Review

Gestational Diabetes and Hypertensive Disorders of Pregnancy as Vascular Risk Signals: An Overview and Grading of the Evidence

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ABSTRACT

The occurrence of common pregnancy-related medical disorders identifies women at high risk of developing future vascular disease. Systematic reviews of cohort studies demonstrate that gestational diabetes confers a 7-fold risk increase for type 2 diabetes, and pre-eclampsia confers a 1.8-fold risk increase for type 2 diabetes and 3.4-fold risk increase for hypertension. Gestational diabetes and hypertensive disorders of pregnancy (HDP) increase the risk of premature vascular disease, but the 2-fold risk increase associated with pre-eclampsia is only partially explained by the development of traditional vascular risk factors. Despite the compelling evidence for gestational diabetes and HDP as vascular risk indicators, there are no published Canadian vascular prevention guidelines that recognize these postpartum women. In contrast, the 2011 American Heart Association guidelines on cardiovascular disease in women include gestational diabetes and HDP in their vascular risk assessment. Studies indicate that the importance surveillance of vascular risk factors in these women after pregnancy is underappreciated by the women themselves and their physicians. Although a prudent diet and physically active lifestyle were demonstrated to reduce diabetes risk in women with a management strategies for postpartum vascular disease prevention. The objectives of this review are to: (1) outline the epidemiologic associations of pregnancy-related disorders with vascular risk factor and vascular disease development; (2) summarize current explanatory pathophysiologic models; and (3) highlight key knowledge gaps and potential future steps toward vascular risk reduction in these young, high-risk women.

Pregnancy-Related Medical Disorders

Gestational diabetes

Gestational diabetes is “glucose intolerance with onset or first recognition during pregnancy.”2 The development of maternal insulin resistance allows for preferential nourishment of the
HDP

HDP occur in 2%-10% of all pregnancies. HDP represent a disease spectrum ranging in severity from gestational hypertension (new hypertension after 20 weeks’ gestation), to preeclampsia (hypertension with proteinuria > 300 mg in 24 hours), to severe preeclampsia (ie, eclampsia [seizure]; HELLP syndrome [hemolysis, elevated liver enzyme and low platelet levels]). During pregnancy, placental cell invasion into the uterine artery endothelial lining normally stimulates the arteries to become more flaccid to support the high blood flow demands for the developing fetus. In women who develop preeclampsia, however, uterine artery transformation remains incomplete. Although the pathophysiology of preeclampsia is complex and not entirely understood, impaired placentation and ischemia are considered to be the primary mechanisms leading to placental release of soluble factors that in turn provoke systemic endothelial dysfunction and, ultimately, preeclampsia (Fig. 1). Defective trophoblast differentiation might be responsible for defective trophoblast invasion of the spiral arteries. Trophoblasts obtained from women with preeclampsia do not demonstrate the normal upregulation of the expression of adhesion molecule. The placental hypoperfusion, hypoxia, and ischemia that follow lead to an imbalance in angiogenic and antiangiogenic circulating factors. Higher levels of antiangiogenic factors (eg, soluble fms-like tyrosine kinase-1/soluble vascular endothelial growth factor receptor 1) antagonize the angiogenic and vasodilatory effects of vascular endothelial growth factor and placental growth factor. Consequently, the cytotrophoblastic epithelial-to-endothelial transformation fails and the production of adhesion molecules, integrins, and cadherins is reduced, resulting in impaired placentation. Other factors that likely contribute to impaired placentation include greater oxidative stress and generation of reactive oxygen species, enhanced placental expression of components of the renin-angiotensin system, and higher sensitivity to angiotensin II.

Genetic factors might also contribute to the pathogenesis of preeclampsia. Seven genetic variants have been more strongly associated with preeclampsia located within or in proximity to the following 6 genes: angiotensin-converting enzyme, a genetic variant involved in the renin-angiotensin system; cytotoxic T-lymphocyte-associated protein 4, a genetic variant involved in inflammation; factor 2, a variant in coagulation; factor V, 2 variants in coagulation; lipoprotein lipase, a variant involved in lipid metabolism; and serine peptidase inhibitor, which encodes the plasminogen activator inhibitor type 1 protein, a variant in fibrinolysis. Importantly, many of these variants have also been implicated in the development of cardiovascular disease (CVD), suggesting that preeclampsia and CVD share genetic risk factors.

Furthermore, altered immune responses might also be implicated in the pathogenesis of preeclampsia, including excessive or atypical maternal immune response to trophoblasts. This leads to secretion of tumour necrosis factor α, which induces apoptosis of the extravillous cytrophoblast. Moreover, interaction between natural killer cells and extravillous trophoblast cells has been suggested to regulate placental implantation. Increased natural killer cell activity and increased dendritic cell infiltration might be involved in abnormal implantation. It has also been proposed that the human leukocyte antigen (HLA) system plays a role in the protective invasion of the spiral arteries, including reduced levels of HLA-E and HLA-G. Enhanced neutrophil activation and activation of the complement system observed in preeclamptic pregnancies can lead to increased inflammation (production of inflammatory cytokines), promote chemotaxis of inflammatory cells, and generate proteolytic fragments that enhance phagocytosis by neutrophils and monocytes. Trophoblastic debris and microparticles carrying antiangiogenic proteins are exaggerated in preeclampsia and might also have a role in the pathogenesis of preeclampsia.

The different factors implicated in the pathogenesis of preeclampsia lead to endothelial cell injury resulting in increased formation of endothelin and activation of coagulation, decreased production of vasodilators, and altered endothelial permeability. Endothelial dysfunction is ultimately responsible for the clinical signs observed in preeclampsia. As suggested by Powe and colleagues “preeclampsia is a disease that begins in the placenta and ends at the maternal
Maternal systemic vascular effects include vasoconstriction (blocked nitric oxide activation), and coagulopathy resulting in diffuse vascular injury and capillary permeability. Multiorgan system involvement leads to the clinical characteristics (hypertension, headaches, edema) and increased morbidity and mortality for the mother (seizures, pulmonary edema, acute kidney injury) and the fetus (intra-uterine growth restriction, prematurity). Preeclampsia treatment includes delivery of the fetus, antihypertensive pharmacotherapy, supportive management, and magnesium sulphate to prevent seizures (eclampsia). The treatment of gestational hypertension is similar and includes antihypertensive therapy and surveillance for the development of preeclampsia. In the short term, preeclampsia and gestational hypertension generally resolve within 3 months postpartum.

Risk factors

Gestational diabetes and HDP share common risk factors including obesity, nulliparity, advanced maternal age, and multifetal gestations. Gestational diabetes and HDP are inversely associated with socioeconomic status. Non-Europid groups (eg, African, South Asian, Latin American, First Nations, and Inuit) develop gestational diabetes and HDP more frequently. Emerging literature suggests a link between maternal sleep-disordered breathing with HDP and gestational diabetes.

Gestational diabetes, pre-existing diabetes, and previous preeclampsia are additional preeclampsia risk factors. Women with primary placental or fetal chromosomal abnormalities also carry a higher risk for preeclampsia. For example, multiple placentas (seen in multifetal gestations), placental thrombosis, and certain fetal trisomies are associated with elevated levels of antiangiogenic proteins, which are associated with preeclampsia.

The prevalence of many of these risk factors for gestational diabetes and HDP continue to increase over time. Overall, pregnant women today are older and more frequently carry excess weight; this partly explains an increase in incidence of gestational diabetes and HDP. For example, Kaiser Permanente records indicate a doubling of gestational diabetes incidence between 1994 and 2002 alone; and an Australian study reported a 45% increase over a similar time frame. Between 1987 and 2005, American hospital discharge data indicate nearly a doubling in the occurrence of HDP.

Postpartum Period

Elevated risks for type 2 diabetes and chronic hypertension

Gestational diabetes and HDP generally resolve soon after delivery, although women with HDP often require short-term antihypertensive therapy in the immediate postpartum period.
metabolic pregnancies (35.6% vs 16.0%).

In terms of overall vascular disease risk, a large Danish administrative database study reported a >1.5-fold risk increase for vascular disease for individuals with HDP. 49 Furthermore, it has been estimated that compared with women without a history of pregnancy-related complications, the calculated 10-year CVD risk based on the Framingham score is 31% greater with preeclampsia; the odds ratio (OR) for vascular disease among women with preeclampsia was associated with ischemic heart disease with a RR of 2.0 (95% CI, 1.8-2.2) for mild preeclampsia and 5.4 (95% CI, 4.0-7.3) for severe preeclampsia. These findings have been replicated in 2 other meta-analyses. 48,59

Gestational diabetes. In a cross-sectional examination of associations between gestational diabetes and prevalent vascular disease among women with a family history of diabetes, the OR for vascular disease among women with gestational diabetes vs those without was 1.85 (95% CI, 1.21-2.82). Associations varied by ethnicity: 1.62 (95% CI, 0.84-3.12) in European women, 1.27 (95% CI, 0.62-2.61) in African American women, and 2.91 (95% CI, 1.06-8.02) in Latin American women.

A Canadian retrospective population-based cohort study examined the effect of gestational diabetes on incident vascular disease over a median of 11.5 years postpartum. 60 The HR for vascular events (i.e., hospitalization for coronary artery disease or cerebrovascular disease) was 1.71 (95% CI, 1.08-2.69), but was markedly attenuated after adjustment for diabetes (HR, 1.1:95% CI, 0.7-1.9); however, this is most likely because diabetes lies along the causal pathway from gestational diabetes to vascular disease. Similarly, the UK prospective Avon Longitudinal Study of Parents and Children cohort study of 3416 women reported increased 10-year cardiovascular risk in women with gestational diabetes. 58 Finally, carotid intima-media thickness (an early surrogate marker of cardiovascular disease) is increased in women with gestational diabetes compared with control subjects. 61 The existing body of evidence supports the importance of gestational diabetes as an early signal of vascular disease risk.

Pathophysiology of vascular disease in women with pregnancy disorders

Pregnancy clearly identifies groups of women with an underlying predisposition for vascular disease. 65 Some researchers propose that gestational diabetes and HDP might additionally directly cause endothelial dysfunction either through hyperglycemia and insulin resistance (in gestational...
diabetes and preeclampsia) or the development of antiangiogenic factors (in preeclampsia) that damage maternal systemic vascular endothelium, thereby accelerating the process of atherosclerosis. Indeed, Berks and colleagues, through mathematical modelling, determined that the risk of cardiovascular disease in women with preeclampsia was not fully explained by the development of traditional vascular risk factors postpartum. Others have theorized that the antecedents of vascular disease unmasked by pregnancy are present even before conception.

Opportunities for Interventions

Lifestyle changes and vascular risk reduction

Although a recent large randomized controlled trial of intensive lifestyle interventions in overweight individuals with type 2 diabetes did not identify a reduction in cardiovascular risk, several studies have demonstrated such interventions to lower diabetes risk. Based on these studies, particularly the American National Institutes of Health’s Diabetes Prevention Program (DPP), recent guidelines recommend lifestyle modifications as first-line therapies for women at risk of cardiovascular disease. The DPP was conducted among adults with impaired glucose tolerance and/or impaired fasting glucose. The DPP compared diabetes incidence in participants randomized to 3 trial arms: an intensive program of dietary and physical activity counselling, treatment with the antihyperglycemic medication metformin, and usual care. In the lifestyle change arm, 16 sessions were delivered by a case manager over 24 weeks, followed by monthly maintenance sessions. The weight reduction goal was 5%-7% of baseline weight and the physical activity goal was 150 minutes of moderate activity per week. In women with gestational diabetes within the previous 10 years, the intensive lifestyle intervention and metformin therapy led to a 50% reduction in diabetes incidence. The lifestyle intervention approach had many additional benefits compared with metformin: less potential for adverse effects, favourable musculoskeletal health impact, and improved psychological well-being. Similar types of interventions are now advocated for women with a gestational diabetes history with or without persistent postpartum glucose abnormalities.

Acting on the evidence

In recent years there has been recognition of the importance of evaluating “global vascular disease risk.” This consists of identifying the number and severity of vascular risk factors to calculate a risk of cardiovascular events over a time period. The score is used to guide treatment targets for specific vascular risk factors. At present, there are no validated risk prediction models specifically for postpartum women with HDP or gestational diabetes; however, the American Heart Association in its “Effectiveness-Based Guidelines for the Prevention of Cardiovascular Disease in Women—2011 Update,” for the first time—included a history of pregnancy complications (gestational diabetes and HDP) in assessing arterial disease risk in women. The American Heart Association Guidelines suggest implementation of the Class I Lifestyle Recommendations that include smoking cessation, a Dietary Approaches to Stop Hypertension (DASH)-like diet, regular physical activity, and weight management for all women with either gestational diabetes or HDP.

There remain enormous gaps in postpartum management of women with a history of gestational diabetes or HDP. In Canada, rates of postpartum screening of women with gestational diabetes for type 2 diabetes are low at 14% with standard care and 28% with reminders by 6 months postpartum. A Canadian study demonstrated that although approximately 50% of physicians (specialists and generalists) involved in obstetrical care were aware of the increased risk of chronic hypertension in women with preeclampsia, only approximately 10% actually informed the patient of these risks. These gaps in postpartum care represent lost opportunities for chronic disease prevention, detection, and management.

An important contributor to lack of postpartum care might actually be the women’s perceptions of future risk and their health service utilization. Studies have shown that women with gestational diabetes and/or HDP tend to perceive their risk of future vascular disease as low and many lack knowledge regarding the role of lifestyle modifications in decreasing risk. At present, approximately half of women with a gestational diabetes history do not undergo the recommended surveillance for vascular risk factors in the years after delivery. A previous study indicates that although 90% of women with a gestational diabetes history are aware that gestational diabetes is an indicator for future development of type 2 diabetes, fewer than 20% view themselves to be at risk.

There are several psychosocial barriers to lifestyle interventions in the postpartum period. For example, in a Kaiser Permanente database study, women with previous gestational diabetes were 40% more likely to be physically inactive and nearly twice as likely to be obese. Many women cite family-related factors as barriers to achieving higher physical activity levels and to adopting a less energy-dense, more nutritionally-balanced dietary intake. These include lack of time because of family responsibilities, lack of child care support, lack of family support to be physically active, and household taste preferences impeding adoption of healthier dietary choices.

Timing of lifestyle interventions

The optimal timing for implementation of lifestyle programs postpartum has not been established, but is likely to be early postpartum. Intervening within 5 years, rather than 10 years, of a gestational diabetes pregnancy as tested in the American DPP, could capture women when the transition to type 2 diabetes is most likely to occur. Engaging women in DPP style prevention efforts has proven challenging particularly closer in time to the first gestational diabetes pregnancy. One trial enrolled women at 6 weeks after a gestational diabetes diagnosis to test an intervention that included 8 healthy-eating classes; 10 physical activity classes; 6 telephone counselling sessions over 9 months; use of a pedometer and sports stroller; and a notebook with healthy food recipes. Active arm participants attended on average fewer than 4 classes and 3 telephone sessions, which could explain the finding that changes in weight and self-reported physical activity did not differ between arms. In another pilot trial (Diet, Exercise and Breastfeeding Intervention [DEBI]), women were enrolled during their third trimester. The aim was to achieve
preferences of postpartum women at risk

In terms of format of delivery of postpartum lifestyle programs, a recent qualitative study of postpartum women with preeclampsia found that women preferred face-to-face counselling, the use of a multidisciplinary team, and a balance with computerized lifestyle advice.93

For women with a gestational diabetes history, participants’ suggestions from the DEBI pilot trial emphasized the need for support from a social network, specific tips on how to exercise with a newborn, and detailed suggestions on low-fat recipes.92

Our own focus group study94 further underscores the importance of social support for behavioural change. We presented participants with a lifestyle program that we had previously validated in adults with type 2 diabetes95 and asked how it could be adapted to women like themselves. They viewed in-person sessions as a means of creating a peer support group. Family-related issues were of high importance, including a need for direct involvement of partners in the program to achieve buy-in for changes in the home food environment and integrating child care to allow participation in sessions. Time constraints were emphasized as a key barrier. Strategies that proactively address these barriers might ultimately improve adherence to lifestyle intervention programs. The mode of delivery of lifestyle intervention programs also requires further study. Although our focus group participants indicated that internet-based communications were a potentially useful adjunct to face-to-face sessions, a previous qualitative study in women with a gestational diabetes history96 suggested stronger support for an internet-based approach.

Summary

We have summarized the evidence presented herein and graded it using the Oxford Centre for Evidence Based Medicine (www.cebm.net) levels of evidence grading system (Table 1):

1. There is Level 1a evidence demonstrating that gestational diabetes is a risk factor for diabetes (greater than 7-fold risk increase)47 and that HDP is a risk factor for type 2 diabetes (1.8-fold risk increase) and hypertension (3.7-fold risk increase).48
2. There is Level 1b evidence indicating that milder forms of HDP also predict chronic hypertension with a graded risk increase across HDP severity categories.49
3. There is Level 1b evidence indicating that gestational diabetes and HDP have synergistic effects on type 2 diabetes risk.50
4. There is Level 1a evidence that preeclampsia signals a greater than 2-fold risk increase for cardiovascular disease events and mortality.48,55,59
5. There is Level 1b evidence that gestational diabetes is a risk factor for cardiovascular disease (1.7-fold risk increase), largely explained by the development of diabetes.61
6. There is Level 1b evidence that dietary changes and greater physical activity levels halve the risk of diabetes in women with a gestational diabetes history and impaired glucose tolerance.78,83 No large scale trials have specifically examined the effects of lifestyle interventions in women with HDP or preeclampsia alone.

The main purpose of the summary and grading of the existing evidence is to stimulate consideration by established committees and policymakers. The importance of gestational diabetes and HDP as vascular risk factors is underappreciated by women and health care professionals.77 It is apparent that in women with gestational diabetes and/or HDP, regular medical assessments focusing on early detection and treatment of diabetes, hypertension, and vascular disease risk is necessary. The optimal frequency and structure of such assessments remains to be established. Additionally, there is a need for further research to establish the utility of health behaviour change strategies and to optimize the delivery of behavioural change information, support, and skills-building in women with a history of gestational diabetes or HDP. Women indicate a need for a high level of support from health professionals, peers, and family members.77 The increasing incidence of HDP and gestational diabetes and the high vascular risk trajectory that these conditions herald mandate lifelong prioritization and action by women, healthcare providers, and policy makers.

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