**Risks of dysglycemia over the first four years**

**after a hypertensive disorder of pregnancy**

Wen, Chuana, b, Metcalfe, Amy b-g, Anderson, Todda,b, Sigal, Ronald J. a-e, Johnson, Jo-Annf, Carson, Michaelh, Nerenberg, Kara A. b-f\*

a: Department of Cardiac Sciences, University of Calgary, Calgary, Alberta, Canada.

b: Libin Cardiovascular Institute of Alberta, University of Calgary, Alberta, Canada.

c: Department of Medicine, University of Calgary, Calgary, Alberta, Canada.

d: Department of Community Health Sciences, University of Calgary, Calgary, Alberta, Canada.

e: O’Brien Institute for Public Health, University of Calgary, Calgary, Alberta, Canada.

f: Department of Obstetrics & Gynecology, University of Calgary, Calgary, Alberta, Canada.

g: Alberta Children’s Hospital Research Institute, University of Calgary, Calgary, Alberta, Canada.

h: Department of Medicine and Obstetrics & Gynecology Hackensack Meridian School of Medicine at Seton Hall, Neptune NJ. USA

\*Corresponding Author

Kara Nerenberg, MD, MSc, FRCPC

HSC 1410, 3330 Hospital Drive, N.W.

Calgary, AB, T2N 4N1, Canada

Phone: 403.220.6376

Fax: 403.283.6151

Email: kara.nerenberg@ucalgary.ca

**Counts:**

Total Word Count:

Abstract: 250

Text:

Figures: 0

Tables: 4

References: 31

**Keywords:**

Hypertensive disorders of pregnancy, preeclampsia, pregnancy, dygslycemia, type 2 diabetes, screening.

**Key Messages:**

Prior to this study, the association between the hypertensive disorders of pregnancy and future dyglycemias in the first four years postpartum was not known.

This study found that women with the hypertensive disorders of pregnancy have double the odds of developing any dysglycemia (i.e., type 2 diabetes, impaired fasting glucose or impaired glucose tolerance) over the first four years postpartum. Thus, further studies evaluating dysglycemia testing and strategies are needed in this high-risk population of women.

**Abstract**

Background: Women with the hypertensive disorders of pregnancy (HDP) [preeclampsia (PE) and gestational hypertension (GHTN)], have increased risks of future diabetes. Postpartum glycemic testing offers early identification and treatment of dysglycemia, though, evidence-based recommendations for this high-risk population are lacking. The objective of this study was to describe the risk of developing dysglycemia in women with normotensive and hypertensive pregnancies over the first four years postpartum.

Methods: The Discharge Abstract Database was used to identify women who delivered singleton live-born infants in Calgary, Canada, between January 2010-December 2012 (N=27,300). This was linked with Calgary Laboratory Services (for glycemic tests) and the Pharmaceutical Information Network databases (for anti-diabetes medication prescriptions) over the first four years postpartum. Logistic regression analyses compared glycemic testing and results adjusted for maternal age, gestational age, parity and the Pampalon deprivation index.

Results: Women with HDP had more glycemic testing (GHTN: 67.8%, PE: 69.9%, vs. Normotensive: 60.9%; P<0.001) and significantly higher results: fasting plasma glucose (mean ± standard deviation) (GHTN: 4.82±0.51mmol/L, PE: 4.84±0.54mmol/L vs. Normotensive: 4.73±0.49mmol/L; p<0.001);random plasma glucose (GHTN: 5.20±0.96mmol/L, PE: 5.39±1.71mmol/L vs. Normotensive: 5.00±0.87mmol/L; p<0.001); and HbA1C levels (PE: 5.62±0.53% vs. Normotensive:5.49±0.32%; p<0.001). Women with HDP had higher adjusted odds (95% confidence interval) of developing type 2 diabetes compared to normotensive women [GHTN: 2.26 (1.50, 13.4); PE: 2.02 (0.91, 4.46)].

Conclusion: The high prevalence of early dysglycemia highlights the importance of targeted postpartum glycemic testing in women after HDP. Research on optimal glycemic testing (specific tests and timing) in these high-risk women is needed.

**Background**

In Canada, diabetes mellitus (DM), has increased in prevalence from 5.6% to 7.8% between 2003-2004 and 2013-2014 and is predicted to reach 12.1% by 20251. Although in general, male adults have a higher prevalence of DM than females (8.7 % vs. 7.6%), females of reproductive ages (25-39 years) have a higher prevalence than males in same age groups1. In addition, the prevalence of prediabetes [i.e., impaired fasting glucose (IFG), impaired glucose tolerance (IGT) or both IFG and IGT] is estimated to increase to 23.2% of the population by 20252. Given the high prevalence of dysglycemia in Canada, early identification of younger populations at risk of dysglycemia may offer an opportunity for the implementation of public health programs for the prevention of type 2 diabetes.

At present, diabetes risk screening tools such as the CANRISK were not developed in people under the age of 403, 4 and generally underestimate the risk of type 2 DM in women after gestational diabetes (GDM)5. Thus, clinicians who care for younger women lack accurate risk predictions tools and must rely on clinical risk factors to guide screening for dysglycemia6. It is, however, well established that GDM is an independent risk factor for the development of future type 2 DM [relative risk (RR) with 95% confidence interval (CI) 7.4; 4.8-11.5]7, up to 30% have persistent dysglycemia when tested early postpartum8, and that lifestyle programs after GDM can reduce the risk of developing future type 2 DM9. Recently, other pregnancy-related complications including the hypertensive disorders of pregnancy (HDP) [i.e., preeclampsia (PE) and gestational hypertension (GHTN)] have been independently associated with the risk of developing type 2 DM in Canada over a 16.5 year period, ranging from 2 times higher in women with HDP to up to 18.4 times higher risk of type 2 DM in women with a history of both HDP and GDM10. However, a recent systematic review demonstrated inconsistent relationships between HDP and future type 2 diabetes11.

While the relationship between HDP and dysglycemia during pregnancy is supported by the increasing prevalence of both GDM and HDP in Canada12, as well as shared clinical risk factors including obesity, insulin resistance and endothelial dysfunction13-15, the relationship between HDP and postpartum dysglycemia requires further study. This information is important as it may increase the understanding of the mechanisms underlying HDP and GDM as well as their relationships with future cardiovascular diseases (CVD). Both HDP and GDM are sex-specific risk factors for the development of premature CVD, though the exact underlying mechanisms remain unclear16. Some of the increased risk of CVD may be related to the development of traditional cardiovascular risk factors after HDP and GDM (i.e., type 2 DM, dyslipidemia, and hypertension)16. Importantly, another emerging pregnancy risk factor for premature CVD is preterm delivery (<37 weeks’ gestation)17, though to date little is known on the association of preterm birth and future maternal dysglycemia. At present, Canadian clinical practice guidelines recommend lipid screening for women after HDP18 and screening for type 2 diabetes after GDM19 but there are no specific evidence-based recommendations for postpartum dysglycemia screening or testing after HDP and other pregnancy complications19. Thus, this window for the early detection and treatment of dysglycemia in women after HDP and other pregnancy complications may be lost.

Given the burden of HDP and risks of both future dysglycemia and CVD, as a first step in informing population-based postpartum cardiovascular risk factor screening programs, the primary objective of this study was to describe the risks of subsequent dysglycemia at a population level in women with normotensive and hypertensive pregnancies over the first four years after delivery.

**Methods**

*Data sources and linkage*

The Alberta Discharge Abstract Database (DAD) was used to identify women who delivered a singleton live-born infant in hospital [The International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Canada (ICD-10-CA) Z37.0, Z37.1] in Calgary, Alberta between 1 January 2010 and 31 December 2012. Women aged ≥18 years at delivery with no subsequent deliveries in the following four years postpartum were included in the cohort in order to facilitate identification of the indication for glycemic testing (i.e., testing for post-partum detection and not for detection of dysglycemia in a subsequent pregnancy). Due to existing dysglycemia testing recommendations20 women with GDM in the current pregnancy using the DAD ICD-10-CA E-24 codes (which has a sensitivity of 83% and specificity of 98% compared with Alberta lab data)21, as well as women with pre-pregnancy type 1 or 2 DM (ICD-10-CA codes E10-E14; sensitivity of 91.4-91.6%, specificity of 93.9-95.4%), were excluded. For similar reasons, this study excluded women with any of the following pre-pregnancy diagnoses: chronic hypertension, heart disease, and kidney disease22.

The Pharmaceutical Information Network (PIN) provides detailed information regarding medications dispensed from approximately 95% of outpatient community-based pharmacies in the province of Alberta from 2010 forward23. The DAD and PIN were linked to identify women with any prescriptions for anti-diabetes agents (oral drugs, injectable drugs or insulin) dispensed during the first four years after the index delivery.

Calgary Laboratory Services (CLS) provides comprehensive out-patient laboratory services for all of Calgary and the surrounding areas. Data on glucose testing [fasting plasma glucose (FPG), two-hour oral glucose tolerance test (2hPG in a 75g OGTT), random plasma glucose (random PG)] and glycated hemoglobin A1c (HbA1c) were extracted in the four years following the index delivery from CLS. Specifically, the postpartum lab results included the first lab tests after index delivery and excluded glycemic tests measured after the first dispensed prescription of anti-diabetes medications.

*Exposure Definitions:*

*Mild PE and severe PE*

The ICD-10-CA codes obtained from the Discharge Abstract Database at the index delivery were used to define mild PE (O14.0) and severe PE (O14.1) including HELLP (hemolysis, elevated liver enzymes and low platelet) syndrome (O14.2).

Preterm delivery

Preterm delivery was defined as delivery before 37 weeks of gestational age.

The Pampalon deprivation index

The Pampalon deprivation index is a small area-based composite index which uses census data to present socioeconomic disparities in the population. This index was derived from postal code data. The index stratifies the population into five quintiles [1-5, from the least deprived (1) to the most deprived (5)] based on both social and material components24. This index is commonly used in Canadian research to describe socioeconomic status25.

*Outcome Definitions:*

Postpartum dysglycemia (diabetes mellitus and prediabetes)

Women who had either their first prescription dispensed for anti-diabetes medications and/or abnormally high glycemic laboratory values (as per Diabetes Canada’s 2018 Clinical Practice Guidelines below) between 43-1460 days postpartum were classified as having new onset type 2 diabetes. The lower time range of 43 days represents the end of the six-week post-partum period which is generally when the majority of the physiologic changes of pregnancy have normalized, with 1460 days representing 4 years after delivery. The anti-diabetes medications included: metformin, sulfonylureas, meglitinides, biguanides, thiazolidinediones, dipeptidyl-peptidase-4 inhibitors, glucagon-like peptide-1 agonists and insulin.

The abnormal glycemic laboratory results were defined as either two abnormal plasma glucose tests (**FPG ≥7.0 mmol/L, random PG ≥11.1 mmol/L**, and/or **2hPG in a 75 gram OGTT≥11.1 mmol/L)** or one abnormal HbA1c (**≥6.5%**) that met the Canadian diagnostic criteria for type 2 DM20 after 42 days postpartum. Prediabetes status was identified by the first impaired fasting glucose (FPG 6.1-6.9 mmol/L), or impaired glucose tolerance (2hPG in a 75g OGTT 7.8-11.0 mmol/L) or an HbA1c of 6.0-6.4% tested after 42 days postpartum (i.e., 43-1460 days).

*Data analyses*

 Descriptive statistics were used to characterize the study population. Demographic characteristics were compared with one-way analysis of variance (ANOVA) for continuous variables and chi-squared test for categorical variables. For glycemic laboratory tests, frequencies were used to summarize the tests performed and compared with chi-squared test; means with standard deviations (SD) were reported for and compared with one-way ANOVA. Only women with glycemic testing were compared. Logistic regression analysis was used to calculate the odds ratios (OR) and 95% confidence intervals (95%CI) of prespecified determinants of dysglycemias (type 2 DM or prediabetes). Maternal age, gestational age at index delivery, parity, and the Pampalon deprivation index were included as covariates. For all comparisons, the referent was women with normotensive pregnancies and the exposure was women with the hypertensive disorders of pregnancy or preterm delivery.

A sensitivity analysis was performed by both including and excluding metformin to assess the effects of metformin as part of the definition of postpartum type 2 DM, given the broad range of non-diabetes indications for metformin’s prescription in young women, including prediabetes and polycystic ovary syndrome26. Analyses were conducted using Stata IC Version 14 (Stata Corp, College Station, TX, USA). Ethics approval for this study was provided by the Conjoint Health Research Ethics Board at the University of Calgary/Alberta Health Services (REB15-2888).

**Results**

Overall, 43,708 women had an in-hospital delivery with singleton live-born infants during the study period. Among these, 16,182 were excluded due to a subsequent delivery by Dec. 31 2016, 89 women had a second pregnancy with a due date beyond Dec. 31. 2016, and 137 women were excluded for uncertain diagnoses of HDP, GDM or DM in the DAD. Thus, 27,300 women were included in the cohort among whom 1,413 women had GTHN and 329 had PE. The average maternal age was 31 years. There were more nulliparous women in the PE and GHTN groups (57.4% and 50.5% respectively) compared to 34.4% of women with a normotensive pregnancy (p<0.05). About half (48.3%) of the women with PE had a preterm delivery (median gestational age of 35.5 weeks). Other demographic and clinical characteristics are reported in Table 1.

In terms of glycemic testing over the first four years after delivery, as outlined in Table 2, 61.4% of the entire cohort had any type of glycemic testing, including 67.8% of women with GHTN, 69.9% of women with PE and 60.9% of normotensive women (p<0.001). The most common glycemic test was a fasting plasma glucose followed by random plasma glucose, then a HgA1C, with the 75-gram OGTT being the least common test (~1% of all women). As outlined in Table 2, in general, women with any form of HDP had higher glycemic measures than normotensive women. Specifically, women with GHTN and PE had higher FPG levels (GHTN: 4.82±0.51mmol/L; PE: 4.84±0.54mmol/L vs. Norm BP: 4.73±0.49mmol/L; p<0.001) and random PG levels (GHTN: 5.20±0.96mmol/L; PE: 5.39±1.71mmol/L vs. Norm BP: 5.00±0.87mmol/L; p<0.001), and women with PE had a higher HbA1C values (5.62±0.53% vs. Norm BP 5.49±0.32%; p<0.001).

In terms of dysglycemia over the first four years post-delivery, the prevalence of type 2 DM was significantly higher among women with GHTN (2.1%) and PE (2.4%) than women who had a normotensive pregnancy (0.8%, p<0.001, Table 3). The incidence of type 2 DM was 1.97 /1,000 person-years (95%CI 1.72-2.27) in women with normotensive pregnancy versus 5.36 /1,000 person-years (95%CI 3.75-7.67, p<0.0001) and 6.13 /per 1,000 person-years (95%CI 3.07-12.26, p=0.007) in women with GHTN and PE respectively . Women with GHTN had a higher odds of developing type 2 diabetes in the first 4 years after the index delivery than women who had normotensive pregnancy when adjusted for maternal age, gestational age, parity, and socio-economic status at delivery [adjusted odds ratio (aOR) GHTN: 2.26, 95% CI (1.50, 3.41); p<0.001; PE: 2.02, 95% CI (0.91, 4.46); p=0.084]. Women with PE had double the odds of being diagnosed with type 2 DM, but this was not statistically significant due to the small sample size. In addition, more women with PE met the diagnostic criteria for prediabetes (either IFG, IGT or both IFG/IGT) than women with GHTN and normotensive pregnancy after adjustment for maternal age, gestational age, parity, and socioeconomic status at delivery [aOR 2.04 95%CI (1.17, 3.56)].

In the sensitivity analysis, when women with metformin prescriptions were excluded, the total new diagnoses of type 2 DM dropped from 239 to 66. Women with GHTN had a higher odds ratio for developing type 2 DM [aOR: 2.33, 95% CI (1.09, 4.95)], which was similar to the relationship of type 2 DM including metformin prescriptions. This analysis was not performed for women with PE given the small sample size.

As an exploratory analysis, the cohort was stratified by term or preterm delivery (PTD) (i.e., <37 weeks’ gestational age) due to emerging evidence of increased CVD risks in women after PTD (see Table 4)27. Amongst normotensive women with a PTD, the odds ratio of subsequent DM was doubled [aOR 2.03, 95% CI (1.31-3.16)]. No comparison was conducted for PTD amongst women with HDP given the small sample sizes across the subgroups. Finally, glycemic parameters were assessed by PTD status and found that all glycemic values were significantly higher amongst women with PTD. Importantly, the mean (SD) HbA1C was higher among women with PTD: normotensive PTD 5.50 (0.31); mild PE 5.64 (0.29); and severe PE/HELLP 5.79 (1.18) vs. compared with the referent normotensive preterm delivery 5.50 (0.31) (p=0.0024).

**Discussion**

The present study examined the patterns of testing for postpartum dysglycemia as well as the risks and prevalence of newly diagnosed type 2 DM and prediabetes in the first four years after delivery among women with the hypertensive disorders of pregnancy compared with normotensive pregnancies. Overall, 61.5% of the entire cohort had glycemic testing over the first four years after delivery. Postpartum glycemic testing occurred more frequently amongst women with gestational hypertension (67.8%) and preeclampsia (69.9%) compared to women with normotensive pregnancies (60.9%). Further, women with GHTN and PE had double the risk of developing diabetes in the 4-year period post-delivery. In addition, the odds of prediabetes was doubled in women with preeclampsia, and was also higher amongst women with preterm delivery prior to 37 weeks’ gestational age. Finally, while all glycemic tests were higher in women with HDP, most importantly, the postpartum HbA1C was significantly higher (mean 5.62%, SD 0.53) in women with PE compared with women with a normotensive pregnancy (mean 5.49, SD 0.32) (p<0.001).

After a thorough review of the literature, this study is the first report an increased prevalence of subsequent diabetes and prediabetes amongst women with HDP as early as 4 years postpartum. Specifically, Feig *et al*. found an increased prevalence of type 2 DM up to 16.5 years postpartum. The early onset (<4 years after delivery) of dysglycemia amongst women with HDP is an important finding as these women on average would be <40 years old, thus generally not included in dysglycemia screening as part of current Canadian clinical practice guidelines28. Given the increased risk of dysglycemia in the first four years after delivery after HDP (which comprises 7% of all deliveries in Canada29), further research is needed to determine the impacts of earlier glycemic testing and treatment on longer-term dyglycemia and health outcomes in women after HDP.

The early incidence of postpartum dysglycemia after HDP is consistent with the findings of a recent Norwegian study that found that women with HDP had a three times higher risk of being treated with anti-diabetes medication by 3.7 years after delivery30. One key difference is that this study defined diabetes only by prescriptions for anti-diabetes medications, and did not use glycemic laboratory data, which could underestimate the actual prevalence of dysglycemia; whereas our study used a combined definition of both prescriptions for anti-diabetes medications as well as standard laboratory definitions of diabetes to increase the accuracy of the classification of all dysglycemias.

The risks of future diabetes after HDP from our study are consistent with the results of a recent systematic review found that GHTN and PE were independently associated with future DM risk [relative risk (RR) (95% CI), GHTN RR: 2.06 (1.57-2.69); PE: RR 2.25 (1.73-2.90)]. A novel finding from this current study is the increased risk of type 2 DM in women with a preterm delivery (<37 weeks) across the hypertensive states from normotensive to severe HDP. This is important as PTD is not only an emerging risk factor for cardiovascular diseases but it is also highly prevalent in Canada (7.8% of all deliveries in 2013)27,17. Further, women with a normotensive pregnancy with PTD had double the risk of developing type 2 DM in the first four years postpartum even after adjustment for maternal age, parity and the social-economic deprivation level.

Another important clinical finding of this population-based cohort study is the pattern of postpartum glycemic testing. First, there was a high proportion of women with normal pregnancies (i.e., normal blood pressure and no gestational diabetes) tested for postpartum dysglycemia. These women may have had other important clinical risk factors for type 2 DM (e.g., family history of type 2 DM, obesity, etc.) which were missing from the administrative data sources. However, in general, this dysglycemia testing practice does not align with current Canadian clinical practice guidelines considering the young age of this cohort and the fact that women with GDM were excluded from this cohort28. Given the costs associated with doing glycemic testing, this finding may represent an opportunity for interventions targeting healthcare providers from a “Choosing Wisely” perspective.

 Second, when specific glycemic tests were examined, the fasting PG (10077/27300, 36.9%) was the most commonly ordered test for dysglycemia screening across all groups of women followed by random PG (8194/27300, 30.0%) and HbA1C (7009/27300, 25.7%). The OGTT (252/27300, 0.9%) was the least common glycemic test. The pattern of glycemic test utilization is notable as the fasting PG tests is generally less sensitive for type 2 DM diagnosis in young women, given the higher prevalence of postprandial dysglycemia, particularly among young women with polycystic ovarian syndrome26, 31. Thus, many young women may have false negative diabetes results with the use of fasting PG alone. This is further supported by data from our study that demonstrates that the average HbA1C levels were less favorable than the FPG among women with and without HDP, thus the HbA1C may be more sensitive in detecting dysglycemia in this young postpartum population. This observation is supported by previous studies demonstrating that the HbA1C test was more sensitive than FPG among younger individuals32, 33 and females33. However, more studies are needed to compare the diagnostic accuracy of the HbA1c and FPG in reproductive-aged women with detailed information on other clinical risk factors for type 2 DM including ethnicity, obesity and family history of DM.

The strengths of our study include the population-based longitudinal follow-up of all women with deliveries in the Calgary area. Importantly, we excluded women with GDM given that current guidelines recommend postpartum screening for type 2 DM and focused on an understudied population of high-risk women with after the hypertensive disorders of pregnancy19. In addition, the study definition of DM was based upon both laboratory criteria (using Canadian definitions) as well as the prescription of anti-diabetes medications, excluding those with DM during pregnancy and pre-pregnancy to ensure an accurate classification of newly diagnosed postpartum DM.

These strengths, however, must be taken into context based upon the limitations of the study’s design. First, the administrative data sets did not include other clinical risk factors for type 2 DM including family history of diabetes or CVD, ethnicity and measures of obesity. Thus, we were unable to account for these risk factors in the analytic models. Second, type 2 DM was, in part, defined by prescriptions for anti-diabetes medication, with the majority (72.4%) of prescriptions being for metformin. While metformin is the first-line glucose-lowering medication for type 2 DM, in young women, metformin is often used for its nonglycemic effects across a broad spectrum of other diseases including polycystic ovary syndrome34 and the PIN administrative data lacked detail on the specific indication for metformin prescription. However, the sensitivity analysis found no difference in the primary association of new postpartum type 2 DM when metformin was excluded.

Another possible limitation to consider is detection bias, whereby women with HDP receive more postpartum dysglycemia testing due to higher risks of future dyglycemia given the recent Canadian evidence demonstrating this association 35. This is unlikely to have impacted the study results as our study cohort was assembled prior to the publication of this Canadian data. Further, this study found comparable numbers of women tested for postpartum dysglycemia in women with normal blood pressure and those with a HDP. Finally, due to low numbers of women with HDP who developed postpartum dysglycemias, we were unable to explore additional statistical testing to describe the patterns of postpartum dysglycemias, including survival analyses which limits the study’s ability to distinguish early postpartum dysglycemias which may represent pre-pregnancy dysglycemia35.

**Conclusion**

This population-based cohort study found that women with a history of the hypertensive disorders of pregnancy (gestational hypertension and preeclampsia) as well as women with preterm delivery, had approximately doubled the risk of developing newly diagnosed type 2 DM over the first four years postpartum. However, current postpartum glycemic testing in Calgary was high and did not target the women at highest risk of dysglycemia. While these findings highlight the importance of early targeted postpartum glycemic testing for dysglycemia, they also demonstrate a compelling need for further research on the optimal testing (specific test) in these high-risk postpartum women.

Funding: No sources of funding were received for this study. Dr. K. Nerenberg acknowledges the support of a Heart and Stroke (HSF) Alberta New Investigator Award as well as CIHR and HSF for the Women’s Heart and Brain Health Mid-Career Research Chair. Dr. A. Metcalfe acknowledges a CIHR New Investigator Award. Dr. T. Anderson holds the Merck Chair for Cardiovascular research.

References:

1. Public Health Agency of Canada. Diabetes in Canada: Highlights from the Canadian chronic disease surveillance system, <https://www.canada.ca/en/public-health/services/publications/diseases-conditions/diabetes-canada-highlights-chronic-disease-surveillance-system.html>; 2017 [accessed 19.02.28].

2. Diabetes Canada. Diabetes statistics in Canada, <https://www.diabetes.ca/how-you-can-help/advocate/why-federal-leadership-is-essential/diabetes-statistics-in-canada>; 2019 [accessed 19.02.28].

3. Robinson C, Agarwal G and Nerenberg KA. Validating the CANRISK prognostic model for assessing diabetes risk in Canada's multi-ethnic population. *Chronic Disease and Injury in Canada*. 2011;32:19-31.

4. Kaczorowoski J, Robinson C and Nerenberg K. Development of the CANRISK questionnaire to screen for prediabetes and undiagnosed type 2 diabetes. *Cdn J Diabetes*. 2009;33:318-385.

5. Chaudhry SN, Doyle M-A, Nerenberg KA, et al. The usefulness of the Canadian Diabetes Risk Assessment Questionnaire (CANRISK) in predicting dysglycemia in women with histories of gestational diabetes. *Canadian Journal Of Diabetes*. 2015;39:491-495.

6. Ekelund M, Shaat N, Almgren P, et al. Prediction of postpartum diabetes in women with gestational diabetes mellitus. *Diabetologia*. 2010;53:452-7. doi: 10.1007/s00125-009-1621-3. Epub 2009 Dec 2.

7. Bellamy L, Casas J-P, Hingorani AD, et al. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. *Lancet*. 2009;373:1773-1779.

8. Carson MP, Frank MI and Keely E. Original research: postpartum testing rates among women with a history of gestational diabetes--systematic review. *Primary care diabetes*. 2013;7:177-86.

9. Wendland EM, Hilgert JB, Duncan BB, et al. Interventions for the prevention of type 2 diabetes mellitus in women wtih previous gestational diabetes. *Cochrane Database of Systematic Reviews - Intervention Protocol*. 2011.

10. Feig DS, Shah BR, Lipscombe LL, Wu CF, Ray JG, Lowe J, Hwee J and Booth GL. Preeclampsia as a risk factor for diabetes: a population-based cohort study. *PLoS Med*. 2013;10:e1001425-.

11. Wang Z, Wang Z, Wang L, et al. Hypertensive disorders during pregnancy and risk of type 2 diabetes in later life: a systematic review and meta-analysis. *Endocrine*. 2017;55:809-821.

12. Nerenberg KA, Johnson JA, Leung B, et al. Risks of gestational diabetes and preeclampsia over the last decade in a cohort of Alberta women. *JOGC*. 2013;35:986-994.

13. Yogev Y, Langer O, Brustman L, et al. Pre-eclampsia and gestational diabetes mellitus: does a correlation exist early in pregnancy? *The Journal of Maternal-Fetal and Neonatal Medicine*. 2004;15:39-43.

14. Wen SW, Xie RH, Tan H, et al. Preeclampsia and gestational diabetes mellitus: Pre-conception origins? *Med Hypotheses*. 2012;79:120-5. Epub 2012 Apr 26.

15. Yogev Y, Xenakis EM, et al. The association between preeclampsia and the severity of gestational diabetes: The impact of glycemic control. *Am J Obstet Gynecol*. 2004;191:1655-1660.

16. Coutinho T, Lamai O and Nerenberg KA. Hypertensive disorder of pregnancy and cardiovascular diseases: Current knowledge and future directions. . *Current Treatment Options in Cardiovascular Medicine*. 2018;7:doi: 10.1007/s11936-018-0653-8.

17. Kessous R, Shoham-Vardi I, Pariente G, et al. An association between preterm delivery and long-term maternal cardiovascular morbidity. *American journal of obstetrics and gynecology*. 2013;209:368.e1-8.

18. Anderson TJ, Grégoire J, Pearson GJ, et al. 2016 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. *Canadian Journal of Cardiology*. 2016.

19. Feig DS, Berger H, Donovan L, et al. Diabetes and Pregnancy. *Canadian journal of diabetes*. 2018;42 Suppl 1:S255-s282.

20. Committee DCCPGE. Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. *Can J Diabetes*. 2018;42(Supple):S1-S325.

21. Bowker SL, Savu A, Donovan LE, et al. Validation of administrative and clinical case definitions for gestational diabetes mellitus against laboratory results. *Diabetic medicine : a journal of the British Diabetic Association*. 2017;34:781-785.

22. Nerenberg KA, Zarnke KB, Leung AA, et al. Hypertension Canada's 2018 Guidelines for Diagnosis, Risk Assessment, Prevention, and Treatment of Hypertension in Adults and Children. *Can J Cardiol*. 2018;34:506-525.

23. Consortium AR. *Alberta health data asset directory*; 2018.

24. Pampalon R, Hamel D, Gamache P, et al. A deprivation index for health planning in Canada. *Chronic diseases in Canada*. 2009;29:178-91.

25. Chan E, Serrano J, Chen L, et al. Development of a Canadian socioeconomic status index for the study of health outcomes related to environmental pollution. *BMC public health*. 2015;15:714.

26. Jeanes YM and Reeves S. Metabolic consequences of obesity and insulin resistance in polycystic ovary syndrome: diagnostic and methodological challenges. *Nutrition research reviews*. 2017;30:97-105.

27. Grandi SM, Filion KB, Yoon S, et al. Cardiovascular Disease-Related Morbidity and Mortality in Women With a History of Pregnancy Complications. *Circulation*. 2019;139:1069-1079.

28. Booth G and Cheng AY. Canadian Diabetes Association 2013 clinical practice guidelines for the prevention and management of diabetes in Canada. Methods. *Canadian journal of diabetes*. 2013;37 Suppl 1:S4-7.

29. Ray JG, Vermeulen MJ, Schull MJ, et al. Cardiovascular health after maternal placental syndromes (CHAMPS): population-based retrospective cohort study. *Lancet*. 2005;366:1797-803.

30. Engeland A, Bjorge T, Daltveit AK, et al. Risk of diabetes after gestational diabetes and preeclampsia. A registry-based study of 230,000 women in Norway. *European journal of epidemiology*. 2011;26:157-63.

31. Dhesi AS, Murtough KL, Lim JK, et al. Metabolic screening in patients with polycystic ovary syndrome is largely underutilized among obstetrician-gynecologists. *American journal of obstetrics and gynecology*. 2016;215:579.e1-579.e5.

32. Carson AP, Reynolds K, Fonseca VA, et al. Comparison of A1C and fasting glucose criteria to diagnose diabetes among U.S. adults. *Diabetes care*. 2010;33:95-7.

33. Rosella LC, Lebenbaum M, Fitzpatrick T, et al. Prevalence of Prediabetes and Undiagnosed Diabetes in Canada (2007-2011) According to Fasting Plasma Glucose and HbA1c Screening Criteria. *Diabetes care*. 2015;38:1299-305.

34. Fujita Y and Inagaki N. Metformin: New Preparations and Nonglycemic Benefits. *Current diabetes reports*. 2017;17:5.

35. Feig DS, Zinman B, Wang X, et al. Risk of development of diabetes mellitus after diagnosis of gestational diabetes. *Cmaj*. 2008;179:229-34.

Table 1. Demographic characteristics of pregnant women in Calgary delivering between 2010-2012.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Normal BPN = 25,558  | GHTNN =1,413 | PEN = 329 | p-value |
| Norm vs. GHTN | Norm vs. PE | GHTN vs. PE |
| Maternal age (years), Mean ± SD | 31.0 ± 5.3 | 31.5 ± 5.7 | 31.3 ± 5.8 | <0.001 | 0.6403 | 0.3261 |
| Gestational age (weeks), median (Q1, Q3) | 38.9 (38, 40) | 38.1 (37, 39) | 35.5 (34, 38) | <0.001 | <0.001 | <0.001 |
| Preterm delivery (<37 weeks) n (%) | 1617 (6.3) | 161 (11.4) | 159 (48.3) | 0.311 | <0.001 | <0.001 |
| Parity n (%) 0 n (%) | 8807 (34.4) | 713 (50.5) | 189 (57.4) | <0.001 | <0.001 | 0.022 |
|  1 n (%) | 10994 (43.0) | 456 (32.3) | 89 (27.1) | <0.001 | <0.001 | 0.066 |
| 2 n (%) | 4001(15.71) | 176 (12.5) | 32 (9.7) | 0.001 | 0.003 | 0.169 |
| ≥3 n (%) | 1750 (6.8) | 68 (4.8) | 19 (5.8) | 0.003 | 0.443 | 0.470 |
| Pampalon index 1ζ, n (%)  | 5344 (21.8) | 256 (19.0) | 59 (18.9) | 0.012 | 0.187 | 0.938 |
| 2, n (%) | 5788 (23.6) | 308 (24.2) | 75 (22.8) | 0.474 | 0.938 | 0.694 |
| 3, n (%) | 4640 (18.9) | 264 (16.8) | 52 (19.5) | 0.616 | 0.272 | 0.222 |
| 4, n (%) | 3455 (14.1) | 223 (15.8) | 49 (16.5) | 0.016 | 0.496 | 0.689 |
| 5ξ, n (%) | 5318 (21.7) | 302 (24.2) | 75 (22.3) | 0.61 | 0.377 | 0.572 |

Legend: Normal BP: normal blood pressure during pregnancy; GHTN: gestational hypertension; PE: preeclampsia.

n: number; SD: standard deviation.

ζ: the least deprived; ξ: the most deprived in the Pamaplon deprivation index.

Table 2. Postpartum glycemic laboratory tests by hypertensive state.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Any glycemictest | Fasting PG  | Random PG  | 2 h OGTT  | HbA1C |
|  | (n, %) | (n, %) | (mean±SD, mmol/L) | (n, %) | (mean±SD, mmol/L) | (n, %) | (mean±SD, mmol/L) | (n, %) | (mean±SD, %) |
| Normal BP  | 15596(60.9) | 10077(39.4) | 4.73±0.49 | 8194(32.1) | 5.00±0.87 | 252(1.0) | 5.90±1.80 | 7009(27.4) | 5.49±0.32 |
| GHTN | 959(67.8)\* | 641(45.4)\*\* | 4.82±0.51\* | 520(36.8)\*\* | 5.20±0.96\*\* | 14(1.0) | 6.29±1.40 | 449(31.8)\*\* | 5.51±0.32 |
| PE | 230(69.9)\*\* | 147(44.7) | 4.84±0.54\*\* | 134(40.7)\* | 5.39±1.71\*\* | 5(1.5) | 6.82±1.52 | 118(35.7)\* | 5.62±0.53\*\*# |
|  Mild PE | 169(70.4) | 105(43.8) | 4.82±0.55 | 101(42.1)\* | 5.25±0.93\* | <5 | \_ | 74(30.8) | 5.64±0.27\*\*# |
| Severe PE/HELLP | 27(71.1) | 21(55.3)\* | 4.88±0.4 | 14(36.8) | 6.67±4.57\*\* | <5 | \_ | 21(55.3)\*\* | 5.73±1.11\*# |

Legend: PG: plasma glucose; 2 h OGTT: two-hour oral glucose tolerance test (75 grams), HbA1C: hemoglobin A1C.

Normal BP: normal blood pressure during pregnancy; GHTN: gestational hypertension; PE: preeclampsia. HELLP: hemolysis, elevated liver enzymes and low platelet syndrome; n: number; SD: standard deviation.

\*: p value >0.05, \*\*: p value <0.001 compared with the normotensive pregnancy;

 #: p value <0.05 compared between preeclampsia and gestational hypertension.

Table 3: Risks of newly diagnosed diabetes and prediabetes among hypertensive disorders of pregnancy subtypes and normotensive pregnancy 4 years after index delivery.

|  |  |  |  |
| --- | --- | --- | --- |
|  | N | Type 2 DM (after 42days postpartum) | Prediabetes (after 42days postpartum) |
|  | n (%)  | Crude odds ratio (95% CI) | Adjusted odds ratioa (95%CI)  | n (%)  | Crude odds ratio (95% CI) | Adjusted odds ratioa (95%CI)  |
| Normal BP | 25,558 | 201(0.8) | Reference | Reference | 473 (1.9) | Reference | Reference |
| GHTN | 1,413 | 30 (2.1) | 2.74 (1.86, 4.03)\*\* | 2.26 (1.50, 3.41)\*\* | 35 (2.5) | 1.35 (0.95, 1.91) | 1.21 (0.85, 1.74) |
| PE | 329 | 8 (2.4) | 3.14 (1.54, 6.43)\* | 2.02 (0.91, 4.46) | 16 (4.9) | 2.71 (1.63, 4.52)\* | 2.04(1.17, 3.56)\* |

a: Adjusted for maternal age, gestation age at delivery, parity and the Pampalon deprivation index.

Legend: DM: diabetes mellitus; Normal BP: normal blood pressure during pregnancy; GHTN: gestational hypertension; PE: preeclampsia; n: number; CI: confidence interval.

\*: p value <0.05, \*\*: p value <0.001 compared with normotensive pregnancy.

Table 4. Risks of newly diagnosed diabetes by preterm birth status among hypertensive disorders of pregnancy subtypes and normotensive pregnancy 4 years after index delivery.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | N | New onset Type 2 DM n (%) | Crude odds ratio(95% CI) | p-value | Adjusted odds ratio (95%CI) | p-value |
| Normal BP term | 23,932 | 178 (0.7) | Reference | - | Reference | - |
| Normal BP preterm | 1,626 | 23 (1.4) | 1.91 (1.24, 2.97) | 0.004 | 2.03 (1.31, 3.16) | 0.002 |
| GHTN term | 1,252 | 30 (2.4) | 3.28 (2.22, 4.84) | <0.001 | 2.85 (1.89, 4.31) | <0.001 |
| GHTN preterm | 161 | <5 | NA | NA | NA | NA |
| PE term | 170 | 5 (2.9) | 4.04 (1.64, 9.96) | 0.002 | 3.80 (1.52, 9.41) | 0.004 |
| PE preterm | 159 | <5 | NA | NA | NA | NA |

Adjusted for maternal age at delivery, parity and the Pampalon deprivation index.

Legend: DM: diabetes mellitus; Normal BP: normal blood pressure during pregnancy; GHTN: gestational hypertension; PE: preeclampsia; n: number; CI: confidence interval; NA; not applicable.