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Original Research

Risks of Dysglycemia Over the First 4 Years After a Hypertensive Disorder of Pregnancy

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Key Messages

- Prior to this study, the association between the hypertensive disorders of pregnancy and future dyglycemias in the first 4 years postpartum was not known.
- Women with the hypertensive disorders of pregnancy have double the odds of developing any dysglycemia over the first 4 years postpartum.
- Further studies evaluating dysglycemia testing strategies are needed in this high-risk population of women.

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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, but evidence-based recommendations for this high-risk population are lacking. The objective of this study was to describe the risks of developing dysglycemia in women with normotensive and hypertensive pregnancies over the first 4 years postpartum.

Methods: The Discharge Abstract Database was used to identify women who delivered singleton live-born infants in Calgary, Alberta, Canada, between January 2010 and December 2012 (N=27,300). This was linked with Calgary Laboratory Services (for glycemic tests) and the Pharmaceutical Information Network databases (for antidiabetes medication prescriptions) over the first 4 years postpartum. Logistic regression analyses compared glycemic testing and results were adjusted for maternal age, gestational age, parity and the Pampalon deprivation index.

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

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

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R É S U M É

Introduction : Les femmes ayant des troubles hypertensifs de la grossesse (THG) (prééclampsie [PÉ] et hypertension artérielle gravidique [HTAG]) ont des risques accrus de diabète dans le futur. L'analyse de la glycémie en postpartum permet le dépistage et le traitement précoces de la dysglycémie, mais il manque de recommandations fondées sur des données probantes pour cette population exposée à un risque élevé. L'objectif de la présente étude était de décrire les risques de dysglycémie chez les femmes enceintes normotendues et hypertendues au cours des 4 premières années du postpartum.
Méthodes : La Base de données sur les congés des patients a été utilisée pour trouver les femmes qui avaient accouché d'un nouveau-né vivant issu d'une grossesse simple à Calgary, en Alberta, au Canada, entre janvier 2010 et décembre 2012 (N = 27 300). Ces données ont été liées aux Calgary Laboratory Services (pour des analyses de la glycémie) et aux bases de données du Pharmaceutical Information Network (pour les ordonnances de médicaments antidiabétiques) au cours des 4 premières années du postpartum. Les analyses de régression logistique ont permis de comparer les analyses de la glycémie et les résultats ajustés selon l'âge de la mère, l'âge gestationnel, la parité et l'indice de défavorisation de Pampalon.
Résultats : Les femmes ayant des THG avaient subi plus d'analyses de la glycémie (HTAG 67,8 % et PÉ 69,9 % *vs* normotendues 60,9 %; p < 0,001) et avaient des résultats significativement plus élevés de la glycémie plasmatique à jeun (HTAG 4,82 ± 0,51 mmol/l et PÉ 4,84 ± 0,54 mmol/l *vs* normotendues 4,73 ± 0,49 mmol/l; p < 0,001), de la glycémie plasmatique aléatoire (HTAG 5,20 ± 0,96 mmol/l et PÉ 5,39 ± 1,71 mmol/l *vs* normotendues 5,00 ± 0,87 mmol/l; p < 0,001) et des concentrations de l'hémoglobine glyquée (PÉ 5,62 ± 0,53 % *vs* normotendues 5,49 ± 0,32 %; p < 0,001). Les femmes ayant des THG montraient des probabilités ajustées plus élevées (intervalle de confiance à 95 %) de diabète de type 2 par rapport aux femmes normotendues (HTAG: 2,26, de 1,50 à 13,4; PÉ: 2,02, de 0,91 à 4,46).
Conclusions : La forte prévalence de dysglycémie précoce montre l'importance des analyses ciblées de la glycémie en postpartum chez les femmes qui avaient eu des THG. D'autres recherches sur les analyses de la glycémie optimale (analyses et périodes précises) chez ces femmes exposées à un risque élevé sont nécessaires.

Introduction

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 2025 (1). Although, in general, male adults have a higher prevalence of DM than females (8.7% vs 7.6%), females of reproductive age (25 to 39 years) have a higher prevalence than males in the same age groups (1). 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 2025 (2). 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 Canadian Diabetes Risk Assessment Questionnaire, have not been developed for people under 40 years of age (3,4) 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 dysglycemia (6). It is, however, well established that GDM is an independent risk factor for the development of future type 2 DM (relative risk [RR] 7.4, 95% confidence interval [CI] 4.8 to 11.5) (7), as up to 30% have persistent dysglycemia when tested early postpartum (8), and that lifestyle programs after GDM can reduce the risk of developing future type 2 DM (9). 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 GDM (10). However, a recent systematic review demonstrated inconsistent relationships between HDP and future type 2 diabetes (11).

Although the relationship between HDP and dysglycemia during pregnancy is supported by the increasing prevalence of both GDM and HDP in Canada (12), as well as shared clinical risk factors such as obesity, insulin resistance and endothelial dysfunction (13–15), 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 (CVDs). Both HDP and GDM are sex-specific risk factors for the development of premature CVD, although the exact underlying mechanisms remain unclear (16). 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), although, to date, little is known about the association of preterm birth and future maternal dysglycemia. At present, Canadian clinical practice guidelines recommend lipid screening for women after HDP (18) and screening for type 2 diabetes after GDM (19), but there are no specific evidence-based recommendations for postpartum dysglycemia screening or testing after HDP and other pregnancy complications (19). 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 4 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 (*International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Canada* [ICD-10-CA] codes Z37.0, Z37.1) in Calgary, Alberta, between January 1, 2010 and December 31, 2012. Women ≥18 years of age at delivery, with no subsequent deliveries in the following 4 years postpartum, were included in the cohort to facilitate identification of the indication for glycemic testing (i.e. testing for postpartum detection and not for detection of dysglycemia in a subsequent pregnancy). Due to existing dysglycemia testing recommendations (20) 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 prepregnancy type 1 or 2 DM (ICD-10-CA codes E10-E14; sensitivity of 91.4% to 91.6%, specificity of 93.9% to 95.4%), were excluded. For similar reasons, our study excluded women with any of the following prepregnancy diagnoses: chronic hypertension, heart disease and kidney disease (22).

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 forward (23). The DAD and PIN were linked to identify women with any prescriptions for antidiabetes agents (oral drugs, injectable drugs or insulin) dispensed during the first 4 years after the index delivery.

Calgary Laboratory Services provides comprehensive outpatient laboratory services for all of Calgary and the surrounding areas. Data on glucose testing (fasting plasma glucose [FPG], 2-hour oral glucose tolerance test [2hPG] in a 75-g oral glucose tolerance test [OGTT], random plasma glucose [random PG] and glycated hemoglobin [A1C]) were extracted in the 4 years after the index delivery from Calgary Laboratory Services. Specifically, the postpartum lab results included the first lab tests after index delivery and excluded glycemic tests measured after the first dispensed prescription of antidiabetes medications.

Exposure definitions

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

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

Pampalon deprivation index: The Pampalon deprivation index is a small area-based composite index that uses census data to present socioeconomic disparities in the population. This index was derived from postal code data. The index stratifies the population into 5 quintiles (1 to 5, from the least deprived [1] to the most deprived [5]) based on both social and material components (24). This index is commonly used in Canadian research to describe socioeconomic status (25).

Outcome definitions

Postpartum dysglycemia (diabetes mellitus and prediabetes): Women who had either their first prescription dispensed for antidiabetes medications and/or abnormally high glycemic laboratory values (as per Diabetes Canada's 2018 Clinical Practice Guidelines, described in what follows) between 43 and 1,460 days postpartum were classified as having new-onset type 2 diabetes. The lower time range of 43 days represents the end of the 6-week postpartum period, which is generally when the majority of the physiologic changes of pregnancy have normalized, with 1,460 days representing 4 years after delivery. The antidiabetes medications included metformin, sulfonylureas, meglitinides, biguanides, thiazolidinediones, dipeptidylpeptidase-4 inhibitors, glucagon-like peptide-1 agonists and insulin.

The abnormal glycemic laboratory results were defined as either 2 abnormal plasma glucose tests (FPG ≥7.0 mmol/L, random PG ≥11.1 mmol/L and/or 2hPG in a 75-g OGTT ≥11.1 mmol/L) or 1 abnormal A1C (≥6.5%) that met the Canadian diagnostic criteria for type 2 DM (20) after 42 days postpartum. Prediabetes status was identified by the first impaired fasting glucose (FPG 6.1 to 6.9 mmol/L), or impaired glucose tolerance (2hPG in a 75-g OGTT 7.8 to 11.0 mmol/L) or an A1C of 6.0% to 6.4% tested after 42 days postpartum (i.e. 43 to 1,460 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-square test for categorical variables. For glycemic laboratory tests, frequencies were used to summarize the tests performed and compared with chi-square test; means with standard deviations (SDs) 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 (ORs) and 95% confidence intervals (CIs) 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 nondiabetes indications for metformin's prescription in young women, including prediabetes and polycystic ovary syndrome (26). Analyses were conducted using Stata IC version 14 (StataCorp, College Station, Texas, United States). 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 December 31, 2016; 89 women had a second pregnancy with a due date after December 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 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 with 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 4 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 an A1C, with the 75-g OGTT being

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

	Normal BP (n=25,558)	GHTN (n=1,413)	PE (n=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 (%)]	1,617 (6.3)	161 (11.4)	159 (48.3)	0.311	<0.001	<0.001
Parity [n (%)]						
0	8,807 (34.4)	713 (50.5)	189 (57.4)	<0.001	<0.001	0.022
1	10,994 (43.0)	456 (32.3)	89 (27.1)	<0.001	<0.001	0.066
2	4,001 (15.71)	176 (12.5)	32 (9.7)	0.001	0.003	0.169
≥3	1,750 (6.8)	68 (4.8)	19 (5.8)	0.003	0.443	0.470
Pampalon index [n (%)]						
1*	5,344 (21.8)	256 (19.0)	59 (18.9)	0.012	0.187	0.938
2	5,788 (23.6)	308 (24.2)	75 (22.8)	0.474	0.938	0.694
3	4,640 (18.9)	264 (16.8)	52 (19.5)	0.616	0.272	0.222
4	3,455 (14.1)	223 (15.8)	49 (16.5)	0.016	0.496	0.689
5†	5,318 (21.7)	302 (24.2)	75 (22.3)	0.61	0.377	0.572

BP, blood pressure; *GHTN*, gestational hypertension; *PE*, preeclampsia; *Q*, quartile; *SD*, standard deviation.
* The least deprived in the Pamaplon deprivation index.
† The most deprived in the Pamaplon deprivation index.

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±0.51 mmol/L and PE 4.84±0.54 mmol/L vs normal BP 4.73±0.49 mmol/L; p<0.001) and random PG levels (GHTN 5.20±0.96 mmol/L and PE 5.39±1.71 mmol/L vs normal BP 5.00±0.87 mmol/L; p<0.001), and women with PE had higher A1C values (5.62±0.53% vs normal BP 5.49±0.32%; p<0.001).

In terms of dysglycemia over the first 4 years postdelivery, 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 per 1,000 person years (95% CI 1.72 to 2.27) in women with normotensive pregnancy vs 5.36 per 1,000 person years (95% CI 3.75 to 7.67; p<0.0001) and 6.13 per 1,000 person years (95% CI 3.07 to 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 socioeconomic status at delivery (GHTN: adjusted odds ratio [aOR] 2.26, 95% CI 1.50 to 3.41; p<0.001; PE: aOR 2.02, 95% CI 0.91 to 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 to 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 aOR for developing type 2 DM (aOR 2.33, 95% CI 1.09 to 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 (Table 4) (27). Amongst normotensive women with a PTD, the OR of subsequent DM was doubled (aOR 2.03, 95% CI 1.31 to 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 it was found that all glycemic values were significantly higher amongst women with PTD. Importantly, mean A1C was higher among women with PTD: normotensive PTD, 5.50 (SD 0.31); mild PE, 5.64 (SD 0.29); and severe PE/hemolysis, elevated liver enzymes and low-platelet syndrome, 5.79 (SD 1.18), as compared with the referent normotensive preterm delivery, 5.50 (SD 0.31) (p=0.0024).

Discussion

In this study we have examined the patterns of testing for postpartum dysglycemia as well as the risks and prevalence of

Table 2
Postpartum glycemic laboratory tests by hypertensive state

	Any glycemic test [n (%)]	Fasting PG		Random PG		2-h OGTT		A1C	
		n (%)	Mean ± SD (mmol/L)	n (%)	Mean ± SD (mmol/L)	n (%)	Mean ± SD (mmol/L)	n (%)	Mean ± SD (%)
Normal BP during pregnancy	15,596 (60.9)	10,077 (39.4)	4.73±0.49	8,194 (32.1)	5.00±0.87	252 (1.0)	5.90±1.80	7,009 (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*,‡

2-h OGTT, 2-hour oral glucose tolerance test (75 g); *A1C*, glycated hemoglobin; *BP*, blood pressure during pregnancy; *GHTN*, gestational hypertension; *HELLP*, hemolysis, elevated liver enzymes and low platelet syndrome; *OGTT*, oral glocose tolerance test; *PE*, preeclampsia; *PG*, plasma glucose; *SD*, standard deviation.
* p>0.05.
† p<0.001 vs normotensive pregnancy.
‡ p<0.05 vs 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 (total)	Type 2 DM (after 42 days postpartum)			Prediabetes (after 42 days postpartum)		
		n (%)	Crude OR (95% CI)	Adjusted OR* (95% CI)	n (%)	Crude OR (95% CI)	Adjusted OR* (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)†

BP, blood pressure; *CI*, confidence interval; *DM*, diabetes mellitus; *GHTN*, gestational hypertension; *NA*, not applicable; *OR*, odds ratio; *PE*, preeclampsia.
* Adjusted for maternal age, gestation age at delivery, parity and the Pampalon deprivation index.
† $p<0.05$ vs normotensive pregnancy.
‡ $p<0.001$ vs normotensive pregnancy.

newly diagnosed type 2 DM and prediabetes in the first 4 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 4 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 postdelivery. 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, although all glycemic tests were higher in women with HDP, most importantly, the postpartum A1C was significantly higher (mean 5.62%, SD 0.53) in women with PE compared to 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 of 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 guidelines (28). Given the increased risk of dysglycemia in the first 4 years after delivery after HDP (which comprises 7% of all deliveries in Canada) (29), 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 findings from a recent Norwegian study showing that women with HDP had a 3-fold higher risk of being treated with antidiabetes medication by 3.7 years after delivery (30). One key difference is that that study defined diabetes only by prescriptions for antidiabetes 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 antidiabetes 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, which found that GHTN and PE were independently associated with future DM relative risk (RR) (GHTN: RR 2.06, 95% CI 1.57 to 2.69; PE: RR 2.25, 95% CI 1.73 to 2.90). A novel finding from our 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 CVDs, but it is also highly prevalent in Canada (7.8% of all deliveries in 2013) (17,27). Furthermore, women with a normotensive pregnancy with PTD had double the risk of developing type 2 DM in the first 4 years postpartum, even after adjustment for maternal age, parity and socioeconomic 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 BP 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) that 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 the cohort and the fact that women with GDM were excluded from the cohort (28). Given the costs associated with glycemic testing, this finding may represent an opportunity for interventions targeting health-care providers from a "choosing wisely" perspective.

Second, when specific glycemic tests were examined, the fasting PG (10,077 of 27,300, 36.9%) was the most commonly ordered test for dysglycemia screening across all groups of women followed by random PG (8,194 of 27,300, 30.0%) and A1C (7,009 of 27,300, 25.7%). The OGTT (252 of 27,300, 0.9%) was the least common glycemic test. The pattern of glycemic test utilization is notable as the fasting PG test 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 ovary syndrome (26,31). 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 showing that the average A1C levels were less favourable than the FPG among women with and without HDP; thus, the A1C may be more sensitive in detecting

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 OR (95% CI)	p value	Adjusted OR (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

BP, blood pressure; *CI*, confidence interval; *DM*, diabetes mellitus; *GHTN*, gestational hypertension; *NA*, not applicable; *OR*, odds ratio; *PE*, preeclampsia.
* Adjusted for maternal age at delivery, parity and the Pampalon deprivation index.

dysglycemia in this young postpartum population. This observation is supported by studies demonstrating that the A1C test was more sensitive than FPG amongst younger individuals (32,33) and females (33). However, more studies are needed to compare the diagnostic accuracy of the A1C 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 pregnancy (19). In addition, the study definition of DM was based on both laboratory criteria (using Canadian definitions) as well as the prescription of antidiabetes medications, excluding those with DM during pregnancy and prepregnancy to ensure an accurate classification of newly diagnosed postpartum DM.

These strengths, however, must be taken into context based on the limitations of the study's design. First, the administrative data sets did not include other clinical risk factors for type 2 DM, such as family history of diabetes or CVD, ethnicity and measures of obesity. Thus, we were unable to account for these risk factors in the analytical models. Second, type 2 DM was, in part, defined by prescriptions for antidiabetes medication, with the majority (72.4%) of prescriptions being for metformin. Although metformin is the first-line glucose-lowering medication for type 2 DM, in young women, it is often used for its nonglycemic effects across a broad spectrum of other diseases, including polycystic ovary syndrome (34), 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 evidence from a Canadian study demonstrating this association (35). This is unlikely to have impacted the study results as our study cohort was assembled before the publication of these data from Canada. Furthermore, our study showed comparable numbers of women tested for postpartum dysglycemia in those with normal BP and those with 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 that may represent prepregnancy dysglycemia (35).

Conclusions

This population-based cohort study has shown that women with a history of the hypertensive disorders of pregnancy (gestational hypertension and preeclampsia) as well as women with preterm delivery, had approximately double the risk of developing newly diagnosed type 2 DM over the first 4 years postpartum. However, current postpartum glycemic testing in Calgary was high and did not target the women at highest risk of dysglycemia. Although these findings highlight the importance of early targeted postpartum glycemic testing for dysglycemia, they also demonstrate a compelling need for further research on optimal testing (specific test) in these high-risk postpartum women.

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Author Disclosures

Conflicts of interest: None.

Author Contributions

All authors were involved in the study design. Data management and statistical analyses were performed by C. Wen and A. Metcalfe. Initial manuscript was drafted by C. Wen and K. Nerenberg. All authors were actively involved in the interpretation of the data, critically revising the manuscript and approved the final version of the paper.

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