the IGT group had a significantly higher risk of labour induction, caesarean section, caesarean section for dystocia/no progress, fetal macrosomia, and shoulder dystocia.

The risk of hypertensive disease and caesarean section for fetal distress/thick meconium-stained amniotic fluid were also higher in the IGT group, but the differences were not statistically significant when maternal age and obesity were excluded. There was no significant difference in the rates of low Apgar scores at 1 and 5 min between the two groups. It is possible that some of the adverse outcomes associated with excess maternal weight were in fact related to GDM. It is also possible that some of the complications attributed to GDM, especially the milder form of IGT, were actually related to excess maternal weight.

Jacobson and Cousins [51] (USA) reported that good glycemiccontrol did not normalize birth weight percentiles, and maternal weight at delivery was the only significant predictor of birth weight percentile. Thus, IGT diagnosed for the first time in pregnancy might only be a feature of excess maternal weight and not in itself a pathological condition. The clinical significance of IGT has also been disputed [Nasrat et al . [45] (Saudi Arabia), Li et al .[52] (Hong Kong)]. Lao and Ho [53] (China) also concluded that some of the complications attributed to GDM are probably related to maternal obesity, but IGT could still affect infant birth weight despite dietary treatment that normalizes maternal gestational weight gain. In another recent study [54] (Denmark) of 2904 pregnant women, the following outcomes measures increased significantly with increasing glucose values on the OGTT: shoulder dystocia, macrosomia, emergency caesarean section, assisted delivery, hypertension, and induction of labour. However, when corrections were made for other risk factors, hypertension and induction of labour were only marginally associated with glucose levels. Aberg et al . [55] (Sweden) conducted a population-based study of maternal and neonatal characteristics and delivery complications in relation to findings for the 75-g, 2-h OGTT at 25–30 weeks' gestation. An increased rate of caesarean section and infant macrosomia was observed in the group with a glucose tolerance of 140–162 mg/dl (7.8–9 mmol/ l) and in the GDM group. Advanced maternal age and high BMI were found to be risk factors for increased OGTT values.

Abnormal GCT as a risk factor for adverse pregnancy outcome Is an abnormal GCT alone, without GDM, a risk factor for adverse pregnancy outcome? Using fetal weight and anthropometric characteristics as their parameters, Mello et al . [56] evaluated 1615 white women with singleton pregnancies who underwent universal screening for GDM in two periods of pregnancy. They divided the population into three groups according to the GCT results: (i) 172 patients with an abnormal GCT in both periods; (ii) 391 patients with a normal GCT in the early period and an abnormal GCT in the late period; (iii) 1052 patients with a normal GCT in both periods (control group). The incidence of large-for-gestational-age (LGA) infants was

significantly higher in group 1 (40.7%) and group 2 (22.0%) than in the control group (8.3%), and significantlyhigher in group 1 than group 2. The newborns of group 1 hada higher birth weight than those of group 2 and the controlgroup, and the newborns of the control group had significantlygreater length and mean cranial circumference. Group 1 babies had a significantly lower ponderal index, thoracic circumference, and weight /length ratio than controls, and a significantly larger cranial /thoracic circumference.

To determine the predictive value of a negative GCT in subsequent pregnancies, Nahum [57] studied 62 pregnancies of women who had given birth twice during the past 4 years and for whom third-trimester 1-h 50-g glucose screening test results were available for both pregnancies. He found that the GCT results were significantly correlated between the two pregnancies ($r = 0.49$, $P < 0.001$) and concluded that a negative GCT of < 140 mg/dl (7.8 mmol/l) during pregnancy is strongly predictive of a negative screening result in a succeeding pregnancy within 4 years.

Accordingly, it is possible that abnormal GCT alone, even without GDM, is a prediabetic state at the lower spectrum of insulin resistance However, in clinical practice we do not use this factor for obstetric management. Early GDM diagnosis as a risk factor for Type II diabetes early diagnosis of GDM, that is, in the first half of pregnancy, is a high risk factor for future development of Type 2 diabetes. Bartha et al . [58] foundthat among 3986 pregnant women, those with early-onset GDM (n= 65) were more likely to be hypertensive (18.46% vs. 5.88%; P= 0.006) and had higher glycemic values and greater need for insulin therapy (33.85% vs. 7.06%, P < 0.001) than those in whom diabetes developed later (n= 170). All cases of neonatal hypoglycemia (n = 4) and all perinatal deaths (n= 3) were in this group.

The women with early GDM also had an increased risk of postpartum diabetes mellitus, whereas those with late-onset GDM had a minimal risk [59]. The percentages of overt diabetes and abnormal glucose tolerance were significantly higher in the early pregnancy group (n= 30) than in the late-pregnancy group (n = 72) (26.7% vs. 1.4% and 40% vs. 5.56%, respectively). Congenital malformations Schaefer-Graf et al . [60], in a review of 4180 pregnancies complicated by GDM (n = 3764) or Type 2 diabetes (n = 416), reported that the congenital anomalies in the offspring affected the same organ systems described in pregnancies complicated by Type 2 diabetes. The risk of anomalies rose with increasing hyperglycaemia at either diagnosis or presentation for care. However, most other reports had conflicting findings.

Bartha et al [58] failed to find an increase in major congenital malformations associated with GDM, as did Kalter [61] in a comprehensive review of the literature. An exception is the recent Swedish Health Registry study covering over 1.2 million births in 1987–1997 [62]. The authors identified 3864 infants born to women with pre-existing diabetes and 8688 infants born to women with GDM. The total malformation rate in the first group was 9.5%, and in the second group, 5.7%— similar to the rate in the general population. However, the GDM group was characterized by an excess of certain malformations, suggesting that a subgroup of GDM patients are at increased risk of diabetic embryopathy, perhaps due to pre-existing but undetected Type 2 diabetes.

Martinez-Frias et al . [63] analysed 19 577 consecutive infants withmalformations of unknown cause and reportedthat GDM was a significant risk factor for holoprosencephaly, upper/lower spine/rib anomalies, and renal and urinary system anomalies. However, owing to the heterogeneous nature of GDM, which includes previously unrecognized and newly diagnosed Type 2 diabetes, they could not rule out the possibility that the teratogenic effect is related to latent Type 2 diabetes. Nevertheless, they concluded that pregnancies complicated by GDM should be considered at risk of congenital anomalies. By contrast, another population-based retrospective study [64] showed that the rate of congenital malformations in the GDM group was only slightly higher than in the control group (OR = 1.3; 95% CI 1.0, 1.6). Interestingly, recent epidemiological data relate maternal obesity per se to congenital malformations;

Mikhail et al. [65] found that compared with non-obese, non-diabetic African- American women, obese non-diabetic African-American women were significantly more likely to have babies with a cardiac anomaly (OR 6.5, 95% CI 1.2, 34.9). Similarly, Watkins and Botto [66] reported that after excluding diabetic mothers and adjusting for potential confounders, overweight women were more likely than average-weight women to have a child with a major isolated heart defect. However, in a large prospective cohort study [67] of 22 951 pregnant women, obese women had no higher risk, overall, of having an offspring with a major defect. Their offspring, nevertheless, did have higher prevalence of minor defects. Another prospective case–control study of 20 248 newborns born in the city of Mainz [68] revealed that the prevalence of major malformations in children of obese mothers was higher than those of the total population (11.1% vs. 4%, OR 1.3, 95% CI 1.0, 1.7).

GDM and hypertensive disorders

Preeclampsia and gestational hypertension are apparently more frequent in women with GDM. A large study by Xiong et al . [69] detected preeclampsia in 2.7% of 2755 patients with GDM compared with only 1.1% of 108 664 patients with normal pregnancy (adjusted OR = 1.3; 95% CI 1.20, 1.41). Similar results were observed for gestational hypertension. Likewise, Dukler et al . [70] studied 380 primiparous women with preeclampsia and 385 primiparous control women for a total of 1207 and 1293 deliveries,respectively. After adjustment for confounding variables, GDM was strongly associated with the recurrence of preeclampsia in the second pregnancy (OR = 3.72; 95% CI 1.45, 9.53). Conditions associated with increased insulin resistance, such as GDM, PCOS, and obesity, may predispose patients to essential hypertension, hypertensive pregnancy, hyperinsulinaemia, hyperlipidaemia, and high levels of plasminogen activator inhibitor-1, leptin, and tumor necrosis factor alpha. These findings may also be associated with a possible increased risk of cardiovascular complications [71].

Joffeet al [72] provided further support for the role of insulin resistance in the pathogenesis of hypertensive disorders of pregnancy. In a prospective study of 4589 healthy nulliparous women, they found that the women with GDM had an increased relative risk of preeclampsia and all hypertensive disorders (RR = 1.67; 95% CI 0.92, 3.05 and RR = 1.54; 95% CI 1.28, 2.11, respectively). Risk ratios were not substantially reduced after further adjustment for

ethnicity and BMI (OR = 1.41 and 1.48, respectively). Furthermore, even within the normal range, multivariate analysis demonstrated that the level of plasma glucose 1 h after a 50-g oral glucose challenge was an important predictor of preeclampsia. Innes et al . [73] evaluated 54 normotensive women who developed hypertension in pregnancy, and 51 controls with normotensive pregnancies, matched for parity. After adjustment for potential confounders, 2-h post load glucose levels remained strongly related to risk for hypertension and to peak mean arterial blood pressure, as did total glucose area under the curve.

Genetics, immunology and GDM

Some patients with GDM have signs of autoimmunity, with insulin autoantibodies and anti-islet cell antibodies), although the prevalence is extremely low (< 10%) [74,75]. Mutations in the glucokinase gene occur in no more than 5% of GDM patients [76]. The inheritability of GDM was studied in 100 women with previous GDM 11 years postpartum [77]. About 60% were found to have either IGT or Type 2 diabetes. Investigation of the parents of this subgroup showed that in a substantial proportion, neither parent had had either IGT or Type 2 diabetes, suggesting a polygenic inheritance or environmental influence, rather than autosomal dominance with high penetration rate. This was supported by animal studies showing that prenatal exposure to a diabetic intrauterine milieu increases the risk of GDM. Harder et al . [78] reported a significantly higher prevalence of Type 2 diabetes in mothers than in fathers of women with GDM, and a significant aggregation of Type 2 diabetes in the maternal–grand maternal line compared with the paternal– grand paternal line. Therefore, a history of Type 2 diabetes on the mother's side might be considered as a particular risk

Factor for GDM:

The possible genetic background of GDM remains unclear. In particular, its association with HLA class II polymorphism has been poorly studied, and the results are conflicting. To clarify these discrepancies, Vambergue et al . [79] comparedthe distribution of HLA class II polymorphism between GDM and IGT samples. They found no significant between-group difference, and no significant variation in DRB1*03 and DRB1*04 allele frequencies. These data provide evidence that Type 1 diabetes HLA class II susceptibility alleles cannot serve as genetic markers for susceptibility to glucose intolerance during pregnancy. Ober et al . [80] studiedthe restriction fragment length polymorphisms near 'candidate diabetogenic genes' in order to identify molecular markers for GDM genes. Genotypes for insulin hyper variable region (HVR), insulin-like growth factor II (IGF2), insulin receptor (INSR), and glucose transporter (GLUT1) were studied in GDM and control subjects. The results supported the hypothesis that GDM has heterogeneous phenotypic and genotypic features and that the risk of GDM in black and Caucasian subjects is not related to obesity per se but to interactions between obesity and INSR alleles. In Caucasian women, INSR and IGF2 alleles interact to confer an additional risk of GDM. Thus, in some women genes responsible for susceptibility to GDM may be similar to the genes conferring risk of Type 2 diabetes, whereas in others novel genes may contribute to GDM.

Risk of future Type 2 diabetes

Women with GDM have a 17–63% risk of Type 2 diabetes within 5–16 years [6]. The risk varies according to different parameters. For example, Greenberg et al . [81], in a study of 94 patients with GDM, reported that the most significant predictor of 6-weeks postpartum diabetes was insulin requirement (RR 17.28, 95% CI 2.46, 134.42), followed by poorglycaemic control, IGT, and GCT ≥ 200 mg/dl (11.1 mmol/ l).All these factors probably represent the magnitude of theinsulin resistance, which is the hallmark of future diabetesand other vascular complications.

Similarly, Bianet al [82]reported a diagnosis of diabetes 5–10 years postpartum in 33.3% of patients with previous GDM (n = 45), but only 9.7% (n = 31) of those with IGT and 2.6% (n = 39) of normal controls. Two or more abnormal OGTT values during pregnancy, a blood glucose level exceeding the maximal values at 1 and 2 h after oral glucose loading, and high pregnancy BMI were all useful predictors of diabetes in later life. To determine if recurrent episodes of insulin resistance (i.e. another pregnancy) contribute to the decline in β -cell function that leads to Type II diabetes in high-risk individuals, Peters et al [83] investigated 666 Latino women with a history of GDM. Among the 87 (13%) who completed an additional pregnancy, the rate ratio of Type 2 diabetes increased to 3.34 (95% CI 1.80, 6.19) compared with women without an additional pregnancy, after adjustment for other potential diabetes risk factors during the index pregnancy (antepartum OGTT, highest fasting glucose, gestational age at diagnosis of GDM) and during follow-up (postpartum BMI, and glucose tolerance,weight change, breast feeding, and months of contraceptive use). Weight gain was also independently associated with an increased risk of Type 2 diabetes; the rate ratio was 1.95 (95% CI 1.63, 2.33) for each 4.5 kg gained during follow-up, after adjustment for the additional pregnancy and the other potential risk factors. These data show that a single pregnancy, independent of the well-known effect of weight gain, accelerates the development of

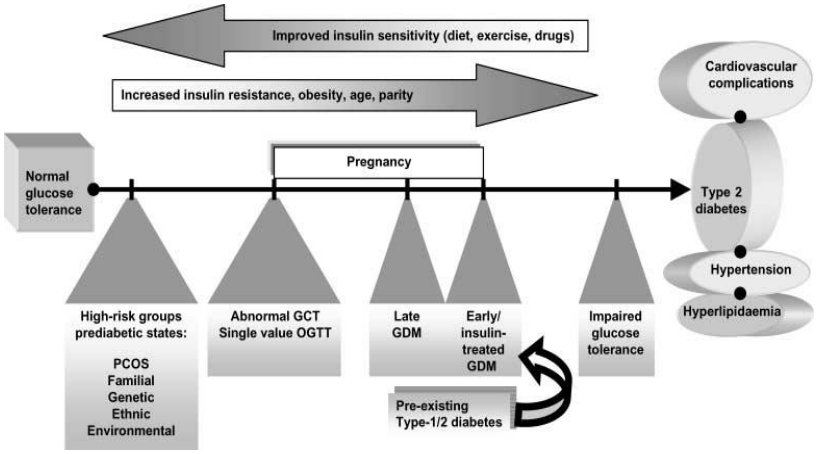
Type 2 diabetes in women with a highprevalence of pancreaticβ-cell dysfunction.

What about milder, diet-controlled GDM? Damm [84] reported abnormal glucose tolerance in 34.4% of 241 women 2–11 years after diabetic pregnancy (3.7% Type 2 diabetes, 13.7% Type 2 diabetes, 17% IGT), in contrast to a control group in which none of the women had diabetes and 5.3% had IGT. The independent risk factors for later development of diabetes were high fasting glucose level at diagnosis of GDM, delivery more than 3 weeks before term, and abnormal OGTT 2 months postpartum. Low insulin secretion at diagnosis of GDM was also an independent risk factor. Even the non-obese glucose-tolerant women with previous GDM had a metabolic profile of Type 2 diabetes, i.e. insulin resistance and impaired insulin secretion. Thus, the first OGTT should probably be performed 2 months postpartum to identify the women who are already diabetic and the women at highest risk of later development of overt diabetes [84]. Interestingly, according to a recent study, both women with a history of GDM as well as their children are at greater risk of progressing to Type 2 diabetes [85]. Whether this effect is due to a genetic or an in utero influence has yet to be determined.

In a recent systematic review, Kim et al [86] found that after the index pregnancy, the cumulative incidence of diabetes ranged from 2.6% to > 70% in studies that examined women 6

weeks postpartum to 28 years postpartum. After adjustment for length of follow-up and cohort retention, they showed that this incidence increased markedly in the first 5 years after delivery and appeared to plateau after 10 years. An elevated fasting glucose level during pregnancy was the most important risk factor for future Type 2 diabetes. Accordingly, the authors suggested that targeting these women may prove to be the most cost-effective intervention.

Suggested insulin resistance pathway



The progression from a normal glucose tolerance state to overt Type 2 diabetes may be accelerated byfactors that increase insulin resistance and attenuated by life-style modifications and insulin-sensitizing drugs (such as metformin). Pregnancy is a periodof increased insulin resistance, and the clinical manifestations may vary from normal glucose tolerance to abnormal screening results [glucose challengetest (GCT)] but normal diagnostic test for gestational diabetes (GDM), and from a single pathological glucose value on the 3-h oral glucose tolerancetest (OGTT) to diagnosis of GDM when two or more such values are detected. Early onset of GDM, in the first half of pregnancy, and the need forinsulin treatment—probably the result of a higher insulin-resistant state—may offer a greater risk of future development of Type 2 diabetes. Pre-existingType 1 or Type 2 diabetes should also be considered.

Prevention of diabetes

As insulin resistance is an early risk factor for diabetes, it iswell recognized that women with PCOS [35] and with GDM [7,81–85] are at high risk of the development of Type 2 diabetes. Two recent large studies have shown that decreasing insulin resistance through diet, exercise, or metformin can decrease the development of diabetes in individuals at high risk [87,88]. In one study the treatment of women with recent GDM with the insulin-sensitizing drug troglitazone led to a 56% decrease in progression to Type 2 diabetes compared with placebo [89]. This protective effect was associated with the preservation of pancreatic β -cell function and appeared to be mediated by a reduction in the secretory demands placed on β -cells by chronic insulin resistance [90]. Thus, it is possible that improving insulin sensitivity with diet, exercise and drugs such as metformin may reduce the risk of diabetes in individuals at high risk, such as women with PCOS, IGT, and a history of GDM [91].

ISSN: 0975-8585

SUMMARY

The 1997 WHO estimates of the prevalence of diabetes in adults showed an expected total rise of > 120% from 135 million in 1995 to 300 million in 2025 [2]. These numbers also include GDM, and should alert physicians to the need to direct special attention to this population, especially in developing countries. The data presented in this review indicate that the epidemiology of GDM is characterized by several features:

- Differences in screening programmes and diagnostic criteria make it difficult to compare frequencies of GDM among various populations. Nevertheless, ethnicity has been proven to be an independent risk factor for GDM, which varies in prevalence in direct proportion to the prevalence of Type 2 diabetes in a given population or ethnic group.
- There are several identifiable predisposing factors for GDM
- In the absence of risk factors, the incidence of GDM is low. Therefore, some authors suggest that selective screening may be cost-effective, especially in view of the forecast rise in the burden of GDM.
- PCOS is an important risk factor for GDM.
- The recurrence rate of GDM (35–80%) is influenced by parity, BMI, early diagnosis of GDM, insulin requirement, weight gain, and the interval between pregnancies.
- Pregnant women with IGT and an abnormal GCT may be at increased risk of an adverse outcome relative to woman with normal glucose tolerance and a normal GCT.
- Women with an early diagnosis of GDM, in the first half of pregnancy, represent a high-risk subgroup, with an increased incidence of obstetric complications, recurrent GDM in subsequent pregnancies, and future development of Type2 diabetes.
- Some of the patients are also at increased risk of diabetic embryopathy, perhaps due to pre-existing but undetected Type 2 diabetes. This should be considered in all patients with early diagnosis of GDM, accompanied by appropriate patient counseling.
- Besides early diagnosis, other factors that place women with GDM at increased risk of Type 2 diabetes are obesity and need for insulin for glycemic control.
- Hypertensive disorders in pregnancy and afterwards may be more prevalent in women with GDM. One possible mechanism is insulin resistance. The epidemiological data suggest an association betweenseveral high-risk prediabetic states, GDM, and Type 2 diabetes. On this basis we suggest an ‘insulin resistance pathway’ as a possible pathogenic linkage (Fig. 1). It is possible that improving insulin sensitivity with diet, exercise and drugs such a metformin may reduce the risk of diabetes in individuals at high risk, such as women with PCOS, IGT, and a history of GDM. Large controlled studies are needed to clarify this issue and to develop appropriate diabetic prevention strategies that address the potentially modifiable risk factors.

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