The development of gestational diabetes and even milder forms of dysglycemia during pregnancy represents a maternal phenotype at increased subsequent risk for developing type 2 diabetes mellitus, metabolic syndrome, and, with time, overt cardiovascular disease. A careful and systematic dissection of the hormonal, metabolic, and vascular changes occurring in such women during pregnancy and over the postpartum years provides a unique opportunity to identify conventional and novel conditions and biomarkers whose modification may attenuate adverse long-term outcomes, particularly cardiovascular risk. The purpose of this review is to summarize current understanding of the magnitude of such risk and its potential causes, with a particular focus on postpartum alterations in endothelial and vascular smooth muscle responsiveness. (J Am Coll Cardiol 2013;62:677–84) © 2013 by the American College of Cardiology Foundation

Gestational diabetes mellitus (GDM), defined as glucose intolerance of varying severity with first onset or recognition during pregnancy (1), represents a failure of the pancreas to respond to the progressive insulin resistance of the latter stages of gestation by appropriately increasing beta-cell mass (2) and insulin secretion (3). Although in the majority of patients, hyperglycemia resolves postpartum, in the years after pregnancy, these women exhibit greater risk for developing type 2 diabetes mellitus (T2DM) (4,5) and overt cardiovascular disease (CVD) (6,7). Thus, detection of GDM affords clinicians opportunities to care longitudinally for a relatively young population at increased risk for cardiovascular events and to intervene early to modify such risk. The purpose of this review is to summarize both epidemiological data concerning the cardiometabolic consequences of gestational dysglycemia and current understanding regarding altered vascular properties that increase the likelihood that these women will experience cardiovascular events.

Gestational Dysglycemia: Diagnosis and Therapy

Over the past 5 decades, a number of diagnostic criteria for GDM with different thresholds have been proposed (8–11). These are still applied, with modifications (12), but the absence of an agreed global diagnostic standard has hindered large-scale evaluation of the prevalence of GDM (13). The American Diabetes Association now advises universal third-trimester screening (12). Earlier American Diabetes Association guidelines incorporated an assessment of GDM risk (Table 1) and recommended either a 1-step approach, with a diagnostic 75-g or 100-g oral glucose tolerance test (OGTT) alone, or a 2-step process with a screening 50-g glucose challenge test (GCT) at first presentation and, if positive, an OGTT (Table 2). Women can be classified into 4 distinct groups by their responses: normal GCT normal glucose tolerance (NGT) (normal GCT result, normal OGTT result), abnormal GCT NGT (elevated GCT result but normal OGTT result), gestational impaired glucose tolerance (GIGT) (1 elevated glucose value on OGTT), and GDM (2 elevated glucose values on OGTT) (14) (Table 2). It is now evident that these milder degrees of glucose intolerance also place the mother (15) at increased postpartum cardiovascular risk. GDM is managed initially with diet and lifestyle modification and, if this fails, with insulin therapy (16). Postpartum, glycemic status should be reassessed by an OGTT at 6 to 12 weeks and then at regular intervals thereafter.
Gestational Dysglycemia: Estimates of Subsequent Cardiovascular Risk

Carr et al. (7) used questionnaire methodology to evaluate CVD risk in women with family histories of T2DM who were on average 29.9 years postpartum. The self-reported prevalence of CVD (stroke and/or coronary artery disease) was significantly greater in those with \( n = 332 \) than without \( n = 662 \) GDM (adjusted odds ratio [OR]: 1.85; 95% confidence interval [CI]: 1.21 to 2.82; \( p = 0.005 \)). This relationship was still significant after adjustment for age, ethnicity, and menopausal status (OR: 1.66; 95% CI: 1.07 to 2.57; \( p = 0.02 \)), suggesting a role for GDM itself in the causality of CVD. Of interest, in that study, women with GDM who self-reported coronary artery disease were on average 7 years younger than those who did not have GDM (45.5 ± 2.2 years vs. 52.5 ± 1.9 years, \( p = 0.02 \)).

In a retrospective population-based study, Retnakaran and Shah (15) linked Ontario databases comprising all live births from 1994 to 1998 with provincial reimbursements for OGTTs. Women were stratified into 3 groups: 1) with GDM \( (n = 13,888) \); 2) with abnormal OGTT results but not GDM (presumed to have milder forms of gestational dysglycemia, e.g., GIGT and elevated GCT NGT; \( n = 71,831 \)); and 3) who did not undergo OGTTs. The latter \( (n = 349,977) \) were presumed to have normal GCT results and normoglycemia during pregnancy. These cohorts then were followed for a median of 12.3 years. Cardiovascular event rates (comprising hospitalizations for myocardial infarction, revascularization by coronary artery bypass grafting or angioplasty, stroke, and carotid endarterectomy) per 10,000 person-years of women with GDM, presumed milder dysglycemia, and presumed normoglycemia were 4.2, 2.3, and 1.9, respectively (Fig. 1). After adjustment for confounding variables the hazard ratios (HRs) for CVD of women with GDM and presumed milder dysglycemia were 1.66 (95% CI: 1.3 to 2.13; \( p < 0.001 \)) and 1.19 (95% CI: 1.02 to 1.39; \( p = 0.03 \)), respectively. However, after adjustment for the development of T2DM, HRs for CVD were no longer significant for GDM (HR: 1.25; 95% CI: 0.96 to 1.62; \( p = 0.06 \)).

### Cardiometabolic Consequences of Gestational Dysglycemia

**Pre-diabetes and T2DM.** Both GDM and milder manifestations of gestational dysglycemia predispose to dysglycemia soon after delivery (4), and 20% to 30% of women with GDM will develop T2DM (17–19) within the first 5 years postpartum (3), in part because of persistent pancreatic beta-cell dysfunction (20–22). In 1 study, >400 women were evaluated 3 months postpartum for glucose intolerance (4) as defined by Canadian Diabetes Association clinical practice guidelines (Table 3) (23). The prevalence of combined T2DM and prediabetes was 3.2% in the normal GCT NGT group, 10.2% in the abnormal GCT NGT group, 16.5% in the GIGT group, and 32.8% in the GDM group (\( p_{\text{trend}} < 0.0001 \)). Most of this dysglycemia was in fact explained by the differing prevalence of postpartum impaired glucose tolerance (i.e., 2.2% impaired glucose tolerance for normal GCT NGT vs. 27% impaired glucose tolerance for GDM). The independent predictors of diabetes and pre-diabetes at 3 months postpartum were GDM (OR: 14.3; 95% CI: 4.2 to 49.1), GIGT (OR: 5.7; 95% CI:

### Table 2 Approaches to the Diagnosis of GDM: 1-Step (12) and 2-Step Algorithms (14)

<table>
<thead>
<tr>
<th>Approach</th>
<th>mmol/l</th>
<th>mg/dl</th>
</tr>
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<tbody>
<tr>
<td>75-g 1-step approach (IADPSG guidelines): requirement</td>
<td>≥1 abnormal value for GDM diagnosis</td>
<td></td>
</tr>
<tr>
<td>FPG</td>
<td>≥5.1</td>
<td>≥92</td>
</tr>
<tr>
<td>1-h plasma glucose</td>
<td>≥10.0</td>
<td>≥180</td>
</tr>
<tr>
<td>2-h plasma glucose</td>
<td>≥8.5</td>
<td>≥153</td>
</tr>
<tr>
<td>2-step approach (NDDG guidelines)</td>
<td></td>
<td></td>
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<tr>
<td>Step 1</td>
<td></td>
<td></td>
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<tr>
<td>50-g CDT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-h plasma glucose</td>
<td>≥7.8</td>
<td>≥140</td>
</tr>
<tr>
<td>Step 2: requirement ≥2 abnormal values for GDM diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100-g OGTT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FPG</td>
<td>≥5.8</td>
<td>≥105</td>
</tr>
<tr>
<td>1-h plasma glucose</td>
<td>≥10.6</td>
<td>≥190</td>
</tr>
<tr>
<td>2-h plasma glucose</td>
<td>≥9.2</td>
<td>≥165</td>
</tr>
<tr>
<td>3-h plasma glucose</td>
<td>≥8.1</td>
<td>≥145</td>
</tr>
</tbody>
</table>

FPG = fasting plasma glucose; GCT = glucose challenge test; GDM = gestational diabetes mellitus; IADPSG = International Association of Diabetes and Pregnancy Study Group; NDDG = National Diabetes Data Group; OGTT = oral glucose tolerance test.
1.6 to 21.1), and abnormal GCT NGT (OR: 3.6; 95% CI: 1.01 to 12.9). An increased risk for dysglycemia was still evident in women with GDM and GIGT at 12 months postpartum and was accompanied by diminished pancreatic beta-cell function (21). This chronic deficiency of pancreatic beta-cell function in women with GDM (3) may in some predate pregnancy (24).

**Metabolic syndrome.** Postpartum metabolic syndrome in GDM has been well described (25,26). When a cohort of women (n/H11005487) were classified 3 months postpartum on the basis of the 2005 International Diabetes Federation guidelines (27), prevalence of the metabolic syndrome was 10% in those with NGT, 17.6% in those with GIGT, and 20% in those with GDM (p/H110050.016) (28). In that series, gestational dysglycemia was the only independent predictor of postpartum metabolic syndrome. For women with GIGT, the OR was 2.16 (95% CI: 1.05 to 4.42), and for those with GDM, the OR was 2.05 (95% CI: 1.07 to 3.94).

**Dyslipidemia.** In a similar study population, Retnakaran et al. (29) found that GDM was an independent predictor of plasma total cholesterol, low-density lipoprotein, and triglyceride concentrations at 3 months postpartum. In addition, there were graded increases in total cholesterol (p/H110050.0047), low-density lipoprotein (p/H110050.0002), and triglyceride (p/H110050.0002) across the classes of gestational dysglycemia, from normal GCT NGT to GDM.

**Hypertension.** An increased risk for postpartum hypertension in women with gestational dysglycemia also has been reported. At 3 months postpartum women with GIGT (median: 110 mm Hg; interquartile range: 103.5 to 115.5 mm Hg; n/H1100591) and those with GDM (median: 111 mm Hg; range: 105 to 119.5 mm Hg; n/H11005137) had significantly higher systolic blood pressures than control subjects (median: 108 mm Hg; interquartile range: 102 to 114 mm Hg; n/H11005259) (p/H110050.0158 for comparison across groups) (28). In another study, a cohort including both obese and nonobese women with GDM examined 1 year postpartum had significantly higher systolic blood pressures than control subjects (median: 108 mm Hg; interquartile range: 102 to 114 mm Hg; n/H11005259) (p/H110050.0158 for comparison across groups) (28). In a previous study, a cohort including both obese and nonobese women with GDM examined >1 year postpartum had significantly higher systolic blood pressures (p = 0.004) and mean (p = 0.004) blood pressures and heart rates but lower stroke volumes and cardiac output than a group of control women without GDM (30).

**Other risk factors.** A prior GDM pregnancy has also been associated with elevated plasma C reactive protein, a marker of chronic subclinical inflammation, and low plasma adi-
ponectin concentrations (30,31). Women with prior GDM are more likely to have higher body mass indexes (BMIs) before pregnancy (4), greater intrapregnancy weight gain (32), and a higher incidence postpartum of polycystic ovary syndrome (33).

Pathophysiology

It is now appreciated that the cardiovascular risk subsequent to a GDM pregnancy resembles that which accrues to the general female population once T2DM develops (34). Indeed, several groups have proposed that cardiometabolic abnormalities detected postpartum might have antedated the gestational dysglycemic pregnancy (24,28,35). As a consequence, attention following a GDM pregnancy has focused on pathophysiological processes now considered to contribute importantly to the vascular injury of T2DM.

Endothelial function. The vascular endothelium is now recognized as a paracrine organ responsible for the production of vasoactive autacoids such as nitric oxide (NO) (36). Dysfunction of the endothelium is recognized as an early precursor of coronary atherosclerosis (37), which when present is systemic (38), can be assessed in peripheral arteries, and is a surrogate for the coronary vasculature (39). As summarized in Table 4, the endothelial function of women with gestational dysglycemia has been assessed in several ways at a number of time points postpartum, but with inconsistent results.

Ex vivo, endothelial and vascular smooth muscle responsiveness to exogenous stimuli can be assessed by placing arterial segments obtained by subcutaneous fat biopsy in wire myographs. One study, involving 14 patients with GDM and 18 controls examined at cesarian section, reported a reduction in the endothelium-mediated vasodilator response to acetylcholine. This was no longer evident after the administration of the prostaglandin inhibitor indomethacin; the smooth muscle response to nitroprusside was similar in the 2 cohorts (40). NO synthase inhibition reduced acetylcholine responsiveness similarly in both groups of women. The investigators proposed that maternal vascular endothelial dysfunction could increase the risk for cardiovascular disorders in women with prior GDM (40).

In a study of the Hyperglycemia and Adverse Pregnancy Outcomes trial (41), Banerjee et al. (42) obtained gluteal fat arteries by biopsy 2 years postpartum and exposed these vessels in myographs to carbachol (to assess endothelium-dependent dilation [EDD]), sodium nitroprusside (to assess smooth muscle responsiveness), and the vasoconstrictor norepinephrine. By the time of biopsy, 5 women had developed postpartum dysglycemia. Maximal EDD of arteries obtained from women with GDM (43.3%) and from women with milder gestational dysglycemia (51.7%) was reduced significantly relative to normoglycemic controls (72.7%) (p = 0.01 and p = 0.04, respectively). BMI at the time of biopsy and hypercholesterolemia proved to be the strongest determinants of EDD, with BMI emerging as the only significant determinant of arterial function. The investigators concluded that potentially reversible vascular pathology was evident very early in women at risk for subsequent T2DM. Although data acquired using this ex vivo approach are instructive, this method has limited application to clinical or population studies.

Flow-mediated dilation (FMD) is a noninvasive, reproducible technique that is used widely to assess EDD, which represents the net of several factors, including endogenous NO synthesis and its local bioavailability (43). This method involves ultrasound and Doppler imaging of a peripheral artery before and then after a period of ischemia, with relative quantification of its resulting dilation (43). Vascular responsiveness to exogenously administered NO is often assessed at the same sitting as an internal control and as an estimate of endothelium-independent dilation (EID). An attenuated FMD response is associated with several conventional cardiovascular risk factors (44-46) as well as established CVD (47) and currently is considered prognostic of increased cardiovascular risk (46,48,49).

Thus far, 4 published cross-sectional studies, conducted at times ranging from intrapartum to 5 years postpartum, have evaluated FMD in women with gestational dysglycemia (50-53). Paradisi et al. (50) assessed, in the third trimester of pregnancy, FMD in women with GDM and with milder degrees of gestational dysglycemia. FMD was significantly lower in both gestational dysglycemic groups compared with controls (GDM: 4.1 ± 0.9%; dysglycemia: 7.6 ± 1.1%; controls: 10.9 ± 1.1%; p < 0.0001 and p < 0.04, respectively). Area under the glucose curve (AUC_{gluc}) during pregnancy and nonesterified fatty acids independently influenced FMD (p < 0.0001 for both). The investigators attributed the relationship with AUC_{gluc} to the effects of hyperglycemia (and possibly secondary insulin resistance) on the generation and bioavailability of endothelium-derived NO.

FMD in dysglycemic women assessed 2 months postpartum was also influenced by AUC_{gluc} (51). These subjects were grouped into those with GDM who had by this time become normoglycemic (n = 10), those with GDM who remained hyperglycemic (with some glucose concentrations in the prediabetes range; n = 10), those normoglycemic during pregnancy (n = 10), and control women who had never been pregnant (n = 10). FMD was impaired in women with GDM who became normoglycemic (4.1 ± 2.3%) and in those who remained hyperglycemic (4.4 ± 0.9%) compared with normoglycemic (10.8 ± 1.3%) and control (>12%) subjects (p < 0.05). However after controlling for postpartum AUC_{gluc} differences in FMD were no longer significant, highlighting the importance of postpartum hyperglycemia in determining endothelial function at this early stage after pregnancy.

The most widely cited report is by Anastasiou et al. (52), whose subjects were studied at 3 to 7 months postpartum, when normoglycemia was restored in all. They compared 3 groups: 1) women with previous GDM (BMI ≈27 kg/m²;
<table>
<thead>
<tr>
<th>First Author (Ref. #)</th>
<th>Duration With Respect to Pregnancy</th>
<th>Population</th>
<th>Methods</th>
<th>Conclusions</th>
<th>Confounding Variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paradisi et al. (50)</td>
<td>Third trimester</td>
<td>Controls (n = 15) Mildly dysglycemia (n = 10) GDM (n = 13)</td>
<td>Brachial FMD</td>
<td>1. FMD was reduced in women with GDM (p &lt; 0.0001) and milder dysglycemia (p &lt; 0.04) vs. controls 2. FMD was lower in GDM vs. milder dysglycemia group (p &lt; 0.04)</td>
<td>AUC_{gluc} accounted for 35% variance of FMD (p = 0.0004) and NEFA for 5% variance (p &lt; 0.0001)</td>
</tr>
<tr>
<td>Savvidou et al. (59)</td>
<td>Third trimester</td>
<td>GDM (n = 34) Controls (n = 34)</td>
<td>Radial artery applanation tonometry</td>
<td>1. Increased augmentation index in GDM pregnancies (p &lt; 0.001) 2. Increased carotid-radial PWV (p = 0.03) in women with GDM</td>
<td>Maternal age, pulse, aortic Tr (p &lt; 0.0001 for all) and presence of GDM (p = 0.003) were independent predictors of augmentation index 2. PWV was not significantly increased in women with GDM after exclusion of women with pre-eclampsia</td>
</tr>
<tr>
<td>Dollberg et al. (73)</td>
<td>At term</td>
<td>GDM (n = 8) Controls (n = 5)</td>
<td>Measurement of NOS activity by arginine-to-citrulline conversion assay of placental vessels</td>
<td>Significantly greater NOS activity in resistance vessels of control pregnancies (p &lt; 0.01)</td>
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<tr>
<td>Knock et al. (40)</td>
<td>At term</td>
<td>Controls (n = 18) GDM (n = 14)</td>
<td>Wire myography of subcutaneous fat biopsies</td>
<td>EDD was decreased in women with GDM vs. controls (p &lt; 0.01)</td>
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</tr>
<tr>
<td>Davenport et al. (51)</td>
<td>2 months</td>
<td>Never pregnant controls (n = 10) NORM (n = 10) GDM-N (n = 10) GDM-H (n = 10)</td>
<td>PWV 1. FMD was significantly decreased in GDM-N and GDM-H vs. NORM groups (p &lt; 0.01) 2. GDM-N and GDM-H groups had decreased brachial and carotid distensibility vs. NORM and control groups (p &lt; 0.05) 3. No significant difference in PWV</td>
<td>1. Difference in FMD nonsignificant after controlling for AUC_{gluc} 2. Difference in brachial and carotid distensibility nonsignificant after controlling for insulin sensitivity, AUC_{gluc} and TG</td>
<td></td>
</tr>
<tr>
<td>Anastasiou et al. (52)</td>
<td>3–7 months</td>
<td>Controls (n = 19) Nonobese GDM (n = 17) Obese GDM (n = 16)</td>
<td>Brachial FMD</td>
<td>1. FMD was significantly decreased in women with GDM vs. controls (p &lt; 0.001) 2. EID was significantly reduced in obese women with GDM (p &lt; 0.05)</td>
<td>BMI was the main determinant of EID (p &lt; 0.05)</td>
</tr>
<tr>
<td>Pleiner et al. (56)</td>
<td>&gt;4 months</td>
<td>Obese women with previous GDM (n = 7) vs. nonobese women with previous GDM (n = 5)</td>
<td>Venous plethysmography (FBF) after ACh infusion 1. Reduced FBF to ACh in the overweight GDM group (p &lt; 0.05) 2. ADMA levels were positively correlated with BMI (p &lt; 0.05)</td>
<td>1. EDD correlated inversely with BMI and hypercholesterolemia on multiple regression 2. BMI was the most powerful determinant of small artery function</td>
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<tr>
<td>Banerjee et al. (42)</td>
<td>2 yrs</td>
<td>Controls (n = 8) UQ (n = 13) GDM (n = 8)</td>
<td>Wire myography of subcutaneous arteries from gluteal fat biopsy</td>
<td>Significantly reduced EDD in both GDM (p = 0.01) and UQ (p = 0.04) vs. controls</td>
<td></td>
</tr>
<tr>
<td>Hu et al. (60)</td>
<td>2–4 yrs</td>
<td>Controls (n = 20) GDM (n = 17)</td>
<td>Aortic and carotid artery stiffness 1. Increased carotid artery stiffness in women with previous GDM pregnancies: Ep (p = 0.0006); β (p = 0.05) 2. Peak perfusion increase in hand and foot skin lower in previous GDM (both p &lt; 0.01 and p = 0.04, respectively); women with GDM had lower increases in perfusion over time in both hands and feet vs. controls (p &lt; 0.001)</td>
<td>Multiple regression of stiffness index found age to be the major determinant (p = 0.008)</td>
<td></td>
</tr>
<tr>
<td>Hannemann et al. (53)</td>
<td>5 yrs</td>
<td>Controls (n = 17) GDM (n = 17)</td>
<td>Laser Doppler fluximetry of skin MMVC to local heating 2. Brachial artery FMD</td>
<td>Impaired MMVC in women with previous GDM (p = 0.008) 2. No difference in EDD or EID in women with GDM vs. controls</td>
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</tr>
</tbody>
</table>

ACh = acetylcholine; ADMA = asymmetric dimethyl-L-arginine; aortic Tr = time between start of systolic curve and inflection point; AUC_{gluc} = area under the glucose curve; β = stiffness index; BMI = body mass index; EDD = endothelium-dependent dilation; EID = endothelium-independent dilation; Ep = pressure strain elastic modulus; FBF = forearm blood flow; FMD = flow-mediated dilation; GDM = gestational diabetes mellitus; GDM-H = prior gestational diabetes mellitus, hyperglycemic postpartum; GDM-N = prior gestational diabetes mellitus, normoglycemic postpartum; MMVC = maximum microvascular vasodilatory capacity; NEFA = nonesterified fatty acids; NORM = normoglycemic pregnancy, normoglycemic postpartum; NOS = nitric oxide synthase; PWV = pulse-wave velocity; TG = triglyceride; UQ = milder forms of gestational dysglycemia.
provide evidence for altered smooth muscle, in addition to altered endothelial, function.

Markers of inflammation. Subclinical inflammation, mediated in part through the paracrine action of adipocytes (61), appears present in both GDM (30) and T2DM (62) and predictive of increased cardiovascular events in the female population (63). Adiponectin expression is reduced in obesity, insulin resistance, and T2DM (64–67) and when measured early in pregnancy, low adiponectin concentrations are associated with increased risk for developing a GDM pregnancy (68,69). A recent study comparing markers of inflammation in women with prior GDM (30) found significantly higher C-reactive protein, interleukin-6, and plasminogen activator 1 and lower adiponectin concentrations than in control subjects, but after adjustment for confounders, only high C-reactive protein and low adiponectin were associated with GDM. Microalbuminuria, a signal of impaired endothelial function in T2DM (70), has been reported also in women whose pregnancies were complicated by GDM (71).

Conclusions

Gestational dysglycemia (GDM and milder forms of gestational glucose intolerance) identifies a group of women who are at increased risk not only for T2DM but also for an earlier age of onset of CVD. The usefulness of identifying a dysglycemic pregnancy is that it will identify a population of women at increased subsequent cardiometabolic risk. Furthermore, much of that risk, expressed as dysglycemia, metabolic syndrome, and altered vascular physiology, becomes evident in the first few months postpartum. Detection of these conventional abnormalities affords clinicians an opportunity to attenuate such risk by targeted intervention. One goal of future investigation is to identify and validate as potential useful postpartum screening tools and biomarkers of subsequent vascular risk, including altered endothelial responsiveness, that may be evident before diabetes, metabolic syndrome, or cardiovascular events emerge.

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Key Words: cardiovascular risk • endothelial function • gestational diabetes • type 2 diabetes mellitus.