

---

**Section** **1** **Epidemiology and  
pathophysiology**

COPYRIGHTED MATERIAL



# 1

# Epidemiologic context of diabetes in pregnancy

David Simmons

Institute of Metabolic Science, Cambridge University Hospitals NHS Foundation Trust, Addenbrookes Hospital, Cambridge, UK

## PRACTICE POINTS

- The prevalence of all forms of diabetes in pregnancy, namely Type 1, Type 2, and gestational diabetes mellitus (GDM), ranges from below 2% to over 20%, although variations in definition, screening, and diagnostic criteria of GDM make comparisons difficult.
- The prevalence of Type 2 diabetes, GDM, and probably Type 1 diabetes in pregnancy is increasing and varies significantly between ethnic groups and between locations.
- The prevalence of some risk factors for GDM and Type 2 diabetes in pregnancy (e.g. obesity) is increasing.
- Adverse pregnancy outcomes are generally increased 2–7-fold in women with pre-existing diabetes and are similar for Type 1 and Type 2 diabetes.
- There is good evidence that intervention for diabetes in pregnancy can reduce adverse pregnancy outcomes: it has been estimated that for every US\$1 invested in diabetes in pregnancy, there is a saving of US\$3–4 on downstream health costs.
- The health, social, and economic impacts of intergenerational transmission of diabetes are unknown.

## BACKGROUND

Historically, the study of diabetes in pregnancy has focused on either women with Type 1 diabetes, whose poor obstetric outcomes once led to an editorial entitled “They give birth astride the grave”<sup>1</sup> or GDM, an entity which remains contentious,<sup>2,3</sup> with variable approaches to definition, screening, and diagnosis.<sup>4</sup> The current epidemic of obesity and diabetes among children, adolescents, and non-pregnant adults<sup>5</sup> has changed the situation, leading to growing numbers with Type 2

diabetes in pregnancy and GDM (including undiagnosed Type 2 diabetes).<sup>6–8</sup> In parallel, our understanding of the impact of diabetes in pregnancy for future generations,<sup>9</sup> and our increasing ability to reduce pregnancy complications,<sup>10</sup> and postpone, if not prevent, diabetes after GDM,<sup>11</sup> have emphasized the epidemiologic and public health importance of diabetes in pregnancy.

## OUTCOMES FROM DIABETES IN PREGNANCY

That there is no common unique pathognomonic complication of diabetes in pregnancy, combined with the apparent continuous relationship between glucose and fetal macrosomia, has resulted in a lack of consensus on the diagnosis of GDM. While diabetes in pregnancy is associated with increased obstetric risk compared with normal pregnancy, the overall contribution of diabetes to most obstetric and neonatal complications on a population basis is actually relatively low, with the largest impact being on shoulder dystocia (through GDM). Table 1.1 shows examples of odds ratios for each obstetric and neonatal complication by diabetes type and the proportion that diabetes in pregnancy contributes on a population basis.<sup>12–15</sup>

Apart from malformations, which are likely to have resulted from preconceptional or periconceptional hyperglycemia, improvements in obstetric practice have led to major reductions in adverse outcomes. Avoidance of such outcomes may dictate the need for complex obstetric decision-making, with the inevitable increase in fetal monitoring (see chapter 12) and which is strongly influenced by the preconceptional and antenatal management of hyperglycemia (see chapters 8 and 10). The importance of other metabolic factors, such as obesity<sup>16–19</sup> and hypertriglyceridemia,<sup>20</sup> in pregnancy are also now increasingly being recognized.

*A Practical Manual of Diabetes in Pregnancy*, 1st Edition.  
Edited by David R. McCance, Michael Maresh and David A. Sacks.  
© 2010 Blackwell Publishing

**Table 1.1** Examples of odds ratios of diabetes for each obstetric and neonatal complication and the proportion that diabetes in pregnancy contributes on a population basis.<sup>12–15</sup>

	Odds ratio	Type 1 diabetes (%)	Type 2 diabetes (%)	Gestational diabetes (%)	No known diabetes (%)
Perinatal mortality	3	0.2	0.9	1.7	97.2
Malformations <sup>1</sup>	7	2.5		0 <sup>2</sup>	97.5
Cesarean Section <sup>1</sup>	2	1.6		4.3	94.1
Birthweight $\geq 4.5$ kg <sup>1</sup>	3	2.6		7.3	90.1
Shoulder dystocia <sup>1</sup>	3	<0.1 <sup>3</sup>		23.5	76.5

<sup>1</sup>Type 1 and Type 2 diabetes combined

<sup>2</sup>Those with malformations considered undiagnosed Type 2 diabetes, small numbers otherwise

<sup>3</sup>Very few on a population basis; many who will likely develop shoulder dystocia are delivered by cesarean section

The long-term implications of diabetes in pregnancy for the offspring, particularly obesity and Type 2 diabetes, are discussed in chapter 25. While there is early evidence that optimal management of diabetes during pregnancy may reduce excess adiposity in the offspring (and hopefully, ergo, subsequent diabetes),<sup>21</sup> this urgently requires confirmation. As yet there is no evidence that poorer neurodevelopmental outcomes, which may be associated with GDM, are amenable to change.<sup>22</sup> Such analyses can be confounded by the associations between socioeconomic status and both GDM and achievement.<sup>23</sup>

## DIAGNOSIS OF GESTATIONAL DIABETES MELLITUS

While it is generally accepted that severe hyperglycemia in pregnancy is associated with adverse maternal fetal outcome, the significance of lesser degrees of hyperglycemia, along with the lack of common pathognomonic sequelae, and the apparent continuum between glucose and, for example, fetal macrosomia<sup>24</sup> have fuelled the lack of consensus on the optimal glycemic threshold for diagnosis of hyperglycemia in pregnancy. This is discussed in chapter 6, but essentially involves deriving a glycemic threshold above which the benefits of intervention outweigh any harm and are cost-effective.

Outside of pregnancy, the 75-g 2-hour oral glucose tolerance test (OGTT) is used. Diabetes and prediabetes are defined by their association with macrovascular and microvascular complications, the clinical appearance of the latter (retinopathy) being largely unique to diabetes. As a result, diabetes in non-pregnant adults has a globally agreed definition, as does impaired glucose tolerance

(IGT) (Table 1.2). There remains disagreement between the World Health Organization (WHO) and the American Diabetes Association (ADA) definition of impaired fasting glucose (Table 1.2). As GDM is defined as carbohydrate/glucose intolerance first identified/with new onset in pregnancy, intuitively it would be thought that by definition, the criteria for diagnosis of GDM would include a fasting glucose of greater than or equal 5.6 or 6.1 mmol/L ( $\geq 101$ – $110$  mg/dL) (ADA or WHO) and/or a 2-hour glucose greater than or equal to 7.8 mmol/L (140 mg/dL), with potentially some modification should pregnancy outcomes be quantitatively worse below these cut-off points. This is discussed more fully in chapter 6.

There have been multiple attempts to define the glycemic thresholds for fetal and maternal outcomes (i.e. diagnostic criteria) for GDM (Table 1.2). These have traditionally been based upon a fasting blood glucose test, 50–100-g glucose load,<sup>4</sup> followed by 1–3 hours of blood glucose testing, and involving interpretation of the results either singly or in combination.

A global move to standardize the diagnostic criteria was the rationale for the Hyperglycaemia and Adverse Pregnancy Outcomes (HAPO) study, a large study among 25 000 women across continents and, importantly, involving many ethnic groups.<sup>24</sup> Of importance is the fact that this study showed that the impact of hyperglycemia for maternal/fetal outcome was applicable to all ethnic groups<sup>24</sup> and independent of maternal obesity, a recognized risk factor *per se* for large babies.<sup>16–19</sup> Further analysis of data from the HAPO study will address the important question of whether different glycemic thresholds are needed to predict a greater risk of glucose-sensitive adverse outcomes.

Table 1.2 Summary of international guidelines for the screening and diagnosis of gestational diabetes (primarily from Cutchie *et al*<sup>1</sup>).

Organization	Screening	Diagnosis				Abnormal values for diagnosis
		Fasting (mmol/L [mg/dL])	1 h (mmol/L [mg/dL])	2 h (mmol/L [mg/dL])	3 h (mmol/L [mg/dL])	
WHO (non-pregnant)	No recommendation	Diabetes $\geq 7.0$ [126] IGT $< 7.0$ [126]	and/or	$\geq 11.1$ [200] 7.8–11.0 [140–198]		One
ADA (non-pregnant)	All $\geq 45$ years If $< 45$ years: BMI $\geq 25$ and one other risk factor Fasting glucose: OGTT if FBG $\geq 5.6$ mmol/L ( $\geq 100$ mg/dL) All except low risk High risk: proceed to OGTT Moderate risk: 50-g GCT; if 1-h BGL $\geq 7.8$ mmol/L ( $\geq 140$ mg/dL), proceed to OGTT 75-g or 100-g OGTT	Diabetes $\geq 7.0$ [126] IGT $< 7.0$ [126]	and/or	$\geq 11.1$ [200] 7.8–11.0 [140–198] $< 11.1$ [200]		One
ADA	All except low risk	5.3 [95]	10.0 [180]	8.6 [155]	7.8 [140] (100 g only)	Two or more values
ACOG	Either screen all except low risk or universal screening. 50-g GCT; if 1-h BGL $\geq 7.8$ mmol/L ( $\geq 140$ mg/dL), proceed to OGTT. 100-g OGTT	C&C 5.3 [95] NDDG 5.8 [104]	10.0 [180] 10.6 [191]	8.6 [155] 9.2 [166]	7.8 [140] 8.0 [144]	Two or more values
CDA	Screen all with a 50-g GCT at 24–28 weeks, but in first trimester if high risk. 1-h glucose $> 10.3$ mmol/L ( $> 185$ mg/dL), diagnostic for GDM. If 1-h glucose 7.8–10.2 mmol/L (140–184 mg/dL) proceed to 75-g OGTT	5.3 [95]	10.6 [191]	8.9 [160]		Two (if only one abnormal defined as IGT of pregnancy)
BCRCP	All except low risk. 50-g GCT. If $\geq 7.8$ mmol/L ( $\geq 140$ mg/dL), 100-g OGTT. If $> 10.3$ mmol/L ( $> 185$ mg/dL), diagnostic for GDM	5.3 [95]	10.0 [180]	8.6 [155]	7.8 [140]	Two or more values

Table 1.2 Continued

Organization	Screening	Diagnosis			Abnormal values for diagnosis	
		Fasting (mmol/L [mg/dL])	1 h (mmol/L [mg/dL]) and/or	2 h (mmol/L [mg/dL])		3 h (mmol/L [mg/dL])
DUK	No routine screening 75-g OGTT	7.0 [126]	and/or	7.8 [140]	–	One
SIGN	All. Random glucose at 28 weeks 75-g OGTT	5.5 [99]	–	9.0 [162]	–	One
CREST	All. Random glucose at 28 weeks 75-g OGTT	5.5 [99]	–	9.0 [162]	–	One
IDF	All except low risk 75-g OGTT	5.3 [95] (75g)	–	8.6 [155]	–	–
JDA	All by casual plasma glucose 75g OGTT	5.5 [99]	10.0 [180]	8.3 [149]	–	Two or more values
ADIPS	All unless resources are limited. 50 g	5.5 [99]	–	75g	–	One
RANZCOG	GCT; if 1-h BGL $\geq 7.8$ mmol/L proceed to 75-g OGTT	5.5 [99]	–	8.0 [144](Aus) 9.0 [162] (NZ)	–	–
WHO (if pregnant)	All except low risk 75-g OGTT	$\geq 7.0$ [126]	and/or	$\geq 7.8$ [140]	–	One
NICE (2008)	Select ethnic groups, BMI $\geq 30$ , first-degree family history, previous GDM, previous baby $\geq 4.5$ kg	$\geq 7.0$ [126]	–	$\geq 7.8$ [140]	–	One

WHO, World Health Organization; ADA, American Diabetes Association; ACOG, American College of Obstetrics and Gynaecology; C&C, Carpenter and Coustan; NDDG, National Diabetes Diagnostic Group; CDA, Canadian Diabetes Association; BCRCP, British Columbia Reproductive Care Program; DUK, Diabetes UK; SIGN, Scottish Intercollegiate Guidelines Network; CREST, Clinical Resource Efficiency Support Team; IDF, International Diabetes Federation; JDA, Japanese Diabetic Association; ADIPS, Australasian Diabetes in Pregnancy Society; RANZCOG, Royal Australasian College of Obstetrics and Gynaecology; NICE, National Institute for Health and Clinical Excellence; OGTT, oral glucose tolerance test; GCT, glucose challenge test; ICT, impaired glucose tolerance; IFG, impaired fasting glucose; GDM, gestational diabetes mellitus; FBG, fasting blood glucose; BGL, blood glucose level; BMI, body mass index

## PREVALENCE OF PREGESTATIONAL DIABETES IN PREGNANCY

The prevalence of Type 1 and Type 2 diabetes in pregnancy would be expected to reflect the rates of diabetes in the background population.<sup>25,26</sup> However, the standard fertility ratio (SFR) is low in Type 1 diabetes (0.80, 95% CI 0.77–0.82), and is particularly low among women with retinopathy, nephropathy, neuropathy, or cardiovascular complications (0.63, 0.54, 0.50, and 0.34, respectively).<sup>27</sup> While fertility rates in Type 2 diabetes have not been reported, they would also be expected to be low (particularly in view of the additional associated obesity, polycystic ovarian syndrome [PCOS], and vascular disease).

The incidence of Type 1 and the prevalence of Type 2 diabetes has been increasing over time,<sup>28</sup> with a reduction in the age at diagnosis of Type 2 diabetes. Both of these factors predict an increasing number of women with pregestational diabetes. However, the more rapid increase in Type 2 diabetes in pregnancy has resulted in some diabetes clinics now seeing a predominance of Type 2 over Type 1 diabetes, which has been accentuated further by ethnicity. In the US, the ratio of women with Type 1 to Type 2 diabetes has shifted from 3:1 to 1:2 between 1980 and 1995.<sup>28</sup> This may be partly due to changes in the population (e.g. in Birmingham, UK the ratio of Type 1 to Type 2 diabetes was 1:2 in South Asians but 11:1 in Europeans<sup>29</sup>). Meanwhile, there have been other important changes. Women with diabetes in pregnancy are now expected to survive. The perinatal mortality for pregnancies complicated by Type 1 diabetes has also dropped from 40% to much nearer the background rate.<sup>23,28</sup> In Type 2 diabetes, the evolving evidence suggests that perinatal mortality and the frequency of congenital malformations are similar to those of Type 1 diabetes,<sup>23</sup> including in those women diagnosed with GDM but found to have Type 2 diabetes postnatally.<sup>6,29</sup> While these trends are more often seen in women of non-European descent, it is likely that a similar picture will be seen in all groups eventually.

To date there are few reports of the prevalence of monogenetic forms of diabetes or secondary diabetes in pregnancy. Glucokinase mutations are present in up to 5–6% of women with GDM and up to 80% of women with persisting fasting hyperglycemia outside pregnancy, a small glucose increment during the OGTT, and a family history of diabetes.<sup>30</sup> Cystic fibrosis is associated with a doubling in the prevalence of diabetes outside of pregnancy, with a further increase during pregnancy (e.g. from 9.3% at baseline to 20.6% during pregnancy, and 14.4% at follow-up).<sup>31</sup>

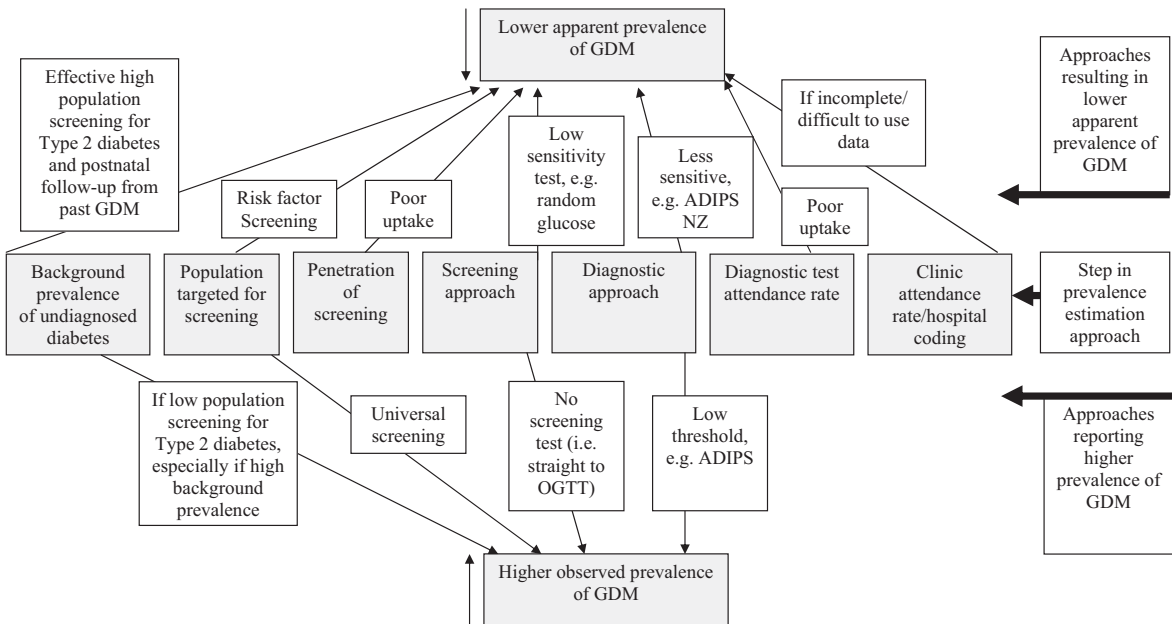
## PREVALENCE OF GESTATIONAL DIABETES

The prevalence of GDM globally in 1998 was examined by King *et al.*<sup>32</sup> An epidemiologic comparison between studies is difficult for the reasons shown in Fig. 1.1 and discussed more fully in chapters 5 and 6. In addition, screening too early (before 24 weeks) will result in fewer cases of GDM being detected. Some women achieve the criteria for GDM only later in pregnancy and will not be diagnosed with the conventional screening approach, which occurs between 24 and 28 weeks.

As highlighted above, there are differences in the rates of GDM when diagnosed by different criteria,<sup>33</sup> both within and between populations (Fig. 1.2). Notwithstanding the different diagnostic criteria, there are major differences in prevalence of GDM between ethnic groups, reflecting both the background prevalence of Type 2 diabetes and the age at onset (the “underwater volcano hypothesis” [Fig. 1.3]).<sup>34</sup> This hypothesis proposes that GDM is more common in people who are temporally closer to developing Type 2 diabetes.

These prevalence rates vary within the same ethnic group in different locations, with migrant populations generally having a higher prevalence than those remaining in traditional rural areas, probably relating to lifestyle change (higher energy diet, less physical activity) and greater adiposity. The prevalence has also generally increased over time (Fig. 1.4).<sup>7,35</sup> While this most likely reflects the epidemics of obesity and Type 2 diabetes in the non-pregnant state, an additional feature is likely to be the increasing age at which pregnancy occurs, and for some total populations, the immigration of high-risk ethnic groups (e.g. in Auckland, New Zealand, numbers of women with GDM doubled over 4 years due to a combination of these factors<sup>36</sup>). Such data need careful scrutiny to recognize these factors and to ensure that no change in ascertainment (e.g. screening approaches) or diagnostic criteria have occurred.

All populations apart from those of non-European descent (and even including some European populations), are now considered at such high risk that most guidelines suggest that these ethnic groups require universal screening.<sup>4</sup> The growth and clinical importance of undiagnosed Type 2 diabetes in pregnancy (i.e. the high end of GDM) also supports a universal screening approach in these populations, both at first antenatal assessment and at the more traditional 24–28 weeks of gestation. With the growing numbers of women with



**Fig. 1.1** Difficulties in comparing prevalence data in gestational diabetes mellitus (GDM) with different approaches (personal observations). ADIPS, Australian Diabetes in Pregnancy Society.

GDM, including undiagnosed Type 2 diabetes in pregnancy, the case for universal screening is becoming persuasive.<sup>37</sup> Prior to the most recent data, the 4th Chicago Workshop on GDM<sup>38</sup> recommended screening of all but those at very low risk (i.e. under 25 years, slim, no risk factors), a group of women who are becoming increasingly uncommon in modern pregnancy clinics. Surprisingly, during an obesity and diabetes epidemic, the latest recommendations from the National Institute for Health and Clinical Excellence (NICE) in the UK,<sup>39</sup> recommend screening using very few risk factors, even excluding older women and those with PCOS from those warranting screening. Decisions underlying these recommendations have been informed by erroneous economic analyses, including the exclusion of (1) identifying women at high risk of future diabetes who could benefit from diabetes preventative intervention, (2) the benefits in the offspring from reduced exposure to maternal hyperglycemia, and (3) future pregnancies complicated by undiagnosed diabetes, as well as an underestimate of reduced benefits when using complex screening approaches.

### Risk factors for gestational diabetes mellitus

While obesity, ethnicity, maternal age, and a family history of diabetes are the major risk factors for GDM, other more traditional factors have been used in selective screening approaches<sup>40</sup> (Table 1.3), including parity and a previous macrosomic baby. Some studies have suggested that multifetal pregnancies (e.g. twins and triplets) may be at increased risk of GDM, although others have not confirmed this.<sup>40</sup> There is increasing evidence of the importance of PCOS as a risk factor for both GDM and undiagnosed Type 2 diabetes in pregnancy. It therefore has been suggested in some countries that prior to treating PCOS with, for example, metformin or clomiphene to assist conception, women should have an OGTT.<sup>41</sup>

Another group of women at risk of GDM are those with a previous history of GDM,<sup>42</sup> particularly in association with excess weight/weight gain between pregnancies and where previous GDM was diagnosed early in pregnancy and required treatment with insulin.<sup>43</sup>

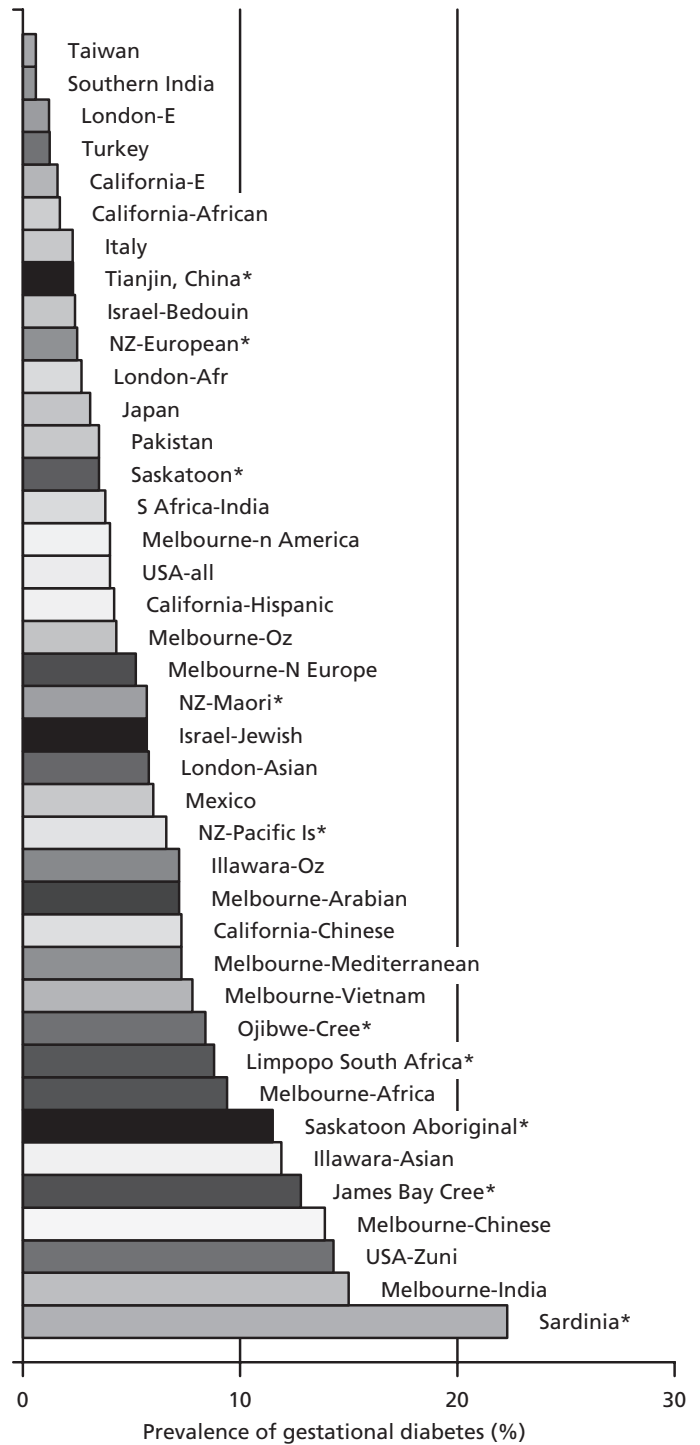
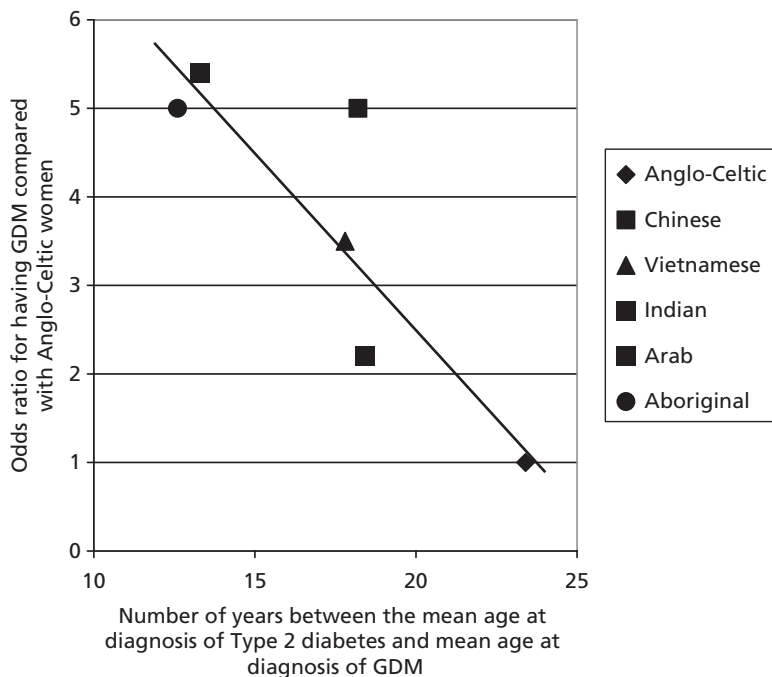


Fig. 1.2 Prevalence of gestational diabetes in different populations at different times (\*since King 1998,<sup>32</sup> includes<sup>63-70</sup>).



**Fig. 1.3** “Underwater volcano” hypothesis: Relationship between risk of gestational diabetes mellitus (GDM) in comparison with Anglo-Celtic women and time between mean age at diagnosis of Type 2 diabetes and diagnosis of gestational diabetes mellitus.<sup>34</sup>

### LONG-TERM IMPLICATIONS OF DIABETES IN PREGNANCY FOR THE MOTHER

The original study by O’Sullivan, from which the current US diagnostic criteria are derived, focused on the long-term risk of permanent diabetes in the mother who had hyperglycemia during pregnancy.<sup>44</sup> The overall literature would suggest a 5–28-year risk of developing permanent diabetes (predominantly Type 2 diabetes) of 17–63%.<sup>45</sup> Approximately 50% of those with autoantibodies develop Type 1 diabetes,<sup>46</sup> and a small number with antibodies are at least initially considered to have Type 2 diabetes.<sup>47</sup> The excess risk of diabetes among those with previous GDM is now seen in all populations studied, with an estimated odds ratio of 6.0 and population attributable risk of 0.10–0.31.<sup>45</sup> Evidence also now suggests that women with additional pregnancies may have an accelerated progression to Type 2 diabetes, as shown in one study by a relative risk of 3.34 (1.80–6.19).<sup>48</sup> This proposal has biologic plausibility in that an additional 9 months of insulin resistance are imposed upon a woman who already has a degree of insulin resistance. Other risk factors for progression to permanent diabetes are largely related to the level of antenatal glycemia, gestational age at diagnosis of GDM, and weight gain.<sup>49</sup>

The incidence of progression to frank diabetes increases markedly in the first 5 years postpartum and then plateaus after approximately 10 years.<sup>49</sup> Such progression to diabetes among women with past GDM can be reduced, as was shown in the Diabetes Prevention Project through both lifestyle- and medication-based interventions beyond the postpartum period.<sup>10</sup> Currently, systems are generally not in place to provide follow-up or intervention. Post-natal follow-up rates can be poor, even for women with Type 2 diabetes, possibly because of family demands.<sup>50</sup>

### DIABETES IN FUTURE GENERATIONS

A small number of babies may experience long-term sequelae from congenital malformations and birth trauma (Table 1.1); however, the impact of growing in an adverse intrauterine milieu is now becoming increasingly evident.<sup>9</sup> Long-term studies of pregnancies complicated by Type 1 diabetes, Type 2 diabetes, and GDM, including different ethnic groups and countries, suggest that exposure to a “diabetic” intrauterine environment is associated with an increase in risk of future obesity, IGT, and diabetes (see chapter 25).<sup>51</sup> Among Pima Indians, diabetes is much more common in the offspring of women with maternal diabetes occurring during rather than after pregnancy<sup>52</sup> (see chapter 25).

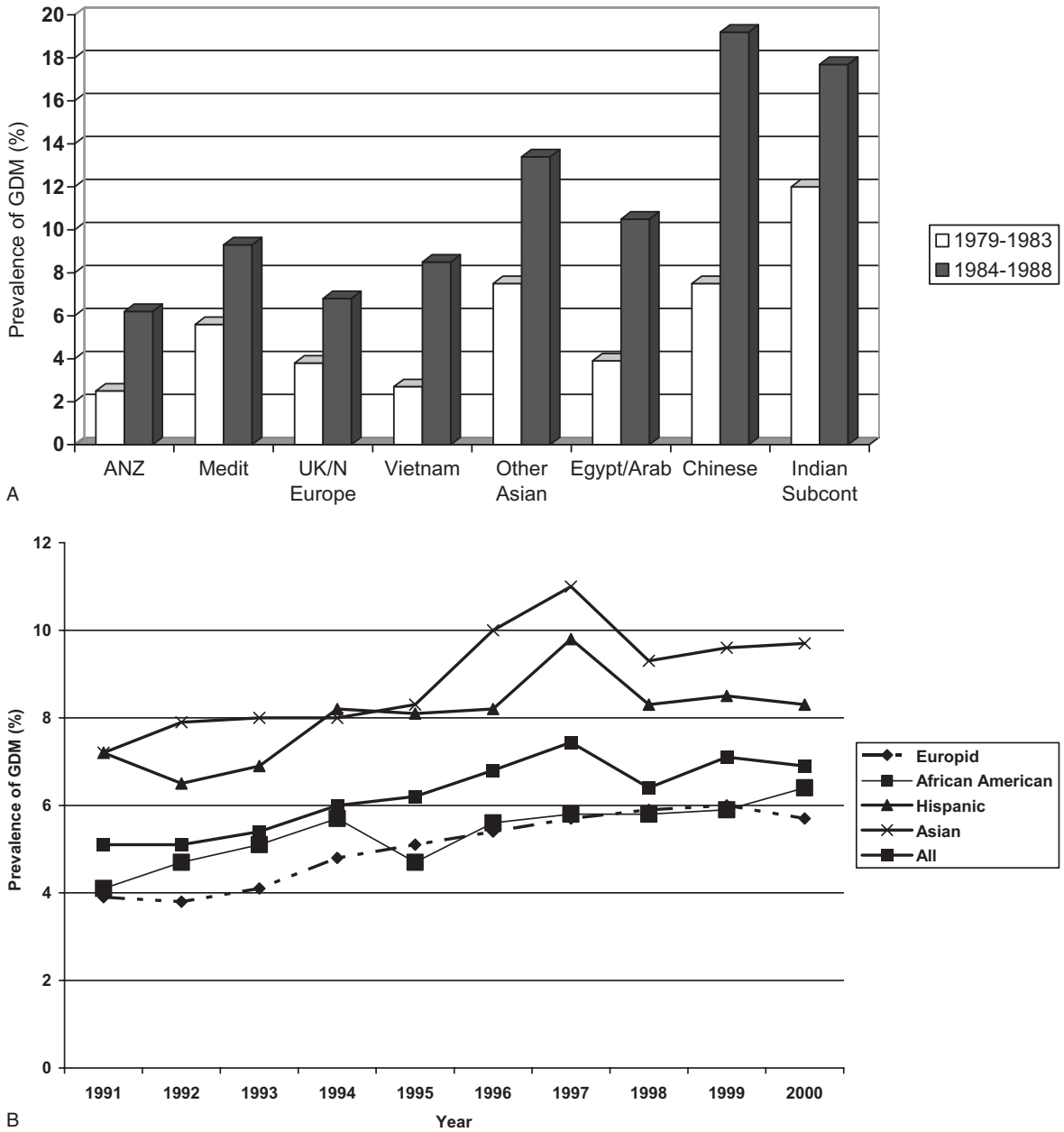


Fig. 1.4 Changing prevalence of gestational diabetes mellitus (GDM) over time in different populations. (A) Increasing prevalence of GDM in Melbourne, Australia 1979–1988.<sup>35</sup>

(B) Increasing prevalence of GDM among different groups in Northern California between 1991 and 2000.<sup>7</sup>

It is not known if intervention during or before pregnancy will ameliorate this “potential amplifier” for the current epidemic of obesity and diabetes. Obtaining long-term data will take many decades. In one small, non-randomized study, adiposity was found less often in the offspring of mothers with GDM treated with insulin than in the offspring of mothers treated with diet alone, but further evidence is needed on whether preconception/

antenatal interventions are of benefit.<sup>21</sup> However, if intrauterine exposure to diabetes is known, then the offspring can be identified as high risk, followed up, and have childhood-based interventions implemented as they become practicable.

**Table 1.3** Risk factors for gestational diabetes mellitus (GDM).

**Maternal demographic and physical factors**

- Ethnicity (non-European)
- Increasing age
- Family history of diabetes
- Short stature
- Low birthweight
- Parity

**Maternal clinical factors**

- Overweight/obesity
- Diet high in red and processed meat
- Pregnancy weight gain
- Physical inactivity
- Polycystic ovarian syndrome
- $\alpha$ -Thalassemia trait
- High blood pressure
- Multiple pregnancy

**Past obstetric history**

- Macrosomia
- Stillbirth
- Past GDM

**HEALTH ECONOMIC IMPLICATIONS**

A thorough health economic analysis regarding diabetes in pregnancy will require an examination of each transitional probability between clinical states and the cost and benefit from each intervention. Table 1.4 summarizes the stages in management and possible interventions. For diabetes in pregnancy, uniquely, such analyses need to include the costs of any long-term effects (beneficial or harmful) on the offspring. Preconception management of Type 1 and Type 2 diabetes, including tight glucose control, has been shown to be cost-effective, with a cost-benefit ratio of 1:3.5<sup>53</sup> for each US dollar invested. While there is also information on obstetric complications (e.g. brachial nerve palsy), it is unknown whether intervention reduces the future risk of obesity, Type 2 diabetes, and neurodevelopmental sequelae. Any such cost-benefit analysis is therefore likely to be incomplete. This is of particular importance in the debate over screening for GDM. Furthermore, implementation costs and uptake need to be included in any analysis, with an awareness that the more complex an approach, the less likelihood that uptake will be complete. The cost-effectiveness of whether or not and how to screen for GDM has been a longstanding issue.<sup>54</sup> It has been suggested that

**Table 1.4** Cost components in diabetes in pregnancy and potential savings from intervention.

	Interventions	Potential savings
<b>Type 1 and Type 2 diabetes</b>		
Preconception	Optimization of metabolic control, folate therapy, medication optimization	Malformations Fetal loss sequelae
Antenatal management	Optimization of metabolic control Optimization of obstetric management	Neonatal, maternal birth complications Offspring risk of diabetes, obesity
Retinal management	Retinal screening, laser if needed	Vitreous surgery, cesarean section
<b>Gestational diabetes mellitus (GDM)</b>		
Diagnosis of GDM	Screening and diagnosis program	
Antenatal management	Optimization of metabolic control Optimization of obstetric management	Neonatal, maternal birth complications Offspring risk of diabetes, obesity
Retinal management	Retinal screening if likely undiagnosed Type 2 diabetes, laser if needed	Vitreous surgery, cesarean section (rare)
Postnatal screening and intervention	Screening Primary prevention (lifestyle, drugs)	Prevention of permanent diabetes Prevention of undiagnosed Type 2 diabetes in pregnancy

approximately US\$3–4 would be saved for every US\$1 expended.<sup>55,56</sup> Improvements in outcomes in the intensive group in the Australian Carbohydrate Intolerance in Pregnancy Study (ACHOIS) suggest that benefits would be even greater if quality of life measures were included, particularly the benefits on postnatal depression.<sup>10</sup> This study has now shown GDM management to be cost-effective with an incremental cost per additional serious perinatal complication of US\$27 503, per perinatal death prevented of US\$60 506, and per discounted life year gained of US\$2988.<sup>57</sup> One small study showed that case management (i.e. allocation of a health professional to manage closely individual cases on a day-by-day basis) of women with diabetes in pregnancy was associated with reductions in the need for hospitalization (a major cost of care), as well as improved glycemic control and increased uptake of a postnatal OGTT.<sup>58</sup>

Intervention to prevent progression from prediabetes to diabetes using either lifestyle measures or medication in women with previous GDM was shown to be cost-effective in the Diabetes Prevention Project.<sup>59</sup> With the population attributable fraction for diabetes estimated at 10–31%, such an approach could have a significant impact on the current diabetes epidemic.<sup>45</sup>

### Postpartum screening

Kim and colleagues examined the efficacy and cost of postpartum screening strategies for diabetes among women with previous GDM and concluded that an OGTT every 3 years had the lowest cost per case of detected diabetes.<sup>60</sup>

---

## THE WAY FORWARD

Epidemiologically, the way ahead differs to some extent according to the type of diabetes. Much is already known about Type 1 diabetes in pregnancy, where the diagnosis is clear and extensive research databases exist. For Type 2 diabetes, there is a growing body of literature regarding prevalence and outcomes, but this remains insufficient for many populations, and relatively little is known of the impact of undiagnosed Type 2 diabetes. Further research must focus on GDM given the current evidence which suggests that this condition has a large population health impact on future diabetes for both mother and offspring.

An epidemiologic comparison of the prevalence of diabetes in pregnancy among various populations is becoming increasingly difficult. The identification and collation

of such descriptive studies is difficult. The recent UK Confidential Enquiry into Maternal and Child Health (CEMACH) study showed that it is possible (with a great deal of effort and good will) to describe a national epidemiologic snapshot of Type 1 and Type 2 diabetes in pregnancy and the related outcomes.<sup>23</sup> This study was able to link outcome with health service quality improvement and audit processes. A similar attempt to develop an Australasian database and benchmarking service has been piloted successfully, involving testing paper, and standalone and networked electronic methods for collecting data.<sup>61</sup> The ultimate goal would be to develop a global database, possibly under the auspices of the International Association of Diabetes in Pregnancy Study Groups, to allow easy description of the epidemiology of diabetes in pregnancy, to benchmark prevalence and outcomes, and to compare process (e.g. proportion of women receiving folate therapy, and proportion of women screened for GDM). This would also support the existence of such databases within nations and facilitate linkage to evaluate and support interventions from pre-conception counseling to postnatal OGTT follow-up in GDM.

The second major area for development remains how to best manage GDM on a population basis. A universally agreed set of diagnostic criteria derived from the HAPO study<sup>24</sup> will be a major step forward. Systematic screening, prevention, monitoring, and quality assurance programs are increasingly being implemented alongside the growth in evidence-based clinical practice. While long-term follow-up studies of the offspring are planned, data from these will take many years and possibly decades to emerge.

If we are, finally, to introduce a systematic approach to the screening for and diagnosis of GDM, similar to screening for syphilis, rubella immunity, and other conditions, with a high penetration, then there will be implications for health providers. The numbers of women diagnosed with GDM will increase dramatically in those places without good penetration of systematic screening currently. Those at the “lower end” of the GDM glycemia range have very different needs from those at the “higher end”. Many of the former may be suitable for obstetric management in the community, rather than specialist clinics, as found in California.<sup>62</sup> Criteria for triaging and referral need further development. If models of care are to shift, then there is an urgent need to implement quality assurance now, so that any changes in trends from the resulting changes in practice and the increase in demands can be monitored and acted upon.

A systematic approach to the follow-up of women with previous GDM and the offspring of all women with diabetes in pregnancy also needs to be put in place. Whether this follow-up is through a centralized (e.g. cervical cancer), devolved (e.g. hypertension) or hybrid approach will depend on the individual health system. Whatever system is implemented, there needs to be linkage with approaches to preventing obesity, promoting physical activity, and preventing or delaying progression to Type 2 diabetes.

In conclusion, the epidemiology of diabetes in pregnancy is constantly changing. The growth in information management, evidence for clinical management, and consensus on how to detect, manage, and follow-up diabetes in pregnancy will clearly continue into the future.

## REFERENCES

- Drury ML. "They give birth astride of a grave". *Diabet Med* 1989;**6**:291–8.
- Jarrett RJ. Gestational diabetes: a non entity? *Br Med J* 1993;**306**:37–8.
- Harris MI. Gestational diabetes may represent discovery of preexisting glucose tolerance. *Diabetes Care* 1988;**11**: 401–11.
- Cutchie W, Simmons D, Cheung NW. Comparison of international and New Zealand guidelines for the care of pregnant women with diabetes. *Diabet Med* 2006;**23**:460–8.
- Zimmet P, Alberti KGMM, Shaw J. Global and societal implications of the diabetes epidemic. *Nature* 2001;**414**: 782–7.
- Feig DS, Palda VA. Type 2 diabetes in pregnancy: a growing concern. *Lancet* 2002;**359**:1690–2.
- Ferrara A. Increasing prevalence of gestational diabetes: a public health perspective. *Diabetes Care* 2007;**30** (Suppl 2): S141–S146.
- Lawrence JM, Chen W, Contreras R, Sacks D. Trends in the prevalence of preexisting diabetes and gestational diabetes mellitus among a racially/ethnically diverse population of pregnant women 1999–2005. *Diabetes Care* 2008;**31**:899–904.
- Freinkel N. Banting Lecture 1980. Of pregnancy and progeny. *Diabetes* 1980;**29**:1023–35.
- Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS. Effect of treatment of gestational diabetes on pregnancy outcomes. Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) Trial Group. *N Engl J Med* 2005;**352**:2477–88.
- Ratner RE. Prevention of Type 2 diabetes in women with previous gestational diabetes. *Diabetes Care* 2007;**30** (Suppl 2):S242–S245.
- Cundy T, Gamble G, Townend K, Henley PG, MacPherson P, Roberts AB. Perinatal mortality in Type 2 diabetes mellitus. *Diabet Med* 2000;**17**:33–9.
- Lang U, Künzel W. Diabetes mellitus in pregnancy. management and outcome of diabetic pregnancies in the state of Hesse, F.R.G.; a five-year-survey. *Eur J Obstet Gynecol Reprod Biol* 1989;**33**:115–29.
- Remsberg KE, McKeown, McFarland KF, Irwin LS. Diabetes in pregnancy and cesarean section. *Diabetes Care* 1999;**22**: 1561–7.
- Tan YY, Yeo GS. Impaired glucose tolerance in pregnancy – is it of consequence? *Aust N Z J Obstet Gynecol* 1996; **36**:248–55.
- Ricart W, Lopez J, Mozas J, et al. Spanish Group for the Study of the Impact of Carpenter and Coustan GDM Thresholds. Body mass index has a greater impact on pregnancy outcomes than gestational hyperglycaemia. *Diabetologia* 2005;**48**:1736–42.
- Jensen DM, Ovesen P, Beck-Nielsen H, et al. Gestational weight gain and pregnancy outcomes in 481 obese glucose-tolerant women. *Diabetes Care* 2005;**28**:2118–22.
- Simmons D. Relationship between maternal glycaemia and birthweight among women without diabetes from difference ethnic groups in New Zealand. *Diabet Med* 2007;**24**:240–4.
- Catalano PM. Obesity and pregnancy – the propagation of a vicious cycle? *J Clin Endocrinol Metab* 2003;**88**:3505–6.
- Knopp RH, Magee MS, Walden CE, Bonet B, Benedetti TJ. Prediction of infant birth weight by GDM screening tests. Importance of plasma triglyceride. *Diabetes Care* 1992;**15**: 1605–13.
- Simmons D, Robertson S. Influence of maternal insulin treatment on the infants of women with gestational diabetes. *Diabet Med* 1997;**14**:762–5.
- Ornoy A, Wolf A, Ratzon N, Greenbaum C, Dulitzky M. Neurodevelopmental outcome at early school age of children born to mothers with gestational diabetes. *Arch Dis Child* 1999;**81**:10F–14F.
- Confidential Enquiry into Maternal and Child Health (CEMACH). *Pregnancy in Women with Type 1 and Type 2 Diabetes in 2002–2003, England, Wales and Northern Ireland*. London: CEMACH, 2005.
- The HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med* 2008;**358**:1999–2002.
- World Health Organisation [homepage on the Internet]. Definition, diagnosis and classification of Diabetes Mellitus and its complications, 1999. [whqlibdoc.who.int/hq/1999/WHO\\_NCD\\_NCS\\_99.2.pdf](http://whqlibdoc.who.int/hq/1999/WHO_NCD_NCS_99.2.pdf)
- IDF Diabetes Atlas. Brussels, 2006. [www.eatlas.idf.org/Prevalence](http://www.eatlas.idf.org/Prevalence)
- Jonasson JM, Brismar K, Sparen P, et al. Fertility in women with Type 1 diabetes: A population-based cohort study in Sweden. *Diabetes Care* 2007;**30**:2271–6.

- 28 Engelgau MM, Herman WH, Smith PJ, German RR, Aubert RE. The epidemiology of diabetes and pregnancy in the U.S., 1988. *Diabetes Care* 1995;**18**:1029–33.
- 29 Dunne FP, Brydon PA, Proffit M, Smith T, Gee H, Holder RL. Fetal and maternal outcomes in Indo-Asian compared to Caucasian women with diabetes in pregnancy. *Q J Med* 2000;**93**:813–18.
- 30 Ellard S, Beards F, Allen LIS, *et al.* A high prevalence of glucokinase mutations in gestational diabetic subjects selected by clinical criteria. *Diabetologia* 2000;**43**:250–3.
- 31 McMullen AH, Pasta D, Frederick P, *et al.* Impact of pregnancy on women with cystic fibrosis. *Chest* 2006;**129**:706–11.
- 32 King H. Epidemiology of glucose intolerance and gestational diabetes in women of childbearing age. *Diabetes Care* 1998;**21**:B9–B13.
- 33 Agarwal, MM, Dhatt GS, Punnose J, Koster G. Gestational diabetes: dilemma caused by multiple international diagnostic criteria. *Diabet Med* 2005;**22**:1731–6.
- 34 Yue DK, Molyneaux LM, Ross GP, Constantino MI, Child AG, Turtle JR. Why does ethnicity affect prevalence of gestational diabetes? The underwater volcano theory. *Diabet Med* 1996;**13**:748–52.
- 35 Beischer NA, Oats JN, Henry OA, Sheedy MT, Walstab JE. Incidence and severity of gestational diabetes mellitus according to country of birth in women living in Australia. *Diabetes* 1991;**40** (Suppl 2):35–8.
- 36 National Women's Annual Clinical Report 2005. Auckland: National Women's Health, Auckland District Health Board.
- 37 Simmons D, Rowan J, Campbell N, Reid R. Screening, diagnosis and services for women with Gestational Diabetes Mellitus in New Zealand: A Technical Report from the National GDM Technical Working Party. *N Z Med J* 2008; **121**:74–86.
- 38 Metzger BE, Coustan DR (eds). Summary and recommendations of the Fourth International Workshop Conference on Gestational Diabetes Mellitus. *Diabetes Care* 1998;**21** (Suppl 2):B161–B167.
- 39 The Guideline Development Group. Guidelines: Management of diabetes from preconception to the postnatal period: summary of NICE guidance. *BMJ* 2008;**336**:714–17.
- 40 Ben Haroush A, Yogev Y, Hod M. Epidemiology of gestational diabetes mellitus and its association with Type 2 diabetes. *Diabet Med* 2004;**21**:103–13.
- 41 Simmons D, Walters BNJ, Rowan JA, McIntyre HD. Metformin therapy and diabetes in pregnancy. *Med J Aust* 2004;**180**:462–4.
- 42 Kim, C, Berger DK, Chamany S. Recurrence of gestational diabetes mellitus: A systematic review. *Diabetes Care* 2007;**30**:1314–19.
- 43 Major CA, de Veciana M, Weeks J, Morgan MA. Recurrence of gestational diabetes mellitus: who is at risk? *Am J Obstet Gynecol* 1998;**179**:1038–42.
- 44 O'Sullivan JB. Diabetes mellitus after GDM. *Diabetes* 1991;**40**:131–5.
- 45 Cheung NW, Byth K. Population health significance of gestational diabetes. *Diabetes Care* 2003;**26**:2005–9.
- 46 Nilsson C, Ursing D, Torn C, Aberg A, Landin-Olsson M. Presence of GAD antibodies during gestational diabetes mellitus predicts Type 1 diabetes. *Diabetes Care* 2007; **30**:1968–71.
- 47 Jarvela IY, Kulmala P, Juutinen J, *et al.* Gestational diabetes identifies women at risk for permanent type 1 and type 2 diabetes in fertile age. *Diabetes Care* 2006;**29**:607–12.
- 48 Peters RK, Kjos SL, Xiang A, Buchanan TA. Long-term diabetogenic effect of single pregnancy in women with previous gestational diabetes mellitus. *Lancet* 1996;**347**:227–30.
- 49 Kim C, Newton K, Knopp R. Gestational diabetes and incidence of Type 2 diabetes mellitus: a systematic review. *Diabetes Care* 2002;**26**:1862–8.
- 50 Simmons D, Fleming C. Prevalence and characteristics of diabetic patients with no ongoing care in South Auckland. *Diabetes Care* 2000;**23**:1791–3.
- 51 Clausen TD, Mathiesen ER, Hansen T, *et al.* High prevalence of Type 2 diabetes and pre-diabetes in adult offspring of women with gestational diabetes mellitus or Type 1 diabetes: The role of intrauterine hyperglycemia. *Diabetes Care* 2008;**31**:340–6.
- 52 Pettitt DJ, Aleck KA, Baird HR, Carraher MJ, Bennett PH, Knowler WC. Congenital susceptibility to NIDDM. Role of intrauterine environment. *Diabetes* 1988;**37**:622–8.
- 53 Klonoff DC, Schwartz DM. An economic analysis of interventions for diabetes. *Diabetes Care* 2000;**23**:390–404.
- 54 Kitzmiller JL. Cost analysis of diagnosis and treatment of gestational diabetes mellitus. *Clin Obstet Gynaecol* 2000;**43**:140–53.
- 55 Jovanovic-Peterson L, Bevier W, Peterson CM. The Santa-Barbara County Health Care Services program: Birth weight change concomitant with screening for and treatment of glucose intolerance of pregnancy: a potential cost effective intervention. *Am J Perinatol* 1997;**14**:221–8.
- 56 Langer O, Conway D, Berkus M, Xenakis EMJ. Conventional versus intensified therapy: Cost/benefit analysis. *Am J Obstet Gynecol* 1998;**178** (Suppl 1):S58.
- 57 Moss JR, Crowther CA, Hiller JE, Willson KJ, Robinson JS. Costs and consequences of treatment for mild gestational diabetes mellitus – evaluation from the ACHOIS randomised trial. *BMC Pregnancy Childbirth* 2007;**7**:27.
- 58 Simmons D, Conroy C, Scott DJ. Impact of a diabetes midwifery educator on the diabetes in pregnancy service at Middlemore Hospital. *Prac Diabet Int* 2001;**18**:119–22.
- 59 Herman WH, Hoerger TJ, Brandle M, *et al.* The cost-effectiveness of lifestyle modification or metformin in preventing type 2 diabetes in adults with impaired glucose tolerance. *Ann Intern Med* 2005;**142**:323–32.
- 60 Kim C, Herman WH, Vijan S. Efficacy and cost of postpartum screening strategies for diabetes among women with

- histories of gestational diabetes mellitus. *Diabetes Care* 2007;**30**:1102–6.
- 61 Simmons D, Cheung NW, Lagstrom J, *et al.* for the ADIPS National Diabetes in Pregnancy Audit Project team. The ADIPS Pilot National Diabetes in Pregnancy Audit Project. *Aust NZ J Obstet Gynaecol* 2007;**47**:198–206.
- 62 Weiderman WC, Marcuz L. Gestational diabetes: a triage model of care for rural perinatal providers. *Am J Obstet Gynecol* 1996;**174**:1719–23.
- 63 Yapa M, Simmons D. Screening for gestational diabetes mellitus in a multiethnic population in New Zealand. *Diabetes Res Clin Pract* 2000;**48**:217–23.
- 64 Rodrigues S, Robinson E, Gray-Donald K. Prevalence of gestational diabetes mellitus among James Bay Cree women in northern Quebec. *CMAJ* 1999;**160**:1293–7.
- 65 Murgia C, Berria R, Minerba L, *et al.* Gestational diabetes mellitus in Sardinia. *Diabetes Care* 2006;**29**:1713.
- 66 Yang X, Hsu-Hage B, Zhang H, *et al.* Gestational diabetes mellitus in women of single gravidity in Tianjin city, China. *Diabetes Care* 2002;**25**:847–51.
- 67 Dyck R, Klomp H, Tan LK, Turnell RW, Boctor MA. A comparison of rates risk factors and outcomes of gestational diabetes between Aboriginal and non-Aboriginal women in the Saskatoon Health District. *Diabetes Care* 2002;**25**:487–93.
- 68 Erem C, Cihanyurdu N, Deger O, *et al.* Screening for gestational diabetes mellitus in northeastern Turkey, Trabazon City. *Eur J Epidemiol* 2002;**18**:39–43.
- 69 Harris S, Caulfield LE, Sugamori ME, Whalen EA, Henning B. The epidemiology of diabetes in pregnant native Canadians. *Diabetes Care* 1997;**20**:1422–5.
- 70 Mamabolo RL, Alberts M, Levitt NS, Delemarre-van de Waal HA, Steyn NP. Prevalence of gestational diabetes mellitus and the effect of weight on measures of insulin secretion and insulin resistance in third-trimester pregnant rural women residing in the Central Region of Limpopo Province, South Africa. *Diabet Med* 2007;**24**:233–9.