Gestational diabetes: the need for a common ground

E Albert Reece, Gustavo Leguizamón, Arnon Wiznitzer

Gestational diabetes mellitus is a substantial and growing health concern in many parts of the world. Certain populations are especially vulnerable to developing this condition because of genetic, social, and environmental factors. Gestational diabetes has serious, long-term consequences for both baby and mother, including a predisposition to obesity, metabolic syndrome, and diabetes later in life. Early detection and intervention can greatly improve outcomes for women with this condition and their babies. Unfortunately, screening and diagnostic tests are not uniform worldwide, which could lead not only to underdiagnosis but also undermanagement of the illness. Here, we report the controversies surrounding the causes, screening, diagnosis, management, and prevention of gestational diabetes, and give specific recommendations for research studies to address the major issues of this medical condition.

Introduction
Gestational diabetes mellitus is characterised by glucose intolerance of variable severity that begins or is first diagnosed during pregnancy and usually resolves not long after delivery.1 Documenting resolution of the condition after birth is crucial because many pregnant women with previously undiagnosed type 2 diabetes are often mistakenly diagnosed as having gestational diabetes.2

Although this medical condition has previously been regarded as benign,1 some studies have recently found increased perinatal morbidity associated with hyperglycaemia during pregnancy. Fortunately, these complications seem to be lessened by better detection and management of this condition,13 which are however hampered by disagreement on many aspects of its diagnosis and treatment. Here, we discuss the epidemiology, pathophysiology, screening, and diagnosis of gestational diabetes. We also examine the available technologies and approaches for the management of this condition and their relative efficacies, and make recommendations about research needed to address controversies.

Epidemiology
Diabetes mellitus and less serious forms of glucose intolerance are widespread in almost every population in the world.4 However, an accurate estimation of the global incidence of gestational diabetes in many countries does not exist because of the lack of uniform standards in glucose tolerance testing around the world.7

In 2000, about 171 million people worldwide had some form of diabetes. By 2030, an estimated 361 million people will be affected by this condition.4 Gestational diabetes is more frequent in certain ethnic groups than in the general population. For example, the frequency of gestational diabetes was measured in 11205 women consecutively attending a multiracial antenatal clinic in UK, and 0-4% white, 1-5% African, 3-5-7-3% Asian, 4-4% Indian, and about 1-4% mixed-origin women were shown to have gestational diabetes.9 The rate of gestational diabetes was also shown to be 5-10 times higher in pregnant Asian women than in white women.9 Additionally, in an ethnic mixed population of women with diabetes entering a prenatal care programme in the USA, African American women had significantly poorer glycaemic control than did other racial groups.10

The increasing incidence of gestational diabetes can be halted or at least slowed. This condition is most widespread in the USA with as many as 200000 women, or 10%, of pregnancies being complicated by the illness every year.11 Although the frequency of occurrence of pre-existing diabetes in pregnancy has increased rapidly in the USA over the past decade (figure 1), that of gestational diabetes has remained relatively stable since the late 1990s,8 and the reasons for this are still not fully understood. However, a high rate of screening nationwide seems to be at least partly responsible.11

Many women who are first diagnosed with diabetes mellitus during pregnancy are classified as having gestational diabetes even though they have pre-existing, or pregestational, diabetes that had gone undiagnosed. This distinction is crucial because pregestational diabetes is associated with more serious consequences for the fetus than is diabetes in the second and third trimester of pregnancy.12 Women with pregestational diabetes who become pregnant are at increased risk of giving birth to a baby with a serious birth defect, including cardiac,11 neurological,11 and vascular anomalies.11

Pathophysiology
Increase in the concentration of pregnancy hormones—including oestrogens and progestins—leads to lower fasting glucose concentrations and deposition of fat, delay in gastric emptying, and increased appetite. As gestation progresses, however, postprandial glucose concentrations steadily increase as tissue sensitivity to insulin decreases.26
To maintain proper glucose control in pregnancy, pancreatic β cells of the mother have to increase insulin secretion enough to counteract the corresponding fall in tissue sensitivity to insulin. For some reason, pregnant women who develop gestational diabetes are unable to increase insulin production to compensate for their increased resistance to insulin.

Post-receptor defects in the insulin-signalling cascade seem to be implicated in the development of insulin resistance. The downregulation of the insulin receptor substrate-1 (IRS-1) might contribute to decreased insulin-mediated glucose uptake in the skeletal muscle. Patients with gestational diabetes also present with a reduced ability of the insulin receptor B to undergo tyrosine phosphorylation. Investigators have suggested that pregnancy triggers a series of metabolic imbalances that lead to a diabetic state in some women who are already genetically predisposed to develop diabetes (figure 2). Some naturally occurring genetic variations are associated with a greater risk of developing this condition. These genes participate in several cell functions, including cell activation, immune response, organ development, and regulation of cell death.

Fetal effects

Glucose travels freely from the mother to the fetus, but maternal insulin does not. Thus, maternal gestational diabetes exposes the fetus to higher concentrations of glucose than normal, which force the fetus to increase its own insulin production. Unfortunately, excess insulin produced by the fetus in response to the mother’s gestational diabetes can cause the fetus to grow excessively, a condition known as large for gestational age. A fetus with a birthweight exceeding 4000–4500 g is referred to as macrosomic.

Mean glucose concentration is strongly associated with neonatal birthweight in women with gestational diabetes. Furthermore, increased insulin concentration in both fetal blood and amniotic fluid correlates with an increased rate of occurrence of fetal macrosomia.

To assess the contribution of maternal carbohydrate metabolism to fetal growth, Catalano and colleagues measured the effect of maternal metabolism, parental demographic and morphometric measures, neonatal sex, and gestational age on placental weight, neonatal birthweight, and newborn body composition. Insulin sensitivity in late gestation had the strongest correlation with placental weight ($R^2=0.28$), neonatal birthweight ($R^2=0.28$), and fat-free mass ($R^2=0.33$).

Large-for-gestational-age fetuses have an increased risk of injury, such as shoulder dystocia and newborn asphyxia, during vaginal birth delivery. Therefore, a caesarean section is often the preferred way to deliver a large-for-gestational-age baby, even though it can lead to increased trauma to the mother.

Fetuses exposed to a high glucose environment have other medical complications after delivery, including infant respiratory distress syndrome, cardiomyopathy, hypoglycaemia, hypocaplaemia, hypomagnesaemia, polycythaemia, and hyperviscosity. Robust evidence linking mild hyperglycaemia and adverse perinatal outcomes has been lacking. However, the hyperglycaemia and adverse pregnancy outcome (HAPO) study, which investigated about 25 000 pregnant women in 15 centres, found that even subclinical hyperglycaemia was significantly and dose-dependently associated with large-for-gestational-age births and increased cord-blood serum C-peptide concentrations. The HAPO study also showed a weaker but still significant association between neonatal hypoglycaemia and primary caesarean delivery. Clausen and colleagues found that a hyperglycaemic intrauterine environment significantly increases the probability of developing type 2 diabetes in adult offspring of white women with either diet-treated gestational diabetes or type 1 diabetes during pregnancy.

After birth, the high glucose environment disappears in infants, but they often have life-long increased risk of glucose intolerance and obesity. Yogev and Visser showed that gestational diabetes is associated with increased risk of early obesity, type 2 diabetes during adolescence, and development of metabolic syndrome in early childhood. Additionally, this condition is a marker for the development of overt type 2 diabetes and metabolic syndrome for the mother in the near term. Children born to mothers with gestational diabetes have nearly double the risk of developing childhood
obesity, metabolic syndrome, or both, compared with children born to non-diabetic mothers.32 Pima Indians, a group of Native Americans residing in the western part of the USA and northwest Mexico, have one of the highest rates of gestational diabetes in the world. Research in Pima Indians has shown that diabetes during pregnancy is a major risk factor for type 2 diabetes and hyperglycaemia in the offspring. Children of Pima Indian women who had diabetes during pregnancy were more obese and had a significantly higher prevalence of type 2 diabetes at 25–34 years of age than children born to Pima women without diabetes.33 Exposure to hyperglycaemia in utero led to the development of type 2 diabetes in 40% of children (5–19 years old) of Pima Indian women. More than two thirds (70%) of Pima Indians between 25 and 34 years of age with prenatal hyperglycaemia exposure developed type 2 diabetes later in life.

Maternal effects
The main maternal effect of gestational diabetes is a higher long-term risk for developing metabolic syndrome and type 2 diabetes. A review of the literature has shown that women with a history of gestational diabetes and obesity (and their children) have a significantly greater risk of developing a metabolic syndrome than mothers (and their children) with no history of gestational diabetes or obesity.34 In the offspring, the increased risk of metabolic syndrome increased with age.

In a multicentre study in France,35 investigators assessed long-term outcomes in healthy women (n=221), women with abnormal glucose tolerance during pregnancy (n=322), and women with gestational diabetes (n=466). The main predictors for women to develop type 2 diabetes were gestational diabetes, or a history of unexplained fetal demise.36 The frequency of gestational diabetes is significantly higher prevalence of type 2 diabetes at 25–34 years of age than children born to Pima women without diabetes. Exposure to hyperglycaemia in utero led to the development of type 2 diabetes in 40% of children (5–19 years old) of Pima Indian women. More than two thirds (70%) of Pima Indians between 25 and 34 years of age with prenatal hyperglycaemia exposure developed type 2 diabetes later in life.

Risk factors
Women with a history of gestational diabetes have also increased risk of developing gestational diabetes in subsequent pregnancies.36 The delivery of a macrosomic infant or a suspected glucose intolerance test in a previous pregnancy are also risk factors for gestational diabetes. Other risk factors include glucosuria, a strong first-degree family history of type 2 diabetes or gestational diabetes, or a history of unexplained fetal demise.37 The frequency of gestational diabetes is 7–10 times higher in pregnant women older than 24 years of age than in those younger than 24,38 suggesting that universal screening is most effective in the older group.39

Obesity also is strongly linked to the development of gestational diabetes. In a population-base cohort study of about 97000 singleton births,40 obese women had a 3-fold increased risk of developing gestational diabetes than non-obese women. Not only obese (body-mass index [BMI] >30) but also overweight women (BMI 25–29) have a greatly increased risk of developing gestational diabetes. Comparison of pregnancy complications and outcomes between obese and non-obese women shows a rate of gestational diabetes of 24–5% for obese versus 2–2% for non-obese women.41 The rate of obesity is rising dramatically worldwide,42 consequently increasing the rate of gestational diabetes.

Screening and diagnostic tests
Screening for gestational diabetes enables identification of risk factors. Furthermore, most clinicians in developed countries recommend a blood test, known as oral glucose tolerance test, between 24 and 28 weeks of pregnancy, or earlier if a woman is at high risk for developing the disease. Glucose tolerance testing is usually done by giving a pregnant woman a drink containing 50 g of glucose 1 h before a blood glucose measurement is taken. After 1 h, a normal blood glucose concentration is anything below 130–140 mg/dL (7.2–7.8 mmol/L) on a 50-g oral glucose tolerance test.

The 1 h oral glucose tolerance test can identify potential cases of diabetes in various populations.43,44 However, in many developed countries, women with a positive 50 g oral glucose tolerance test receive a more invasive follow-up diagnostic test to avoid false-positive results, which is typically a 100 g, 3 h oral glucose tolerance test. Some investigators have reported that
even a single abnormal test is associated with mild glucose intolerance later on.\textsuperscript{45,46} However, the diagnosis of gestational diabetes usually requires at least two abnormal values in this test.\textsuperscript{27}

The 100 g, 3 h oral glucose tolerance test has been the gold standard for diagnosing gestational diabetes for many years in North America. However, this two-step approach to diagnosis (table), which has a reported reproducibility of about 78%,\textsuperscript{19} is expensive to administer and, therefore, not practical in many developing countries. The WHO recommends a one-step, 75 g oral glucose tolerance test\textsuperscript{29} in the developing world. The results of the HAPO study support the usefulness of the one-step, 75 g screening approach for detecting gestational diabetes in the general population.\textsuperscript{25,31,32} The panel shows a screening strategy for gestational diabetes based on a one-step or two-step approach. The usefulness of the WHO one-step screening approach for gestational diabetes in a group of more than 1600 pregnant women has recently been assessed:\textsuperscript{33} this approach showed an acceptable sensitivity rate of 85% and could rule out gestational diabetes in more than two-thirds of women.

Fasting blood glucose and random blood glucose tests are becoming popular because they are easy to do and do not cause major inconvenience to the patient. Unfortunately, reproducibility, sensitivity, and specificity of these tests are not proven.\textsuperscript{34} Although some evidence exists that the measurement of fasting glucose can reliably detect gestational diabetes, some patients were later found to have gestational diabetes but had high blood glucose only after a meal, with normal fasting concentrations.\textsuperscript{35}

Other commonly available screening tests include glycosylated haemoglobin, capillary blood glucose measurement with a haemocue, breakfast tests, lunch tests, glucosuria, blood fructosamine, and the fetal abdominal circumference. However, all these tests have weak sensitivity and are not recommended in most cases.\textsuperscript{36-39}

A study has shown that women younger than 25 years old and without high risk factors for gestational diabetes have a very low risk of developing this condition at a later stage and, ultimately, do not need follow-up diagnostic tests.\textsuperscript{60} However, in another study, certain risk factors, such as obesity, a first-degree relative with type 2 diabetes, history of gestational diabetes or macrosomia, advanced maternal age, non-white ethnic origin, and any poor obstetric outcome, were all high-risk indicators for developing gestational diabetes, and these women needed further diagnostic testing.\textsuperscript{61}

Despite evidence that risk-factor screening is effective in the detection of women who could develop gestational diabetes, it is nevertheless controversial. One review of the literature has shown that screening tests are not very effective in detecting gestational diabetes: their positive likelihood ratio of screening for risk factors is only 1·75.\textsuperscript{62} Therefore, women who are deemed only by risk-factor screening to be likely to develop gestational diabetes have only a minimally increased likelihood of developing the disease.

The North American diabetes in pregnancy study group and the Canadian Diabetes Association recommend universal screening for all pregnant women. The American Diabetes Association (ADA) and the British Diabetic Association recommend selective, risk-related screening. As previously mentioned, rates of gestational diabetes are so low in some populations that universal screening might not be cost effective.\textsuperscript{63,64} Diagnosis of gestational diabetes is controversial, with different international bodies issuing slightly different.

<table>
<thead>
<tr>
<th>Plasma glucose concentration cutoff (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Screening test</strong></td>
</tr>
<tr>
<td>50 g, 1 h screening</td>
</tr>
<tr>
<td><strong>Diagnostic test</strong></td>
</tr>
<tr>
<td>100 g, 3 h OGTT</td>
</tr>
<tr>
<td>Fasting</td>
</tr>
<tr>
<td>1 h</td>
</tr>
<tr>
<td>2 h</td>
</tr>
<tr>
<td>3 h</td>
</tr>
</tbody>
</table>

OGTT: oral glucose tolerance test. Cutoff values were taken from reference 48.

**Table: Screening and diagnostic tests**

Panel: Screening strategy for detection of gestational diabetes

**Risk assessment of gestational diabetes should be ascertained at the first prenatal visit**

**Low risk:** blood glucose testing not routinely required if all of the following characteristics are present:
- Member of an ethnic group with a low prevalence of gestational diabetes
- No known diabetes in first-degree relatives
- Age <25 years old
- Weight normal before pregnancy
- Weight normal at birth
- No history of abnormal glucose metabolism
- No history of poor obstetric outcome

**Average risk:** do blood glucose testing at 24–28 weeks’ gestation using either:
- Two-step procedure: 50-g glucose challenge test followed by a diagnostic oral glucose tolerance test in those meeting the threshold value in the glucose challenge test
- One-step procedure: diagnostic oral glucose tolerance test done in all individuals

**High risk:** do blood glucose testing as soon as possible, using the procedures described above if one or more of these are present:
- Severe obesity
- Strong family history of type 2 diabetes
- Previous history of: gestational diabetes, impaired glucose metabolism, or glucosuria

If gestational diabetes is not diagnosed, blood glucose testing should be repeated at 24–28 weeks’ gestation or at any time a patient has symptoms or signs that are suggestive of hyperglycaemia.

Reproduced, with permission, with minor modifications from Metzger and colleagues.\textsuperscript{48}
recommendations. Shirazian and colleagues recently compared the different diagnostic criteria for gestational diabetes proposed by various international organisations—including ADA, WHO, and the Australian Diabetes in Pregnancy Society (ADIPS)—in a group of 670 pregnant women diagnosed with 75 g, 2 h oral glucose tolerance test. The investigators diagnosed gestational diabetes in 41 (6·1%), 81 (12·1%), and 126 (18·8%) women on the basis of ADA, WHO, and ADIPS criteria, respectively. Women who were gestational-diabetes positive only on the basis of WHO criteria had lower fasting plasma glucose concentration (4·9 vs 5·7 mmol/L; p<0·0001) and 1 h plasma glucose concentration (8·1 vs 11·1 mmol/L; p<0·0001), but higher 2 h plasma glucose concentration (8·3 vs 6·1 mmol/L; p<0·0001) than women diagnosed only on the basis of ADA criteria.

**Rationale for screening and intervention**

The effect of screening, diagnosis, and treatment of gestational diabetes has been controversial for many years, leading to lack of agreement. The Australian carbohydrate intolerance study in pregnant women (ACHOIS) trial group did a randomised clinical trial to assess whether treating women with gestational diabetes reduced the risk of perinatal complications. 1000 pregnant women with gestational diabetes at 24–28 weeks of gestation were randomly assigned to receive dietary advice, blood glucose monitoring, and insulin therapy, or routine care.

Serious perinatal outcomes were reduced from 4% to 1% in pregnant women treated for gestational diabetes. Furthermore, induction rate and admission to the neonatal nursery increased in women of the intervention group. The rate of cesarean section was similar for both intervention and control groups. However, at 3 months after delivery, rates of depression were lower and quality of life scores were higher, which is consistent with improved health status, in the intervention group.

Langer and colleagues found a 2-fold to 4-fold increase in metabolic complications and large-for-gestational-age births for an untreated group of women with gestational diabetes compared with a treated group.

**Management**

Close monitoring and treatment of gestational diabetes are important to the long-term health of a pregnant woman and her baby. The fifth international workshop-conference on gestational diabetes recommended the following blood glucose concentrations: fasting plasma glucose of 90–99 mg/dL (5·0–5·5 mmol/L); 1-h postprandial plasma glucose below 7·8 mmol/L (<140 mg/dL); and 2-h postprandial plasma glucose below 6·7–7·1 mmol/L (<120–127 mg/dL).

**Glucose monitoring**

Self-glucose monitoring enables a pregnant woman with gestational diabetes to check her blood glucose concentration at any time and to take steps to decrease the long-term risks of diabetic complications for her and her baby. Many different kinds of blood glucose meters exist, but they all work in a similar way and are reasonably accurate (these are less accurate during episodes of hypoglycaemia than during episodes of hyperglycaemia). Researchers are currently assessing less intrusive continuous glucose monitoring systems, the efficacy of which has mainly been tested in patients with type 1 diabetes. However, continuous glucose monitoring systems technology is becoming of increasing clinical interest for the management of gestational diabetes.

**Nutrition and diet**

In addition to blood glucose monitoring, the first line of management of women with gestational diabetes consists of medical nutrition therapy with adjunctive exercise for at least 30 min per day. Patients who fail to maintain glycaemic targets through diet and exercise therapy receive insulin injections or other antihyperglycaemia medications.

Although a growing number of studies suggest that nutritional support during pregnancy can have a substantial effect on incidence and severity of gestational diabetes, nutritional management of this condition is controversial.

A 2003 Cochrane review showed no difference in the prevalence of birthweights greater than 4000 g or cesarean deliveries in women with gestational diabetes...
who were randomly assigned to primary dietary therapy or no specific treatment. The authors concluded that insufficient evidence exists to recommend dietary therapy in patients with altered glucose metabolism. Nevertheless, ADA recommends that women with gestational diabetes receive nutrition counselling and follow a diet that adequately meets the needs of their pregnancy but restricts carbohydrates to 35–40% of daily calories. This recommendation is based on research showing that restricting carbohydrates to 35–40% of calories decreases maternal glucose concentrations and improves maternal and fetal outcomes. Research has also shown that restricting carbohydrates to 30–33% of daily calories (to about 25 kcal/kg actual weight per day) could be beneficial for obese women (BMI >30).

**Exercise**

Investigators have shown that prenatal exercise can delay or prevent the development of gestational diabetes, and exercise during pregnancy can prevent complications to the baby. Zhang and colleagues did a prospective cohort study in about 22 000 women to assess whether the amount, type, and intensity of pregravid physical activity and sedentary behaviours are associated with the risk of developing gestational diabetes. Women who spent 20 h per week or more watching television and did not do any vigorous activity had a higher risk of developing the condition than women who spent less than 2 h per week watching television and did physical activity. Women with gestational diabetes who exercised regularly during pregnancy were less likely than those who did not exercise to deliver a large-for-gestational-age infant.

**Treatment**

For several years, human insulin has been the only treatment option for diabetes that could not be controlled by diet and lifestyle modifications alone. Diet-controlled gestational diabetes is classified as class A1 diabetes. Gestational diabetes needing insulin therapy is classified as class A2 diabetes. Insulin therapy for class A2 diabetes needs substantial patient training to keep the number of injections that patients need on a daily basis to a minimum to bring their blood glucose values within the normal range.

Some insulin analogues have recently come on the market. Of the three rapid-acting insulin analogues, only two—28B-L-lysine-29B-L-proline insulin (lispro) and 28B-aspartic-acid insulin (aspart)—have been investigated in pregnancy. Both have shown clinical effectiveness, minimal transfer across the placenta, and no evidence of teratogenesis. Both analogues improve postprandial glucose excursions in type 1 diabetes patients compared with human insulin, and might be associated with a lower risk of delayed postprandial hypoglycaemia. Oral antihyperglycaemic drugs have not been used in pregnant women because of reports of fetal anomalies and other adverse outcomes in animal studies and in some human cases. However, recent evidence suggests that some oral antihyperglycaemic drugs can be beneficial in pregnancy.

Using the single-cotyledon placental model, Elliot and colleagues reported almost no transfer of glibenclamide, in spite of maternal glibenclamide being 100 times above therapeutic concentrations. In a later study, Langer and colleagues examined more than 400 women with pregnancies complicated by gestational diabetes requiring treatment. They observed no significant differences between patients receiving glibenclamide or insulin in mean maternal blood glucose, proportion of large-for-gestational-age fetuses (12% vs 13%, respectively), macrosomia (7% vs 4%), lung complications (8% vs 6%), hypoglycaemia (9% vs 6%), admission to neonatal intensive-care unit (6% vs 7%), or fetal anomalies (2% vs 2%). Additionally, a similar percentage of women achieved the desired glycaemic control in the glibenclamide and insulin groups (82% vs 88%, respectively). Glibenclamide was not found in the cord serum of any infants.

The effectiveness of three oral antihyperglycaemic drugs used in pregnancy—glibenclamide, metformin, and acarbose—was assessed. In two prospective studies, one of which was a randomised controlled trial, glibenclamide seemed to be as effective and safe as insulin in the treatment of gestational diabetes. Furthermore, metformin did not increase fetal anomalies or malformations in several small trials in pregnant women with polycystic ovary syndrome. Metformin also prevents early pregnancy loss, decreases insulin resistance, reduces insulin and testosterone concentrations, and reduces the incidence of gestational diabetes. In one small study, acarbose also did not cause any adverse effects during pregnancy.

In a systematic review of evidence, maternal glycaemic control, caesarean delivery rates, and birthweights did not differ greatly between insulin and glibenclamide groups. Furthermore, there was no difference in the rate of congenital malformations between individuals treated with insulin and those treated with oral agents. Thus, although evidence is still scarce, glibenclamide and metformin seem to be safe and might be used to treat patients with gestational diabetes.

**Conclusions**

Gestational diabetes is a growing health concern, especially in certain predisposed populations. Although traditionally deemed not as dangerous for the developing fetus as pregestational diabetes, gestational diabetes has serious, long-term consequences for both baby and mother. Evidence now suggests that screening, early detection, and management can greatly improve outcomes for women with this condition and their babies. Unfortunately, screening and diagnostic standards are
not uniform worldwide, which might lead to under-diagnosis and under-management of the disease.

Regular finger stick monitoring is still the preferred method for measurement of glucose concentrations. However, continuous glucose monitoring seems to be not only accurate, but might also detect transient episodes of hyperglycaemia and hypoglycaemia, both of which can be detrimental to the fetus.

Although human insulin or human insulin analogues have been the preferred treatment for gestational diabetes for some time, oral antihyperglycaemic agents—such as glibenclamide and metformin—could be just as effective for the management of the disease.

To resolve the controversies on causes, diagnosis, and management of gestational diabetes, the diagnostic definition of the condition needs to be revised on the basis of the new information obtained from the HAPO study. Furthermore, additional research is needed on: mechanisms of insulin resistance; ideal glucose targets to decrease perinatal morbidity in women with gestational diabetes; effectiveness of oral antihyperglycaemic drugs versus insulin analogues; identification of all predictors of future development of diabetes; and effectiveness of postpartum interventions to decrease the later incidence of diabetes in women with gestational diabetes and in their children.

Contributors
EAR was responsible for the initial literature search and selection of articles to include in the Seminar. GL and AW suggested additional articles to include in the Seminar and appropriate figures and tables. Each author contributed equally to the writing of the Seminar and to addressing reviewers’ comments.

Conflicts of interest
EAR routinely receives honoraria for invited lectures on diabetes and diabetic embriopathy by medical societies and academic medical institutions around the world, and owns a patent for a dietary intervention to reduce the risk of birth defects in pregnant women with pregestational diabetes (Patent No DE399; US5 1299; 031). AW is the chairman of the Department of Obstetrics and Gynecology at Soroka University Medical Center (NY, USA). GFL declares that he has no conflicts of interest.

Acknowledgments
We thank Jim Swyers who helped in the early stages of the development of this manuscript.

References
9 Chawla A, Amundsen AL, Hansen KF, Iversen PO. Gestational diabetes in women from South Asia. Tidskr Nor Lægeforen 2006; 126: 1041–43.


