# Prevention of Type 2 Diabetes in Women With Previous Gestational Diabetes

ROBERT E. RATNER, MD

The consequences of hyperglycemia appearing during pregnancy were well described in 1917, when Elliot P. Joslin described Case 309, which "showed sugar in 1897 during pregnancy, but following confinement, with resulting dead baby, it disappeared, but returned in 9 years in the form of moderate to severe diabetes. . . . [W]ith our present knowledge, it is quite possible that such an outcome could be prevented by active treatment of the glycosuria from the very start" (1). Subsequently, O'Sullivan and Mahan's definition of gestational diabetes mellitus (GDM) in 1964 was a formal recognition of the mother's increased risk of future development of diabetes (2). They defined GDM if a pregnant woman undergoing a 3-h 100-g oral glucose tolerance test had glucose values exceeding 2 SDs above the mean on two of the four values. This landmark study described a population of pregnant women with a lifetime risk of diabetes exceeding 70% (3). Multiple studies worldwide have demonstrated a broad ethnic and geographic distribution of GDM, but all studies share the increased risk of subsequent diabetes after delivery (4).

## PREVALENCE OF DIABETES AFTER GDM

— Assessment of diabetes risk postpartum is influenced by the criteria used to define GDM, the testing undertaken postpartum, and the length of follow-up. Diagnosis of carbohydrate intolerance in the first trimester of pregnancy may reflect the ascertainment of previously undiagnosed and, presumably, asymptomatic diabetes. Alternatively, pregnancy creates a metabolic stress that may push a woman with compensated type 1 or type 2 diabetes into a decompensated hyperglycemic state. Under these circumstances, one would anticipate a high rate of persistent hyperglycemia in the postpartum state. In fact, the presence of GDM doubles the risk of diabetes within 4 months postpartum, whereas a fasting plasma glucose >121 mg/dl during the pregnancy increased the risk 21-fold (5).

Differential criteria for diagnosis of GDM affects the denominator for the assessment of proportion of women affected (6). Reliance on fasting glucose screens with failure to perform oral glucose tolerance tests reduces the sensitivity of identifying subsequent diabetes (7). At the Fifth International Workshop, Kitzmiller presented data from a multiethnic cohort further demonstrating the limitations of the fasting glucose as a screen, with only 34% of impaired glucose tolerance or diabetes being picked up by those women with impaired fasting glucose levels (J.L. Kitzmiller, personal communication). As will be shown subsequently, there does not appear to be a temporal window for postpartum diabetes development, but rather the risk persists, requiring lifelong evaluation to completely capture the risk of diabetes.

A systematic review of GDM and ensuing diabetes was published by Kim et al. (8). The review encompassed 36 years and included studies that specified the criteria for the diagnosis of both GDM and type 2 diabetes and included the risk of diabetes in women with a history of GDM. A total of 28 studies met criteria, and together they demonstrate a consistent pattern of diabetes occurrence over time. Differences among studies were explained by differential follow-up, ethnicity, and retesting rates. When cumulative incidence of diabetes is plotted against follow-up after delivery (Fig. 1), rapid conversion to diabetes is seen over the first 5 years, with a slower progression subsequently.

The Diabetes Prevention Program (DPP) sought involvement of women with a history of GDM and impaired glucose tolerance to participate in a long-term diabetes prevention study (9). A total of 350 women (of 1,810 parous women randomized) provided a history of GDM with a mean of 12 years since the index GDM pregnancy. Women who rapidly transitioned from GDM to type 2 diabetes before entry into the DPP were excluded from entry, yielding a survival cohort of high-risk women who had impaired glucose tolerance. Women with a history of GDM were 8 years younger than the non-GDM cohort, but were otherwise well matched for ethnicity, parity, BMI, level of glucose intolerance, or insulin resistance. Even after adjusting for age (Fig. 2), the women with a history of GDM in the placebo group had a 74% increased hazard for developing diabetes than their non-GDM control subjects (17.1%/year compared with 9.8%/year over 3 years, respectively) (10). So, even temporally removed from the index pregnancy, GDM confers a markedly increased risk for developing diabetes, even when compared with a comparably glucose-intolerant population.

## PREDICTORS OF TYPE 2 DIABETES AFTER GDM

— As previously mentioned, fasting plasma glucose is the strongest predictor of early postpartum development of diabetes (5), but it also remains the strongest independent predictor of long-term development of type 2 diabetes in the mother (8). Area under the oral glucose tolerance test curve, as well as 1- and 2-h glucose levels, typically correlate with diabetes risk, as well.

Once these glycemic parameters are controlled for in multivariate analysis, maternal BMI, either before or during pregnancy, correlated with diabetes risk,

From the MedStar Research Institute and Georgetown University School of Medicine, Washington, DC.

Address correspondence and reprint requests to Robert E. Ratner, MD, MedStar Research Institute, 6495 New Hampshire Ave., Hyattsville, MD 20783. E-mail: robert.ratner@medstar.net.

Received for publication 5 June 2006 and accepted in revised form 9 November 2006.

This article is based on a presentation at a symposium. The symposium and the publication of this article were made possible by an unrestricted educational grant from LifeScan, Inc., a Johnson & Johnson company.

**Abbreviations:** ACOG, American College of Obstetrics and Gynecology; DPP, Diabetes Prevention Program; GDM, gestational diabetes mellitus; PIPOD, Pioglitazone in Prevention of Diabetes; TRIPOD, Troglitazone in Prevention of Diabetes.

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

DOI: 10.2337/dc07-s223

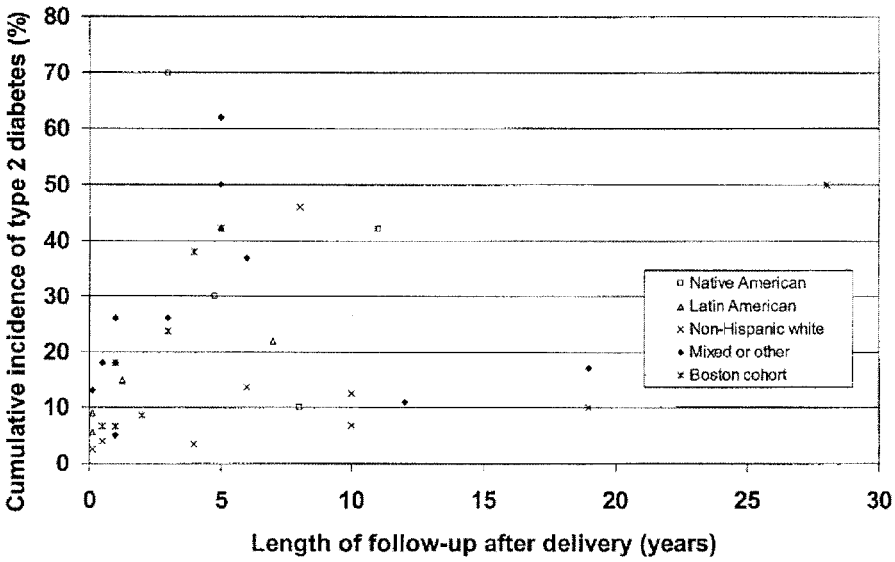


**Figure 1**—*Cumulative incidence of type 2 diabetes by ethnicity and length of follow-up. Adapted from Kim et al. (8).*

but neither gestational weight gain nor postpartum BMI remained significant predictors. Similarly, maternal age, parity <5, prior GDM, or family history of diabetes are not independently associated with subsequent diabetes in multivariate analysis when glycemic variables are included (8,11,12). Insulin therapy during pregnancy frequently predicts subsequent maternal diabetes (13), but may simply be a reflection of the degree of fasting hyperglycemia. Fetal outcomes have not been predictive of maternal risk of diabetes.

Although not routinely obtained, assessment of insulin secretion, both during and after pregnancy, provides the strongest independent predictors of diabetes in the mother (14,15). Perhaps the best pathophysiological assessment of predictors of progression to diabetes after GDM stem from the Troglitazone in Prevention of Diabetes (TRIPOD) study of Buchanan et al. (16). Protection from conversion to type 2 diabetes was conferred by a reduction in insulin resistance, resulting in large reductions in insulin output. They concluded that reduction in β-cell workload may preserve subsequent β-cell function. This was further explored in the open-label observational study, Pioglitazone in Prevention of Diabetes (PIPOD), in which lower glucose levels and higher acute insulin responses during an intravenous glucose tolerance test were seen in women remaining diabetes free (17). Independent predictors of diabetes development were the lack of change in insulin area after the intravenous glucose tolerance test in the first year of follow-up and the higher the baseline oral glucose tolerance test glucose area.

## CURRENT RECOMMENDATIONS FOR POSTPARTUM FOLLOW-UP

— At the present time, the American Diabetes Association on the basis of expert consensus recommends that "women with gestational diabetes should be screened for diabetes 6 weeks postpartum and should be followed up with subsequent screening for the development of diabetes or pre-diabetes" (18). The American College of Obstetrics and Gynecology (ACOG) makes no specific recommendation on follow-up other than to suggest that postpartum testing may be performed, despite the absence of data demonstrating a clear benefit (19). Survey data suggest that 75% of practicing obstetricians who are ACOG fellows routinely test patients with GDM in the postpartum state (20); however, a more detailed chart review revealed far fewer women with GDM actually receive any glucose follow-up (21). Two-thirds of women with GDM history underwent some form of glycemia assessment at a mean of 136 days postpartum. Only 37% underwent either a fasting glucose or oral glucose tolerance test at a median of ~14 months after delivery.

Recommendations for actual intervention to prevent progression to diabetes are even less clear. Without clearly specifying GDM as a risk factor, the American Diabetes Association (18) recommends the following: *1*) individuals at high risk for developing diabetes need to become aware of the benefits of modest weight loss and participating in regular physical activity, and 2) monitoring for the development of diabetes should be performed every 1–2 years.

ACOG suggests that "individuals at increased risk should be counseled regarding diet, exercise, and weight reduction or maintenance to forestall or prevent the onset of type 2 diabetes" (19).

The National Diabetes Education Program (NDEP) is currently promoting a GDM Diabetes Prevention Initiative, targeting both providers and women with a

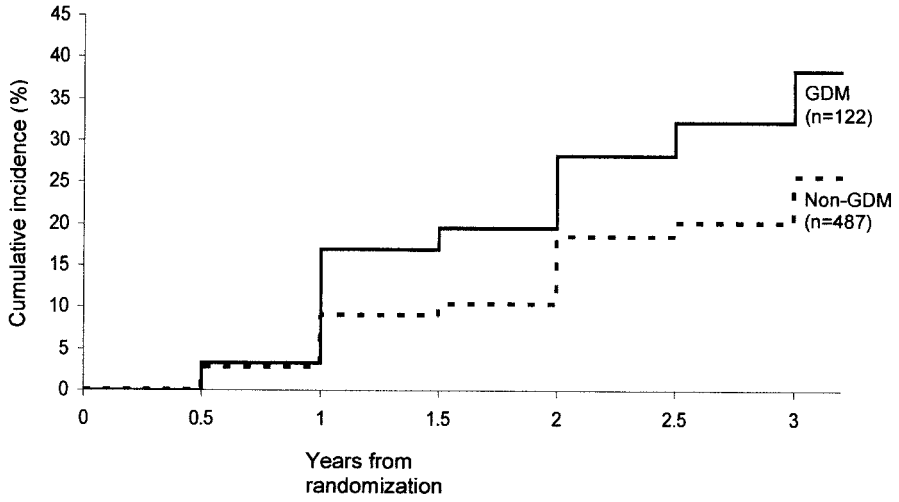


**Figure 2**—*Cumulative incidence of diabetes among the placebo group (adjusted for age in DPP by history of GDM). Adapted from the Diabetes Prevention Program Research Group (10).*

**Table 1—*GDM diabetes prevention initiative from the National Diabetes Education Program***

- GDM imparts lifelong risk for diabetes, mostly type 2.
- Modest weight loss and physical activity can delay or prevent type 2 diabetes.
- Offspring can lower risk by eating healthy foods, being active, and not becoming overweight.

Conservative recommendations to patients include:

- Let health care practitioners know of any history of GDM.
- Get tested 6–12 weeks postpartum, then every 1–2 years.
- Reach prepregnancy weight 6–12 months postpartum.
- If still overweight, lose at least 5–7% of weight slowly, over time, and keep it off.

Adapted from the National Diabetes Education Program (22).

GDM history (22). Key messages are illustrated in Table 1.

The rationale for such recommendations is now being developed from a variety of clinical trials; however, these are based on clinical expert committee recommendations.

## CLINICAL TRIALS INTERVENING POSTPARTUM TO PREVENT OR DELAY DIABETES

— Of the six published diabetes prevention clinical trials, three specifically targeted and analyzed women with a history of GDM. The TRIPOD study exclusively enrolled women with prior GDM, regardless of impaired glucose tolerance or normal glucose tolerance (16). Women were obese (mean BMI 30 kg/m$^2$), with approximately two-thirds with impaired glucose tolerance at study entry and the rest with normal glucose tolerance. Randomization to placebo or troglitazone treatment demonstrated a 55% risk reduction in the development of diabetes in the troglitazone group from 12.1%/year for placebo to 5.4%/year. The early termination of the trial, because of the recall of troglitazone from the market, provided a unique opportunity to assess the durability of the benefit and to clarify whether hyperglycemia was simply being treated or actually prevented. With 86% ascertainment at ~8 months after discontinuation of the interventions, incidence rates for diabetes remained highly significantly different with a risk reduction for troglitazone therapy of 87% (21.2%/year down to 3.1%/year). The authors conclude that delay or prevention, rather than masking, occurred as a result of the active intervention.

With the withdrawal of troglitazone therapy from the American market, the issue of comparable response post-GDM to therapy with other available thiazolidinediones was studied in the observational PIPOD study (17). Women completing the TRIPOD study without developing diabetes were invited to participate and were given 30 mg pioglitazone and titrated to 45 mg daily. Over the subsequent 3 years, the incidence of diabetes was 4.6%/year compared with the historical observation of 12.1% diabetes per year in the placebo group of TRIPOD. Without the concurrent control group, these data only infer a durable effect of thiazolidinedione therapy, since they were comparable to the 3.1%/year incidence seen with troglitazone. PIPOD further substantiated that the protective effect of thiazolidinediones lies in their capacity to offload the β-cell by preventing the 33% reduction in β-cell compensation for insulin resistance seen during TRIPOD.

The DPP was a multicenter clinical trial of both men and women with impaired glucose tolerance randomized to receive standard lifestyle intervention and placebo, metformin therapy, or an intensive lifestyle intervention (9). The population enrolled included a multiethnic population spanning the age range of 25–89 years (23). As previously reported for the cohort as a whole, intensive lifestyle intervention delayed or prevented the onset of diabetes in 58%, whereas metformin was successful in 31%, compared with the placebo control group (24). As previously stated, the women with a GDM history enrolled in the DPP were younger, but otherwise comparable to those women without the GDM history (10). Despite less weight loss resulting from intensive lifestyle intervention, the women with GDM histories had a comparable reduction in the development of diabetes (55%). Metformin therapy was even more effective in the GDM cohort, with a 50% risk reduction, compared with 14% in the non-GDM group. This latter finding may be explained by the younger age of those with a history of GDM and the previously identified relationship between age and metformin response (24).

## CONCLUSIONS

— In summary, it is clear that GDM confers a lifelong increased risk for the development of diabetes, and in most cases, this turns out to be type 2 diabetes. Progression from GDM to type 2 diabetes correlates with progressive β-cell failure to compensate for the ongoing insulin resistance. Postpartum follow-up of at-risk women is inadequate, and the recommendations for screening from ACOG and the American Diabetes Association are at variance. Consistent recommendations, together with a professional and public health campaign to raise the awareness of GDM as a diabetes predictor, will be necessary to improve postpartum care of women at highest risk.

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

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

Reproduced from the Summary and Recommendations of the Fifth International Workshop-Conference on Gestational Diabetes Mellitur (25). OGTT, oral glucose tolerance test. *Classification of glucose metabolism by criteria recommended by the American Diabetes Association (19).

Recommendations for follow-up of GDM stemming from the Fifth International Workshop-Conference are elucidated elsewhere in this publication, but are summarized in Table 2.

Clinical trials now provide level A evidence for the impact of multiple interventions to prevent the progression to type 2 diabetes in women with a history of GDM. Both lifestyle modification and pharmacological therapies (metformin, troglitazone, and pioglitazone) have been shown to reduce diabetes development by 50% or more. The diagnosis of GDM should initiate a long-term intervention and diagnostic process to minimize the risk of developing diabetes or to diagnose it as early in the course of disease as possible.

**References**


1. Joslin EP: *The Treatment of Diabetes Mellitus With Observation Upon the Disease Based Upon 1300 Cases*. Philadelphia, PA, Lea & Febiger, 1917
2. O'Sullivan JB, Mahan CM: Criteria for the oral glucose tolerance test in pregnancy. *Diabetes* 13:278–285, 1964
3. O'Sullivan JB: Diabetes mellitus after GDM. *Diabetes* 40 (Suppl. 2):131–135, 1991
4. Buchanan TA, Xiang AH: Gestational diabetes mellitus. *J Clin Invest* 115:485–491, 2005
5. Schaefer-Graf UM, Buchanan TA, Xiang AH, Peters RK, Kjos SL: Clinical predictors for a high risk for the development of diabetes mellitus in the early puerperium in women with recent gestational diabetes mellitus. *Am J Obstet Gynecol* 186:751–756, 2002
6. O'Sullivan J: Quarter century of glucose intolerance: incidence of diabetes mellitus by USPHS, NIH, WHO criteria. In *Advances in Diabetes Epidemiology*. Eschwege E, Ed. New York, Elsevier, 1982, p. 123–131
7. Woerle HJ, Pimenta WP, Meyer C, Gosmanov NR, Szoke E, Szombathy T, Mitrakou A, Gerich JE: Diagnostic and therapeutic implications of relationships between fasting, 2-hour postchallenge plasma glucose and hemoglobin a1c values. *Arch Intern Med* 164:1627–1632, 2004
8. Kim C, Newton KM, Knopp RH: Gestational diabetes and the incidence of type 2 diabetes. *Diabetes Care* 25:1862–1868, 2002
9. Diabetes Prevention Program Research Group: The Diabetes Prevention Program: Design and methods for a clinical trial in the prevention of type 2 diabetes mellitus. *Diabetes Care* 22:623–634, 1999
10. Diabetes Prevention Program Research Group: Prevention of diabetes in women with a history of gestational diabetes. *J Clin Endocrinol Metab*. In press
11. Seghieri G, DeBellis A, Anichin R, Alviggi L, Franconi F, Breschi MC: Does parity increase insulin resistance during pregnancy? *Diabet Med* 22:1574–1580, 2005
12. Lobner K, Knopff A, Baumgartner A, Mollenhauer U, Marienfeld S, Garrido-Franco M, Bonifacio E, Ziegler AG: Predictors of postpartum diabetes in women with GDM. *Diabetes* 55:792–797, 2006
13. Catalano P, Vargo K, Bernstein I, Amini S: Incidence and risk factors associated with abnormal postpartum glucose tolerance in women with gestational diabetes. *Am J Obstet Gynecol* 165:914–919, 1991
14. Metzger B, Cho N, Roston S, Radvany R: Prepregnancy weight and antepartum insulin secretion predict glucose tolerance five years after gestational diabetes mellitus. *Diabetes Care* 16:1598–1605, 1993
15. Buchanan T, Xiang A, Kjos S, Trigo E, Lee W, Peters R: Antepartum predictors of the development of type 2 diabetes in Latino women 11–26 months after pregnancies complicated by gestational diabetes. *Diabetes* 48:2430–2436, 1999
16. Buchanan TA, Xiang AH, Peters RK, Kjos SL, Marroquin A, Goico J, Ochoa C, Tan S, Berkowitz K, Hodis HN, Azen SP: Preservation of pancreatic beta cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk Hispanic women. *Diabetes* 51:2796–2803, 2002
17. Xiang A, Peters R, Kjos S, Marroquin A, Goico J, Ochoa C, Kawakubo M, Buchanan TA: Effect of pioglitazone on pancreatic beta cell function and diabetes risk in Hispanic women with prior gestational diabetes. *Diabetes* 55:517–522, 2006
18. American Diabetes Association. Standards of medical care in diabetes (Position Statement). 28 (Suppl. 1):S4–S36, 2005
19. American Association of Obstetricians and Gynecologists. Gestational Diabetes, ACOG Practice Bulletin No. 30. *Obstet Gynecol* 98:525–538, 2001
20. Gabbe SC, Gregory RP, Powers ML, Williams SB, Schulkin J: Management of diabetes mellitus by obstetricians-gynecologists. *Obstet Gynecol* 103:1229–1234, 2004
21. Smirnakis KV, Chasen-Taber L, Wolf M, Markenson G, Ecker JL, Thadhani R: Postpartum diabetes screening in women with a history of gestational diabetes. *Obstet Gynecol* 106:1297–1303, 2005
22. National Diabetes Education Program: http://www.ndep.nih.gov/diabetes/pubs/NeverTooEarly_Tipsheet.pdf. Accessed 1 June 2006
23. Diabetes Prevention Program Research Group: The Diabetes Prevention Program: baseline characteristics of the randomized cohort. *Diabetes Care* 23:1619–1629, 2000
24. Diabetes Prevention Program Research Group: The Diabetes Prevention Program: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 346:393–403, 2002
25. Metzger BE, Buchanan TA, Coustan DR, de Leiva A, Dunger DB, Hadden DR, Hod M, Kitzmiller JL, Kjos SL, Oats JN, Pettitt DJ, Sacks DA, Zoupas C: Summary and recommendations of the Fifth International Workshop-Conference on Gestational Diabetes Mellitus. *Diabetes Care* 30 (Suppl. 2):S251–S260, 2007