Gestational Diabetes After Delivery

Short-term management and long-term risks

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After the intensified treatment often required for treating gestational diabetes mellitus (GDM), clinicians may be tempted to relax after delivery of the baby. If it is assumed that no further management is needed, an excellent opportunity to improve the future health status of these high-risk women may be lost. There are special concerns for the early postpartum care of women with GDM. Encouragement and facilitation of exclusive breastfeeding is very important because of the profound short-term as well as long-term health benefits to the infant and the reduced risks for subsequent obesity and glucose intolerance demonstrated in many breastfeeding women. A method of contraception should be chosen that does not increase the risk of glucose intolerance in the mother. Some women with GDM will have persisting hyperglycemia in the days after delivery that will justify medical management for diabetes and perhaps for hypertension, microalbuminuria, and dyslipidemia. Treatment should be maintained according to the guidelines of the American Diabetes Association and other relevant organizations and adjusted for the needs of lactation. Treatment should be continued in adequate fashion to minimize risks to the early conceptus if there is a subsequent planned or unplanned pregnancy.

Most women with GDM will not have severe hyperglycemia after delivery. This group should be followed for at least 6–12 weeks to determine their glucose status. Many studies over 3 decades on all continents of the globe demonstrate the high risk of subsequent diabetes in this female population. The degree of this risk is best assessed by glucose tolerance testing. Randomized controlled trials have proven that several interventions (diet and planned exercise 30–60 min daily at least 5 days per week and antidiabetic medications) can significantly delay or prevent the appearance of type 2 diabetes in the women with impaired glucose tolerance (IGT). The high-risk women can also be assessed for cardiovascular risk factors, with appropriate management and follow-up to reduce the risk of coronary heart disease, cardiomyopathy, and stroke. These women should be educated to seek specific preconception consultation before the next pregnancy to avoid the teratogenic effect of unrecognized diabetes.

EARLY POSTPARTUM CARE — Provision of puerperal obstetrical and neonatal care is the first concern after vaginal or cesarean delivery of women diagnosed with GDM (1). GDM mothers who had imperfect glycemic control, obesity, or hypertension may have an increased frequency of preterm delivery and postpartum complications (2–8). Hopefully, a minority of babies will need to be managed in the neonatal intensive care unit (9,10), but if they do, parental anxieties need to be addressed and mother-infant bonding encouraged. Cesarean delivery and neonatal intensive care unit admissions are affected by parental and clinician input and institutional policies, as well as determined by glycemic control, obesity, and hypertension during pregnancy. If medication has been used to treat GDM, it is usually stopped at delivery. Encouragement and training for healthy nutrition, planned physical activity, and weight reduction as needed, continued cessation of smoking, facilitation of breastfeeding, and effective planning for the next or no more pregnancies are of high importance for all GDM mothers after delivery. Considerations concerning lactation (11,12) and contraception (13) in women with GDM are presented elsewhere in this supplement.

Immediate postpartum persistence of hyperglycemia at the level of type 2 diabetes is uncommon in women diagnosed with GDM, and type 1 diabetes is even more unusual. Both can be ruled out by a few fingerstick glucose tests in the first days after delivery (to rule out diabetes: fasting plasma glucose [FPG] <126 mg/dl, <7 mmol/l; casual plasma glucose <200 mg/dl, <11.1 mmol/l). If diabetes is suspected and is confirmed by laboratory fasting or casual glucose tests (14), medical nutrition therapy, self-monitoring of blood glucose, and planned physical activity are continued. The diabetic food plan should be designed for good glycemic control, effective lactation, and infant health. Consultation with a registered dietitian is desirable. If type 1 diabetes is suspected and confirmed (14), insulin therapy is reinstituted.

If type 2 diabetes is suspected immediately postpartum, the addition of oral agents can be considered. Glyburide (glibenclamide) or glipazide do not appear in the breast milk of treated women (15), and any type of insulin can be used if needed during breastfeeding or bottle-feeding. Three small studies show that metformin is excreted into breast milk with a range of milk/plasma ratios of 0.35–0.71, but with no indication of harmful effects on the infants (16–18). Larger studies are needed to be able to determine that metformin therapy is indicated for diabetic

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Abbreviations: CVD, cardiovascular disease; FPG, fasting plasma glucose; GDM, gestational diabetes mellitus; GTT, glucose tolerance test; hsCRP, highly sensitive C-reactive protein; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

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

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Table 1—*Reasons to perform glucose tolerance testing after pregnancies complicated by GDM*

1. The substantial prevalence of glucose abnormalities detected by 3 months postpartum.
2. Abnormal test results identify women at high risk of developing diabetes over the next 5–10 years.
3. Ample clinical trial evidence in women with glucose intolerance that type 2 diabetes can be delayed or prevented by lifestyle interventions or modest and perhaps intermittent drug therapy.
4. Women with prior GDM and IGT or IFG have CVD risk factors. Interventions may also reduce subsequent CVD, which is the leading cause of death in both types of diabetes.
5. Identification, treatment, and planning pregnancy in women developing diabetes after GDM should reduce subsequent early fetal loss and major congenital malformations.

women during lactation. The use of acarbose is attractive during lactation because absorption of the oral drug is quite limited, but there are no studies of the pharmacological effect of delayed gastrointestinal absorption of carbohydrate on the quality of lactation. Use of a thiazolidinedione could also be an attractive choice, since the drugs are highly protein-bound "and the large volume of distribution of the maternal compartment should ensure that relatively little crosses into breast milk" (19), but there are no studies as yet of the use of pioglitazone or rosiglitazone in diabetic lactating women. Finally, the woman with diabetes should be educated about *1*) the risk of early fetal loss and major congenital malformations if hyperglycemia is not controlled before the next pregnancy, *2*) the possibility of prevention of diabetic complications with good control of glucose and blood pressure, and *3*) the long-term risks of cardiovascular disease (CVD) with type 2 diabetes and means of its prevention (20,21). Women with GDM but without diabetes diagnosed immediately postpartum should be advised to have later glucose tolerance testing, to have a prepregnancy consultation before the next pregnancy, and to request early glucose screening in the next pregnancy.

In the absence of obvious diabetes soon after delivery, the timing of delayed postpartum glucose tolerance testing (6–12 weeks or later) may depend on the length of continuation of health insurance coverage. Obstetrical or medical care should continue until delayed postpartum glucose status is determined and the patient is educated about indicated preventive therapy or diabetes/CVD risk reduction. Patient referral may be necessary to continue this management.

POSTPARTUM GLUCOSE TESTING

— The rationale for delayed postpartum glucose testing (at 6–12 weeks) of women with prior GDM is based on five sets of facts (Table 1). The first is the prevalence of abnormal results by 3 months postpartum (cited references published since the last International GDM Workshop in 1998: 22–33). Impaired fasting glucose (IFG) is defined as FPG ≥100 or ≥110 mg/dl (≥5.6 or ≥6.1 mmol/l), depending on study and guideline (14,34,35). IGT is defined as a 75-g glucose tolerance test (GTT) 2-h plasma glucose of 140–199 mg/dl (7.8–11.0 mmol/l). Diabetes is defined as repeated FPG ≥126 mg/dl (≥7 mmol/l) or 2-h glucose ≥200 mg/dl (≥11.1 mmol/l) (14,34,35). The prevalence of isolated IFG is 3–6%, that of IGT is 7–29%, and that of diabetes is 5–14% 4–20 weeks after pregnancy in women who were diagnosed with GDM and received treatment during gestation (Table 2). The variance in prevalence may depend on the frequency of obesity in the sample and different diagnostic standards for GDM in the pregnancy, but does not seem to depend much on geographic location of the study. The majority of recent studies of early postpartum follow-up after GDM yield an IGT prevalence of 17–23%.

The second reason to identify glucose intolerance after pregnancy is that abnormal test results identify women at increased risk of developing type 1 diabetes or especially type 2 diabetes over 1–15 years follow-up (cited references published since the last International GDM Workshop in 1998: 36–46). Systematic reviews of older studies conclude that 35–60% of subjects develop type 2 diabetes by 10–20 years after a GDM pregnancy, at rates much greater than control groups who did not have glucose intolerance during pregnancy (47–49). The higher rates were in studies of particular ethnic groups in the U.S. Recently, follow-up programs elsewhere also have identified increasing rates of type 2 diabetes by 5–10 years after GDM (Table 2): 9–43% type 2 diabetes in Europe (37,40–42,45,46) and 11–21% in Asia (38,43,44). The frequency of type 2 diabetes is influenced by BMI, weight gain after pregnancy, family history of diabetes, fasting and postchallenge glucose levels during and after pregnancy, postpartum insulin resistance and inadequate β-cell secretion, and the need for pharmacological treatment during pregnancy (24,27–30,36,38,42,46,50–52). However, the risk factors are unable to predict all cases of subsequent type 2 diabetes: the biggest risk factor is a GDM pregnancy. The prevalence of type 1 diabetes identified 1–10 years after GDM in mostly European studies is 2.3–9.3% (Table 2) (40–42,45) and can usually be predicted by detection of β-cell–related autoantibodies during or after the GDM pregnancy (26,46,53–58).

The important third reason to identify glucose abnormalities postpartum is that six randomized clinical trials demonstrate the benefit of several interventions (diet and exercise 30–60 min daily at least 5 days per week, acarbose, metformin, or peroxisome proliferator–activated receptor-γ agonists: thiazolidinediones, "glitazones") in delaying or preventing type 2 diabetes in women with glucose intolerance (59–72). These trials are reviewed elsewhere in this supplement (73).

The fourth reason is that women with prior GDM have a high frequency of CVD risk factors (30,43,46). Reduction of type 2 diabetes in these women should be of great health benefit (74–77), since coronary heart disease, heart failure, stroke, and their associated mortality are common in this population (78). Clinical trials are ongoing to test this hypothesis. Intensified multifactorial treatment of type 2 diabetes already present is of demonstrated benefit in reducing diabetic and cardiovascular complications (79). Clinical trials are also needed to determine the best methods to reduce CVD risk factors in women with prior GDM and to measure the impact on long-term health.

The fifth reason to predict or identify diabetes after GDM, but not least important, is that women with undiagnosed hyperglycemia entering subsequent pregnancy have high rates of major congenital malformations in their infants (80–83), which can be reduced by planning pregnancy and using intensified preconception care of diabetes (84,85). Unfortunately, for many reasons, women with type 2 diabetes have been less likely to use preconception care (83,86,87), so major public efforts are required to improve this dangerous situation.

Table 2—*Observational studies published since 1998 identifying glucose abnormalities after pregnancies complicated by GDM (short- and longer-term follow-up)*

Study	Region	Number GDM followed	Follow-up after delivery	Percent isolated IFG	Percent IGT	Percent type 2 diabetes
Short-term follow-up						
Conway and Langer (22)	Texas	179	4–13 weeks	3.3*	16.7	7.8
Ko et al. (23)	China	801	6 weeks	NA	22.7	13.1
Pallardo et al. (24)	Spain	788	3–6 months	5.8*	14.1	5.4
Costa et al. (25)	Spain	120	2–12 months	2.5*	10.8	2.5
Bartha et al. (26)	Spain	102	3 months	NA	6.9	8.8
Aberg et al. (27)	Sweden	193	12 months	NA	21.8	9.2
Schaefer-Graf et al. (28)	California	1,636	1–4 months	NA	21.8†	14.1
Jang et al. (29)	Korea	311	6–8 weeks	2.3*	23.2	16.7
Pallardo et al. (30)‡	Spain	838	3–6 months	4.8*	10.4	3.5
Agarwal et al. (31)	United Arab Emirates	549	4–8 weeks	5.5*	15.3	9.1
Winzer et al. (32)	Austria	98	12 months	5.0§	20.0	15.0
Lin et al. (33)	China	127	>6 weeks	NA	29.1	13.4
Current study	California	527	6–21 weeks	6.3§	23.3	4.7
Longer-term follow-up						
Buchanan et al. (36)	California	91	1–2 years	NA	NA	15.4
Kousta et al. (37)	U.K.	192	1–86 months	9.4*	27.1	24.0
Bian et al. (38)	China	86	5–10 years	NA	7.0	20.9
Linne et al. (39)	Sweden	28	15 years	NA	NA	35
Albareda et al. (40)	Spain	352	6 years	7.1*	17.3	11.1 (2.6% type 1 diabetes)
Cypryk et al. (41)	Poland	193	1–8 years	0.5*	13.5	18.7 (9.3% type 1 diabetes)
Lauenborg et al. (42)	Denmark	330	6–10 years	NA	26.4†	37.0 (3.9% type 1 diabetes)
Cho et al. (43)	Korea	170	1–5 years	NA	25.3	10.6
Cheung and Helmink (44)	Australia	102	1–8 years	NA	16	29
Hunger-Dathe et al. (45)	Germany	173	2–10 years	NA	19.1†	9.2 (2.3% type 1 diabetes)
Lobner et al. (46)	Germany	302	2–11 years	NA	NA	43.1‡

*1997 American Diabetes Association criteria (34). †Includes IFG by 1997 American Diabetes Association criteria. ‡Some overlap with prior study. §2003 American Diabetes Association criteria (14). ‡May include type 1 diabetes. NA, not available.

The purpose of delayed postpartum glucose testing is to identify any type of glucose abnormality present: IFG, IGT, type 1 diabetes, or type 2 diabetes (14). Both isolated IFG and isolated IGT predict (to different degrees) later risks of type 2 diabetes and of CVD, and combined IFG-IGT generally has the greatest predictive power (30,88–99). There has been debate about the applicability and efficacy of different types of glucose testing in the postpartum state. It is claimed that the greater stability and reproducibility of FPG compared with GTT suggests that FPG would be more easily and widely applied for clinical screening and diagnosis (14). In the case of women with GDM, the pregnancy has already been the screening test for "glucose abnormality," so what is needed after GDM is a diagnostic test. It is generally agreed that random glucose testing is not systematic and that assays for glycosylated hemoglobin or proteins are not sensitive to moderate hyperglycemia or glucose intolerance (14).

CURRENT STUDY: FAILURE OF FPG TO IDENTIFY CASES OF IGT OR TYPE 2 DIABETES 6–21 WEEKS AFTER PREGNANCY IN A MULTIETHNIC POPULATION

In San Jose, CA, we evaluated the yield of postpartum 2-h 75-g GTTs performed in clinical laboratories in a multiethnic population of women with GDM treated during 2000–2003. GDM was diagnosed by private clinicians based on a 50-g 1-h glucose screening test value >199 mg/dl (>11.1 mmol/l) or a 100-g 3-h GTT with any two values ≥95 mg/dl fasting, 1-h 180 mg/dl, 2-h 155 mg/dl, and 3-h 140 mg/dl (5.3, 10.0, 8.6, 7.8 mmol/l, respectively) (14). Patients were then referred to one of two diabetes and pregnancy education and treatment centers for coordinated multidisciplinary management under the supervision of one physician. All patients were trained in daily fingerstick capillary self-monitoring of blood glucose at fasting and 1 hour after main meals. All patients received medical nutrition therapy from registered dietitians and were trained to keep daily food records of carbohydrate intake in their own languages. They were taught to use daily planned physical activity whenever possible. When the majority of glucose values exceeded 99 mg/dl (5.5 mmol/l) fasting or 129 mg/dl (7.2 mmol/l) postprandial in any given week, medical therapy was instituted with glyburide (26.6%) or one of several insulin regimens (36.8%). If hyperglycemia exceeded the stated limits using glyburide therapy up to a maximum of 20 mg/day, patients were changed to insulin therapy (45.7% of those on glyburide), with dosage adjusted sequentially as needed. All patients were given laboratory requisitions before delivery and encouraged to go for a postpartum 75-g 2-h GTT at 6–12 weeks after delivery, with the timing depending on the continuation of their health insurance coverage.

Of 527 women with GDM complet-

Table 3—*Ethnicity and postpartum glucose abnormalities on 75-g 2-h GTTs 6–21 weeks after delivery in women with prior GDM in San Jose, CA*

Ethnic group	Normal GTT	Isolated IFG	Isolated IGT	Combined IFG-IGT	Type 2 diabetes	Total
Asian Indian	51 (66.2)	5	9	8	4	77
Far East Asian	48 (51.1)	10	26	6	4	94
Southeast Asian	105 (68.2)	7	26	10	6	154
Hispanic	64 (66.7)	3	15	9	5	96
Non-Hispanic white*	78 (73.6)	8	11	3	6	106
Total	346 (65.7)	33 (6.3)	87 (16.5)	36 (6.8)	25 (4.7)	527

Data are *n* or *n* (%). *Caucasian: European, Russian, or Middle Eastern origin.

ing the postpartum testing at 5–21 weeks after delivery, the GTTs were diagnostic of isolated IFG in 6.3%, isolated IGT in 16.5%, combined IFG-IGT in 6.8%, and type 2 diabetes in 4.7% (14). Thus, 34.3% of the group demonstrated postpartum glucose abnormalities, a rate similar to those in other recent U.S. reports (22,28). Only 4 of the 25 women (16%) diagnosed with type 2 diabetes had an FPG ≥126 mg/dl (≥7 mmol/l) on the GTT. The results of the postpartum GTTs in the different ethnic groups are presented in Table 3 (100). There were just a few black/African-American, Native American, and Pacific Islander women in this population, and they were excluded from the analysis. It is apparent that postpartum glucose abnormalities were common (26.4–48.9%) in all represented ethnic groups.

Prepregnancy BMI (101,102) was atypical in this population of women with GDM in that 60.1% had BMI <25 kg/m^2, 25.6% were overweight (BMI 25–29.9 kg/m^2), and only 14.3% were obese (BMI ≥30 kg/m^2), probably because of the high proportion of Far East and Southeastern Asian women (only 0.9% obese by National Institutes of Health standards). It has been suggested that specific BMI classifications should be validated for Asian women in the U.S. (103,104). Postpartum glucose abnormalities were of similar frequency in all the prepregnancy BMI categories: 33.4% with BMI <25 kg/m^2, 36.2% in those overweight, and 35.2% in the obese group. The distribution of postpartum glucose abnormalities in the BMI categories of the represented ethnic groups is presented in Table 4. Even in Caucasian and Hispanic women, postpartum glucose abnormalities were common (19 and 26%, respectively) in the groups with BMI <25 kg/m^2, although they were more common in groups with BMI ≥30 kg/m^2.

Postpartum glucose abnormalities were found in all GDM treatment groups, although there was the expected variation in frequency with increasing intensity of treatment required to maintain normoglycemia (Table 5). For women with prior GDM not requiring pharmacotherapy during pregnancy, 20.9% had postpartum GTT abnormalities (mostly IGT). Previous investigators demonstrated many antepartum and postpartum predictors of a higher rate of type 2 diabetes after pregnancy. These predictors include advanced maternal age, elevated BMI in some studies, the degree of fasting and postchallenge hyperglycemia during or after pregnancy, earlier diagnosis of GDM, the need for pharmacotherapy, and poor pancreatic β-cell compensation for increased insulin resistance (26,28, 29,36,40,43,105–108). These predictors are not to be denied, but many so-called "low-risk" women with prior GDM also have postpartum glucose abnormalities, so we recommend universal testing at 6–12 weeks or later after pregnancy. Although lactation may improve glucose tolerance (109–111), neither breastfeeding status nor use of low-dose combination oral contraceptives influenced the diagnosis of postpartum glucose abnormalities in the present and other studies (105,112–114). Progestin-only preparations were not used in this population.

In our analysis of women with prior GDM, impaired fasting glucose (FPG ≥100 mg/dl, ≥5.6 mmol/l) (14) was not sensitive (34%) in identifying IGT and type 2 diabetes on the postpartum GTTs, although of course it identifies its own category of glucose abnormality (Table 6). Regarding type 2 diabetes only, 44% had FPG <100 mg/dl (<5.6 mmol/l) on the GTT. The lack of sensitivity of FPG persisted among the different ethnic groups and BMI categories (data not shown). The two-by-two tables show that lower values of FPG set at ≥95 or ≥90 also miss a substantial number of cases (51 and 38%, respectively) of IGT + type 2 diabetes. All other studies but one (115) also show that postpartum IFG has low sensitivity of predicting "postprandial" glucose intolerance and type 2 diabetes after pregnancy (22,25,30,31,37,41, 116,117) and at other times in women (93,96,118–121). Therefore, the 75-g GTT with fasting and 2-h glucose measurements is the best diagnostic test to identify important glucose abnormalities after pregnancy in women with prior GDM. Use of the simpler FPG test alone is not recommended.

Table 4—*Cross-tabulation of pre-pregnancy BMI, ethnic groups, and 6- to 21-week postpartum glucose abnormalities in women with prior GDM in San Jose, CA*

BMI (kg/m^2)	Asian Indian	Far East Asian	Southeast Asian	Hispanic	Caucasian
<25	51.4 (35)	78.4 (46)	82.5 (31)	28.1 (26)	51.0 (19)
25–29.9	32.4 (28)	21.6 (60)	16.1 (40)	41.7 (35)	21.6 (35)
≥30	16.2 (42)	0	1.5 (0)	30.2 (38)	27.5 (34)

Data are percent of cases in different BMI categories (percent with abnormal glucose tolerance).

MANAGEMENT OF IGT AFTER PREGNANCY

— How should the clinician manage the woman with prior GDM and IGT identified after pregnancy? Certainly weight loss or weight maintenance medical nutrition therapy and 30–60 min exercise daily at least 5 days per week should be applied (64,76). The 2-h 75-g GTT should be repeated at some interval, since it can revert to normal or abnormal "spontaneously." For women with persisting IGT after a good effort of medical nutrition therapy and planned physical activity, clinical trials support the clinician adding pharmacotherapy (73,74,122). Acarbose delays carbohydrate absorption and helps with postprandial glucose control, but side effects limit usage (123). Metformin decreases hepatic glucose production and lipid oxidation, improves peripheral tissue insulin sensitivity and helps with weight loss (123,124). Thiazolidinediones (glitazones) as peroxisome proliferator–activated receptor-γ agonists increase

Table 5—*Frequency of postpartum glucose abnormalities according to GDM treatment group (San Jose data)*

Treatment group	*n*	Normal GTT (%)	Isolated IFG (%)	IGT (%)	Type 2 diabetes (%)
MNT only	192	79.1	1.8	17.2	1.9
Glyburide	77	62.5	4.7	31.2	1.6
Glyburide > insulin	64	49.1	8.5	35.6	6.8
Insulin	194	59.3	9.5	23.8	7.4

MNT, medical nutrition therapy.

insulin sensitivity and may improve lipid balance and cardiovascular and renal function (72,125–127). Metformin and glitazones may help "take the load off" the overworked pancreatic β-cells (75,128). As noted above, it is important to identify and control type 2 diabetes before a subsequent pregnancy. This may justify continued follow-up in the gynecological setting of women with the potential to become pregnant, or close collaboration with other physicians.

Published data are less helpful in deciding management of women with isolated IFG. At least follow-up with delayed repeat GTT testing is justified, since IFG predicts risk of development of impaired glucose tolerance or type 2 diabetes (71) and perhaps risk of CVD (88,89,96).

CARDIOVASCULAR RISKS IN WOMEN WITH PRIOR GDM

— The question arises whether and how to evaluate CVD risk markers in women with glucose abnormalities persisting after pregnancies with GDM. Inflammatory processes are now known to contribute to atherosclerosis (129,130). Research continues on the role of lipoproteins, cytokines, oxidative stress, loss of nitric oxide bioactivity in the vessel wall (131), and effects of angiotensin and aldosterone (132,133). Addition of LDL subfractions (to detect small dense particles, LDL phenotype B) to the standard lipid profile may help in predicting risk of CVD events (68). Assays of inflammatory markers for potential clinical use include white blood cells, soluble adhesion molecules, cytokines (the interleukins and tumor necrosis factor-α), and acute-phase reactants (fibrinogen and highly sensitive C-reactive protein [hsCRP]) (134). C-reactive protein is a correlate of obesity in women with GDM (135). The American Heart Association/Centers for Disease Control Scientific Statement concluded that class IIA evidence supported use of hsCRP as the best inflammatory marker currently available (134). "Other inflammatory markers (cytokines, other acute-phase reactants) should not be measured for the determination of coronary risk in addition to hsCRP." Measurement of hsCRP using standardized assays should be done (in the absence of current infection or estrogen/progestogen hormone use) "twice (averaging results), optimally 2 weeks apart, fasting or nonfasting in metabolically stable patients. If hsCRP level is >10 mg/l, the test should be repeated and the patient examined for sources of infection or inflammation." Otherwise, hsCRP levels are categorized as low risk (<1 mg/l), average risk (1.0–3.0 mg/l), and high risk (>3.0 mg/l) (134).

Several investigators have studied lipids in women with previous GDM. Latina women diagnosed with IGT 6–12 weeks after pregnancies with GDM in Los Angeles showed elevated triglycerides compared with GDM women with normal glucose tolerance postpartum. The women with IGT destined to develop type 2 diabetes by 36 months also initially demonstrated reduced HDL cholesterol. LDL cholesterol levels were not different postpartum in any of the GDM groups compared with control subjects, but LDL subfractions were not reported (136). The authors concluded that factors other than lipids might contribute to the high prevalence of cardiovascular morbidity in a similar cohort of women with prior GDM followed for 12–18 years in Los Angeles (137). A total of 56 former GDM mothers without IFG or IGT studied 5–6 years after pregnancy in Rhode Island had significantly increased proportions of subjects with elevated total cholesterol (39%), elevated LDL cholesterol (13%), and systolic blood pressure >140 mmHg (9%) compared with control subjects with similar BMI distribution (138). Elevated triglycerides and LDL cholesterol levels 6–11 years after pregnancy were also noted in women with prior GDM compared with control subjects with similar glucose and BMI parameters in Boston (139). Women with prior GDM were more likely to have elevated triglycerides and low HDL cholesterol than a control group in Denmark (140). Increased intramyocellular lipid concentration identified IGT in Austrian women with prior GDM, compared with a glucose-tolerant control group (141). In Asia, total cholesterol, LDL cholesterol, and triglycerides were significantly higher, and HDL cholesterol was significantly lower in 801 women with prior GDM versus control subjects after adjustment for age, BMI, and smoking (23), but only triglycerides discriminated between IGT and normal glucose tolerance in the women who had GDM (23,43).

On the other hand, standard lipoprotein concentrations were not different in women with prior GDM compared with

Table 6—*Predictive value of FPG measurements on postpartum oral GTT to identify 2-h glucose abnormalities (San Jose data)*

FPG values (mg/dl)	IGT + type 2 diabetes	2-h glucose normal	Predictive values of FPG ≥100 mg/dl	Predictive values of FPG ≥95 mg/dl	Predictive values of FPG ≥90 mg/dl
≥100	50	33	Sensitivity 0.338	Sensitivity 0.486	Sensitivity 0.623
≥95	72	66	Specificity 0.913	Specificity 0.826	Specificity 0.646
≥90	92	134			
<100	98	346	PPV* 0.602	PPV 0.522	PPV 0.417
<95	76	313	PNV† 0.779	PNV 0.805	PNV 0.814
<90	56	245			

*Predictive value of a positive test; †predictive value of a negative test.

control subjects 1–3 years after pregnancy in Italy (142) and in Spain, despite the increased BMI and waist circumference (30). In the latter study, women with IFG had significantly increased odds ratios for obesity and hypertension than the women with postpartum IGT (30). Also in Spain, the only lipid abnormality was increased VLDL cholesterol levels at a 5-year follow-up of 262 women with prior GDM (143). Similar concentrations of plasma lipids were found in white nonobese women with prior GDM and in control subjects matched for age, BMI, and waist-to-hip ratio in a retrospective case-control study in Brazil (52) and in a similar study in China (33). More research is needed on lipid abnormalities in women with prior GDM, with or without IFG and IGT, and the relationship to subsequent CVD.

Recent studies of insulin resistance and components of the "metabolic syndrome" in women with prior GDM suggest that a chronic systemic inflammatory response may be present in glucose-intolerant women and may be an early feature of the cluster of CVD risk factors known as the metabolic syndrome (144–147). A total of 23 women studied 1–10 years after pregnancy with GDM in New England had higher mean levels of BMI, waist circumference, triglycerides, hsCRP, and interleukin-6 compared with 23 control subjects (148). Insulin sensitivity was similar to control subjects in women with prior GDM in Barcelona, but insulin secretion was lower and waist circumference was higher, and the proportion with blood pressure >130/85 mmHg was 42 versus 29% in the control subjects (143). Average hsCRP and interleukin-6, but not tumor necrosis factor-α, were higher in a prior GDM group than in control subjects 3 months after delivery in Austria, with or without direct measures of insulin resistance (149). In Italy, hsCRP and fibrinogen concentrations were significantly elevated in women 1–3 years after pregnancy with GDM, even excluding women with IGT (142). Gestational hyperglycemia predicted a high risk of later metabolic syndrome after adjustments for age and prepregnancy BMI in another Italian study (150). In the large 4- to 23-year follow-up program in Denmark, the prior GDM group of 481 women had 68% impaired glucose regulation, 59% elevated fasting serum insulin, 54% central obesity, 28% hypertension, and 35% dyslipidemia, mainly characterized by elevated triglycerides and reduced HDL cholesterol. Inflammatory markers were not measured (140). Total plasma homocysteine level was a risk factor for the development of diabetes after GDM in Korea (43). As with lipids, continuing investigation of the metabolic syndrome CVD risk factors is justified after GDM, to determine the likelihood of CVD events and means of their prevention.

CONCLUSIONS — The initial postpartum management of women with GDM should focus on maternal-infant well-being, encouragement and training for healthy nutrition, planned physical activity, weight reduction as needed, continued smoking cessation, breastfeeding, and provision of appropriate contraception. We conclude that women with prior GDM have substantial rates of IFG, IGT, and type 2 diabetes after pregnancy best identified by a 75-g 2-h oral GTT 6–12 weeks or later postpartum. Continued prolonged follow-up is indicated to *1*) offer and apply treatment in women with IGT designed to delay or prevent development of type 2 diabetes, *2*) follow women with IFG or normal GTT to detect later conversion to IGT or type 2 diabetes (more research is needed to better define the conversion rate in women receiving appropriate advice on nutrition and physical activity 30–60 min daily at least 5 days per week), and *3*) identify diabetes for intensified treatment before a subsequent pregnancy to lower the risk of major congenital malformations in their infants.

During pregnancy women with GDM should be educated that glucose intolerance may not be temporary, that it can be modified by behavior changes and that postpartum testing will be important. Presuming an increased risk for cardiovascular events in glucose-intolerant women with prior GDM (151), large long-term follow-up studies are needed to identify the frequency and value of CVD risk markers and to determine if interventions (antioxidants, aspirin, behavior modification, glucose and blood pressure control, and specific pharmacological agents) can reduce the frequency or mortality of coronary heart disease, heart failure, or stroke in these women. Recent reports of low rates of postpartum glucose tolerance testing (152,153) and of lifestyle modification (154–158) in women with prior GDM show that a dramatic paradigm shift in clinical practice is necessary to improve the lifelong health of these women.

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