

## Review Article

# Gestational diabetes mellitus and its complications

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Gestational diabetes mellitus (GDM) is a new epidemic among Australian women, especially those with Asian backgrounds. The 1998 Australia National Diabetes Strategy and Implementation Plan recognises GDM as an independent glucose metabolic disorder affecting sub-groups of Australians. Gestational diabetes mellitus is an Australian national diabetes priority area, along with insulin dependent diabetes mellitus (IDDM) and non-insulin dependent diabetes mellitus (NIDDM). This paper reviews the many issues relating to GDM that continue to be debated by researchers and clinical service providers. These issues include the diagnosis of GDM, the effect of GDM on fetal outcomes, the long-term health effects on the offspring of GDM mothers, the effect of GDM on maternal outcomes and the long-term health effects on women with a history of GDM.

**Key words:** gestational diabetes, fetal outcome, inter generational diabetes, Asian women, obesity, carbohydrate intolerance, glucose metabolism.

## Introduction

Gestational diabetes mellitus (GDM) is defined as carbohydrate intolerance of variable severity with onset or first recognition during pregnancy. The definition applies regardless of whether insulin is used for treatment or whether the condition persists after pregnancy. It does not exclude glucose intolerance that may have antedated the pregnancy.<sup>1,2</sup> By this definition, there are three subtypes of GDM: previously undiagnosed abnormal glucose tolerance; pregnancy-induced intolerance; and the early auto-immune beta-cell-destruction phase of insulin-dependent diabetes mellitus (IDDM), although this is rare.<sup>3</sup> The local background incidence of impaired glucose tolerance (IGT) and non-insulin dependent diabetes mellitus (NIDDM) may not only influence the incidence of GDM, but also maternal and neonatal outcomes of GDM. However, there is still a lack of consensus about how to diagnose GDM world-wide.

The perinatal outcome of pregnancy complicated by GDM varies greatly from study to study. Also, the effectiveness of treatment is controversial. It has been suggested that the existing standard of care and widespread screening in the USA and some other parts of the world are based on imperfect data, and that it is appropriate to stop and obtain more data.<sup>4</sup> Jarrett<sup>5</sup> argued that gestational diabetes is no more than a special case of impaired glucose tolerance temporarily associated with pregnancy. Any maternal-fetal morbidity is more likely to be due to maternal age or obesity or, indeed, to the effects and consequences of diagnosis rather than to the glucose intolerance.

## Diagnosis

The diagnostic criteria vary from country to country and, even in a single country such as Australia,<sup>6</sup> several criteria for diagnosis of GDM coexist. In 1985, the World Health Organization (WHO)<sup>7</sup> recommended that the diagnostic criteria for the non-pregnant state be used as the diagnostic criteria for the diagnosis of GDM, which would be based on a 75 g oral

glucose tolerance test (OGTT). The use of the WHO's criteria in the pregnant state allows comparison of glucose levels during pregnancy and non-pregnancy. The diagnostic criteria also differentiate an intermediate state: namely, impaired glucose tolerance (IGT). However, the criteria have been criticised as being derived from the consensus of experts, rather than being based on population studies.<sup>8</sup> In other words, they are based on neither the risk of late progression to diabetes in the mothers nor pregnancy outcome in the babies. The WHO criteria have also been criticised by Dornhorst and Beard as having created a great deal of scepticism, given that two or three times more women are diagnosed with GDM using WHO criteria than with other methods previously validated.<sup>9</sup> Conversely, Beischer *et al.*<sup>10</sup> suspected that the WHO criteria underestimated the incidence of glucose intolerance in pregnancy. Garner<sup>11</sup> considered that the criteria were not suitable for pregnancy, as fasting levels were normally lower and postprandial levels higher in normal pregnancy when compared with the non-pregnant state.

In order to remedy the lack of studies to determine the reference values for 75 g OGTT, Hatem *et al.*<sup>12</sup> studied distributions of plasma glucose levels of fasting 1 hour and 2 hours after a 75 g oral glucose load in 212 normal women with no conventional risk factors for GDM. It was proposed that the upper limits of normal for plasma glucose concentration 2 hours after a 75 g glucose load for the second and third trimesters were 7.5 and 9.6 mmol/L, respectively; these values were based on the rounded-up 97.5 percentile measurements.

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Li *et al.*<sup>13</sup> studied the glucose response of 75 g OGTT in 618 unselected pregnant Chinese women between 24 and 28 weeks gestation. It was found that the 2 hour glucose levels at 2-standard deviation and 4-standard deviation above the mean came very close to the criteria of abnormality suggested by WHO: 8.3 mmol/L and 10.8 mmol/L, respectively. The area under the glucose response curve also correlated best with the glucose levels at 2 hours during the OGTT ( $y = 2.1x + 4.6$ ,  $r = 0.885$ ). Therefore, the authors proposed that the 75 g OGTT, interpreted using the WHO criteria, seemed appropriate for pregnant Chinese women.

O'Sullivan and Mahan developed criteria for the OGTT based on the subsequent risk of progression to diabetes later in life, and this forms the basis for the diagnosis of GDM in North America today.<sup>14</sup> The proposed diagnostic procedure uses venous whole blood, a 100 g glucose load, and involves taking blood samples at fasting and 1, 2 and 3 hours after ingesting the glucose load. A diagnosis is made if two of these values meet or exceed the standard. The National Diabetes Data Group (NDDG) endorsed the adoption of O'Sullivan and Mahan criteria and released derived values based on a shift from venous whole blood to venous plasma.<sup>15</sup> The O'Sullivan and Mahan criteria and the values have also been adopted by the American Diabetes Association (ADA)<sup>16</sup> and the American College of Obstetricians and Gynecologists (ACOG).<sup>17</sup> Nevertheless, criticisms have been voiced. These included concerns that the population tested was a mixed racial and socio-economic inner-city population, that the criteria did not deal with the significance of the various plasma glucose levels in relation to the outcome of pregnancy,<sup>11,18</sup> that obesity was not considered as a confounding variable, and that a 100 g glucose load frequently caused nausea and vomiting.<sup>11</sup>

Several attempts have been made to compare the 100 g glucose tolerance test with the 75 g glucose tolerance test in pregnancy. A comparison of the NDDG and WHO criteria for detecting GDM was made by Deerochanawong<sup>19</sup> in a population in Thailand. A 75 g OGTT and a 50 g glucose challenge test (GCT) were administered to 709 pregnant women and those with a positive screening value (1 h  $\geq 7.8$  mmol/L) underwent a 100 g OGTT within 7 days of undergoing a 75 g OGTT. The prevalence of GDM was found to be 1.4% (10/709) and 15.7% (111/709) using the NDDG and WHO criteria (2 h  $\geq 7.8$  mmol/L), respectively. It was also noted in the study that of 14 women with macrosomic infants, six had an abnormal WHO test while only three had an abnormal NDDG test.

Similarly, in a study of a population with a very high prevalence of NIDDM, Pettitt *et al.* reported that the one-step WHO test for glucose tolerance during pregnancy was abnormal in a greater percentage of women with adverse outcomes than the more cumbersome two-step NDDG test.<sup>20</sup> Pettitt *et al.* considered, therefore, that the WHO test was at least as good as the NDDG test in predicting adverse pregnancy outcomes.<sup>20</sup> A study from Hong Kong revealed that, after re-administering a 75 g OGTT, 347 pregnant women with a mean gestational age of 29.2 weeks were found to be abnormal using NDDG criteria within 2 weeks of a 100 g OGTT. Forty-five per cent had normal glucose tolerance, 51% had impaired glucose tolerance and 3% had GDM if the subsequent 75 g OGTT was interpreted by the WHO criteria.<sup>21</sup> The

plausible low incidence of GDM detected by the WHO criteria in the Hong Kong study may be partially explained by the order in administering OGTT and the imperfect reproducibility of the OGTT during pregnancy.

Sacks *et al.*<sup>22</sup> found that a 50 g 1 hour GCT was only moderately reproducible and that reliance could not be placed on a single normal test result, particularly among patients with risk factors. Catalano *et al.*<sup>23</sup> evaluated the reproducibility of a 3 hour 100 g OGTT during pregnancy and found that the test was not reproducible for diagnosis of GDM in as high as 24% of pregnant women. To date, no report about the reproducibility of a 75 g OGTT during pregnancy has been found. The size of the glucose load in the first testing was also reported to influence the blood glucose response, and even the fasting glucose value, on the second testing.<sup>24</sup> Therefore, a comparative study of WHO and NDDG criteria with a randomized order of 75 g OGTT and 100 g OGTT is still needed to investigate their relative power in detecting GDM if the results of these two sets of major GDM diagnostic criteria are to be comparable.

In order to determine meaningful cut-off values of the 75 g OGTT, Sacks *et al.* studied a group of pregnant women who underwent the 75 g 2 hour OGTT.<sup>25</sup> After not finding glucose threshold values relevant to birth weight or macrosomia, it was concluded that criteria defining GDM would probably be established by consensus. In 1989, the Australasian Diabetes in Pregnancy Study Group initiated an *ad hoc* working party in an attempt to establish an agreed definition of GDM and to recommend a standard screening procedure for Australia.<sup>26</sup> The working party recommended the use of a 75 g glucose load and a fasting plasma glucose level of greater than or equal to 5.5 mmol/L and/or a 2 hour plasma glucose level of greater than or equal to 8.0 mmol/L as being gestational diabetes. The criteria were reached by consensus.

A Melbourne study involving 1371 pregnant women using the 75 g OGTT showed that GDM incidence according to various criteria was present in 4.2% (2 hour plasma glucose greater than or equal to 8.0 mmol/L), 5.2% (2 hour plasma glucose greater than or equal to 7.8 mmol/L) and 5.5% of the women using the proposed Australian criteria.<sup>27</sup> Nord *et al.* supported the use of the 75 g 2 hour OGTT with a cut-off value of greater than or equal to 9.0 mmol/L. Women in the group with a 2 hour glucose value of 8.0–8.9 mmol/L had similar neonatal mortality, morbidity or birth trauma. They were significantly older and heavier, had a higher body mass index (BMI), gave birth to heavier children and had a significantly increased number of larger than gestational age (LGA) infants.<sup>28</sup>

More recently, Lao and Lee<sup>29</sup> compared differences in maternal age, parity, fasting values in the 75 g OGTT, maternal body mass index, gestational age at delivery, incidence of larger than date infants, and placental weight among four groups of pregnant women. The women had plasma glucose levels of 8–8.9 mmol/L (Group A), 9–10.9 mmol/L (Group B), 11.0 mmol/L or above (Group C) and normal glucose tolerance (Group D) 2 hours after ingestion of a 75 g glucose load. Lao and Lee found that Group A patients were significantly different from Group D in the aforementioned parameters, but were similar to Group B for most of these parameters. Group C was found to be significantly different from both the Group D and Group A for most of the above

parameters. The authors suggested that the current WHO criteria for the diagnosis of GDM should be maintained. It seems that a study of the risk of perinatal morbidity in the small proportion of pregnant women detected by Australasian, but not by WHO criteria, is warranted.

### Fetal outcomes

There is a heated debate as to whether GDM is associated with a higher incidence of fetal mortality and morbidity. Many studies have failed to observe a higher perinatal mortality rate in women with glucose intolerance during pregnancy.<sup>30–33</sup> It has been said that the risk of perinatal mortality does not appear to be higher in infants born to women with GDM. In contrast, a study by Aberg *et al.* shows that intra-uterine deaths were significantly increased among previous siblings of women with GDM compared with the siblings of controls.<sup>34</sup> Some earlier studies showed that perinatal mortality was increased in untreated GDM.<sup>35–37</sup> Ales and Santini<sup>38</sup> questioned the importance of GDM in perinatal mortality because of insignificant findings in some studies. Separate analyses of perinatal mortality in women with differing severity of glucose intolerance will help shed light on the contradictory findings.

In the Pima Indians of Arizona, a population with a very high incidence of NIDDM,<sup>39</sup> the perinatal mortality rate is higher in women previously known to have diabetes. This rate varies with the third-trimester glucose concentration (2 hours after a 75 g glucose load without fasting) in those not previously known to have diabetes.<sup>40</sup> Johnstone *et al.* conducted a prospective case-control study in Kuwait and found that prepregnancy diabetes had a perinatal mortality rate nearly fourfold greater than non-diabetics.<sup>41</sup> They also found that the relative risk for gestational diabetes (fasting plasma glucose greater than 5.8 mmol/L on at least two occasions) was 2.0. Cases with IGT (a plasma glucose level of greater than 8 mmol/L 2 hours after a 75 g glucose load, with a fasting glucose less than 5.8 mmol/L) did not have a statistically significant perinatal loss compared with controls. Roberts *et al.*<sup>42</sup> reported no association between perinatal mortality and gestational glucose intolerance in women with IGT.

It has been observed that there is high perinatal morbidity (e.g. macrosomia, neonatal hypoglycaemia, hypocalcaemia, hypomagnesaemia, hyperbilirubinaemia, birth trauma and respiratory distress syndromes) in infants<sup>43,44</sup> and subsequent childhood and adolescent obesity in offspring of women with GDM.<sup>45,46</sup> Mild carbohydrate intolerance was also associated with high rates of neonates with birth weights of more than 4000 g or LGA,<sup>47</sup> and high rates of neonates with hypoglycaemia or hyperbilirubinaemia.<sup>48</sup> Even in pregnant women without GDM, the incidence of macrosomia (defined as a birth weight of greater than 4 kg) increased from 1.2 to 9.5% when plasma glucose levels 2 hours after a 75 g GCT increased from less than 4.5 mmol/L to greater than 7.8 mmol/L.<sup>49</sup> In addition, a graded increase in adverse maternal-fetal outcomes was associated with increasing maternal carbohydrate intolerance in women without GDM.<sup>50</sup>

Maresh *et al.*, however, found that birth weight was not related to maternal age or severity of diabetes but to maternal obesity. Neonatal morbidity indices such as admission to the special care baby unit for longer than 48 h and polycythaemia were related significantly to the severity of the diabetes and

not to maternal age or obesity.<sup>51</sup> A study of Pima Indians by Pettitt *et al.*<sup>40</sup> showed that the percentage of pregnancies associated with LGA increased with increasing third trimester glucose concentration. After maternal age and weight were accounted for in a binary multiple regression analysis, the third trimester glucose concentration was no longer significantly associated with the LGA rate. The congenital malformation and prematurity rates did not vary significantly with third-trimester glucose, but were high in infants of previously diabetic mothers.

Roberts *et al.* studied the fetal outcomes of 826 pregnant women with normal glucose tolerance, 120 with IGT, 7 with diabetes by the WHO criteria and 135 with pre-existing Type 1 diabetes. There was no significant difference between the infants of the normal and IGT mothers in the rate of admission to the special care baby unit, or in the incidence of hyperbilirubinaemia, transient tachypnoea of the newborn or major congenital malformations. In comparison, all of these measures of neonatal morbidity were increased in infants of mothers with pre-existing Type 1 diabetes.<sup>42</sup> Neither mean birth weight nor proportion of babies weighing between 4000 and 4500 g or over 4500 g were different in infants of the four groups of women in this study.

Lucas *et al.*<sup>52</sup> also failed to detect any significant differences in neonatal outcome variables, including percentage of LGA neonates delivered by women with class A<sub>1</sub> gestational diabetes ( $n = 159$ ), when compared with controls ( $n = 151$ ) using a normal 3 hour OGTT. In a study of pregnant women with GDM diagnosed using a 2 hour value greater than or equal to 9.0 mmol/L 75 g OGTT, Koukkou *et al.*<sup>33</sup> found that both maternal obesity and the diagnosis of GDM influenced the time and the mode of delivery. Perinatal mortality and morbidity did not differ significantly between women with GDM and women with a normal glucose tolerance. An association between the OGTT glucose area and the gestational age and ethnicity-adjusted birth weight was observed in women with normal glucose tolerance test in the study, but was absent in the GDM pregnancies. Some authors considered that it was the treatment of GDM that reduced the perinatal morbidity of infants.<sup>53,54</sup>

Hod *et al.*<sup>55</sup> advocated further reductions in plasma glucose levels for glycaemic control in women with GDM in order to shift the rate of perinatal complications nearer to that of the normal population. This is supported by a large prospective population-based study.<sup>56</sup> Langer *et al.* demonstrated that intensified management using memory reflectance meters was associated with a significant reduction in adverse pregnancy outcomes, compared with the conventional method for GDM treatment. In contrast, a New Zealand study showed that the most significant variables influencing birth weight in the diabetic pregnancy were gestational age at delivery; prepregnancy body mass index; maternal height; estimated weight gain during pregnancy; presence of hypertension; and cigarette smoking (the latter two having negative effects on birth weight).<sup>57</sup> The authors suggested that, within the limits of glycaemic control obtained in the study, birth weight was largely determined by maternal factors other than hyperglycaemia. Green *et al.* verified that maternal BMI played a role in the birth weight or BMI of infants.<sup>58</sup> Maternal weight gain correlates with birth weight in underweight and average-weight control women,

but not in overweight controls or in other patients with GDM.<sup>59</sup>

Sacks reviewed the link between macrosomia and gestational diabetes and suggested a consensus definition of fetal macrosomia be reached. Randomized trials were necessary, in which all factors influencing fetal growth and development were uniformly analysed to develop differential clinical interventions.<sup>60</sup> Nasrat *et al.* did not detect differences in the proportion of babies with birth weights larger than or equal to 2 SD above the mean, neonatal capillary blood glucose less than 1.5 mmol/L or a haematocrit reading larger than or equal to 65%, in between IGT women and controls.<sup>61</sup>

Li *et al.* conducted a small randomized controlled trial involving 216 women with an abnormal 100 g GTT.<sup>62</sup> Women with normal glucose tolerance (NGT) or IGT (as defined by the WHO criteria) were randomized to either treatment or control groups. The perinatal outcome in these two groups was comparable irrespective of glycaemic status. Women who were treated for IGT had smaller babies and 1 week earlier deliveries than the control group. Garner *et al.* carried out a prospective randomized controlled trial to compare fetal-neonatal maternal outcome in 300 women with gestational diabetes.<sup>63</sup> The result suggests that intensive treatment of GDM may have little effect on birth weight, birth trauma, operative delivery, or neonatal metabolic disorders.

### Long-term health outcomes of offspring

Freinkel developed the hypothesis of fuel-mediated teratogenesis; namely, that maternal fuels may influence the development of the fetus and that alterations occurring subsequent to organogenesis during the differentiation and proliferation of fetal cells could cause long-range effects on behavioural, anthropometric and metabolic function.<sup>64</sup> A study in rats reported by Gauguier *et al.* showed that mild hyperglycaemia in the fetus of female rats, induced by continuous glucose infusion during the last week of pregnancy, led to impairment of insulin secretion in the adult offspring independent of genetic or toxic interference.<sup>65</sup> This impairment can be transmitted to the subsequent generation by the mother via a non-genetic process. Similar findings in rats have been reported by others.<sup>66–68</sup> The CODIAB Study found a familial aggregation of diabetes that suggests a strong genetic component with a mode of inheritance that may be influenced by the maternal environment.<sup>69</sup> Findings from Simmons *et al.* also indicate that those with NIDDM are more likely to have a diabetic mother than father and that the mother was a more important conduit of inheritance for diabetes.<sup>70</sup>

In the population with the highest reported incidence and prevalence of NIDDM, Pettitt *et al.* revealed that NIDDM during pregnancy resulted in offspring having a higher prevalence of NIDDM between the age of 20 and 24 years than in offspring of non-diabetic women or offspring of women who developed diabetes immediately after the pregnancy.<sup>71</sup> After reviewing the long-term effects of a diabetic pregnancy on the offspring among Pima Indians, Pettitt *et al.* found that the offspring of women who had diabetes during pregnancy were, on average, more obese, had higher glucose concentrations and a higher incidence of diabetes than offspring of women who developed diabetes after pregnancy or who remained non-diabetic.<sup>72</sup> The authors of this study concluded

that the diabetic pregnancy, in addition to its effects on the newborn, compromises the subsequent growth and glucose metabolism of the offspring and that these effects are additional to genetically determined traits.

Other studies also suggest a pathogenic role of fetal and neonatal hyperinsulinism for the development of IGT in offspring of diabetic mothers<sup>58</sup> and a correlation of childhood obesity in offspring of diabetic mothers with amniotic fluid insulin (AFI).<sup>73</sup> In an attempt to test the hypothesis that long-term postnatal development may be modified by metabolic experiences *in utero*, Silverman and colleagues enrolled the offspring of women with IDDM, NIDDM or GDM from 1977 through to 1983 and assessed fetal beta-cell function by AFI at 32–38 weeks gestation.<sup>46</sup> They found that the 88 offspring of diabetic mothers had higher 2 hour glucose and insulin concentrations compared with the 80 control subjects of the same age and pubertal stage, and that the prevalence of IGT in the 10 to 16-year-old offspring of diabetic mothers was significantly higher than in the control group. However, IGT in the offspring was not associated with the aetiology of the mother's diabetes (gestational vs. pregestational) or macrosomia and treatment of GDM with insulin was not related to the development of IGT in the offspring.

The following concern was expressed by Pettitt: 'Diabetes is a vicious cycle; not only does the mother have problems in pregnancy, but the infants are likely to go on to be obese and to develop diabetes; they may already have diabetes by childbearing age'.<sup>4</sup> However, more studies are needed to learn whether this is true for other populations, particularly in populations with a low prevalence of NIDDM and/or high prevalence of GDM. More studies are also warranted in order to observe the effectiveness of intensive management of GDM during pregnancy on childhood obesity and on obesity developed later in life, and on IGT prevalence in the offspring of women with a history of prior GDM. This is because, theoretically, good glucose control in women with GDM would be expected to reduce insulin secretion in the fetus.

Apart from exploring somatic and metabolic changes in the offspring of mothers with diabetes during pregnancy, efforts have been made to investigate the influences of metabolic disturbances during pregnancy and prenatal and perinatal morbidity on neurodevelopment in infants of diabetic mothers. Petersen *et al.* identified a higher rate of early growth delay in diabetic pregnancies, associated with psychomotor deficits in the progeny at an age of 4–5 years.<sup>74</sup> Rizzo *et al.* reported that there was a significant correlation between second and third trimester glycaemic regulation (haemoglobin A<sub>1c</sub> and fasting plasma glucose levels) and three of four newborn behavioural dimensions of the Brazelton neonatal behavioural assessment scale, their responses were poorer as maternal glucose increased.<sup>75</sup> In the study of Silverman *et al.*,<sup>73</sup> similar findings were reported. The childhood intelligence quotient (IQ) at 4 years of age was found to be inversely correlated with second and third trimester maternal lipid metabolism (serum free fatty acids and beta-hydroxybutyrate). The inverse correlation between children's mental-developmental-index scores and maternal lipid metabolism in the second and/or third-trimester has also been shown by other studies of Rizzo.<sup>76,77</sup>

Sells *et al.* recently reported findings in 90 control infants and 109 infants of diabetic mothers, the latter including 70 'early entry' (good controlled) subjects and 39 'late entry' (poorly controlled) subjects.<sup>78</sup> Late-entry infants scored less well on language measures than the other groups. The less than optimal intellectual development was associated with reduced head circumference and the mean head size was correlated negatively with glycosylated haemoglobin levels during all three trimesters. Yet there were no differences identified in Bayley scores at 6, 12 and 24 months of age or in cognitive development at 3 years of age among control, early entry infants and late-entry infants. In another study of Rizzo *et al.*<sup>79</sup> involving 89 pregestational diabetic women, 99 gestational diabetic women and 35 normal gestational glucose women, no significant correlation emerged between either measure of child's IQ and any prevalent perinatal complications; the authors attributed this to prevailing practices in diabetes management and obstetric and neonatal care. Due to the fact that most of the subjects recruited in these studies had NIDDM or were mixed with GDM and normal control women, a question should be asked as to what extent GDM and its intensive treatment influences neurodevelopment in the fetus.

### Maternal outcomes

In some studies, there are higher risks of hypertension, pre-eclampsia,<sup>80–82</sup> polyhydramnios,<sup>82</sup> caesarean section<sup>32,83</sup> and diabetes later in life<sup>84</sup> in women with GDM. Among the risks, the most concerning is that these women are at an increased risk of developing overt diabetes, particularly NIDDM, later in life.<sup>81</sup>

Normal pregnancy is a state of relative insulin resistance<sup>85</sup> and independent of the well-known effect of weight gain, accelerates the development of NIDDM in women with a high prevalence of pancreatic beta-cell dysfunction, as indicated by a history of GDM.<sup>86</sup> Using the euglycaemic glucose clamp technique and erythrocyte insulin binding, Ryan *et al.* found that, during an insulin infusion of 40 mU/m<sup>2</sup>-min, with blood glucose clamped at a concentration of 75 mg/dL, glucose infusion rates were 213 ± 11 mg/m<sup>2</sup>-min, 143 ± 23 mg/m<sup>2</sup>-min and 57 ± 18 mg/m<sup>2</sup> in non-pregnant, non-diabetic pregnant and gestational diabetic women, respectively.<sup>87</sup> When the insulin infusion rate was increased to 240 mU/m<sup>2</sup>-min, the glucose infusion rates were 327 ± 11 mg/m<sup>2</sup>-min in non-pregnant women, 270 ± 31 mg/m<sup>2</sup>-min in non-diabetic pregnant women and 157 ± 26 mg/m<sup>2</sup>-min in gestational diabetic women. Insulin binding was similar in all three groups. It was suggested that the insulin resistance of pregnancy may include a decrease in presumed 'maximum' insulin responsiveness that results from a postreceptor defect in insulin action.

A longitudinal study in non-obese pregnant women was carried out by Catalano *et al.*<sup>88</sup> A significant 3.0- to 3.5-fold increase was found throughout gestation in first-phase and second-phase insulin releases during the intravenous glucose tolerance test. It was also demonstrated in the study, using the hyperinsulinaemia-euglycaemic clamp technique, that there was a significant 56% decrease in insulin sensitivity between 34 and 36 weeks' gestation. Of note, 39% of the total decrease in insulin sensitivity was evident by 12–14 weeks' gestation. Buchanan *et al.* used the minimal model analysis

of a frequently sampled intravenous glucose tolerance test to obtain concurrent measurement of whole-body insulin sensitivity and pancreatic beta-cell responsiveness to glucose during the third trimester of pregnancy.<sup>89</sup> They found that late normal pregnancy in lean and moderately obese women was associated with a two-thirds reduction in insulin sensitivity, as compared with the non-gravid state. This insulin resistance was compensated for by threefold increases in first- and second-phase insulin responses to intravenous glucose. Women with mild GDM in this study were found to have similar insulin sensitivity to those of normal pregnant women. However, insulin responses to glucose, especially the first-phase responses, were impaired in GDM.

Catalano *et al.* recently studied the pregravid status and longitudinal changes in carbohydrate metabolism during normal pregnancy and islet cell antibody-negative women with GDM.<sup>90</sup> This study also showed that there was a significant increase in the first-phase insulin response with advancing gestation in both the control and GDM groups, but the increase in the first-phase insulin response during pregnancy was significantly smaller in the GDM group. There was a significant decrease in insulin sensitivity in both groups with advancing gestation, but a significantly greater decrease in insulin sensitivity was found in the GDM group compared with the control group. In more recent studies,<sup>91–93</sup> the glucose intolerance in GDM was shown to be associated with more pronounced insulin resistance and impaired insulin secretion, which persisted after delivery.<sup>91,92</sup> Damm *et al.* recently reported a longitudinal study of plasma insulin and glucagon in women with previous GDM. Women who developed GDM had a relative insulin secretion deficiency, the severity of which was predictive for later development of diabetes.<sup>94</sup> However, it remains unanswered whether beta-cell dysfunction or insulin resistance develops first in the pathogenesis of GDM.

### Long-term health outcomes of women

In a sense, the insulin resistance during pregnancy could be regarded as a physiological glucose tolerance test which unmasks the subclinical abnormality either in beta-cell secretion function or insulin action. It has been demonstrated in several studies that women with a prior history of GDM are at high risk of developing NIDDM later in life. Kjos *et al.* performed 2 hour OGTT between 5 and 8 weeks postpartum in 246 women with recent GDM.<sup>95</sup> It was found that 48 (19%) of the patients had an abnormal OGTT in the early postpartum period, among which 25 (10%) had postpartum NIDDM and 23 (9%) had IGT. The prevalence of postpartum diabetes mellitus was found, in this study, to increase in parallel with the degree of maternal metabolic de-compensation during pregnancy. Greenberg *et al.* also found that at 6 weeks after delivery, glucose intolerance occurred in 34%, IGT in 18% and overt diabetes in 16% of women.<sup>96</sup> Predictive variables for postpartum glucose intolerance were identified as being a requirement for insulin (insulin vs. diet: 25 vs. 3% impaired glucose tolerance, 26 vs. 0% diabetes;  $P = 0.001$ ), poor glycemic control (any 2-hour postprandial blood sugar level of 150 mg/dL or higher: 34 vs. 5% diabetes;  $P = 0.005$ ), and the 50 g GCT value (200 mg/dL or higher: 32 vs. 6% diabetes;  $P = 0.01$ ).

Metzger *et al.* evaluated glucose tolerance during the first year postpartum in 113 women with GDM and found the incidence of abnormal glucose tolerance to be very high, 38% with diabetes and 19% with IGT.<sup>97</sup> They also found that virtually all women with antepartum fasting plasma glucose greater than or equal to 130 mg/dL (7.2 mmol/L) remained abnormal postpartum. Another study in Australia showed that 12 months after delivery, the cumulative prevalence of abnormal glucose tolerance in women with prior GDM was 33.3% (14 of 42), with 26% (10 of 42) being frankly diabetic, including two women with IDDM.<sup>98</sup> These findings suggest that unrecognized glucose intolerance may have accounted for quite a proportion of GDM diagnosed during pregnancy.

Catalano *et al.* found that abnormalities of insulin response and insulin resistance were present in 50% of women with previous GDM but with normal oral glucose tolerance.<sup>99</sup> Both impaired insulin response and insulin sensitivity have been identified in other studies.<sup>100,101</sup>

In line with subclinical abnormalities of glucose metabolism in women with a history of GDM, many long-term follow-up studies have observed high rates of progression to NIDDM in these women.<sup>84,102,103</sup> In the 15 years follow-up study of O'Sullivan, the incidences of diabetes in overweight and normal weight women with prior GDM were as high as 46.7 and 25.6%, respectively.<sup>102</sup> In contrast, the incidences in concurrent overweight and normal weight controls were only 4.5 and 1.9%, respectively. In a group of Latino women with prior GDM who did not have diabetes 4–16 weeks after delivery, Kjos *et al.*, using life table analysis, revealed a 47% cumulative incidence rate of NIDDM 5 years after delivery.<sup>103</sup> Similar findings were also reported in other populations.<sup>84,104,105</sup>

Henry *et al.* identified the ethnic difference in incidence of diabetes in women with prior GDM, finding that Vietnamese-born mothers had a greater risk of diabetes mellitus on follow-up; 25% of those who underwent follow-up testing had developed diabetes mellitus within 9 years of diagnosis of gestational diabetes, in comparison with 9% of Australian-born mothers.<sup>106</sup> Nevertheless, Pettitt *et al.* failed to show that among Pima Indians, women with IGT during pregnancy were at a higher risk of NIDDM than were women with normal glucose tolerance.<sup>107</sup> More follow-up studies of women with GDM are warranted, particularly in Asian women with GDM given the fact that very high incidences of GDM have been found among other Asian populations.<sup>10,108</sup> Such studies, however, require the evaluation of putative preventive strategies.

The most important long-term benefit of universal screening for GDM may be the possible prevention or delay of diabetes mellitus in women.<sup>109</sup> Although no reduction in subsequent diabetes due to insulin therapy during pregnancy was found in a 16 year prospective study of 615 GDM subjects,<sup>110</sup> the Da Qing IGT and Diabetes Study<sup>111</sup> and others showed that diet and/or physical exercise are able to retard the progress of IGT to NIDDM.<sup>112,113</sup> It can be expected that life-style intervention may reduce the subsequent IGT and NIDDM in women who have previously experienced GDM.

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