# Summary and Recommendations of the Fifth International Workshop-Conference on Gestational Diabetes Mellitus

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The Fifth International Workshop-Conference on Gestational Diabetes Mellitus (GDM) was held in Chicago, IL, 11–13 November 2005 under the sponsorship of the American Diabetes Association. The meeting provided a forum for review of new information concerning GDM in the areas of pathophysiology, epidemiology, perinatal outcome, long-range implications for mother and her offspring, and management strategies. New information and recommendations related to each of these major topics are summarized in the report that follows.

The issues regarding strategies and criteria for the detection and diagnosis of GDM were not reviewed or discussed in detail, since it is anticipated that the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study will provide data in mid-2007 that will foster the development of criteria for the diagnosis of GDM that are based on perinatal outcomes. Thus, for the interim, the participants of the Fifth International Workshop-Conference on GDM endorsed a motion to continue use of the definition, classification criteria, and strategies for detection and diagnosis of GDM that were recommended at the Fourth Workshop-Conference. Those guidelines are reproduced (with minor modifications) in this article in APPENDIX Tables 1 and 2.

**SUMMARY AND RECOMMENDATIONS** — The invited lectures, topical discussions, and posters presented at the conference and the invited manuscripts that appear in this issue of *Diabetes Care* served as the basis for the following summary and recommendations.

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**Abbreviations:** CVD, cardiovascular disease; GDM, gestational diabetes mellitus; IGT, impaired glucose tolerance; MNT, medical nutrition therapy; SMBG, self-monitoring of blood glucose.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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## PANEL I: PATHOPHYSIOLOGY AND EPIDEMIOLOGY

### Pathophysiology

**General considerations.** Current diagnostic criteria assign the diagnosis of GDM to women with glucose levels in the upper ~5–10% of the population distribution. The hyperglycemia varies in severity from glucose concentrations that would be diagnostic of diabetes outside of pregnancy to concentrations that are asymptomatic and only slightly above normal, but associated with some increased risk of fetal morbidity.

Like all forms of hyperglycemia, GDM is characterized by insulin levels that are insufficient to meet insulin demands. The causes of pancreatic β-cell dysfunction that lead to insulin insufficiency in GDM are not fully defined. Three general categories have been identified: *1*) autoimmune β-cell dysfunction, *2*) highly penetrant genetic abnormalities that lead to impaired insulin secretion, and *3*) β-cell dysfunction that is associated with chronic insulin resistance.

It has long been held that pregnancy-induced insulin resistance unmasks the onset of β-cell defects that underlie GDM. Evidence presented at the meeting indicated that the defects are chronic rather than of acute onset. Although studies to date are limited in scope, they uniformly reveal a chronic β-cell defect that is present before and after pregnancy and accompanied by increasing blood glucose concentration. This hypothesis suggests that when GDM is diagnosed, it includes some women with preexisting glucose intolerance that is revealed by routine glucose tolerance screening in pregnancy.

The majority of women with GDM eventually develop diabetes after pregnancy. Published reports indicate a nearly linear increase in the cumulative incidence of diabetes during the first 10 years after pregnancy. The risk is similar among all ethnic groups with GDM. Two studies presented reported that new cases of diabetes continue to appear 1–2 decades after GDM.

**GDM and insulin resistance.** Two forms of insulin resistance exist in women who develop GDM. The first is the physiological insulin resistance of late pregnancy. Evidence presented suggests the postreceptor mechanisms that contribute to the insulin resistance of normal pregnancy appear to be multifactorial, but are exerted in skeletal muscle at the β-subunit of the insulin receptor and at the level of insulin receptor substrate-1. In addition, increased free intracytoplasmic p85α subunit of phosphatidylinositol 3-kinase appears to be involved. These alterations in insulin signaling may contribute to reduced insulin-mediated glucose uptake in skeletal muscle, a major tissue for whole-body glucose disposal. Insulin resistance abates soon after pregnancy, and the signaling changes have returned to normal within 1 year postpartum in women with normal glucose tolerance. These findings suggest that the insulin resistance is driven by pregnancy-induced factors, with placental growth hormone and tumor necrosis factor-α currently being the most likely candidates.

The second form of insulin resistance in GDM is a more chronic form that is present before pregnancy and is exacerbated by the physiological changes that lead to insulin resistance during pregnancy. Thus, most women with GDM have a combination of acquired and chronic insulin resistance and are therefore, as a group, slightly more insulin resistant than normal women during late pregnancy. Phosphorylation of insulin receptor tyrosine results in the transmission of the insulin signal to enable glucose uptake. Evidence presented identified a significant decrease in maximal insulin receptor tyrosine phosphorylation in muscle as one potential mechanism for the additional insulin resistance in obese women. Evidence was also presented for a role of increased serine phosphorylation of the insulin receptor and insulin receptor substrate-1, competitively inhibiting insulin receptor substrate-1 tyrosine phosphorylation and further inhibiting downstream insulin signaling.

**GDM and pancreatic β-cell function.** Compared with women with normal glucose tolerance, those with GDM have lower insulin secretion for their degree of insulin resistance. Over the long term (i.e., years), insulin secretion deteriorates in relation to chronic insulin resistance, leading to progressive hyperglycemia and predominantly type 2 diabetes. In a Latino population of women with prior GDM, this deterioration has been slowed or arrested by treatment of insulin resistance, which takes advantage of short-term insulin sensitivity secretion changes to reduce insulin secretory demands on β-cells. In the Diabetes Prevention Program, lifestyle intervention and therapy with metformin also improved insulin sensitivity and preserved β-cell function in women with or without previous GDM.

Whereas most women who develop GDM have evidence for β-cell dysfunction related to chronic insulin resistance, an important minority do not. Some of these women appear to have autoimmune β-cell dysfunction. Evidence was presented for the presence of cytoplasmic islet cell antibodies and antibodies directed against GAD65, the membrane tyrosine phosphatase, and insulin in some women with GDM. These autoantibodies have also been used to identify individuals at high risk for the development of autoimmune diabetes in other settings, such as in first-degree relatives of subjects with classic type 1 diabetes. The frequency of such autoimmunity tends to parallel the frequency of type 1 diabetes in a given ethnic group. These findings suggest that autoimmune β-cell problems and related hyperglycemia represent a specific biological subtype of GDM that is distinct from insulin resistance and type 2 diabetes. Women with this subtype of GDM have clinical characteristics that are typically considered to impart a low risk of GDM (lean, Caucasian). Autoimmune GDM should be suspected in such patients. They may experience relatively rapid metabolic deterioration during or after pregnancy, so they require more aggressive follow-up. No specific disease-modifying therapies are currently available for autoimmune GDM.

**Genetics of GDM.** Monogenic forms of diabetes such as maturity-onset diabetes of the young (MODY; autosomal dominant inheritance) and mitochondrial diabetes (maternal inheritance, often with other clinical manifestations) appear to contribute in a relatively minor way (<5% of cases) to GDM. These conditions generally have a young age at onset and relatively mild hyperglycemia, at least initially, so they may be detected by the routine glucose screening that is commonly practiced in pregnancy. The genes involved in these subtypes of diabetes and GDM appear to have important effects on β-cell function, and patients often do not have evidence of chronic insulin resistance. Clinical suspicion of these subtypes is based on lack of clinical evidence for insulin resistance, coupled with a suggestive family history. Diagnosis requires genotyping that has recently become available for clinical practice.

The contribution of genetics to other forms of GDM is not well established. The sparse data that are available suggest modest heritability but are confounded by incomplete case ascertainment. Nonetheless, the autoimmune and insulin-resistant forms of diabetes outside of pregnancy, diseases for which GDM is often a precursor, are heritable, and some contributory genetic variants have been defined. Evidence was presented that some of the variants may contribute to GDM or its physiological phenotypes (insulin resistance, β-cell dysfunction), but the studies to date are relatively small, as are the potential genetic contributions.

## The placenta in GDM

The placenta serves as the primary interface between the mother and fetus. Alterations in placental transport functions can modify the impact of maternal metabolic abnormalities of GDM on the developing fetus. Evidence presented that was obtained from human term placentas studied in vitro indicates that placental glucose transport and metabolism are normal in GDM pregnancies, despite increased glucose fluxes from mother to fetus that result from increased glucose concentrations on the maternal side. Transfer and metabolism of other maternal nutrients (e.g., lipids, amino acids, micronutrients) in GDM are not yet well characterized. The placenta is a rich source of steroids, lipid-derived molecules, and peptides that can directly affect maternal metabolism and fetal development. Increased expression and production of cytokines such as TNF-α, interleukin-6, and leptin by placentas from women with GDM could be relevant to the development of exaggerated insulin resistance in pregnancies complicated by GDM. Evidence was presented that insulin from the fetus can modify placental gene expression, glycogen deposition, and vascular expansion. These findings reveal a potential role of the fetus in regulating placental function but do not indicate whether fetal influences mitigate or exaggerate the impact of GDM on fetal development.

**Recommendations for future research.** The following topics were identified as important opportunities for research:

- Pancreatic β-cell function: *1*) research into the effect of pregnancy on β-cell autoimmunity, the clinical utility of antibody screening, and the development of disease-modifying therapies of autoimmune GDM; *2*) development of effective disease-modifying strategies (e.g., to preserve β-cell function); and *3*) tailoring interventions to subsets of patients with specific genetic or pathophysiological abnormalities.
- Mechanisms of insulin resistance: *1*) explore later steps in the insulin-signaling pathway; *2*) identify the primary cellular triggers that lead to reduced insulin signaling in normal pregnancy and GDM; *3*) examine the effects of placental products (e.g., cytokines and placental growth hormone) and the influence of maternal fat accumulation and fatty acids on insulin sensitivity; and *4*) consider ethnic, nutritional, and environmental influences on fat distribution and adipose tissue biology that may play important roles in the development of insulin resistance.
- Studies of genotype-phenotype relationships, gene-environment interactions, and pre-diabetic phenotypes with primary focus on genetics within specific subtypes of GDM and within or between ethnic groups, rather than on GDM in general because of the biological heterogeneity of GDM. Pharmacogenetic studies may also be relevant to development of strategies for prevention of diabetes after GDM.
- In the placenta of GDM study: *1*) placental structure and function before 20 weeks' gestation, where the maternal environment of GDM could alter placental development and function with consequences for fetal growth and development later in gestation; *2*) placental metabolism and transfer of nonglucose nutrients, especially lipids; *3*) fetal-placental crosstalk to better characterize fetal signals that alter placental growth and function; and *4*) the role of placental cytokines as potential modulators of fetal fat accretion or metabolic programming (e.g., appetite regulation, β-cell function).

### Epidemiology

**Current observations.** In recent years, there has been a global increase in the prevalence of both obesity and type 2 diabetes. Recent reports provide convincing evidence for an increasing prevalence of GDM in the U.S. as well. Multivariate analyses that were reviewed at the conference demonstrated an increase in GDM within ethnic groups as well as an apparent disproportionate increase in the prevalence of GDM among younger, compared with older, pregnant women. Determining whether, and to what extent, a concurrent increase in prevalence of GDM has occurred globally is made difficult by a number of confounders including lack of uniformity in glucose tolerance testing (glucose load, glycemic thresholds, and number and timing of test results required to define GDM). Another is the variation in the prevalence of GDM associated with maternal age and ethnicity.

Causal factors for the apparent increase in GDM are likely to be multiple, including the prevalence of obesity, particularly in youth (due to low levels of physical activity and high levels of caloric intake) and improved survival of female infants whose birth weights were at the extremes of the normal range. As adults, the latter individuals have altered insulin action and/or insulin secretory capacity that may predispose them to the development of GDM. Birth weight history may be a valuable aid in risk assessment for GDM (APPENDIX Table 1).

**Recommendations for the future**

- Diagnostic criteria and definitions: *1*) clinical translation of Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study results regarding diagnostic criteria for GDM is of a high priority, and *2*) standardize definitions of maternal weight gain and fetal phenotype to facilitate the study of factors that influence fetal growth, perinatal morbidity, and long-term development of offspring of GDM mothers.
- Studies of GDM incidence: Such studies are of high priority and should include the following: *1*) data from populations throughout the world and concurrent correlation with pregnancy outcome; *2*) determining if the relationship between the globally occurring weight increase in women of reproductive age is causal for, or a concomitant of, glucose intolerance in pregnancy; *3*) clarification of reasons for different rates of increase in incidence of GDM in different ethnic groups and whether their geographical location plays an important role; and *4*) studies of the influence of socioeconomic factors, social deprivation, stress, and/or depression on GDM incidence, care, and outcome.
- Risk factors for GDM: Identification of other potentially alterable factors that put women at risk for the development of GDM is important for developing clinical strategies for its prevention.

## PANEL II: THERAPEUTIC INTERVENTIONS DURING PREGNANCY

### Perinatal implications

Identification and intensive management of GDM are associated with a decrease in mortality and morbidity in infants. With appropriate therapy, the likelihood of intrauterine fetal death is not detectably higher than in the general population. Morbidity can be increased, however, and this is likely to remain an issue until optimal management of the altered intrauterine environment is understood and appropriate interventions are implemented.

Excessive fetal growth remains an important perinatal concern in GDM. Maternal hyperglycemia continues to be viewed as the primary determinant of increased fetal growth via delivery of glucose to the fetus, which leads to fetal hyperinsulinemia. Other factors influencing growth include nutrients such as amino acids and lipids, specific growth factors, placental function, and the fetal response to a given nutrient environment. Fetal growth in women with GDM is typically monitored antenatally by ultrasound scan, and diabetes-related macrosomia is characterized by disproportionately increased growth of the abdominal circumference. Risk of macrosomia (variously defined as large-for-gestational-age or birth weight ≥4,000/4,250/4,500 g) is great when GDM is not recognized or is treated casually. Consequences of excessive fetal growth include birth trauma, maternal morbidity from operative delivery, and possible lifelong increased risks of glucose intolerance and obesity in the offspring. The cesarean delivery rate is increased in patients with GDM, in part to avoid birth trauma. Some reports suggest that overtreatment of GDM resulting in sustained levels of glucose that are below the normal range may lead to small-for-gestational-age infants (variously defined as <10th or <5th percentile of birth weight for gestational age and sex).

Other neonatal morbidities that potentially occur more frequently in infants of women with GDM include hypoglycemia, hyperbilirubinemia, hypocalcemia, erythremia, and poor feeding. Prevalence and severity of morbidities depend on gestational age at delivery as well as on metabolic factors. GDM with onset in

**Table 1—*Ambulatory glucose values in pregnant women with normal glucose tolerance***

| Study | Subjects (*n*) | Fasting | Postprandial (60 min) | Postprandial (peak) |
|---|---|---|---|---|
| Paretti et al. (3)* | 51 | 69 (57–81) | 108 (96–120) | |
| | | 3.8 (3.2–4.5) | 6.0 (5.3–6.7) | |
| Yogev et al. (2)† | 57 | 75 (51–99) | 105 (79–131) | 110 (68–142)‡ |
| | | 4.2 (2.8–5.5) | 5.8 (4.4–7.3) | 6.1 (3.8–7.9) |

Data are conventional and SI units (95% CI). *Glucose measured by capillary glucose meter with values adjusted to reflect plasma concentration (3). †Values obtained by continuous monitoring of interstitial fluid (2). ‡The time of the "peak" postprandial glucose concentration = 70 min (44–96).

mid-pregnancy or later pregnancy is not associated with an increased prevalence of congenital malformations. However, GDM diagnosed with elevated fasting plasma glucose (>120 mg/dl, >6.7 mmol/l) or A1C ≥7.0%, especially when detected early in pregnancy, possibly represents preexisting type 2 diabetes and is associated with a rate of anomalies that is higher than that found in the general obstetrics population.

Whether intensive management of GDM may also provide benefit to the mothers by reducing preterm labor, preeclampsia, maternal birth trauma, or postpartum complications is being addressed by ongoing clinical trials. A recently reported randomized controlled trial of GDM management (intervention) versus routine prenatal care (no intervention) of women with GDM showed less preeclampsia but a higher rate of induction of labor with intervention, as well as improved postpartum maternal health status including less depression (1).

## Metabolic management during pregnancy

In the randomized controlled trial recently reported by Crowther et al. (1), it was found that treating GDM (mean values in the diagnostic 75-g oral glucose tolerance test: fasting plasma glucose 86 ± 13 mg/dl [4.8 ± 0.7 mmol/l]; 2-h 140–198 mg/dl [7.8–11.0 mmol/l]) significantly reduced the likelihood of serious neonatal morbidity compared with routine prenatal care. Treatment included individualized medical nutrition therapy (MNT), daily self-monitoring of blood glucose (SMBG), and insulin when needed (20%). Similar randomized controlled trials are in progress. Pending their conclusion, based on the Crowther et al. randomized controlled trial, as well as other lower-level data on pregnancy outcome in untreated GDM, diagnosis and management of GDM are supported (preferably with onset of treatment by 30 weeks' gestation). Attention should be paid to minimizing untoward effects of labeling women with GDM such as increased cesarean sections and neonatal intensive care unit admissions.

## Goals and surveillance

**Maternal glycemia.** It is important to have normative data when formulating therapeutic goals. Evidence presented at the conference from ambulatory continuous glucose monitoring of interstitial fluid in nondiabetic pregnancies indicates that the mean of peak postprandial glucose concentration approximates 110 ± 16 mg/dl (6.1 ± 0.9 mmol/l) and that there is substantial intra- and intersubject variation of the time to the peak glucose excursion after starting the meal (range 45–120 min) (2). These normative values are similar to those found in a prospective study of ambulatory fingerstick capillary glucose monitoring in normal pregnant women (adjusted for plasma) (Table 1) (3).

Specific glucose values used as "upper boundary" treatment targets in clinical trials in GDM include capillary blood glucose in the following ranges: fasting 90–99 mg/dl (5.0–5.5 mmol/l), 1-h postprandial blood glucose <140 mg/dl (<7.8 mmol/l), or 2-h postprandial blood glucose <120–127 mg/dl (<6.7–7.1 mmol/l). The trials achieved satisfactory clinical outcomes, including frequency of fetal macrosomia <11%, suggesting that the treatment targets were appropriate. However, there are no data from controlled trials of lower versus higher targets or 1-h versus 2-h postprandial testing to identify ideal goals for prevention of fetal risks. There was consensus that the recommendations of the Fourth International Workshop-Conference on GDM to maintain maternal capillary glucose concentrations at <96 mg/dl (<5.3 mmol/l) in the fasting state, <140 mg/dl (<7.8 mmol/l) at 1 h, and <120 mg/dl (<6.7 mmol/l) 2 h after starting the meal need not be revised until data addressing optimal goals are available. Evidence from observational studies suggests that when mean capillary glucose levels in GDM are maintained at <87 mg/dl (<4.8 mmol/l), there is an increased likelihood of small-for-gestational-age infants.

Daily SMBG, using meters (preferably with memory capability) appears to be superior to less frequent monitoring in the clinic for detection of glucose concentrations that may warrant intensification of therapy beyond individualized MNT. Many providers decrease the frequency of SMBG when MNT is successful in achieving goals for metabolic control; available data do not address such issues as the duration of good control sufficient to reduce the frequency of SMBG or the appropriate frequency of testing in GDM that is well controlled on MNT. New technologies for glucose surveillance should enable future research to determine optimal goals for metabolic control. When alternate site testing is used, consideration should be given to the lag time for changes in postprandial glucose concentration when compared with fingerstick capillary glucose testing. Validation of the accuracy of patients' monitoring techniques is also essential.

**Ultrasound measurement of fetal abdominal circumference.** Assessing the fetal response to maternal GDM by ultrasound measurement of fetal abdominal circumference starting in the second and early third trimesters and repeated every 2–4 weeks can provide useful information (in combination with maternal SMBG levels) to guide management decisions. Evidence reviewed at the conference from randomized controlled trials indicates that modification of metabolic management based on fetal growth measurements may improve perinatal outcome or at least be equivalent to standard intensified management. Less intensified management may be allowed with normal growth (fetal abdominal circumference <75th percentile for gestational age), although the consensus was that some SMBG should be continued. Lower targets for glycemic control may be selected when size of the fetal abdomen is excessive, or pharmacological therapy can be added or intensified if a large abdominal circumference is detected despite seemingly good glycemic control. For this approach to be effective in clinical practice, attention should be given to the

accuracy of the measurements of fetal size and maternal glucose.

**Other methods of surveillance.** Urine ketone testing has been recommended in GDM patients with severe hyperglycemia, weight loss during treatment, or other concerns of possible "starvation ketosis." Fingerstick blood ketone testing is available and is more representative of laboratory measurements of β-hydroxybutyrate. However, the effectiveness of ketone monitoring (urine or blood) in improving fetal outcome has not been tested. Insufficient data are available to determine whether measurement of glycosylated hemoglobin or other circulating proteins is of value in the routine management of GDM. Psychosocial assessment of women with GDM is encouraged to detect issues such as depression, eating disorders, stress, and anxiety that can block effective response to prescribed treatment. Many patients will need support to be able to cope with the requirements of intensified care; however, the most effective approaches have not yet been defined.

## MNT and planned physical activity

MNT is the cornerstone of treatment for GDM. However, relatively little information is available to allow evidence-based recommendations regarding specific nutritional approaches such as total calories and nutrient distribution to the management of GDM. The food plan should be designed to fulfill minimum nutrient requirements for pregnancy set by the Institute of Medicine and to achieve glycemic goals without inducing weight loss or excessive weight gain. Adequate energy intake that provides appropriate weight gain is recommended during pregnancy. For overweight and obese women with GDM, modest energy and carbohydrate restriction may be appropriate. Ketonemia from starvation ketosis should be avoided.

MNT is best prescribed by a registered dietitian or qualified individual with experience in the management of GDM. Food plans should be culturally appropriate and individualized to take into account the patient's body habitus, weight gain, and physical activity and modified as needed throughout pregnancy to achieve treatment goals. Adjusting the amount and type of carbohydrate to achieve the target for postprandial glucose concentrations is an important part of the treatment regimen. Training patients in "carbohydrate counting," use of food records, and testing postprandial fingerstick capillary blood glucose can facilitate this goal. Nutrition interventions for GDM should emphasize overall healthy food choices, portion control, and cooking practices that can be continued postpartum and may potentially help prevent later diabetes, obesity, cardiovascular disease (CVD), and cancer. Training patients for subsequent lifestyle modifications aimed at losing weight and increasing physical activity are recommended.

In normal pregnancy, expected weight gain varies according to the prepregnancy weight. The Institute of Medicine report (4) recommended a relatively small gain during pregnancy of ≥7 kg or 15 lb for patients who are obese (BMI ≥30 kg/m$^2$) and a proportionally greater weight gain (up to 18 kg or 40 lb) for patients who are underweight (BMI <18.5 kg m$^2$) at the onset of pregnancy. However, there are no data on optimal MNT and weight gain for women with GDM. Furthermore, many individuals have reached or exceeded their prepregnancy-based weight gain target before the diagnosis of GDM is made. By contrast, some obese women will not gain much weight in spite of good nutritional intake, and fetal growth is usually normal. Excess gestational weight gain can be associated with fetal macrosomia and unhealthy maternal postpartum weight retention. Plotting weekly body weights on a weight gain grid specific to BMI classification is encouraged to facilitate recognition of inadequate or excess weight gain.

Planned physical activity of 30 min/day is recommended for all individuals capable of participating. Advising GDM patients to walk briskly or do arm exercises while seated in a chair for at least 10 min after each meal accomplishes this goal. Safety precautions on use of exercise during pregnancy have been published. Regular aerobic exercise with proper warm-up and cool-down has been shown to lower fasting and postprandial glucose concentrations in several small studies of previously sedentary individuals with GDM.

## Intensified metabolic therapy

Patients who fail to maintain glycemic goals or who show signs of excessive fetal growth should receive treatment in addition to standard nutritional management. Treatment with insulin has been used most frequently in such circumstances. There are no data demonstrating superiority of a particular insulin or insulin analog regimen in GDM. It is recommended that insulin administration be individualized to achieve the glycemic goals stated above.

**Human insulin.** This is the least immunogenic of commercially available preparations, but the rapid-acting insulin analogs, lispro and aspart, develop antibodies at rates and titers that are comparable to human regular insulin. No reports of glulisine use in pregnancy are available. Using insulin preparations of low antigenicity minimizes the transplacental transport of insulin antibodies. Of the three rapid-acting insulin analogs, lispro and aspart have been investigated in pregnancy, demonstrating clinical effectiveness, minimal transfer across the placenta, and no evidence of teratogenesis. These two insulin analogs both improve postprandial glucose excursions compared with human regular insulin and may be associated with lower risk of delayed postprandial hypoglycemia. A randomized controlled trial of 322 subjects with type 1 diabetes found similar safety in the use of aspart insulin compared with regular human insulin (5). Randomized controlled trials have not been carried out using long-acting insulin analogs of any type in diabetic pregnant women (insulin glargine, insulin detemir). Thus, human NPH insulin as part of a multiple injection regimen should be used for intermediate-acting insulin effect in GDM.

**Oral antihyperglycemic agents.** Of the sulfonylurea family of drugs, only glyburide (glibenclamide) has been demonstrated to have minimal transfer across the human placenta (4% ex vivo) and has not been associated with excess neonatal hypoglycemia in clinical studies. There is evidence from one randomized controlled trial during pregnancy (6) and several supporting observational studies that glyburide is a useful adjunct to MNT/physical activity regimens when additional therapy is needed to maintain target glucose levels. Glyburide action must be carefully balanced with meals and snacks to prevent maternal hypoglycemia (as with insulin therapy). There is some evidence that glyburide may be less successful in obese patients or those with marked hyperglycemia earlier in pregnancy. As with MNT/physical activity and insulin regimens, SMBG and fetal measurements of abdominal circumference or other parameters of fetal size need to be followed closely in women using glyburide.

***Metformin*** does cross the placenta, and at present there is no evidence to recommend metformin treatment for GDM

except in clinical trials, which should include long-term follow-up of infants. Metformin has been used in women with polycystic ovarian syndrome to improve fertility and decrease the spontaneous abortion rate, and in nonrandomized studies, its use has been continued throughout pregnancy. However, two randomized trials demonstrated a lowering of the spontaneous abortion rate, even when metformin was discontinued as soon as pregnancy was diagnosed. There is insufficient evidence that metformin prevents GDM.

***Acarbose***, an α-glucosidase inhibitor, is poorly absorbed from the gastrointestinal tract, and two preliminary studies have suggested efficacy in reducing postprandial glucose excursions in GDM, but with the expected high frequency of abdominal cramping. A small proportion of this drug may be absorbed systemically, and safety and potential transplacental passage have not been fully evaluated.

Use of thiazolidinediones, glinides, and glucagon-like peptide 1 agonists during pregnancy is considered experimental. There are no controlled data available in pregnancy, and one study reported that rosiglitazone crossed the human placenta at 10–12 weeks' gestation, with fetal tissue levels measured at about half of maternal serum levels. Ex vivo human placental perfusion studies of glucagon-like peptide 1 agonist detected minimal levels on the fetal side.

## Obstetric management

**Fetal surveillance.** Fetal ultrasound screening for congenital anomalies is recommended for women with GDM who present with A1C ≥7.0% or fasting plasma glucose >120 mg/dl (>6.7 mmol/l) as an increased risk of major congenital malformations has been reported in such pregnancies. Use of ultrasound measurements to detect fetal macrosomia as a guide to GDM treatment is considered above (GOALS AND SURVEILLANCE). Type and frequency of surveillance for fetal well-being and its frequency should be influenced by the severity of maternal hyperglycemia or the presence of other adverse clinical factors. Mothers with GDM should be taught to monitor fetal movements during the last 8–10 weeks of pregnancy and to report immediately any reduction in the perception of fetal movements. Data are not available to demonstrate the optimal application of more intensive fetal monitoring or which method is superior in women with GDM. No fetal surveillance method is always able to detect fetal compromise. Data are insufficient to determine whether surveillance beyond self-monitoring of fetal movements is indicated in women with GDM who continue to meet the targets of glycemic control with MNT/physical activity regimens alone and in whom fetal growth is appropriate for gestational age.

**Maternal surveillance.** The frequency of spontaneous preterm birth may be increased in women with untreated GDM. When otherwise indicated, the use of corticosteroids to enhance fetal lung maturity should not be withheld because of a diagnosis of GDM, but intensified monitoring of maternal glucose levels is indicated and temporary addition or increase of insulin doses may be necessary. The risk of hypertensive disorders is also increased in women with GDM. Measurement of blood pressure and urinary protein is recommended at each prenatal visit to detect the development of preeclampsia.

Based on studies of women with preexisting diabetes, blood glucose monitoring during labor is often used in women with GDM treated with insulin or glyburide to guide correction of maternal hyperglycemia and prevent fetal hypoxia and neonatal hypoglycemia. However, the ideal target glucose concentration during labor has not been established.

## Timing and route of delivery

There are no data supporting delivery of women with GDM before 38 weeks' gestation in the absence of objective evidence of maternal or fetal compromise. Data are not available to indicate whether or not there is greater risk of perinatal morbidity/mortality in the infants of women with well-controlled GDM if pregnancy is allowed to proceed past 40 weeks' gestation. Nevertheless, it is reasonable to intensify fetal surveillance when pregnancy is allowed to continue beyond 40 weeks' gestation. Some evidence indicates that delivery past 38 weeks can lead to an increase in the rate of large-for-gestational-age infants without reducing the rate of cesarean deliveries.

Amniocentesis for assessment of fetal lung maturity is not indicated in well-controlled patients who have indications for induction of labor or cesarean section as long as there is reasonable certainty about the estimation of gestational age. When delivery is necessary at an earlier gestational age for the well-being of mother or fetus, delivery should be effected without regard to lung maturity testing.

Delivery of a large-for-gestational-age fetus in the setting of GDM is associated with an increased risk of birth injury compared with the nondiabetic population. Strategies to reduce the risk of birth injury include a liberal policy toward cesarean delivery when fetal overgrowth is suspected. However, no controlled trials are available to support this approach. In planning the timing and route of delivery, consideration of fetal size using clinical and ultrasound estimation of fetal weight, despite inherent inaccuracies, is frequently used. Using ultrasound estimated fetal weight or abdominal circumference to make decisions regarding timing and route of delivery may be associated with a lower rate of shoulder dystocia, but larger studies are needed to determine if this approach affects the rate of neonatal injury.

## Recommendations for the future

There is need for data from controlled clinical studies to determine the following:

- Optimal target ranges for glucose control in GDM
- Optimal MNT regimens
- The role of gestational weight gain in perinatal and long-term maternal outcomes
- The role of SMBG in patients treated only with MNT/physical activity
- Comparison of different insulin and insulin analog regimens
- Glyburide effects on *1*) maternal and neonatal outcomes in comparison to therapy with insulin; *2*) potential postpartum progression of the woman with GDM toward glucose intolerance/diabetes; *3*) the possibility of GDM recurrence; and *4*) the intermediate- and long-term development of offspring
- The potential role of other oral antihyperglycemic agents during pregnancy
- Psychosocial approaches to enhance glycemic control and perinatal outcome
- Optimal strategies for fetal monitoring and determining timing and route of delivery to prevent fetal and maternal complications. Both cost-benefit analysis and determination of the psychological impact of therapies should be included in the assessment of outcomes.
- Whether monitoring maternal blood glucose is indicated during labor in women with GDM, and if so, the frequency of measurement and the optimal glucose levels that are associated with the best perinatal outcome

## PANEL III: OFFSPRING

### Clinical implications

Presentations focused on determinants of birth weight; determinants of the phenotype of infants of women with GDM; fetal, neonatal, and infant risk factors for future growth and development; and the health effects of breastfeeding in infants of women with GDM. In addition to classic risk factors associated with macrosomic infants of women with GDM, there is increasing awareness of childhood risk for obesity, for GDM, and subsequently for type 2 diabetes.

Traditionally, the marker of offspring risk has been macrosomia. Definitions of macrosomia in current use are probably now obsolete, and some measure of adiposity at birth may be more appropriate. Size at birth is a complex interaction between maternal environment and fetal genes. A major component of maternal intrauterine environment is the glucose concentration, and there appears to be a continuum in the relationship with birth weight. However, this relationship is modulated by parity and probably by putative genes for type 2 diabetes and obesity. Maternal restraint of fetal growth, evident especially during the first pregnancy, is inherited through the maternal line related to mitochondrial DNA or maternally expressed genes. Genetic predisposition for type 2 diabetes and obesity may also be inherited from one or both parents by offspring of GDM mothers. Maternal prepregnancy BMI is an independent risk factor for large size at birth, an effect with certain genetic determinants but possibly also environmental components operating in utero.

The importance of the intrauterine environment is highlighted by studies in the general population that indicate an association between poor fetal growth followed by rapid childhood weight gain and subsequent risk of diabetes and CVD in adulthood. Measures aimed at reducing or preventing obesity by modification of lifestyle may also decrease the risk of obesity and diabetes in the offspring. The child's primary care provider should be aware that the child of a mother with GDM has inherent risks of future obesity and diabetes.

Newborn infants of women with GDM have increased adiposity and reduced fat-free mass even if they are not macrosomic. A degree of "catch down" growth occurs over the first year or two, followed by excessive weight, resulting in risk of obesity by age 5 years. There are few detailed studies of body composition and none relating to appetite, exercise, and other confounders such as psychosocial and ethnic differences.

The extent to which strict control of maternal GDM or postnatal modification in diet such as breastfeeding or bottle-feeding modifies childhood risks is unknown. There are few data on infants of women with GDM who were breastfed, and although reports are conflicting, all but one study show favorable or no significant effect on subsequent health. A study reported after the conference (7) found that children of GDM mothers who were breastfed for >3 months had a 45% decrease in rates of being overweight (BMI ≥90th percentile) at 2–8 years compared with those who were bottle-fed.

### Recommendations for the future

- Educate providers regarding the lifelong risk of obesity and type 2 diabetes for the offspring of women with GDM.
- Provide early counseling to families to avoid excessive weight gain, since this may be the first sign of risk. Apply American Diabetes Association guidelines for screening high-risk children and adolescents for future type 2 diabetes.
- Studies are needed that evaluate changes in adiposity over the first 5 years of life, using sophisticated methods that are correlated with standard office measures to derive appropriate standards.
- Follow-up studies that involve large numbers of subjects, that commence at birth and continue long term, are needed to *1*) disentangle the relative contribution of GDM and obesity without hyperglycemia or frank GDM during pregnancy on offspring's risk for obesity and diabetes and *2*) establish the attributable risk of GDM for development of obesity and type 2 diabetes in other populations in addition to the Pimas.
- Studies on breastfeeding with careful attention to the maternal glucose control during this critical period of infant development are needed to determine if there are additional factors that influence the risk of obesity in these children. Data are insufficient to suggest a change in the current recommendations that promote breastfeeding.

## PANEL IV: MATERNAL FOLLOW-UP

### Clinical implications

Communication between the health care providers and with the patient should establish a postdelivery health plan including surveillance for and prevention of diabetes.

There are immediate short- and long-term medical issues to consider after GDM pregnancy. These were addressed by presentations that focused on strategies for *1*) evaluation of glucose metabolism and CVD risk factors postpartum, *2*) breastfeeding by mothers after GDM, *3*) appropriate use of contraception, *4*) links between various types of gestational hypertension and long-term risk of CVD, and *5*) preventing or delaying progression to diabetes after GDM.

Although the majority of women with GDM return to normal glucose tolerance immediately after delivery, a significant number will remain diabetic or continue to have impaired glucose tolerance (IGT). Many will have additional pregnancies in the future. Appropriate family planning and contraception are necessary because of known risks of congenital malformations and early fetal loss if overt diabetes has ensued and of a high risk of abnormal glucose metabolism during subsequent pregnancy, even if glucose metabolism is initially normal after GDM. A majority of women are overweight or obese before the index GDM pregnancy and gain additional weight during pregnancy.

### Status of glucose metabolism

**Post-delivery.** Persistent hyperglycemia in the early puerperium is uncommon and can be excluded by measuring fasting or random capillary blood glucose levels before discharge from the hospital (Table 2). Elevated values (diabetes) should be confirmed with laboratory measurements of fasting plasma glucose (fasting plasma glucose ≥126 mg/dl, ≥7 mmol/l) or postprandial glucose (≥200 mg/dl, >11.1 mmol/l) (8). In such patients, MNT and, if necessary, pharmacological therapy should be continued to maintain good glycemic control and provide sufficient calories for lactation and infant well-being. All types of insulin, glyburide, or glipizide can be safely used by breastfeeding women. Limited data suggest that metformin, while excreted into breast milk, does not appear to have harmful neonatal effects; however, larger studies are needed to demonstrate the safety to

**Table 2—*Metabolic assessments recommended after GDM***

| Time | Test | Purpose |
|---|---|---|
| Post-delivery (1–3 days) | Fasting or random plasma glucose | Detect persistent, overt diabetes |
| Early postpartum (around the time of postpartum visit) | 75-g 2-h OGTT | Postpartum classification of glucose metabolism* |
| 1 year postpartum | 75-g 2-h OGTT | Assess glucose metabolism |
| Annually | Fasting plasma glucose | Assess glucose metabolism |
| Tri-annually | 75-g 2-h OGTT | Assess glucose metabolism |
| Prepregnancy | 75-g 2-h OGTT | Classify glucose metabolism |

*Classification of glucose metabolism by criteria recommended by the American Diabetes Association (8). OGTT, oral glucose tolerance test.

the infant of breastfeeding women using metformin as well as acarbose and glitazones.

**Postpartum.** Glucose tolerance testing should be delayed until 6–12 weeks after delivery in the GDM women who do not have diabetes immediately postpartum. A 75-g oral glucose tolerance test can be coordinated with the postpartum visit (Table 2). Several studies have shown that measuring only the fasting plasma glucose level postpartum is not sufficiently sensitive to identify all women who have IGT or type 2 diabetes. Data presented at the conference indicated that, postpartum, only 34% of the women with IGT or type 2 diabetes had impaired fasting glucose and that 44% of those with type 2 diabetes had fasting levels <100 mg/day (<5.5 mmol/l).

It is important to carefully evaluate those who do not have clinical characteristics associated with type 2 diabetes. Measurement of serum anti-GAD antibodies is useful to identify subjects with autoimmune β-cell dysfunction and, when present, close follow-up is warranted, since their carbohydrate tolerance may deteriorate rapidly into overt diabetes. In general, the frequencies of these less common forms of diabetes tend to parallel the background prevalence of these disorders in a given population.

**Long term.** Published studies show that after GDM, 35–60% of women develop type 2 diabetes within 10 years. Thus, accurate diagnosis of glucose abnormalities permits the initiation of strategies for primary prevention of diabetes, a primary goal of follow-up care. It is recommended that glucose metabolism be assessed periodically with an oral glucose tolerance test because of the low sensitivity of fasting plasma glucose alone to detect IGT and diabetes. Currently, large population studies have not established an optimum testing frequency or evaluated modified testing strategies based on risk factors. In the absence of such data, the panel recommended that after initial postpartum testing, an oral glucose tolerance test should be repeated in 1 year and, at a minimum, every 3 years thereafter (Table 2).

## CVD risk factor assessment

A substantial number of women with prior GDM share many characteristics with subjects that have the metabolic syndrome (e.g., glucose intolerance, insulin resistance, central obesity, elevated triglycerides, and low HDL cholesterol) and inflammatory markers (e.g., high-sensitivity C-reactive protein and interleukin-6). Evidence was reviewed suggesting that women with GDM may manifest short-term endothelial dysfunction during late pregnancy that is manifested as transient hypertension. Long-term endothelial dysfunction may be associated later in life with increased risk of chronic hypertension and CVD. Insulin resistance may be implicated in transient hypertension and has been associated with inflammatory responses. It has been suggested that chronic states of insulin resistance may produce chronic inflammation, adversely affecting vascular reactivity and atherogenesis, and may set up future hypertension and ischemic vascular disease in these women. In the absence of established specific strategies for women with GDM, standard screening guidelines for CVD risk factor assessment should be followed at the times that glucose metabolism is evaluated (Table 2).

## Breastfeeding

The effect of breastfeeding per se on subsequent risk of diabetes is not clear. Limited studies show lower rates of postpartum diabetes and fasting glucose levels in breastfeeding women with prior GDM and a protective effect with lower diabetes rates in healthy women who breastfed. Pending clarification of these issues, all women, including those with prior GDM, should be actively encouraged to exclusively breastfeed to the greatest extent possible during the first year of life.

## Contraception or pregnancy planning

Contraceptive options can be tailored to individual lifestyle and preference. Nonhormonal methods can be prescribed using standard guidelines. Combination oral contraceptives containing the lowest doses should be prescribed and can be started 6–8 weeks after delivery if the woman is breastfeeding. However, in the Latino population of breastfeeding women, the use of progestin-only oral contraceptives (e.g., 0.35 mg/day norethindrone) and long-acting injectable depomedroxyprogesterone acetate (150 mg every 3 months) was associated with a two- to threefold increase in diabetes risk. Thus, progestin-only agents should be used with caution during breastfeeding. Pregnancy planning should include evaluation of glucose tolerance and, if abnormal, treatment of hyperglycemia before discontinuation of contraception.

## Diabetes prevention

During pregnancy, women are routinely screened for GDM, by assessing risk factors, doing blood glucose testing, or both. A diagnosis of GDM identifies women at high risk for diabetes. This routine clinical identification represents a unique opportunity and a responsibility for caregivers to educate the patient and health care system for the need for primary diabetes prevention. There is substantial research evidence that lifestyle change and use of metformin or thiazolidinediones (troglitazone and pioglitazone) can prevent or delay the progression of IGT to

type 2 diabetes after GDM. Researchers and health care providers should actively support public health initiatives such as the Diabetes in Women Action Plan to educate public, patients, and providers about the risk of GDM and cooperate with the National Diabetes Education and Prevention for GDM Initiative (NDEP@hagersharp.com) for implementation of the Diabetes Prevention Program lifestyle program into the public sector.

### Recommendations for the future

Studies indicated below are needed for optimal postpartum and long-term health of women who have had GDM.

- Risks and timeline for progression to diabetes: The timeline for the development of diabetes after delivery appears to vary depending on risk factors and whether IGT is present after GDM. An optimal follow-up and testing strategy needs to be established for those who do not have IGT at initial postpartum testing.
- Prevention of diabetes: Women with prior GDM who develop IGT are an identified high-risk group, already linked to the health care system. Studies are needed to *1*) establish optimal timing and cost-effectiveness of diabetes prevention interventions; 2) find effective ways to deliver preventive interventions in this population (both translational research and health care funding are needed to accomplish this objective); and 3) link prevention of diabetes in women with GDM to the equally important goal of preventing childhood obesity and metabolic syndrome in their offspring.
- Risks of CVD: The risks and mechanisms for the development of CVD (hyperlipidemia, hypertension, and atherosclerosis) need to be established by follow-up studies in women with prior GDM. Women with prior GDM share many characteristics with people who have the metabolic syndrome, and these relationships need clarification.
- Inter-pregnancy care: Research is needed to achieve optimal outcome in pregnancies after GDM. Issues to be addressed by prospective clinical trials include *1*) whether it is beneficial to delay or avoid subsequent pregnancy, 2) whether to breastfeed and for how long, and 3) optimal choice of hormonal contraceptive.

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## APPENDIX

### Panel members

**Panel I.** Thomas A. Buchanan,* Alberto de Leiva, Gernot Desoye, Assiamira Ferrara, Jed Friedman, Sylvie Hauguel-de Mouzon, David Hadden,* Boyd Metzger, Jeremy Oats,* David J. Pettitt, David Sacks,* Richard Watanabe. (*Panel chairpersons.)

**Panel II.** Deborah Conway, Donald Coustan,* Moshe Hod, Lois Jovanovic, John Kitzmiller,* Siri Kjos, Mark Landon, Alberto de Leiva,* Thomas Moore, Diane Reader, Janet Rowan. (*Panel chairpersons.)

**Panel III.** Patrick M. Catalano, Dana Dabelea, David B. Dunger,* Erica P. Gunderson, David J. Pettitt*. (*Panel chairpersons.)

**Panel IV.** Marshall Carpenter, Andrea Dunaif, John L. Kitzmiller, Siri Kjos,* Robert E. Ratner, Christos Zoupas*. (*Panel chairpersons.)

**Table 1—*Screening strategy for detecting GDM***

GDM risk assessment: 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 GDM
  - No known diabetes in first-degree relatives
  - Age <25 years
  - Weight normal before pregnancy
  - Weight normal at birth
  - No history of abnormal glucose metabolism
  - No history of poor obstetric outcome
- Average risk: Perform blood glucose testing at 24–28 weeks using either:
  - Two-step procedure: 50 g glucose challenge test (GCT) followed by a diagnostic oral glucose tolerance test in those meeting the threshold value in the GCT.
  - One-step procedure: Diagnostic oral glucose tolerance test performed on all subjects.
- High-risk: Perform blood glucose testing as soon as feasible, 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: GDM, impaired glucose metabolism, or glucosuria

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

Reproduced with minor modifications from Metzger et al. (9). "Weight normal at birth" is an additional low-risk criterion that must now be met.

**Table 2—*Diagnosis of GDM by an oral glucose tolerance test***

| | Oral glucose load* | | | |
|---|---|---|---|---|
| | 100-g glucose† | | 75-g glucose† | |
| Fasting‡ | 95 mg/dl | 5.3 mmol/l | 95 mg/dl | 5.3 mmol/l |
| 1-h‡ | 180 mg/dl | 10.0 mmol/l | 180 mg/dl | 10.0 mmol/l |
| 2-h‡ | 155 mg/dl | 8.6 mmol/l | 155 mg/dl | 8.6 mmol/l |
| 3-h‡ | 140 mg/dl | 7.8 mmol/l | — | — |

Data are from Metzger et al. (9). *The test should be performed in the morning after an overnight fast of at least 8 h but not more than 14 h and after at least 3 days of unrestricted diet (≥150 g carbohydrate/day) and physical activity. The subject should remain seated and should not smoke throughout the test. †Two or more of the venous plasma glucose concentrations indicated below must be met or exceeded for a positive diagnosis. ‡The cutoff values are those proposed by Carpenter and Coustan (10) for extrapolation of the whole blood glucose values found by O'Sullivan and Mahan (11) to plasma glucose concentrations.

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