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Gestational diabetes mellitus: What does it predict for the future?

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Gestational diabetes mellitus (GDM), is defined as glucose intolerance of varying severity with onset or first recognition during pregnancy. It is a common condition affecting 2%-3% of all pregnant women.[1] Generally, the long-standing debate over the role of screening for GDM has focused on fetal and obstetrical outcomes. It is important to recognize, however, that the diagnosis of GDM also identifies a population of women at high risk of type 2 diabetes mellitus in the future. This issue of *Endocrinology Rounds* reviews the implications of a history of previous GDM. The following topics will be considered in turn:

- **the risks of future metabolic disease**
- **the pathophysiologic changes exhibited by women with a history of GDM**
- **antepartum clinical predictors of the risk of progression to type 2 diabetes**
- **interventional strategies to modify the risk.**

Risk of type 2 diabetes mellitus and the metabolic syndrome

A history of previous GDM confers a significantly elevated lifetime risk of type 2 diabetes mellitus (T2DM). This risk has been variously estimated to be between 17% to 63% within 5 to 16 years after the index pregnancy.[2] The wide variation in the magnitude of reported risk between studies has been attributed to several factors, including differences in:

- ethnic composition of study populations
- duration of follow-up
- cohort retention
- diagnostic criteria for GDM
- definition of T2DM.

To examine the relative importance of these factors as sources of variation in the reported risk, Kim et al conducted a systematic review of 28 studies, in which subjects underwent testing for GDM during pregnancy followed by subsequent postpartum testing for T2DM.[3] In the 28 studies analyzed, the cumulative incidence of diabetes after the index pregnancy ranged from 2.6% to >70% between 6 weeks to 28-years postpartum. Nevertheless, adjustment for length of follow-up and retention rate markedly reduced the differences between studies to a cumulative incidence of between 30% and 50% at 5 years. Moreover, after a diagnosis of GDM, women from mixed or non-Caucasian cohorts appeared to progress to T2DM at similar rates (there was insufficient data to assess progression in predominantly Caucasian cohorts). Across ethnic groups, the cumulative incidence to T2DM showed a sharp increase within the first 5 years after delivery and appeared to plateau after 10 years. These findings support the identification of women with previous GDM as a high-risk population and emphasize the importance of the early postpartum years in the progression to T2DM.

In addition to diabetes, women with a history of GDM are at increased risk for other metabolic abnormalities. Several studies have demonstrated increased rates of obesity, systolic hypertension, and dyslipidemia, as manifest by elevated total cholesterol, low-density lipoprotein cholesterol (LDL), and triglyceride concentrations.[4,5] Given the constellation of metabolic abnormalities in this cohort, Verma et al studied the prevalence of the metabolic syndrome in women with previous GDM. Metabolic characterization of 106 women with previous GDM and 101 controls was performed on 6 occasions between 4 and 11 years after delivery.[6] By 11 years, 27.2% of the previous GDM subjects had developed the metabolic syndrome compared

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Figure 1: Disposition curves for control subjects (solid line) and post-GDM subjects (broken line)[9]

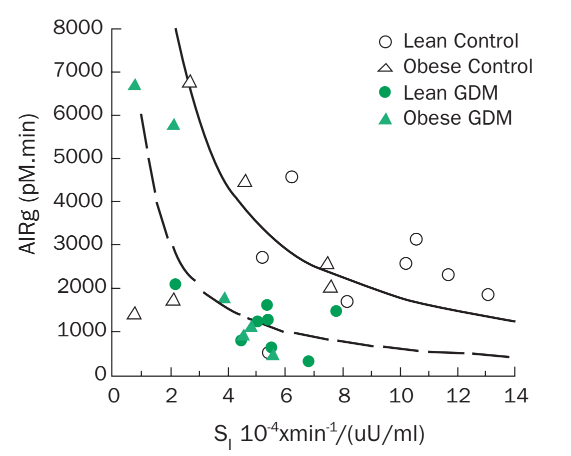
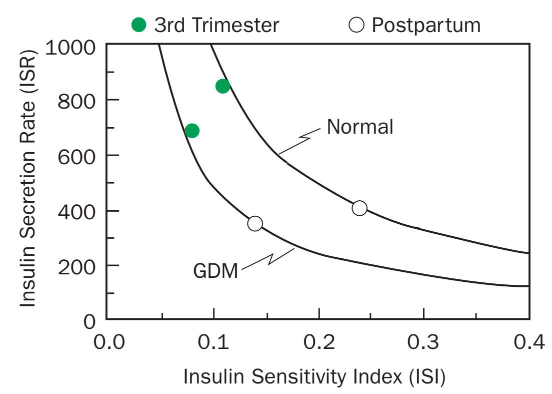


Figure 2: Insulin sensitivity-secretion relationships in normal women and women with GDM[11]



with 8.2% of controls. The risk was greatest in women with pre-pregnancy obesity, such that, at 11 years, the cumulative hazard for developing metabolic syndrome in the next 2 years was 26 times higher in women with previous GDM and pre-pregnancy obesity, compared to lean controls (defined as pre-pregnancy body mass index < 27.3 kg/m^2). Moreover, the association between previous GDM and the metabolic syndrome is also supported by the converse relationship: components of the metabolic syndrome have been shown to predict future GDM.[7] As such, it has been hypothesized that the diagnosis of GDM may represent the transient unmasking of a latent metabolic syndrome, one that may become clinically apparent later in life as either T2DM or the metabolic syndrome.[7]

Pathophysiologic changes in women with previous GDM

Since it identifies a population of women at high risk of subsequent T2DM, GDM offers a unique opportunity to study early events in the natural history of T2DM. Therefore, careful pathophysiologic characterization of the cohort of women with previous GDM is of clear interest. This section considers the following pathophysiologic features in this cohort: ß-cell dysfunction, insulin resistance, endothelial dysfunction, and inflammation.

ß-cell dysfunction and insulin resistance

Normal pregnancy is characterized by a progressive decline in insulin sensitivity, ultimately leading to significant insulin resistance by the 3rd trimester.[8] GDM develops in a subset of women whose ß-cell compensation for this acquired insulin resistance is insufficient to maintain euglycemia. Since insulin resistance and ß-cell dysfunction are hallmarks of T2DM, it is of particular interest to assess these features postpartum in women with a history of GDM.

Ryan et al studied 14 normoglycemic women with a history of GDM in the preceding 8 years compared to controls who were matched for body mass index (BMI) and waist-to-hip ratio (WHR).[9] All subjects underwent oral glucose tolerance testing (OGTT) and frequently sampled intravenous glucose tolerance testing (FSIGT). Insulin sensitivity index (S_I), using the Bergman minimal model, was significantly decreased in subjects with a history of previous GDM compared to controls. First-phase insulin release to intravenous glucose was also lower in the previous GDM group. Considering the increased insulin resistance in these subjects, their insulin secretory response was particularly impaired. The disposition index, which models the hyperbolic relationship between S_I and the acute insulin response to glucose (AIR_g), provides a measure of ß-cell compensation for insulin resistance. As shown in Figure 1, previous GDM was associated with an unfavourable leftward shift of the disposition curve, in both lean and obese subjects. Thus, it is apparent that abnormalities in both insulin secretion and action are present before the development of hyperglycemia (ie, progression to T2DM) in women with a history of previous GDM.

Homko and colleagues employed a different approach to study these apparent defects.[10] They determined prehepatic insulin secretion rates (determined by deconvolution of peripheral C-peptide concentrations using individually determined C-peptide kinetic parameters) in 7 patients with GDM and 8 age- and weight-matched patients with normal glucose tolerance (NGT) during the 3rd trimester and again at 3 months postpartum. As would be expected, insulin sensitivity index improved postpartum in both the NGT and the GDM group. However, the difference in insulin sensitivity between late pregnancy and postpartum was much greater in the NGT group. This finding suggests that women who develop GDM have chronic insulin resistance compared with NGT women. If one again considers the insulin sensitivity-secretion relationship (Figure 2), it is apparent that NGT and GDM subjects regulate insulin secretion on 2 separate hyperbolae.[11] The women with GDM exhibited lower insulin responses for their degree of insulin resistance during pregnancy. After pregnancy, the insulin response remained inappropriately low for the degree of insulin resistance in women with previous GDM. Moreover, using the disposition index as a quantitative measure of ß-cell function, the ß-cell defect in these women was found to be of similar magnitude both during and after pregnancy.[11] These findings suggest that the underlying ß-cell defect, which becomes clinically apparent as GDM during the high insulin resistance of late gestation, is still present postpartum (though less readily apparent, given the improved insulin sensitivity of the nonpregnant state).

The pro-insulin-to-insulin (PI:I) ratio, which is elevated in T2DM, has also been studied in GDM as a marker of ß-cell dysfunction. Conflicting evidence has emerged regarding this measure in the setting of GDM. Some studies have demonstrated an increased PI:I ratio in patients with GDM compared to pregnant women with NGT.[12,13] On the other hand, Festa et al found no difference in circulating pro-insulin concentrations, both in absolute terms and relative to levels of specific insulin, as measured by the PI:I ratio.[14] Reasons for the lack of consistency between studies include differences in the size and characteristics of study populations (eg, inclusion criteria, definition of GDM, gestational age, mean weight). In terms of previous GDM, Persson and associates have shown an increased molar PI:I ratio in lean, normoglycemic, former GDM patients compared to control subjects, 3 to 4 years after the index pregnancy.[15] This finding was consistent on repeat testing of the same cohort 3-years later (ie, 6-7 yrs after the index pregnancy) with a significant correlation between the PI:I ratio in the first and second follow-up studies.[16] As there was no correlation between the PI:I ratio in the first follow-up and the outcome of the OGTT in the second follow-up, the investigators' hypothesis that an elevated PI:I ratio may predict the subsequent development of glucose intolerance in the setting of previous GDM could not be supported. At present, this measure can only be interpreted as a marker of ß-cell dysfunction in this cohort.

The basis of the ß-cell defect in women with a history of GDM remains unclear. Candidate mechanisms include glucotoxicity, lipotoxicity, and amyloid deposition. While there is an increased risk of type 1 DM in this cohort, autoimmune destruction of ß-cells does not appear to be a factor in most patients with previous GDM.[17] In particular, there is a low incidence of immunologic markers predictive of type 1 DM, such as islet cell antibodies, insulin autoantibodies, and glutamic acid decarboxylase (GAD) autoantibodies.[1] Moreover, the frequency of HLA-DR2, DR3, and DR4 antigens is similar both in healthy pregnant women and in women who develop GDM.[1]

Buchanan has postulated that the ß-cell defect in women with GDM is caused by chronic insulin resistance.[11] This hypothesis links the two typical metabolic abnormalities present in both GDM and T2DM. Most importantly, this theory has potential implications for the management of patients with a history of GDM, since it suggests that the reduction of chronic insulin resistance could possibly limit or improve concomitant ß-cell dysfunction.

Endothelial dysfunction

Endothelial dysfunction, an early sign in the development of cardiovascular disease, has been demonstrated in T2DM and in components of the metabolic syndrome, including hypertension, dyslipidemia, and obesity.[18-22] It has been suggested that endothelial dysfunction precedes the development of glucose intolerance in individuals at risk of developing diabetes.[23] Thus, patients with a history of GDM, who are typically young, healthy women with a low burden of co-morbid disease, represent an important study population in which to evaluate endothelial function.

Anastasiou et al assessed vasodilatory response of the brachial artery during reactive hyperemia (a measure of endothelium-dependent vasodilatation) in 33 women with a history of previous GDM (16 obese, 17 non-obese) and 19 healthy controls, 3 to 6 months after delivery.[24] Flow-mediated dilatation (FMD) was impaired by over 80% in both the obese and non-obese subsets of patients with previous GDM compared to controls. FMD correlated inversely with basal insulin resistance, as estimated by homeostasis model assessment (HOMA). Thus, chronic insulin resistance in patients with a history of GDM, as demonstrated earlier, may provide a basis for the impaired endothelial-dependent vasodilation observed in this cohort.

Asymmetric dimethylarginine (ADMA), an endogenous inhibitor of nitric oxide synthase, is a recently-described marker of endothelial dysfunction. Elevated serum concentrations of ADMA are associated with endothelial dysfunction and increased cardiovascular risk.[25] Increased ADMA levels have been observed in various conditions associated with cardiovascular disease, including hypertension, dyslipidemia, T2DM, hyperhomocysteinemia, and renal failure.[26-29] Therefore, increased ADMA has been suggested as one cause of abnormal endothelial function in these conditions. Stuhlinger and colleagues demonstrated a significant positive relationship between ADMA concentration and insulin resistance (measured by insulin suppression test), independent of other cardiovascular risk factors.[30] Moreover, they found that treatment with rosiglitazone, an insulin-sensitizing thiazolidinedione, reduced ADMA levels while enhancing insulin sensitivity. Taken together, these findings have led to the hypothesis that ADMA may be a factor in the endothelial dysfunction observed in insulin resistance.

Mittermayer et al measured ADMA concentrations in 77 normoglycemic women with a history of GDM (46 obese, 31 non-obese) and 17 healthy controls, at 14 to 16 weeks after delivery and again after 1 year.[31] Serum concentrations of ADMA were approximately 20% higher in both obese and non-obese women with a history of GDM compared to controls at both time points. Interestingly, in contrast to the findings of Stuhlinger et al, ADMA concentration was not significantly related to the insulin sensitivity index determined by FSIGT. This discrepancy may be due to differences in study populations or in the measures used to estimate insulin sensitivity. Further study in this area is clearly warranted.

Inflammation

Chronic subclinical inflammation, as manifest by elevated serum levels of acute phase proteins, has been associated with T2DM, metabolic syndrome, and cardiovascular disease.[32-36] Acute phase bio-markers such as C-reactive protein (CRP), plasminogen activator inhibitor 1 (PAI-1), and interleukin-6 have emerged as predictors of incident T2DM, potentially implicating a role for chronic subclinical inflammation in the pathogenesis of diabetes.[37-40] In this context, the status of inflammatory bio-markers in women with a history of previous GDM is of clear interest.

Total sialic acid provides an integrated marker of the acute phase response, since most acute phase reactants contain a sialic acid residue. Therefore, Sriharan et al measured sialic acid levels in 46 women with a history of GDM and 50 controls, 7 years after their index pregnancy.[41] Mean total sialic acid was significantly higher in women with previous GDM compared to controls, after adjustment for BMI and insulin sensitivity. These findings suggest that previous GDM may be associated with a chronic inflammatory response. Interestingly however, GDM *per se* does not appear to be an inflammatory state, independent of the inflammatory effects of maternal obesity.[42] Further study to reconcile these findings is indicated.

Clinical predictors of risk for T2DM

Despite the recommendation that women with GDM should undergo a postpartum OGTT to classify their glucose tolerance status, < 50% of patients return for such testing.[43] A recent study of women diagnosed with GDM in Ottawa in 1997 and 2000, showed that none had undergone a postpartum OGTT.[44] Thus, antepartum clinical predictors for risk of future progression to T2DM at the time of diagnosis of GDM in pregnancy could be of particular value in identifying those women at greatest risk. In the largest study addressing this question, Schaefer-Graf and colleagues studied 1636 patients with GDM who underwent an OGTT within 1 to 4 months postpartum.[43] Postpartum DM was diagnosed in 230 women (14.1%). From these data, 6 independent predictors for the development of T2DM were identified by multivariate logistic regression. All of the predictors were related to either the severity or duration of hyperglycemia. The final model of independent predictors included the following parameters in order of decreasing significance:

- the highest fasting plasma glucose in pregnancy
- any fasting plasma glucose level ≥5.8 mmol/L
- the area under the curve of the OGTT in pregnancy
- gestational age at diagnosis
- history of previous GDM
- result on the 50 g glucose challenge test.

Table 1: Parameters associated with highest risk of future type 2 DM in women with GDM[43]

- Highest fasting plasma glucose in pregnancy > 6.7 mmol/L
- Diagnosis before 19 weeks of gestation
- History of previous GDM
- 1 hr pc glucose > 11.2 mmol/L on 50 g glucose challenge test

Parameters associated with the highest risk of postpartum T2DM included:

- a highest fasting plasma glucose value >6.7 mmol/L
- diagnosis of GDM before 19 weeks of gestation
- a history of previous GDM
- a glucose measurement >11.2 mmol/L on the glucose challenge test (Table 1).

All of these parameters are routinely acquired during the management of women with GDM and can thus be used antenatally to identify those women at highest risk.

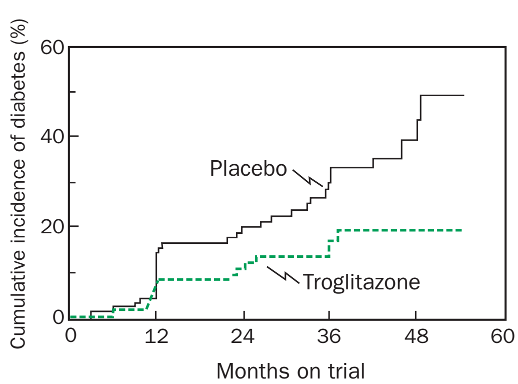
Interestingly, no measure of maternal weight emerged as an independent predictor of postpartum T2DM in this study. Pre-pregnancy obesity has been identified as an important factor in other smaller studies. This discrepancy may have been due to the high prevalence of obesity in this study cohort (mean pre-pregnancy BMI 29 +/- 5.7 kg/m^2).

Intervention strategies in women with a history of previous GDM

Having established that women with a history of GDM represent a population at high risk of future T2DM, intervention strategies to modify their risk of progression are clearly needed. Glycemic surveillance with an OGTT between 6 weeks to 6 months postpartum and subsequent fasting plasma glucose screening is recommended. Regular exercise and dietary modification to promote postpartum weight loss should also be considered in this population. In addition, attention to modifiable cardiovascular risk factors is indicated.

Buchanan's hypothesis that the ß-cell defect in women with GDM may be due to chronic insulin resistance suggests that amelioration of chronic insulin resistance may preserve ß-cell function in this population. This concept provided the basis for the Troglitazone in Prevention of Diabetes (TRIPOD) Study.[45] In this double-blind, randomized, control trial, 266 Hispanic women with previous GDM were randomized to either the now off-the-market thiazolidinedione, troglitazone, or placebo and treated for a median of 30 months. Subjects were assessed by OGTT annually and by intravenous glucose tolerance test at baseline,

Figure 3: Cumulative incidence rates of type 2 DM in women with placebo or troglitazone in the TRIPOD Study[45]



at 3 months of treatment and at 8 months after stopping the study drug. As shown in Figure 3, the incidence of T2DM was reduced by >50% among former GDM patients treated with troglitazone compared to those treated with placebo. In the troglitazone arm of the study, protection from diabetes was associated with an initial increase in insulin sensitivity at 3 months, with the most prominent protection noted in those women who responded to their increased insulin sensitivity with a large reduction in insulin secretion. In addition, the persistence of protection from diabetes 8 months after the study drug was stopped suggested that the thiazolidinedione might have altered the course of progression to T2DM in this high-risk population. Lastly, while placebo-treated patients displayed a worsening of their disposition index, patients treated with troglitazone showed stable ß-cell compensation for ambient insulin resistance over the course of the study, suggesting that the study drug was associated with preservation of ß-cell function. Taken together, these findings suggest that thiazolidinedione treatment in women with a previous history of GDM may preserve ß-cell function and prevent or delay progression to T2DM. Further study is now needed to determine if these findings can be extended to other ethnic groups and other thiazolidinediones. Nevertheless, the results of the TRIPOD study raise the exciting possibility of effective risk modification in the high-risk cohort of women with previous GDM.

Conclusions

In summary, GDM identifies a population of women at high risk of developing T2DM. Following the index pregnancy, this cohort exhibits several pathophysiologic changes that may reflect early events in the pathogenesis of T2DM, including chronic insulin resistance, ß-cell dysfunction, and endothelial dysfunction. Clinical predictors of progression to T2DM include the highest fasting plasma glucose in pregnancy, gestational age at diagnosis, previous history of GDM, and the result on glucose challenge test. Thus, women with a history of previous GDM represent an important population in which to consider preventative interventions. In particular, strategies for amelioration of insulin resistance need to be further explored, given recent evidence that the reduction of secretory demands on the ß-cell may delay or even prevent progression to T2DM. Strategies to be studied include lifestyle modifications to promote weight loss (diet, exercise) and pharmacologic therapy with thiazolidinediones.

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References

1. Kuhl C. Etiology and pathogenesis of gestational diabetes. *Diabetes Care* 1998;21(suppl 2):B19-B26.
2. Kjos S, Buchanan TA. Gestational diabetes mellitus. *N Engl J Med* 1999;341(23):1749-1756.
3. Kim C, Newton K, Knopp R. Gestational diabetes and the incidence of type 2 diabetes. *Diabetes Care* 2002;25:1862-1868.
4. O'Sullivan JB. Subsequent morbidity among GDM women. In: Sutherland HW, Stowers JM, eds. *Carbohydrate metabolism in pregnancy and the newborn*. New York: Churchill Livingstone; 1984:174-180.
5. Meyers-Seifer CH, Vohr B. Lipid levels in former gestational diabetes mothers. *Diabetes Care* 1996;19:1351-1356.
6. Verma A, Boney C, Tucker R, Vohr B. Insulin resistance syndrome in women with prior history of gestational diabetes mellitus. *J Clin Endocrinol Metab* 2002;87:3227-3235.
7. Clark CM Jr, Qui C, Amerman B, et al. Gestational diabetes: should it be added to the syndrome of insulin resistance? *Diabetes Care* 1997;20:867-871.
8. Buchanan TA, Metzger BE, Freinkel N, Bergman RN. Insulin sensitivity and ß-cell responsiveness to glucose during late pregnancy in lean and moderately obese women with normal glucose tolerance and mild gestational diabetes. *Am J Obstet Gynecol* 1990;162:1008-1014.
9. Ryan E, Imes S, Liu D et al. Defects in insulin secretion and action in women with a history of gestational diabetes. *Diabetes* 1995;44:506-512.
10. Homko C, Sivan E, Chen X, Reece EA, Boden G. Insulin secretion during and after pregnancy in patients with gestational diabetes mellitus. *J Clin Endocrinol Metab* 2001;86:568-573.
11. Buchanan TA. Pancreatic ß-cell defects in gestational diabetes: implications for the pathogenesis and prevention of type 2 diabetes. *J Clin Endocrinol Metab* 2001;86(3):989-993.
12. Dornhorst A, Davies M, Anyaoku V, et al. Abnormalities in fasting proinsulin concentration in mild gestational diabetes. *Clin Endocrinol* 1991;34:211-213.
13. Kautzky-Willer A, Thomaseth K, Ludvik B, et al. Elevated islet amyloid, pancreatic polypeptide and proinsulin in lean gestational diabetes. *Diabetes* 1997;46:607-614.
14. Festa A, Shnawa N, Schernthaner G, Haffner S. Proinsulin in pregnant women with normal glucose tolerance or mild gestational diabetes mellitus. *Exp Clin Endocrinol Diabetes* 1999; 107:447-452.
15. Persson B, Hanson U, Hartling SG, Binder C. Follow-up of women with previous GDM: insulin, C-peptide and proinsulin responses to oral glucose load. *Diabetes* 1991;40 (suppl 2):136-141.
16. Hanson U, Persson B, Hartling SG, Binder C. Increased molar proinsulin-to-insulin ratio in women with previous gestational diabetes does not predict later impairment of glucose tolerance. *Diabetes Care* 1996;19(1):17-20.
17. Damm P, Kuhl C, Bertelsen A, Molsted-Pedersen L. Predictive factors for the development of diabetes in women with previous gestational diabetes mellitus. *Am J Obstet Gynecol* 1992;167:607-616.
18. Sandeman DD, Pym CA, Green EM, Seamark C, Shore AC, Tooke JE. Microvascular vasodilatation in feet of newly diagnosed non-insulin dependent diabetic patients. *Br Med J* 1991;302:1122-123.

19. Pinkney JH, Stehouwer CD, Coppack SW, Yudkin JS. Endothelial dysfunction: cause of the insulin resistance syndrome. *Diabetes* 1997;46(suppl 2):S9-S13.
20. Iiyama K, Nagano M, Yo Y, et al. Impaired endothelial function with essential hypertension assessed by ultrasonography. *Am Heart J* 1996;132:779-782.
21. Chowienczyk PJ, Watts GF, Cockcroft JR, Ritter JM. Impaired endothelium-dependent vasodilation of forearm resistance vessels in hypercholesterolemia. *Lancet* 1992;340:1430-1432.
22. Steinberg HO, Chaker H, Leaming R, Johnson A, Bretchel G, Baron AD. Obesity/insulin resistance is associated with endothelial dysfunction: implications for the syndrome of insulin resistance. *J Clin Invest* 1996;97:2601-2610.
23. Hannerman M, Liddell W, Shore A, Clark P, Tooke J. Vascular function in women with previous gestational diabetes. *J Vasc Res* 2002;39:311-319.
24. Anastasiou E, Lekakis J, Alevizaki M, et al. Impaired endothelium-dependent vasodilatation in women with previous gestational diabetes. *Diabetes Care* 1998;21(12):2111-2115.
25. Cooke JP. Does ADMA cause endothelial dysfunction? *Arterioscler Thromb Vasc Biol* 2000;20:2032-2037.
26. Lundman P, Eriksson MJ, Stuhlinger M, Cooke JP, Hamsten A, Tomvall P. Mild-to-moderate hypertriglyceridemia in young men is associated with endothelial dysfunction and increased plasma concentrations of asymmetric dimethylarginine. *J Am Coll Cardiol* 2001;38:111-116.
27. Abbasi F, Asagami T, Cooke JP, et al. Plasma concentrations of asymmetric dimethylarginine are increased in patients with type 2 diabetes mellitus. *J Am Coll Cardiol* 2001;88:1201-1203.
28. Surdacki A, Nowicki M, Sandmann J, et al. Reduced urinary excretion of nitric oxide metabolites and increased plasma levels of asymmetric dimethylarginine in men with essential hypertension. *J Cardiovasc Pharmacol* 1999;33:652-658.
29. Kielstein JT, Boger RH, Bode-Boger SM, et al. Asymmetric dimethylarginine plasma concentrations differ in patients with end-stage renal disease: relationship to treatment method and atherosclerotic disease. *J Am Soc Nephrol* 1999;10:594-600.
30. Stuhlinger M, Abbasi F, Chu J, et al. Relationship between insulin resistance and an endogenous nitric oxide synthase inhibitor. *JAMA* 2002; 287:1420-1426.
31. Mittermayer F, Mayer BX, Meyer A, et al. Circulating concentrations of asymmetrical dimethyl-L-arginine are increased in women with previous gestational diabetes. *Diabetologia* 2002;45:1372-1378.
32. Pickup JC, Crook MA. Is Type 2 DM a disease of the innate immune system? *Diabetologia* 1998;41:1241-1248.
33. Pickup JC, Mattock MB, Chusney GD, Burt D. NIDDM as a disease of the innate immune system: association of acute-phase reactants and interleukin-6 with metabolic syndrome X. *Diabetologia* 1997;40(11):1286-92.
34. Festa A, D'Agostino R Jr, Howard G, Mykkanen L, Tracy RP, Haffner SM. Chronic subclinical inflammation as part of the insulin resistance syndrome. *Circulation* 2000; 102:42-47.
35. Yudkin JS, Stehouwer CDA, Emeis JJ, Coppack SW. C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction. *Arterioscler Thromb Vasc Biol* 1999;19:972-978.
36. Ross R. Atherosclerosis: an inflammatory disease. *N Engl J Med* 1999;340: 115-126.
37. Pradhan AD, Manson JE, Rifai N, Buring J, Ridker PM. C-Reactive protein, interleukin 6 and risk of developing Type 2 Diabetes Mellitus. *JAMA* 2001;286(3):327-334.
38. Freeman DJ, Norrie J, Caslake MJ, et al. C-reactive protein is an independent predictor of risk for the development of diabetes in the West of Scotland Coronary Prevention Study. *Diabetes* 2002;51:1596-600.
39. Barzilay JI, Abraham L, Heckbert SR, et al. The relation of markers of inflammation to the development of glucose disorders in the elderly: the Cardiovascular Health Study. *Diabetes* 2001;50:2384-2389.
40. Festa A, D'Agostino R Jr, Tracy RP, Haffner SM. Elevated levels of acute-phase proteins and plasminogen activator inhibitor-1 predict the development of type 2 diabetes. The Insulin Resistance Atherosclerosis Study. *Diabetes* 2002;51:1131-1137.
41. Sriharan M, Reichelt AJ, Opperman ML, et al. Total sialic acid and associated elements of the metabolic syndrome in women with and without previous gestational diabetes. *Diabetes Care* 2002;25(8):1331-1335.
42. Retnakaran R, Hanley AJ, Raif N, Connelly PW, Sermer M, Zinman B. C-reactive protein and gestational diabetes: the central role of maternal obesity. *J Clin Endocrinol Metab* 2003; in press.
43. 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* 2002;186(4):751-756.
44. Clark HD, van Walraven C, Code C, Karovitch A, Keely E. Did publication of a clinical practice guideline recommendation to screen for type 2 diabetes in women with gestational diabetes change practice. *Diabetes Care* 2003;26(2): 265-268.
45. Buchanan TA, Xiang AH, Peters RK et al. Preservation of pancreatic ß-cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk Hispanic women. *Diabetes* 2002; 51(9):2796-2803.

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