Journal of Diabetes & Clinical Practice

Piotr, J Diabetes Clin Prac 2023, 6:1

Review Article Open Access

Risk and Clinical Treatment of Oxidative Stress in Hypertensive Diseases Pregnancy with Gestational Diabetes Mellitus: A Prospective Cohort Study

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Abstract

Introduction: Oxidative stress is linked to the development of gestational diabetes mellitus (GDM). Maternal antioxidant vitamins in early pregnancy may play a role in GDM occurrence. We aimed to investigate the associations of vitamins A and E in early pregnancy with the risk of GDM and to explore whether these antioxidant vitamins can be biomarkers for the early prediction of GDM.

Methods: We carried out a prospective cohort study conducted in Beijing and enrolled pregnant women with vitamins A and E measurements at 9 weeks of gestation and having one-step GDM screened with a 75-g oral glucose tolerance test between 24 and 28 weeks of gestation.

Results: The vitamin A levels in early pregnancy were significantly higher in women with GDM than in those without GDM and positively correlated with fasting blood glucose. In multivariate models, vitamin A levels were significantly associated with GDM per SD. A significant trend of risk effect on GDM risk across quartiles of vitamin A was observed. No significant association of serum vitamin E with GDM was observed overall. However, a noted trend of protective effect on GDM risk across quartiles of vitamin E/cholesterol ratio was observed. In ROC analysis, the multivariate model consisting of vitamin A and other risk factors showed the best predictive performance.

Conclusions: Higher levels of vitamin A in early pregnancy were significantly associated with an increased risk of GDM. Vitamin A has the potential to be a biomarker indicating pathogenesis of GDM.

Introduction

Increased understanding of the epidemiologic context, pathophysiology, and treatment efficacy of gestational diabetes mellitus (GDM) has raised corollary questions regarding subsequent morbidities, in addition to diabetes, sustained by patients with this diagnosis. Both hypertension and vascular disease have been examined as conditions that may be predicted by GDM. Obesity and insulin resistance are central attributes of both GDM and the metabolic syndrome. These characteristics and dyslipidemia are associated with endothelial dysfunction, oxidative stress, and overexpression of inflammatory responses, all of which contribute to vascular disease [1]. These associations have significant public health ramifications because of the current epidemic of obesity, affecting individuals of all age-groups. The recent report of Crowther et al. confirming the efficacy of screening for and treatment of mild-to-moderate levels of glucose intolerance in mid-pregnancy in reducing both perinatal and maternal morbidity has set the stage for universal maternal screening and thereby identifies a cohort of young women who may be at risk for subsequent hypertension and vascular disease. Recent trials of exercise and dietary interventions and pharmacological treatments suggest that such interventions may reduce late post-gestational morbidity among women with prior GDM. Consequently, questions about the association of GDM and subsequent hypertension and vascular disease are timely and important.

Nondiabetic and GDM Pregnancy

Pregnancy produces transient insulin resistance, manifest as elevated postprandial glycemia, fasting hyperlipidemia in the form of increased triglycerides, LDL particles, and free fatty acids and accelerated ketosis. Nondiabetic pregnancy is also associated with increased blood levels of plasminogen activator inhibitor-1, tumor necrosis factor-α, and C-reactive protein (CRP), all markers of increased inflammatory response [2]. Despite these metabolic characteristics, pregnancy also induces increased venous capacitance, reduced systemic arterial resistance, and vasodilation associated with a 50% increase in circulating blood volume.

Gravidas with GDM generally demonstrate higher degrees of post pregnancy insulin resistance, β-cell dysfunction, higher BMI, central obesity, and exaggerated hyperlipidemia, which suggests that GDM is a transient manifestation of longstanding metabolic dysfunction. As such, GDM may be expected to have an association with gestational hypertension, a hypothesis ascribed to Vorzimer et al. in 1937.

Insulin Resistance, GDM and Gestational Hypertension

Bryson et al. found significantly elevated odds ratios (ORs) for GDM among women with gestational hypertension and preeclampsia among 60,000 maternal hospital discharges in Washington state. Nonproteinuric GH but no preeclampsia has been associated with insulin resistance documented by the hyperinsulinemic-euglycemic clamp technique. Caruso et al. examined 26 sequential subjects with third trimester hypertension with a euglycemic-hyperinsulinemic clamp. On day 1 of the study protocol [3], subjects performed an oral glucose tolerance test, during which plasma glucose, insulin, lipids, and lipoprotein were measured. On day 2, bioelectrical impedance was measured and the clamp was performed. Women with gestational

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Received: 03-Jan-2023, Manuscript No: jdce-23-87726, **Editor assigned:** 05-Jan-2023, PreQC No: jdce-23-87726 (PQ), **Reviewed:** 18-Jan-2023, QC No: jdce-23-87726, **Revised:** 25-Jan-2023, Manuscript No: jdce-23-87726 (R), **Published:** 31-Jan-2023, DOI: 10.4172/jdce.1000177

Citation: Piotr B (2023) Risk and Clinical Treatment of Oxidative Stress in Hypertensive Diseases Pregnancy with Gestational Diabetes Mellitus: A Prospective Cohort Study. J Diabetes Clin Prac 6: 177.

hypertension demonstrated a 40% reduction in the steady-state insulin sensitivity index compared with the control subjects, but no insulin sensitivity index differences were found between control subjects and either of the two other hypertensive groups. In fact, preeclampsia subjects had lower insulin and glucose area under the curve than control subjects, with there being no differences among the other groups. When the four groups were pooled, insulin sensitivity index was negatively associated with triglyceride concentration and insulin area under the curve and persisted after adjustment for percent body fat. These data suggest that insulin resistance, independent of degree of obesity, contributes to transient hypertension identified in late pregnancy. These data, from gravidas already diagnosed with hypertension, suggest that preeclampsia may not result solely from insulin resistance [4].

However, these and other studies of gravidas with established hypertension did not address whether obesity per se or insulin resistance was primarily associated with new-onset hypertension in late pregnancy. Cohort studies, in which metabolic characteristics were measured before the onset of hypertension in pregnancy, have provided more insight into this association. Mid-pregnancy fasting hyperinsulinemia has been associated with subsequent development of preeclampsia alone in African-Americans and with GH alone in a Japanese cohort, both independent of maternal BMI. In contrast, another mixed racial cohort found no association between mid-pregnancy hyperinsulinemia and subsequent gestational hypertension when controlling for BMI and race.

Several other cohort studies of surrogate markers for insulin resistance in early pregnancy suggest that it is insulin resistance that predisposes to new-onset hypertension in pregnancy. A prospective cohort case-control study (10) examined first trimester sex hormone–binding globulin and second trimester glucose challenge test glucose values in 45 patients with preeclampsia and 90 normotensive control subjects. Sex hormone–binding globulin production is inhibited by insulin and thereby serves as evidence of hyperinsulinemia and insulin resistance [5]. Those who later developed preeclampsia had lower sex hormone–binding globulin and higher glucose challenge test values, suggesting an association between early insulin resistance and late pregnancy preeclampsia. Of note, the sex hormone–binding globulin association with preeclampsia reached statistical significance only among women with BMI values <25 kg/m2, suggesting an obesity-related threshold effect.

Further, among nondiabetic gravidas, mid-pregnancy postprandial glycemia has been noted to be positively associated with odds of subsequent gestational hypertension and preeclampsia. A retrospective case-control study of 97 women with new-onset hypertension in late pregnancy and 77 normotensive control gravidas demonstrated that after adjustment of BMI and baseline systolic and diastolic blood pressures, the post–50-g challenge 1-h glucose value at 24–28 weeks was significantly higher among those developing hypertension [6].

Indirect evidence for an association with early-pregnancy insulin resistance and subsequent preeclampsia has been provided in a nested case-control study of 24-h urine insulin excretion in a cohort of nondiabetic singleton pregnancies. Patients with preeclampsia and nonproteinuric gestational hypertension were compared with 429 normotensive control subjects, matched by enrollment site and specimen storage time. The association of 24-h insulin secretion and preeclampsia or gestational hypertension was adjusted for BMI and smoking. Patients with mild preeclampsia, but not those with gestational hypertension, demonstrated increased 24-h insulin secretion. Possible confounding by variable hepatic insulin clearance notwithstanding, the increased 24-h insulin excretion suggests that insulin resistance, not hyperglycemia, characterizes a predisposition to preeclampsia.

Patients with GDM have a high prevalence of insulin resistance and were studied to examine the effect of insulin resistance versus other potential pathogenic factors in the development of preeclampsia. Among 184 gravidas with diagnosed GDM, mid-pregnancy anthropometry, blood pressure, micro albuminuria, fasting lipids, inflammatory and endothelial damage markers, and family disease history were examined in a predictive model for subsequent preeclampsia. Compared with the remaining patients, the 22 who developed preeclampsia demonstrated increased mid-pregnancy BMI, blood pressure, fasting glucose and insulin, urate, CRP, and micro albuminuria and a higher prevalence of family history of hypertension and gestational diabetes. No association of preeclampsia with mid-pregnancy lipid measurements was found [7]. These data suggest that among gravidas with characteristics of the metabolic syndrome, fasting dyslipidemia is not an independent pathogenic factor in the development of preeclampsia.

Subclinical Inflammation, Vascular Dysfunction, and GDM

A case-control study of patients with and without prior GDM demonstrated that post-GDM women had higher mean levels of inflammatory biomarkers and peripheral vascular resistance and decreased stroke volume, measured ~4 years postpartum, compared with those without. Though maternal age and years postpartum were comparable, those with a history of GDM had higher levels of CRP [8], interleukin-6, and plasminogen activator inhibitor. The same subjects also demonstrated increased vascular resistance and decreased stroke volume after adjustment for BMI. These data suggest that the gestational diabetic condition, characterized by inflammatory dysregulation and vascular dysfunction, both independent risks for cardiovascular disease, may predict its later clinical development.

The mechanisms that may link GDM with pregnancy hypertension are only partly examined. Brachial artery post-occlusion flow-mediated vasodilation but not nitrate-dependent vasodilation has been found to be reduced in gravidas with impaired glucose tolerance. Paradisi et al. performed stepwise linear regression analysis of data among 10 gravidas with impaired glucose tolerance, 13 gravidas with GDM and 15 gravidas with normal glucose tolerance and found that glucose area under an oral 3-h glucose tolerance test curve could account for 35%, and fasting free fatty acid levels accounted for 5% of the variance in flow-mediated vasodilation. However, neither BMI nor insulin response to an oral glucose challenge were independently associated with flow-mediated vasodilation. Moreover, moderate weight reduction does not affect the reduced brachial artery flow-mediated vasodilation in women with a history of GDM. These data suggest that, at least macrovascular, endothelial dysfunction may be a response to mildly elevated ambient glucose concentrations but may not reflect insulin resistance [9].

The association between preeclampsia and later hypertension also appears to be partly independent of insulin resistance and β-cell function. In a 15-month cohort study of 150 gravidas with GDM enlisted between 28 and 34 weeks' gestational age, 29 were found to meet criteria for preeclampsia. A thorough characterization of insulin response and glucose disposal was carried out during and after pregnancy, including oral glucose tolerance test glucose levels, insulin sensitivity index, glucose effectiveness, acute response to glucose, disposition index, and euglycemic clamp measures of basal or steady-state levels of glucose, insulin, free fatty acid, hepatic glucose output, peripheral glucose clearance, C-peptide, and glucagon. In the

third trimester and at 15 months after delivery, compared with the remainder of the cohort, those with preeclampsia did not demonstrate greater insulin resistance, but did demonstrate significantly higher blood pressures [10]. Though no subjects in this short follow-up study became clinically hypertensive, this cohort study suggests that new-onset proteinuric hypertension in pregnancy may reflect underlying vascular dysfunction that is independent of insulin resistance or hyperglycemia.

Conclusion

The complexity of the several pathogenic pathways that cause hypertension and vascular disease and the prolonged interval that appears to predate clinical morbidity have hindered inquiry into the association between GDM and vascular disorders. As a former fruste of later type 2 diabetes, GDM-affected gravidas are identified as at risk of diabetes-related atherosclerosis, glomerular disruption, and pathogenic retinal angiogenesis. That GDM is evidence for underlying chronic conditions such as dysregulation of innate immune response that, independent of the diabetic state, produces vascular disease is difficult to assert with the present published literature. Cross-sectional studies of patients with established gestational hypertension or preeclampsia are ambiguous as to the possible pathogenic effect of insulin resistance. Cohort studies initiated in early and mid-pregnancy show evidence that both gestational hypertension and preeclampsia may be more prevalent in gravidas with greater insulin resistance. The association of gestational glucose intolerance with gestational hypertension appears to be independent of obesity and ambient glycemia but explained in part by insulin resistance.

Late pregnancy preeclampsia is associated with elevated mid-pregnancy BMI, blood pressure, fasting glucose and insulin, urate, and C-reactive protein, suggestive of metabolic and immune dysregulation. GDM appears to be associated with overexpressed innate immune response, which, in turn, is associated with vascular dysfunction and vascular disease. Among women with GDM, markers of insulin resistance do not appear to correlate with hypertension in short-term cohort studies. However, when non-GDM subjects are compared with subjects with GDM, post pregnancy studies do show an association of insulin resistance with both inflammatory dysregulation and vascular dysfunction.

Cohort studies that have used population-based pregnancy databases consistently identify a clinically significant association of both gestational hypertension and preeclampsia with later hypertensive disorders. Associations with coronary artery disease or stroke are less consistent, requiring further investigation.

Preventing the evolution of diabetes and lipid and immune dysregulation of the metabolic syndrome has become a salient public health issue because of the epidemic of childhood and early adulthood obesity and the opportunity at hand to treat insulin resistance by behavioral and pharmacological interventions. However, limited available literature highlights the need for long-term cohort studies of women with well-characterized metabolic and vascular profiles during pregnancy and decades later. Our present knowledge suggests that screening for GDM provides an opportunity of pregnancy outcome improvement. Limited studies of diabetes prevention in at-risk patient groups suggest that we may have the opportunity to reduce the risk of later diabetes. Additional investigation is required to determine if interventions that prevent or postpone diabetes also delay the onset of vascular disease.

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