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ORIGINAL RESEARCH

CARDIO-OBSTETRICS

Risk Factors and Outcomes Associated With Hypertensive Disorders of Pregnancy in Maternal Congenital Heart Disease

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ABSTRACT

BACKGROUND Among women with congenital heart disease (CHD), risk factors for hypertensive disorders of pregnancy (HDP) and the association of HDP with adverse outcomes are unknown.

OBJECTIVES The purpose of this study was to identify risk factors for HDP among women with and without CHD and to assess the association of HDP with adverse events.

METHODS This retrospective cohort study included the first live birth for each woman who was pregnant in Alberta, Canada, between January 1, 2005, and December 31, 2018. The prevalence of HDP among women with and without CHD was compared. Multivariable models were used to determine the independent associations between maternal characteristics and HDP and to assess the strength of associations between HDP and CHD with adverse events.

RESULTS Of the total birth events, 0.6% (N = 2,575) occurred in women with CHD. HDP were more common among women with CHD (11.2% vs 8.1%, $P < 0.0001$). Chronic hypertension and diabetes mellitus were strongly associated with HDP among women with CHD (adjusted odds ratio [aOR]: 4.56; 95% confidence interval [CI]: 2.95-7.03; and aOR: 3.33; 95% CI: 1.48-7.49, respectively). Coarctation of the aorta was the only CHD lesion independently associated with increased risk for HDP (aOR: 1.76; 95% CI: 1.02-3.02). HDP, as opposed to CHD, was more strongly associated with having a complicated delivery admission, preterm delivery, and small for gestational age infant.

CONCLUSIONS HDP were more common among women with CHD. The strongest risk factors for HDP among women with CHD were acquired. The presence of HDP, rather than CHD, was more strongly associated with certain adverse outcomes. (JACC Adv 2022;1:100036) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

aHR = adjusted hazard ratio

aOR = adjusted odds ratio

CHD = congenital heart disease

CI = confidence interval

HDP = hypertensive disorders of pregnancy

PEE = preeclampsia/eclampsia

SGA = small for gestational age

With improved pediatric outcomes, the population of women with congenital heart disease (CHD) who reach childbearing age is rapidly growing.[1-3] Maternal CHD is associated with higher rates of maternal, obstetric, and infant adverse events compared with the general obstetric population.[4-9]

Hypertensive disorders of pregnancy (HDP) affect 5% to 10% of all pregnancies and are associated with significant morbidity and mortality, accounting for up to 16% of pregnancy-related deaths worldwide.[10] HDP are associated with physiological abnormalities, including reduced arterial compliance, increased vascular resistance, reduced cardiac output, and diastolic dysfunction that may be poorly tolerated in women with CHD.[11] Furthermore, women with CHD may be predisposed to vascular dysfunction prior to conception, potentially increasing their risk of HDP.[12-19]

Previous studies suggest an increased prevalence of HDP among women with CHD compared with the general obstetrical population, but these analyses have primarily included small or historical cohorts or did not examine HDP in detail.[8,20-22] Although risk factors for HDP have been identified in the general population, whether HDP are associated with similar clinical factors among women with CHD is unknown.[23] Furthermore, the association of HDP with adverse pregnancy-related outcomes among women with CHD has not been studied. The main objectives of this analysis were to: 1) assess and compare the prevalence of HDP among women with and without CHD; 2) identify and compare clinical factors associated with the development of HDP among women with and without CHD; and 3) assess the association of HDP and CHD with adverse pregnancy-related events.

METHODS

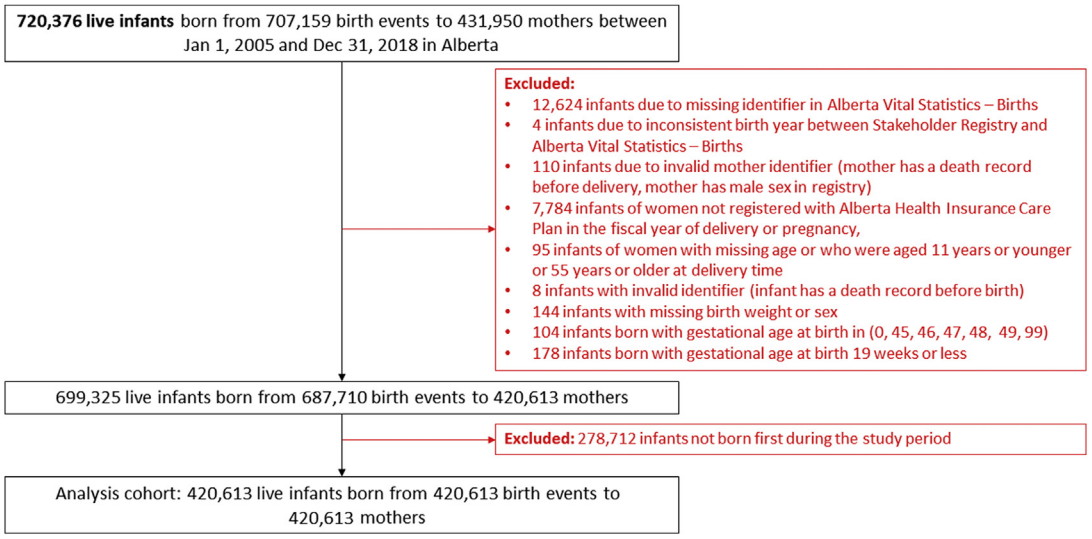
DATA SOURCE. This retrospective cohort study utilized data from the longitudinal Alberta Pregnancy-Birth cohort, which has been previously described.[24] Briefly, infant and mother identifiers and infant date of birth from the Stakeholder Newborn Database were used to link to the following data sources: 1) infant sex, birth weight, gestational age, singleton/multiple birth status, maternal age at delivery, and parity from the Alberta Vital Statistics-Birth Database; 2) demographic data from the Alberta Health Care Insurance Population registry; 3) data on the neighborhood-level household income from the 2010 Population Census; 4) physician office visits from the practitioners' claims database; 5) ambulatory care data from the National Ambulatory Care Reporting System database; 6) hospitalization data from the Discharge Abstract Database; and 7) date of death from the Vital Statistics-Death Database.[25] These health databases are collected primarily for administration and information on the health system in Alberta. Trained health information management professionals review administrative documents to create medical abstracts and generate codes that are collected in the databases.[26]

Data for this analysis were obtained from the Alberta Ministry of Health (Alberta Health). The data are proprietary and not available publicly. This study was approved by the University of Alberta Ethics Board. Due to the retrospective nature of this study, the requirement for informed consent was waived. This study complies with the Declaration of Helsinki.

STUDY POPULATION AND DEFINITIONS. The study population consisted of pregnant women with a live birth in Alberta, Canada, between January 1, 2005, and December 31, 2018. The first live birth for each woman during the study time period was retained for analysis. For nonsingleton pregnancies, only neonatal outcomes associated with the first-born infant were included. As such, the final analysis cohort included only 1 delivery and 1 infant for each woman (**Figure 1**). International Classification of Diseases version 9 and 10 codes were used to identify CHD and all comorbidities of interest. The presence of CHD codes in any diagnosis field associated with a health care encounter (hospitalizations, emergency department visits, outpatient clinic visits or physician office visit) between April 1, 2002, and March 31, 2019, was used to identify CHD. CHD diagnoses were grouped into simple, moderate, or complex CHD categories (Supplemental Table 1). Lesion severity groupings were based on the Bethesda criteria.[27] Women with diagnostic codes representing nonspecific CHD (ie, could not be categorized into a severity group) were qualified as a CHD case only if they had 2 or more physician office visits associated with the diagnosis. When lesions of different severity were present, the CHD severity of the case was ascertained based on the most severe lesion (complex > moderate > simple). Cases with only nonspecific CHD were considered as having simple lesions.

HDP was defined as gestational hypertension and preeclampsia and/or eclampsia (PEE). Gestational hypertension and PEE were identified when present in at least 1 inpatient/emergency room encounter or 2 outpatient clinic/physician office visits between 20 weeks of gestation and delivery.[28] Chronic

FIGURE 1 Derivation of the Study Cohort



hypertension, if recorded prior to pregnancy or during the first 20 weeks of gestation, was considered a preexisting condition and not included as HDP. If a code for chronic hypertension first appeared between 20 weeks of gestation and delivery, it was included as gestational hypertension. Women coded as having both chronic hypertension and gestational hypertension were considered to have chronic hypertension. Women with more than 1 diagnosis consistent with HDP were considered to have the most severe type (PEE > gestational hypertension). Covariates were considered present if a relevant diagnosis code was present in at least 1 hospitalization, 1 emergency department visit, or 2 outpatient clinic/physician office visit records between April 1, 2002, and delivery.

STATISTICAL ANALYSIS. Prevalence of HDP, overall and stratified by category, was reported for women with and without CHD. Maternal characteristics and adverse pregnancy-related event rates between women with and without HDP were compared, stratified by the presence of CHD. Continuous variables were reported as means with standard deviations or median with interquartile range and compared using *t*-test or Kruskal-Wallis test. Categorical variables were summarized as counts and percentages and compared using chi-square tests.

Multivariable logistic regression was used to examine the association between maternal characteristics and HDP, stratified by the presence of CHD. Maternal variables of interest were selected based on risk factors for HDP in the general obstetrical population identified in prior studies, as well as by clinical plausibility. To avoid interaction, lesion severity and lesion type were assessed in separate models.

Logistic regression was used to determine the relative strength of the adjusted association of the HDP-CHD-interaction with maternal or infant adverse events as well as a composite representing a complicated birth admission (ICU admission or length of stay >72 hours during birth admission). A Cox proportional hazard model was used to assess the interaction with a composite of 1-year death or readmission. Time to event was defined as the time to first readmission, death, departure from province, 1-year postpartum, or March 31, 2019, (end of follow-up). For this analysis, women were stratified into 4 groups: those with either CHD or HDP alone (+CHD/−HDP or −CHD/+HDP), those with both CHD and HDP (+CHD/+HDP), and those with uncomplicated pregnancies (−CHD/−HDP) as the reference.

RESULTS

PREVALENCE OF HYPERTENSIVE DISORDERS OF PREGNANCY. Of the 707,159 birth events among 431,950 women in the Alberta Pregnancy-birth cohort, 420,613 were included in our analysis (Figure 1). There were 2,575 women with CHD representing 0.6% of the study population.

Among women with CHD, 11.2% of pregnancies were complicated by HDP compared with 8.1% among women without CHD ($P < 0.0001$) (Table 1, Central Illustration). When examined individually, both gestational hypertension and PEE were more

TABLE 1 Prevalence of HDP Among Women With and Without CHD

	With CHD (n = 2,575; 0.6%)	Without CHD (n = 418,038; 99.4%)	*P* Value
Any HDP	288 (11.2)	33,675 (8.1)	<0.0001
Gestational hypertension	203 (7.9)	23,774 (5.7)	<0.0001
Preeclampsia/eclampsia	85 (3.3)	9,901 (2.4)	0.0019
Preeclampsia/eclampsia without chronic hypertension	66 (2.6)	8,660 (2.1)	0.0811
Preeclampsia/eclampsia superimposed on chronic hypertension	19 (0.7)	1,241 (0.3)	<0.0001
Early-onset preeclampsia/eclampsia	24 (0.9)	2,165 (0.5)	0.0036

Values are n (%).
CHD = congenital heart disease; HDP = hypertensive disorders of pregnancy.

common among women with CHD (7.9% vs 5.7%, $P < 0.0001$; 3.3% vs 2.4%, $P = 0.0019$, respectively). Among women with PEE, PEE superimposed on chronic hypertension also occurred more frequently among women with CHD (0.7% vs 0.3%, $P < 0.0001$). Women with CHD were more affected by early-onset PEE, defined as PEE diagnosed prior to 34 weeks of gestation (0.9% vs 0.5%, $P = 0.0036$).

MATERNAL CHARACTERISTICS ASSOCIATED WITH HYPERTENSIVE DISORDERS OF PREGNANCY. There was a greater burden of comorbidities among women with CHD, including chronic hypertension (4.5% vs 1.8%, $P < 0.0001$) and diabetes mellitus (1.3% vs 0.8%, $P = 0.0118$) (Table 2).

Adjusted analyses showed that, when compared with mild disease, the presence of neither moderate nor severe CHD was associated with greater risk for HDP (adjusted odds ratio [aOR]: 1.19; 95% confidence interval [CI]: 0.91-1.56, and aOR: 0.78; 95% CI: 0.45-1.36, respectively) (Figure 2). Of the specific CHD lesions examined, coarctation of the aorta was the only congenital lesion independently associated with an increased risk for HDP (aOR: 1.76; 95% CI: 1.02-3.02) (Supplemental Table 3). Chronic hypertension and diabetes mellitus were strongly associated with HDP in pregnancies of women with CHD (aOR: 4.56; 95% CI: 2.95-7.03, and aOR: 3.33; 95% CI: 1.48-7.49, respectively), as well as in those without CHD (aOR: 4.80; 95% CI: 4.55-5.07, and aOR: 3.34; 95% CI: 3.08-3.63, respectively). Additional patient characteristics that were associated with HDP among both women with and without CHD included nulliparity and nonsingleton pregnancy. Overall, when leaving aside those predictors that are specific to patients with CHD, the direction of the association between maternal characteristics and HDP was similar between patients with and without CHD with the exception of South Asian and Chinese ethnicity.

THE ASSOCIATION OF HYPERTENSIVE DISORDERS OF PREGNANCY AND CONGENITAL HEART DISEASE WITH ADVERSE PREGNANCY-RELATED MATERNAL AND INFANT OUTCOMES. One-year maternal and neonatal death rates were low irrespective of the presence of maternal CHD and/or HDP (Table 3). Otherwise, with the exception of cesarean delivery which occurred at a similar rate in both groups, all examined adverse events occurred more commonly in women with CHD than in those without CHD.

Compared with women with uncomplicated pregnancies (−CHD/−HDP), women with both CHD and HDP (+CHD/+HDP), as well as those with HDP alone (−CHD/+HDP), had higher odds of having a complicated delivery admission (maternal composite 1) (aOR: 4.75; 95% CI: 3.71-6.08, and aOR: 4.00; 95% CI: 3.90-4.11, respectively) (Figure 3A, Central Illustration). In contrast, women with CHD alone (+CHD/−HDP) were at lower of risk of experiencing a complicated delivery admission than women with uncomplicated pregnancies (aOR: 1.35; 95% CI: 1.19-1.53). Women with either −CHD/+HDP or +CHD/−HDP, as well as those with +CHD/+HDP, had an increased risk of 1-year readmission or death (maternal composite 2) compared with women with uncomplicated pregnancies (adjusted hazard ratio [aHR]: 1.44; 95% CI: 1.38-1.51, aHR: 1.69; 95% CI: 1.47-1.94, aHR: 1.92; 95% CI: 1.35-2.73, respectively).

Infants born to mothers with −CHD/+HDP or +CHD/+HDP had the highest odds of preterm delivery (aOR: 2.56; 95% CI: 2.47-2.64, aOR: 3.06; 95% CI: 2.28-4.10, respectively) (Figure 3B, Central Illustration). Infants born to mothers with +CHD/−HDP also had increased odds of preterm delivery (aOR: 1.39; 95% CI: 1.20-1.60), but the magnitude was lower. Infants born to women with −CHD/+HDP and +CHD/−HDP had higher odds of being small for gestational age (SGA); however, the magnitude of risk was higher among pregnancies complicated by HDP (aOR: 1.50; 95% CI: 1.46-1.55 vs aOR: 1.25; 95% CI: 1.11-1.42). Infants born to mothers with +CHD/−HDP or +CHD/−HDP had the highest odds of having a congenital anomaly (aOR: 4.90; 95% CI: 4.32-5.56, aOR: 5.86; 95% CI: 4.26-8.06, respectively). Infants born to mothers with −CHD/+HDP also had increased odds of having a congenital anomaly, but the magnitude was lower (aOR: 1.37; 95% CI: 1.30-1.46). Finally, infants born to mothers with +HDP/−CHD, +CHD/−HDP, or +CHD/+HDP all had similarly increased risk of 1-year readmission or all-cause death (infant

TABLE 2 Baseline Characteristics

	With CHD				Without CHD				
	Total (n = 2,575; 0.6%)	−HDP (n = 2,287; 88.8%)	+HDP (n = 288; 11.2%)	*P* Value[a]	Total (n = 418,038; 99.4%)	−HDP (n = 384,363; 91.9%)	+HDP (n = 33,675; 8.1%)	*P* Value[b]	*P* Value[c]
Demographics									
Age, y	28.6 ± 5.8	28.6 ± 5.7	29.1 ± 6.0	0.1464	29.4 ± 5.6	29.3 ± 5.6	29.9 ± 5.8	<0.0001	<0.0001
Age <20 y	168 (6.5)	153 (6.7)	15 (5.2)	0.3373	16,743 (4.0)	15,563 (4.0)	1,180 (3.5)	<0.0001	<0.0001
Age >35 y	303 (11.8)	262 (11.5)	41 (14.2)	0.1676	58,164 (13.9)	52,377 (13.6)	5,787 (17.2)	<0.0001	0.0017
General population	2,470 (95.9)	2,198 (96.1)	272 (94.4)	0.1784	388,860 (93.0)	356,881 (92.8)	31,979 (95.0)	<0.0001	<0.0001
South Asian	55 (2.1)	45 (2.0)	<11 (3.5)	0.096	13,268 (3.2)	12,258 (3.2)	1,010 (3.0)	0.0566	0.0027
Chinese	50 (1.9)	44 (1.9)	<11 (2.1)	0.8534	15,910 (3.8)	15,224 (4.0)	686 (2.0)	<0.0001	<0.0001
Married	1,681 (65.3)	1,485 (64.9)	196 (68.1)	0.2941	286,039 (68.4)	263,030 (68.4)	23,009 (68.3)	0.6881	0.0006
Rural	591 (23.0)	512 (22.4)	79 (27.4)	0.0551	80,920 (19.4)	73,694 (19.2)	7,226 (21.5)	<0.0001	<0.0001
Annual income, $	75,764 (68,090-96,647)	75,764 (68,090-96,257)	76,315 (68,090-98,140)	0.2821	76,315 (68,280-96,647)	76,315 (68,280-96,647)	76,592 (68,538-96,758)	<0.0001	0.0727
Obstetrical history									
Nulliparous	1,835 (71.3)	1,600 (70.0)	235 (81.6)	<0.0001	287,291 (68.7)	259,938 (67.6)	27,353 (81.2)	<0.0001	0.0056
Nonsingleton pregnancy	60 (2.3)	44 (1.9)	16 (5.6)	0.0001	8,171 (2.0)	6,697 (1.7)	1,474 (4.4)	<0.0001	0.1703
Comorbidities									
Chronic hypertension	115 (4.5)	76 (3.3)	39 (13.5)	<0.0001	7,629 (1.8)	5,470 (1.4)	2,159 (6.4)	<0.0001	<0.0001
Diabetes mellitus	33 (1.3)	22 (1.0)	11 (3.8)	<0.0001	3,467 (0.8)	2,550 (0.7)	917 (2.7)	<0.0001	0.0118
Gestational diabetes	160 (6.2)	137 (6.0)	23 (8.0)	0.1861	26,958 (6.4)	23,447 (6.1)	3,511 (10.4)	<0.0001	0.6282
Renal disease	11 (0.4)	<11 (0.3)	<11 (1.0)	0.0898	726 (0.2)	522 (0.1)	204 (0.6)	<0.0001	0.0022
Lupus	13 (0.5)	11 (0.5)	<11 (0.7)	0.63	613 (0.1)	504 (0.1)	109 (0.3)	<0.0001	<0.0001
Pulmonary embolism	29 (1.1)	24 (1.0)	<11 (1.7)	0.298	1,479 (0.4)	1,318 (0.3)	161 (0.5)	<0.0001	<0.0001
VTE	41 (1.6)	31 (1.4)	<11 (3.5)	0.0068	2,178 (0.5)	1,906 (0.5)	272 (0.8)	<0.0001	<0.0001
CHD severity									
Mild	1,499 (58.2)	1,342 (58.7)	157 (54.5)	0.1768	n/a	n/a	n/a	n/a	n/a
Moderate	889 (34.5)	775 (33.9)	114 (39.6)	0.0554	n/a	n/a	n/a	n/a	n/a
Severe	187 (7.3)	170 (7.4)	17 (5.9)	0.3456	n/a	n/a	n/a	n/a	n/a
CHD lesion type									
Secundum type atrial septal defect	595 (23.1)	535 (23.4)	60 (20.8)	0.3314	n/a	n/a	n/a	n/a	n/a
Ventricular septal defect	363 (14.1)	321 (14.0)	42 (14.6)	0.8013	n/a	n/a	n/a	n/a	n/a
Bicuspid aortic valve	239 (9.3)	208 (9.1)	31 (10.8)	0.3576	n/a	n/a	n/a	n/a	n/a
Aortic coarctation	104 (4.0)	81 (3.5)	23 (8.0)	0.0003	n/a	n/a	n/a	n/a	n/a
Tetralogy of Fallot	71 (2.8)	67 (2.9)	<11 (1.4)	0.1324	n/a	n/a	n/a	n/a	n/a
Transposition of the great arteries	53 (2.1)	46 (2.0)	<11 (2.4)	0.6368	n/a	n/a	n/a	n/a	n/a
Atrioventricular septal defect, ostium primum atrial septal defect, endocardial cushion defect	53 (2.1)	46 (2.0)	<11 (2.4)	0.6368	n/a	n/a	n/a	n/a	n/a
Ebstein anomaly	23 (0.9)	21 (0.9)	<11 (0.7)	0.7036	n/a	n/a	n/a	n/a	n/a
Subaortic stenosis	17 (0.7)	14 (0.6)	<11 (1.0)	0.3963	n/a	n/a	n/a	n/a	n/a
Pulmonary artery stenosis and atresia	117 (4.5)	106 (4.6)	11 (3.8)	0.5312	n/a	n/a	n/a	n/a	n/a
Anomalous pulmonary venous return	14 (0.5)	11 (0.5)	<11 (1.0)	0.2227	n/a	n/a	n/a	n/a	n/a
Pulmonary valve stenosis	55 (2.1)	52 (2.3)	<11 (1.0)	0.1729	n/a	n/a	n/a	n/a	n/a
Patent ductus arteriosus	85 (3.3)	72 (3.2)	13 (4.5)	0.2215	n/a	n/a	n/a	n/a	n/a

Values are mean ± SD, n (%), or median (IQR). General population represents women who do not identify as either Chinese or South Asian. Based on the demographics of Alberta, Canada, this group is predominantly Caucasian. Annual income represents an annual median household income in 2010 at neighborhood level reported in the Canadian dollar. [a]For testing differences between +CHD/−HDP and +CHD/+HDP. [b]For testing differences between −CHD/−HDP and −CHD/+HDP. [c]For testing differences between women without CHD and with CHD.

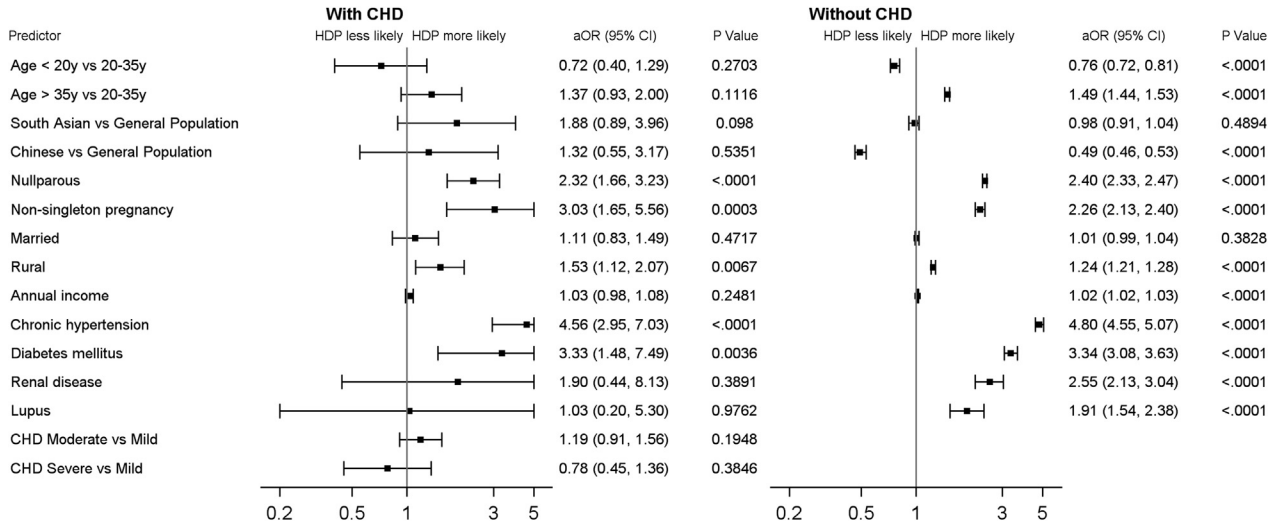
CHD = congenital heart disease; HDP = hypertensive disorders of pregnancy; IQR = interquartile range; SD = standard deviation; VTE = venous thromboembolism/deep vein thrombosis.

composite 1) compared with infants born to −HDP/−CHD mothers (aHR: 1.40; 95% CI: 1.36-1.44, aHR: 1.56; 95% CI: 1.42-1.72, aHR: 1.40; 95% CI: 1.06-1.83, respectively).

DISCUSSION

Our real-world retrospective examination of HDP and CHD in a large contemporary cohort of pregnant

FIGURE 2 Clinical Factors Associated With HDP Among Women With and Without CHD



General population includes women who do not identify as either Chinese or South Asian. Based on the demographics of Alberta, Canada, this group is predominantly Caucasian. Annual income represents the annual median household income in 2010 at neighborhood level reported in the Canadian dollar. Effect is estimated per 10,000 dollars. aOR = adjusted odds ratio; CHD = congenital heart disease; CI = confidence interval; HDP = hypertensive disorders of pregnancy.

women had several notable findings. First, women with CHD had a higher risk of having a pregnancy complicated by HDP. Both gestational hypertension and PEE were more common among women with CHD. Second, among women with CHD, coarctation of the aorta was the only CHD lesion that was independently associated with increased risk for HDP; otherwise, the strongest risk factors for HDP, chronic hypertension and diabetes mellitus, were acquired and potentially modifiable. Finally, the strengths of the associations of CHD and HDP with adverse maternal and infant outcomes varied depending on the outcome.

PREVALENCE OF HYPERTENSIVE DISORDERS OF PREGNANCY. HDP are a leading cause of pregnancy-related maternal and perinatal morbidity and mortality worldwide.[10,29,30] Additionally, HDP is an important risk factor for future maternal cardiovascular diseases, including heart failure, coronary artery disease and stroke, and early all-cause mortality.[31-34] Increased rates of HDP have previously been reported among women with CHD.[7,20-22,35] Our study supports these findings and additionally found that, when examined individually, both gestational hypertension and PEE were more common among women with CHD. Additionally, among those diagnosed with PEE, PEE superimposed on chronic hypertension was more common among women with CHD. Importantly, women with CHD also experienced a higher rate of early-onset PEE. Early-onset PEE is associated with increased risk of maternal morbidity, early and late maternal mortality, fetal and perinatal death, and severe neonatal morbidity compared with PEE with onset after 34 weeks.[36-38]

MATERNAL CHARACTERISTICS ASSOCIATED WITH THE DEVELOPMENT OF HYPERTENSIVE DISORDERS OF PREGNANCY. Although clinical factors associated with HDP have been described among the general obstetric population, risk factors have not been well defined among women with CHD. Our analysis found that the strongest risk factors for HDP were similar irrespective of the presence or absence of maternal CHD.

Coarctation of the aorta was independently associated with HDP, even after adjustment for the presence of chronic hypertension.[20,39,40] Prior studies suggested that increased prevalence of HDP among patients with coarctation of the aorta may primarily be driven by a high prevalence of chronic hypertension.[41] Our results, however, suggest that coarctation of the aorta may predispose patients to HDP even in the absence of chronic hypertension. Patients with both repaired and unrepaired coarctation of the aorta are susceptible to underlying endothelial dysfunction, endothelium-independent vascular dysfunction, and diffuse vasculopathy with increased arterial stiffness which may contribute to the development of HDP.[15-19]

TABLE 3 Adverse Pregnancy-Related Events by CHD and HDP Status

	With CHD				Without CHD				
	Total (n = 2,575; 0.6%)	−HDP (n = 2,287; 88.8%)	+HDP (n = 288; 11.2%)	*P* Value[a]	Total (n = 418,038; 99.4%)	−HDP (n = 384,363; 91.9%)	+HDP (n = 33,675; 8.1%)	*P* Value[b]	*P* Value[c]
Cesarean delivery	790 (30.7)	664 (29.0)	126 (43.8)	<0.0001	123,589 (29.6)	109,033 (28.4)	14,556 (43.2)	<0.0001	0.2162
Preterm delivery (<37 wk)	293 (11.4)	226 (9.9)	67 (23.3)	<0.0001	33,909 (8.1)	27,569 (7.2)	6,340 (18.8)	<0.0001	<0.0001
Preterm delivery without induction of labor	215 (8.3)	177 (7.7)	38 (13.2)	0.0016	24,804 (5.9)	21,330 (5.5)	3,474 (10.3)	<0.0001	<0.0001
Preterm delivery with induction of labor	78 (3.0)	49 (2.1)	29 (10.1)	<0.0001	9,105 (2.2)	6,239 (1.6)	2,866 (8.5)	<0.0001	0.0032
Delivery hospitalization >72 h	431 (16.7)	312 (13.6)	119 (41.3)	<0.0001	50,975 (12.2)	39,093 (10.2)	11,882 (35.3)	<0.0001	<0.0001
ICU admission during delivery hospitalization	23 (0.9)	16 (0.7)	<11 (2.4)	0.0033	613 (0.1)	393 (0.1)	220 (0.7)	<0.0001	<0.0001
Any hospitalization other than delivery (within 1 y of delivery)	228 (8.9)	197 (8.6)	31 (10.8)	0.2261	21,027 (5.0)	18,582 (4.8)	2,445 (7.3)	<0.0001	<0.0001
Death (within 1 y of delivery)	<11 (0.0)	0 (0.0)	<11 (0.3)	n/a	49 (0.0)	35 (0.0)	14 (0.0)	<0.0001	0.2083
Composite outcomes									
Delivery admission with ICU admission and/or length of stay >72 h	433 (16.8)	314 (13.7)	119 (41.3)	<0.0001	51,063 (12.2)	39,162 (10.2)	11,901 (35.3)	<0.0001	<0.0001
1-y death or readmission	228 (8.9)	197 (8.6)	31 (10.8)	0.2261	21,048 (5.0)	18,596 (4.8)	2,452 (7.3)	<0.0001	<0.0001
Infant outcomes									
Preterm delivery (<37 wk)	293 (11.4)	226 (9.9)	67 (23.3)	<0.0001	33,909 (8.1)	27,569 (7.2)	6,340 (18.8)	<0.0001	<0.0001
Low birth weight (<2,500 g)	276 (10.7)	212 (9.3)	64 (22.2)	<0.0001	28,308 (6.8)	22,545 (5.9)	5,763 (17.1)	<0.0001	<0.0001
Small of gestational age	353/2,567 (13.8)	298/2,279 (13.1)	55/288 (19.1)	0.0052	47,375/417,669 (11.3)	41,881/383,997 (10.9)	5,494/33,672 (16.3)	<0.0001	0.0001
Congenital anomaly	329 (12.8)	283 (12.4)	46 (16.0)	0.0848	12,032 (2.9)	10,643 (2.8)	1,389 (4.1)	<0.0001	<0.0001
Congenital heart defect	360 (14.0)	308 (13.5)	52 (18.1)	0.0343	12,670 (3.0)	11,191 (2.9)	1,479 (4.4)	<0.0001	<0.0001
Birth hospitalization length of stay >72 h	433 (16.8)	351 (15.3)	82 (28.5)	<0.0001	41,534 (9.9)	33,758 (8.8)	7,776 (23.1)	<0.0001	<0.0001
Any hospitalization (between 1 d and 1 y of life)	426 (16.5)	375 (16.4)	51 (17.7)	0.5725	47,024 (11.2)	41,587 (10.8)	5,437 (16.1)	<0.0001	<0.0001
Death (between 1 d and 1 y of life)	45 (1.7)	41 (1.8)	<11 (1.4)	0.6221	1,977 (0.5)	1,826 (0.5)	151 (0.4)	0.494	<0.0001
Composite outcomes									
Birth admission with ICU admission and/or length of stay >72 h	600 (23.3)	496 (21.7)	104 (36.1)	<0.0001	63,868 (15.3)	53,873 (14.0)	9,995 (29.7)	<0.0001	<0.0001
1-y death or readmission	454 (17.6)	402 (17.6)	52 (18.1)	0.841	48,618 (11.6)	43,078 (11.2)	5,540 (16.5)	<0.0001	<0.0001

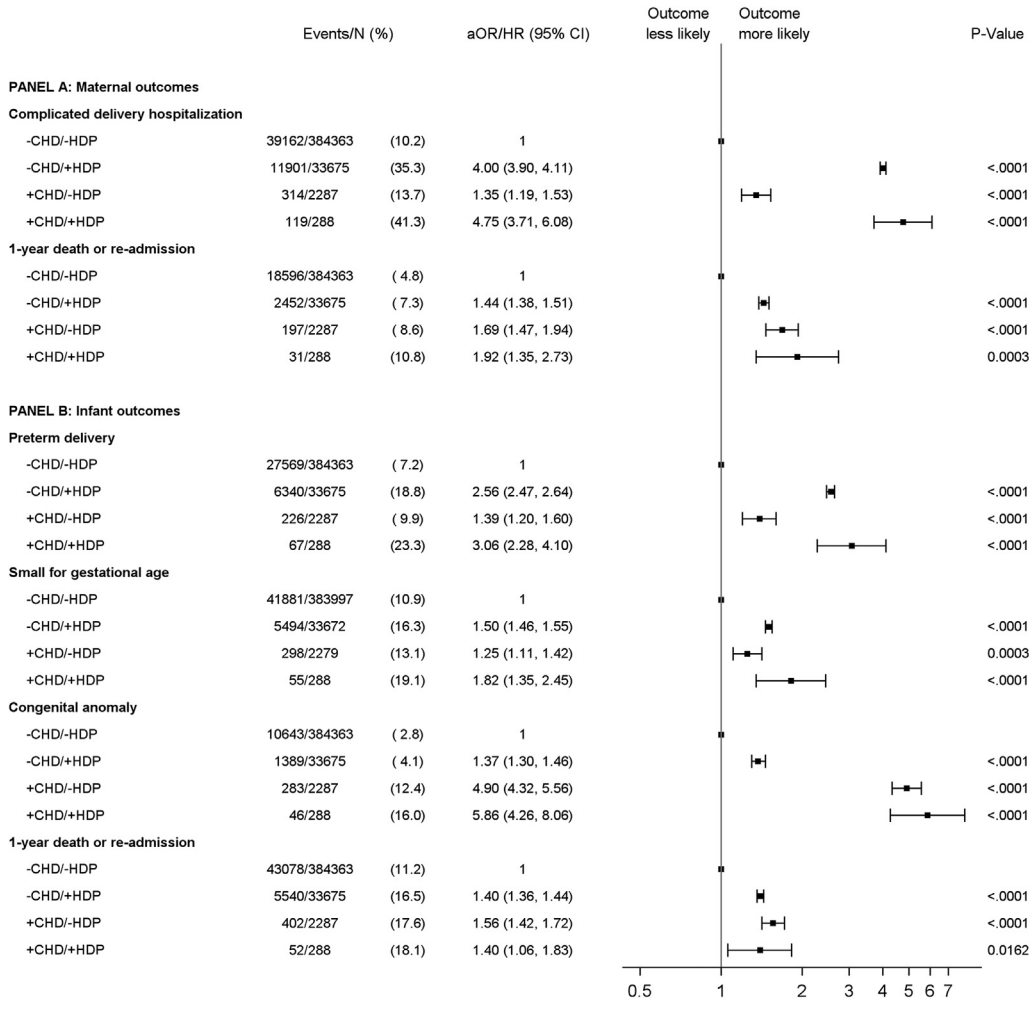
Values are n (%) or n/N (%). [a]For testing differences between +CHD/−HDP and +CHD/+HDP. [b]For testing differences between -CHD/−HDP and -CHD/+HDP. [c]For testing differences between women without CHD and with CHD.

CHD = congenital heart disease; HDP = hypertensive disorders of pregnancy; ICU = intensive care unit.

Although more complex congenital lesions such as Fontan circulation and Eisenmenger syndrome have also been associated with unfavorable vascular derangements that could predispose to HDP, our analysis did not identify an association between severe CHD and HDP. This could be related to the small number of included patients with severe CHD. Alternatively, women with severe CHD more commonly deliver at an earlier gestation, which may reduce their risk of HDP, which most commonly occur toward the end of pregnancy.[20] Prior studies have identified increased rates of HDP among women with other specific CHD lesions such as transposition of the great arteries, atrial septal defects, and ventricular septal defects.[20-22,35] These lesions were not associated with increased risk for HDP after covariate adjustment in our analysis.

Our results suggest that the most important risk factors for HDP among women with CHD are acquired and potentially modifiable. Chronic hypertension is a known risk factor for the development of PEE in the general obstetrical population and, in fact, was also the clinical characteristic most strongly associated with the development of HDP among women with CHD in our analysis. Diabetes mellitus was also an important risk factor. When compared with age-matched controls in the general population, chronic hypertension and diabetes mellitus are more common among young adults with CHD, likely in part related to self- and physician-imposed activity restrictions and an increased burden of obesity.[42-44] Our analysis cohort also demonstrated a higher prevalence of chronic hypertension and diabetes mellitus among women with CHD than among those without CHD. Education and encouragement surrounding the importance of physical activity and healthy living habits to prevent the development of chronic hypertension and diabetes mellitus may help to mitigate the burden of HDP among women with CHD. Women with CHD and chronic hypertension and/or diabetes mellitus should receive preconception counseling regarding their risk of HDP, and preconception care

FIGURE 3 The Association Between CHD and HDP Status and Pregnancy-Related Adverse Maternal and Infant Outcomes



Maternal adverse outcomes are presented in **A**, and infant adverse outcomes are presented in **B**. Complicated delivery hospitalization refers to a delivery admission with intensive care unit admission or length of stay >72 hours. Adjustment variables included age, ethnicity, parity, multiple pregnancy, married, rural residence, annual income, chronic hypertension, diabetes mellitus, renal disease, lupus, gestational diabetes, pulmonary embolus, venous thromboembolism/deep vein thrombosis. HR = hazard ratio; other abbreviations as in Figure 2.

should focus on control of these comorbidities with pregnancy-safe medications.

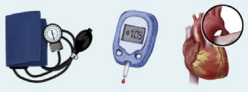
THE ASSOCIATION OF HYPERTENSIVE DISORDERS OF PREGNANCY AND CONGENITAL HEART DISEASE WITH ADVERSE PREGNANCY-RELATED MATERNAL AND INFANT OUTCOMES. Women with CHD are at increased risk for adverse pregnancy-related maternal and fetal outcomes compared with the general obstetric population.[8-10] Almost all examined adverse pregnancy outcomes occurred more commonly among women with CHD in our cohort than among those without CHD. The relative strength of CHD and HDP as risk factors for adverse pregnancy-related events differed based on the outcome assessed, suggesting that, among women with CHD, certain adverse outcomes may not solely be a result of their underlying cardiac disease but could also be related to an increased burden of HDP.

The expected physiological changes that occur during pregnancy may present a hemodynamic challenge for women with CHD. The intrapartum and immediate postpartum periods can be particularly hazardous due to extreme changes in cardiac output, circulating blood volume, and systemic vascular resistance. Although most women with CHD tolerate these changes well, complications during the

CENTRAL ILLUSTRATION **The Impact of HDP Among Women With CHD**

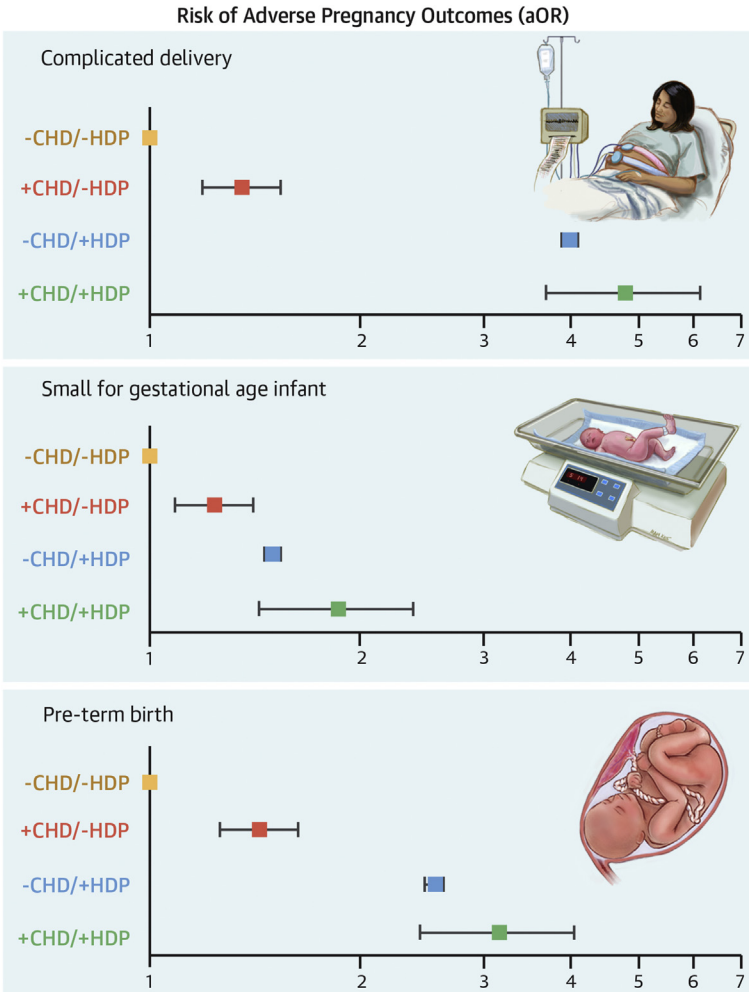
11.2% of women with CHD develop HDP

Risk factors for HDP among women with CHD:
- chronic hypertension
- pre-existing diabetes
- coarctation of the aorta



8.1% of women without CHD develop HDP

Risk factors for HDP among women without CHD:
- chronic hypertension
- pre-existing diabetes



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aOR = adjusted odds ratio; CHD = congenital heart disease; HDP = hypertensive disorders of pregnancy.

peripartum period remain a concern.[8,45] In our analysis, although the presence of CHD did confer increased odds of having a complicated delivery hospitalization, the presence of HDP was more strongly associated with this adverse pregnancy outcome. This suggests that all women with CHD, but especially those with HDP, should be monitored closely throughout their delivery admission so that prompt evaluation and management can be pursued in the event of decompensation. Conversely, when examining 1-year readmission or death, women with CHD, HDP, or both experienced similarly increased risk compared with women who had uncomplicated pregnancies.

The relative association of maternal CHD and HDP as risk factors for infant adverse outcomes also varied. Women with CHD more commonly experience preterm delivery than the general obstetric population.[6,8,20] This finding was reproduced in our cohort. Preterm delivery, the majority of which was related to spontaneous preterm labor, was strongly associated with the presence of HDP, with women with CHD alone having a lower magnitude of risk than those with HDP. Similarly, the risk of having an SGA infant was also more strongly associated with HDP than CHD alone.

Both maternal CHD and HDP are associated with congenital defects in offspring.[46] Our data revealed

that the risk for congenital anomalies in the infant, which were primarily CHD in our cohort, was highest among women with CHD although infants born to mothers with HDP alone were also at increased risk for having a congenital anomaly. There was not an additive effect of risk in women with both CHD and HDP.

Finally, infants born to mothers with either CHD or HDP or both were at increased risk for 1-year readmission and death compared with infants born to women with uncomplicated pregnancies. There was no additive risk in women with both CHD and HDP. The risk for 1-year readmission and death in infants born to women with CHD could be related to increased rates of other adverse infant outcomes such as congenital anomalies, SGA, and preterm delivery. Further investigation is necessary to better understand the cause of long-term complications among infants born to mothers with CHD and/or HDP and the impact of novel programs to reduce that risk.

STUDY LIMITATIONS. Although our study represents the largest contemporary population-based analysis of HDP in women with CHD to date, it has several limitations. First, the use of International Classification of Diseases codes to identify CHD and HDP, as well as comorbid diagnoses, could have resulted in misclassification related to undercoding or inappropriate coding. Additionally, certain CHD lesions, particularly lesions consistent with severe CHD, are difficult to accurately code.[47-49] To mitigate these risks, algorithms used to identify these diagnoses were based on data from multiple health care settings. Second, details regarding surgical repair for CHD were not available. Third, despite our large cohort, the number of women with uncommon or complex congenital lesions was low, likely related to their low prevalence in the general population and the aforementioned difficulties with coding. The translation of our findings to women with complex CHD is therefore limited. Fourth, pregnancies that resulted in termination, miscarriage, or stillbirth, which account for about 20% of pregnancies in women with CHD, were not included in our database.[20] This may have affected our results, as it is possible that women with 1 of these pregnancy outcomes may represent a cohort with more severe CHD. Fifth, some baseline characteristic data were not collected in the Alberta Pregnancy-Birth cohort database. Finally, data for this analysis were collected exclusively from within the universal health care system in Alberta, Canada, which may affect the generalizability of our results.

CONCLUSIONS

As compared with women without CHD, women with CHD experienced higher rates of HDP, both overall and for gestational hypertension and PEE when considered individually. Coarctation of the aorta was the only CHD lesion that was independently associated with having a pregnancy complicated by a hypertensive disorder. Other risk factors for HDP were similar among women with and without CHD; chronic hypertension and diabetes mellitus, potentially modifiable comorbidities that occur disproportionately among young adults with CHD, were most strongly associated. The relative strength of CHD and HDP as risk factors for adverse pregnancy-related outcomes differed based on the specific outcome assessed. Interventions during childhood and early adulthood to reduce the prevalence of modifiable risk factors may lead to a lesser burden of HDP and related adverse outcomes among women with CHD.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: HDP are more common among women with CHD than among the general obstetrical population. The strongest risk factors for HDP are acquired, potentially modifiable, and similar to those observed among women without CHD. Coarctation of the aorta is the only CHD lesion independently associated with HDP. Certain adverse pregnancy-related outcomes among women with CHD may be related to increased rates of HDP.

TRANSLATIONAL OUTLOOK: Future research should assess the effect of preconception clinical interventions to reduce the burden of risk factors for HDP among women with CHD and the resulting effect on the prevalence of HDP as well as adverse pregnancy-related outcomes in this population.

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KEY WORDS congenital heart disease, hypertensive disorders of pregnancy, outcomes, preeclampsia

APPENDIX For supplemental tables, please see the online version of this paper.