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Neonatal outcomes of twins <29 weeks gestation of mothers with hypertensive disorders of pregnancy

Katherine Yurkiw[1], Belal Alshaikh[1], Shabih U. Hasan[1], Deepak Louis[2], Julie Emberley[3], Martine Claveau[4], Marc Beltempo[4], Kamran Yusuf[1]✉ and on behalf of the Canadian Neonatal Network Investigators

BACKGROUND: Hypertensive disorders of pregnancy (HDP) are associated with dysfunctional placentation and are a major cause of maternal and neonatal morbidity and mortality. Twin pregnancies have a larger placental mass and are a risk factor for HDP. The effect of HDP on neonatal outcomes in twin pregnancies is unknown.
METHODS: Retrospective cohort study using the Canadian Neonatal Network database from 2010–2018 of twin infants <29 weeks gestation born to mothers with HDP and normotensive pregnancies. Using multivariable models, we determined adjusted odds ratios (AORs) and 95% confidence intervals (CI) for mortality, bronchopulmonary dysplasia, severe neurologic injury, severe retinopathy of prematurity (ROP), necrotizing enterocolitis, and nosocomial infection in twin infants of mothers with HDP compared to twin infants of normotensive mothers.
RESULTS: Of the 2414 eligible twin infants <29 weeks gestational age, 164 (6.8%) were born to mothers with HDP and had higher odds of severe ROP (AOR 2.48, 95% CI 1.34–4.59). Preterm twin infants born to mothers with HDP also had higher odds of mortality (AOR 2.02, 95% CI 1.23–3.32). There was no difference in other outcomes.
CONCLUSION: Preterm twin infants <29 weeks gestation of HDP mothers have higher odds of severe ROP and mortality.

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IMPACT: Hypertensive disorders of pregnancy, associated with placental dysfunction, are a major cause of maternal and neonatal morbidity and mortality.Twin pregnancy, associated with a larger placental mass, is a risk factor for hypertensive disorders of pregnancy.The effect of hypertensive disorders of pregnancy on outcomes of preterm twins is unknown.Preterm twins of mothers with hypertensive disorders of pregnancy are at higher risk of severe retinopathy of prematurity and mortality.Our data can be used to counsel parents and identify infants at higher risk of severe retinopathy of prematurity and mortality.

INTRODUCTION

Globally, 5–10% of women have elevated blood pressure during pregnancy.[1] Hypertensive disorders of pregnancy (HDP) are among the leading causes of maternal and neonatal mortality and morbidity across all gestational ages.[1,2]

HDP comprise chronic or pre-pregnancy hypertension, and a spectrum of pregnancy-induced hypertensive disorders, ranging from gestational hypertension to preeclampsia to eclampsia.[3] Preeclampsia is the most frequently encountered HDP and is characterized by hypertension with signs of maternal end-organ involvement such as proteinuria, thrombocytopenia, hepatic, renal or neurologic impairment.[2,3] With the increasing prevalence of predisposing factors such as advanced maternal age, obesity, diabetes, and utilization of assisted reproductive technologies, the worldwide incidence of HDP is increasing.[2]

HDP are known to increase the risk of iatrogenic (medically induced) and spontaneous preterm delivery and can detrimentally impact fetal growth, resulting in intrauterine growth restricted infants.[4] In addition, preterm singleton infants born to mothers with HDP have an increased risk of several morbidities including respiratory distress syndrome, need for respiratory support, and bronchopulmonary dysplasia (BPD).[5–8] Some studies have demonstrated decreased risks of necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), and neurologic sequelae in infants of HDP pregnancies, while others did not show a difference.[5,6,8] Conflicting evidence exists with regards to the risk of retinopathy of prematurity (ROP) with HDP, with studies showing increased, decreased, or no difference in risk compared to infants of normotensive pregnancies.[6–11] Overall mortality often appears to be decreased in infants of HDP mothers compared to normotensive mothers, although this too is controversial.[7,8,12–16]

Preeclampsia and other HDP are thought to develop from malimplantation and dysfunction of developing placentas, which results in an ischemic, anti-angiogenic, and pro-inflammatory milieu that may have severe maternal and fetal consequences.[3,17] One well documented risk factor for the development of HDP is

[1]Pediatrics, University of Calgary, Calgary, AB, Canada. [2]Pediatrics and Child Health, University of Manitoba, Winnipeg, MB, Canada. [3]Pediatrics, Memorial University, St. John's Newfoundland and Labrador, St. John's, NF, Canada. [4]Pediatrics, McGill University, Montreal, QC, Canada. A list of members and their affiliations appears in the Supplementary Information. ✉email: kyusuf@ucalgary.ca

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multifetal gestation.[18–20] The risk of HDP increases with increasing chorionicity.[21] This increased risk is believed to be conferred due to higher placental mass in twins compared to singleton pregnancies, leading to higher-than-normal circulating levels of pro-inflammatory and anti-angiogenic factors consistent with HDP pathology.[20]

When compared to singleton pregnancies, twin pregnancies have poorer outcomes and more complications across all gestational ages.[22] We, and others, have reported on the outcomes of singleton preterm neonates of HDP mothers compared to normotensive mothers.[5,6,8,23] However, there is limited data on the neonatal outcomes of premature twins born to mothers with HDP. Given the rising prevalence of twin pregnancies, and the higher risk of HDP in twin pregnancies, we believe this to be a significant gap in the literature on infants of mothers with HDP.[24] The aim of our study was to compare the neonatal outcomes of premature infants <29 weeks gestation born to mothers with HDP with infants born to normotensive mothers using the Canadian Neonatal Network (CNN) database.

METHODS

Study population

The Canadian Neonatal Network (CNN) comprises all level III neonatal intensive care units (NICUs) across Canada and is responsible for maintaining an electronic database of demographic and outcome data of NICU admissions. Anonymized maternal and neonatal data using standardized definitions are electronically recorded at each participating institution by trained data abstractors. The details of data collection and management have been described previously.[25] The internal consistency and reproducibility of the CNN database have been previously demonstrated.[26] The study population consisted of twin infants born at <29 weeks gestation admitted to participating CNN NICUs between January 1, 2010 and December 31, 2018. Infants who were moribund, had major congenital abnormalities, or were missing maternal data on hypertension were excluded. Singletons and higher-order multiples were excluded, as were any twins who lacked data on a matched twin. The infants meeting inclusion criteria were subsequently divided into two groups: infants born to mothers with a history of HDP and infants born to normotensive mothers. The study was approved by the Research Ethics Board of the University of Calgary (REB 19-1894) and the Steering Committee of the CNN.

Definitions

Study variables were defined using the CNN Abstractor's Manual.[27]

Maternal hypertension was defined by Canadian standards as a hospital or office measured systolic blood pressure of >140 mmHg and/or diastolic blood pressure of >90 mmHg averaged across a minimum of two measurements in the same arm, at least 15 min apart.[8] Hypertension existing at the beginning of pregnancy (chronic hypertension) and hypertension that developed at or after 20 weeks gestation (pregnancy-induced hypertension, PIH) were both included. The term HDP included chronic hypertension, PIH without proteinuria, preeclampsia, eclampsia, and preeclampsia superimposed on chronic hypertension.[8] Maternal smoking was based on maternal self-report and extraction from prenatal records and defined as any cigarette smoking during pregnancy. Duration of smoking and number of cigarettes smoked are not collected as part of the CNN database. Maternal diabetes was defined as either pre-pregnancy diabetes or gestational diabetes.

Infant gestational age was documented based on the following order of preference: date of in-vitro fertilization, first trimester ultrasound, last menstrual period, obstetric estimate, and neonatal estimate. Antenatal steroid use was classified as any steroid use prior to birth and complete course of steroids.

The Score for Neonatal Acute Physiology (SNAP II) score was calculated as a physiologic illness severity measure at the time of admission.[28] BPD was defined as the persistent requirement for supplemental oxygen at 36 weeks corrected gestation or at the time of discharge to a level I or II NICU.[29] Severe neurologic injury (SNI) was defined as > Grade 2 intraventricular hemorrhage according to the Papile criteria and/or periventricular leukomalacia (PVL), defined as persistent periventricular echogenicity according to ultrasound findings.[30] ROP was defined as ≥Stage 3 in one or both eyes, according to the International Classification of ROP.[31] NEC was defined as ≥Stage 2, according to the Bell criteria.[32] A patent ductus arteriosus (PDA) was documented based on consistent clinical findings, or confirmation by echocardiography. Surfactant use was defined as any administration of surfactant at any point during NICU admission. Nosocomial infection was defined as the presence of a pathogenic organism in either blood or cerebrospinal fluid culture after 48 h of age. Growth discordance between twins was defined as a birth weight discrepancy of >18%.[33]

Outcomes

The outcomes assessed in our study included neonatal mortality, along with clinically significant morbidities including: BPD, SNI, ROP ≥ Stage 3, NEC ≥ Stage 2, and nosocomial infection.

Statistics

Maternal and infant baseline characteristics were compared using the X^2 test for categorical variables and the *t* test or the Mann–Whitney *U* test for continuous variables. Odds ratios for neonatal outcomes were calculated using logistic regression models, corrected for potential confounders including maternal age, antenatal steroid use, maternal smoking, infant gestational age, infant sex, C-section, out born status, SNAP II > 20, and the presence of twin growth discordance. A generalized estimating equations (GEE) model was used to account for the correlation between the twins from the same mother.

The difference in outcomes between the HDP and normotensive group was expressed as the ratio of two geometric means and was transformed back to the original scale for reporting. The normotensive group was the reference for the percentage change. A two-sided $p < 0.05$ was used to determine statistical significance. All analyses were conducted using SAS 9.3 (SAS Institute Inc, Cary, North Carolina).

Results

There were 2414 twin infants <29 weeks gestation that were admitted to participating Canadian NICUs during the study period that met study inclusion criteria. Of these infants, 164 (6.8%) were born to mothers with HDP and 2250 (93.2%) were born to normotensive mothers (Fig. 1).

Table 1 shows the maternal and neonatal characteristics of the two study groups. Maternal age and rates of diabetes, antenatal steroid use, and C-section were higher in the HDP group. Rates of cigarette smoking and chorioamnionitis were higher in the normotensive group. Growth discordance and surfactant use were higher in infants of HDP mothers, while birth weight, proportion of infants with Apgar score at 5 min <7, SNAP II > 20, and duration of hospital stay were lower in infants of HDP mothers. There was no difference in the gestational age between the two groups.

Table 2 shows the adjusted odds ratios and 95% confidence intervals of the outcomes of the cohort. Compared to twin infants in the normotensive group, the odds of ROP ≥ Stage 3 were significantly higher in twin infants in the HDP group (AOR 2.48, 95% CI 1.34–4.59). Infants born to mothers with HDP had increased odds of neonatal mortality compared to infants of normotensive mothers (AOR 2.02, 95% CI 1.23–3.32). Although the incidence of BPD and NEC were higher in infants of mothers with HDP, the difference was not statistically significant. The decreased odds of SNI and nosocomial infection in infants of mothers with HDP compared to infants of normotensive mothers were similarly not statistically significant. There was no significant difference in any of the other outcomes in the analysis of the cohort.

DISCUSSION

In this large national cohort of preterm twin infants <29 weeks gestation, we demonstrate that infants of mothers with HDP have increased odds of severe ROP compared to infants born to normotensive mothers. In addition, preterm twin infants born to mothers with HDP have increased odds of neonatal mortality compared to preterm twin infants of normotensive mothers. Other clinically significant morbidities including BPD, SNI, NEC, and nosocomial infection were not statistically different between the HDP and normotensive groups.

Hehir et al. (2016) reported on the outcomes of twin infants born to mothers with HDP compared to normotensive mothers.[34]

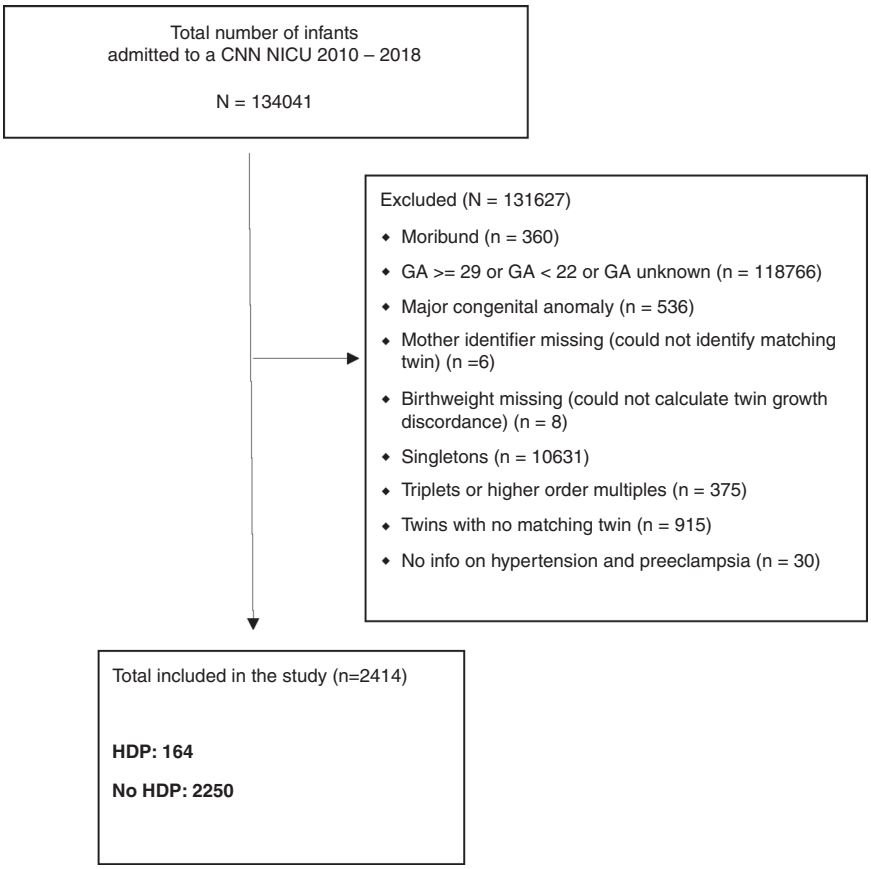

Fig. 1 Flow diagram of the study cohort.

Using data from the ESPRIT (Evaluation of Sonographic Predictors of Restricted growth in Twins) study of eight Irish tertiary care NICUs, they conducted a secondary analysis of perinatal outcomes in twins born to mothers with HDP compared to twins of normotensive mothers. Their cohort included mothers with gestational hypertension and preeclampsia, and they assessed infants of all gestational ages. They reported mothers with HDP had higher rates of diabetes, increased risk for emergency caesarian section delivery, and more twin–twin growth discordance, similar to the findings in our study. Smoking during pregnancy is reported to be protective of preeclampsia and gestational hypertension and as in our study, a larger proportion of normotensive mothers smoked. They found no significant difference in composite morbidity of respiratory distress syndrome, hypoxic ischaemic encephalopathy, PVL, NEC, and sepsis between infants of HDP mothers and infants of normotensive mothers, consistent with our findings. They found no significant difference in overall mortality between infants of HDP mothers compared to normotensive mothers, which is inconsistent with our findings. Their cohort included infants of all gestational ages and the mean gestational age in their HDP group was 35.8 weeks, and in the normotensive group was 36 weeks, significantly older than our study population, and no gestational age-based subgroup analysis was reported. In their cohort, 9.4% (92/977) of mothers comprised the HDP group which was comparable to our cohort where 6.8% (164/2414) of mothers had HDP.

Our findings show increased odds of ROP in twin infants <29 weeks gestation born to hypertensive mothers. This is consistent with some studies in singleton pregnancies that have shown an increased risk of ROP in infants of hypertensive mothers.[6] However, the literature on the relationship between HDP and ROP is conflicting; with some studies suggesting that preeclampsia is protective for ROP and other studies presenting preeclampsia as a risk factor for ROP, and yet others showing no association.[6–10,35]

ROP is an ischemic retinopathy that affects the immature retinal vascular system of the premature infant, and occurs in two phases.[36] The first phase is characterized by cessation of retinal vascular growth; low levels of cytoprotective factors such as insulin-like growth factor (IGF-1) have been implicated in oxidative damage in this phase.[36] The second phase of retinopathy is characterized by excessive and aberrant neovascularization of the hypoxic retina; elevated levels of proangiogenic factors such as vascular endothelial growth factor (VEGF) have been implicated in the pathophysiology in this second phase of ROP.[36] HDP, specifically preeclampsia, is postulated to arise from altered extra-villous trophoblast cell invasion and inadequate remodelling of maternal placental spiral arteries, leading to hypoperfusion of the developing placenta.[3] The hypoxic placenta releases anti-angiogenic factors and proinflammatory factors resulting in the endothelial cell dysfunction, hypertension, and maternal end organ damage seen in preeclampsia and other HDP.[3]

The relationship between HDP and ROP was first described by Holmstrom et al. in 1996, however since then, opposing results have been reported, and the relationship remains inconclusive.[37] Proponents of the model of preeclampsia as being protective for ROP attribute lower levels of circulating VEGF and elevated levels of antiangiogenic factors such as soluble-fms-like tyrosine kinase 1 (sFlt1) and soluble endoglin in preeclampsia as creating an in-utero environment that is protective against the development of retinopathy.[38] However, it is unclear to what extent these maternal factors transmit to the infant, as studies looking at infant and umbilical cord levels of antiangiogenic versus proangiogenic factors have not consistently shown differences

Table 1. Maternal and infant characteristics of twin infants born at <29 weeks gestation to mothers with HDP and normotensive mothers.

Characteristics	Maternal HDP Group $n = 164$	Maternal Normotensive Group $n = 2250$	p value
Maternal age (y), mean (SD)	33.1 (6.9)	30.9 (5.4)	0.002
Gravida, median (IQR)	2 (1, 3)	2 (1, 3)	0.14
Substance use	4 (2%)	96 (4%)	0.31
Cigarette smoking	12 (7%)	282 (13%)	0.04
Diabetes (pre-existing or gestational)	36 (22%)	222 (10%)	<0.001
Antenatal steroid use	155 (96%)	2033 (91%)	0.03
Chorioamnionitis	12 (9%)	265 (14%)	0.08
Caesarian section birth	134 (82%)	1428 (64%)	<0.001
Male gender	102 (62%)	1247 (55%)	0.09
Twin growth discordance	54 (33%)	465 (21%)	0.002
Out born	14 (9%)	268 (12%)	0.19
Gestational age (week), mean (SD)	26.4 (1.5)	26.2 (1.6)	0.07
Gestational age group			
<26 weeks	47 (29%)	706 (31%)	0.46
26–28 weeks	117 (71%)	1544 (69%)	
Birth weight (g), mean (SD)	862 (267)	930 (235)	0.001
APGAR score <7 at 5 min	59 (36%)	890 (40%)	0.29
SNAP II score (>20)	40 (25%)	604 (27%)	0.46
Surfactant use	136 (83%)	1694 (75%)	0.02
PDA	99/162 (61%)	1363/2210 (62%)	0.88
Duration of Hospitalization, median (IQR)	69.5 (41, 100.5)	70 (42, 101)	0.72

HDP hypertensive disorders of pregnancy, *IQR* interquartile range, *PDA* patent ductus arteriosus, *SNAP* score for neonatal acute physiology.

between infants of hypertensive and normotensive mothers.[17,39] It has also been suggested that the chronic mild hypoxia experienced by an infant of a HDP mother may actually accelerate retinal vascularization, thereby reducing the risk of ROP associated with premature delivery.[40]

However, investigators have reported preeclampsia to be a risk factor for ROP through a series of postulated mechanisms not fully elucidated, but consistent with the results from our study.[6,41–43] Increased oxidative stress, pro-inflammatory factors, and lower circulating levels of maternal IGF-1 have all been implicated as potential contributors to increased risk of ROP in preeclampsia.[43]

Two recent systematic review- meta-analyses have shown no significant association between gestational hypertensive disorders and the development of ROP.[11,44] The potential causes for the discrepancy in the literature regarding the association between HDP and ROP are several, but may result from variation in the definition of HDP and the gestational ages and birthweights of the cohorts studied. These previous studies are confined to singleton pregnancies with HDP; importantly, no study to our knowledge has reported on ROP in twin gestation with HDP. Certainly, further robust data is required to help elucidate the relationship and underlying pathophysiology linking ROP and HDP.

In our cohort there was higher antenatal steroid use in the HDP group. This has been described in studies on singleton pregnancies with HDP. Mothers with HDP may be admitted to stabilize their hypertension, giving more time for administration of antenatal steroids. Normotensive mothe present in preterm labour with little time for antenatal steroid use.[45] The lower rates of chorioamnionitis in HDP is also reported by several other studies.[45–47] The number of males in the HDP group was higher but was not statistically significant. Although there is preponderance of males in preeclampsia, the ratio reverses the more preterm the delivery, with a preponderance of female fetuses. This has been attributed to male embryos being more susceptible to implantation disorder with some of those destined to develop preeclampsia resulting in spontaneous abortion.[48] The statistically non-significant number of males in the HDP group may been due to our cohort confined to <29 weeks gestation.

Another result from our study was an increased odds of neonatal mortality in infants <29 weeks gestational age that were born to HDP mothers compared to normotensive mothers. There is controversy in the literature regarding the impact of HDP on neonatal mortality; some studies show reduced mortality with HDP, some show no difference, and yet others show increased mortality with HDP.[13–16] In a large Australian cohort that included infants of all gestational ages, Roberts et al. demonstrated that infants of any gestational age born to mothers with any subtype of HDP had increased risk of neonatal mortality compared to normotensive pregnancies.[16] Other studies looking specifically at preterm singletons showed that after correction for various confounders, preterm infants of HDP pregnancies had decreased mortality compared to preterm infants of normotensive pregnancies.[13–15] Various mechanisms have been proposed to explain these differences including differences in in-utero environments, the underlying indication for preterm delivery, differences in prenatal treatments such as steroids and magnesium sulfate, and variations in the intensity of prenatal monitoring/surveillance between the two populations. Reasons for the discrepancy in results between different studies may be due to differences in definitions or subdivisions of HDP, differences in gestational ages of study cohorts, differences in statistical approaches, and difference in the variables selected for multivariate analyses. Additionally, while all these studies looked at preterm singletons, the contribution of multifetal gestation to the risk of mortality such as in our study, has not been well studied and remains an area of future research.

Our study has several strengths. Firstly, the CNN database is a robust and highly standardized and validated data source. Our large population and detailed demographic data allowed for adjustment for several potential confounding variables, improving

Table 2. Comparison of neonatal outcomes of twin infants born at <29 weeks gestation to mothers with HDP and normotensive mothers.

Outcomes	Maternal HDP Group *n*/*N* (%)	Maternal Normotensive Group *n*/*N* (%)	*p* value	Adjusted[a] OR (95% CI)
Composite Outcome[b]	113/164 (69%)	1484/2250 (66%)	0.44	1.40 (0.92, 2.13)
Mortality	28/164 (17%)	311/2250 (14%)	0.24	2.02 (1.23, 3.32)
BPD	74/140 (53%)	962/1951 (49%)	0.41	1.32 (0.87, 2.02)
SNI (IVH/PVL > Grade 2)	11/154 (7%)	245/2180 (11%)	0.11	0.72 (0.37, 1.39)
ROP ≥ Stage 3	21/110 (19%)	225/1624 (14%)	0.12	2.48 (1.34, 4.59)
NEC ≥ Stage 2	13/164 (8%)	158/2245 (7%)	0.66	1.21 (0.63, 2.35)
Nosocomial Infection	32/164 (20%)	528/2250 (23%)	0.24	0.83 (0.52, 1.34)

Generalized estimating equations (GEE) model was used to account for the correlation between the twins from the same mother.
HDP hypertensive disorder of pregnancy, *BPD* bronchopulmonary dysplasia, *SNI* severe neurologic injury, *IVH* intraventricular hemorrhage, *PVL* periventricular leukomalacia, *ROP* retinopathy of prematurity, *NEC* necrotizing enterocolitis, *SNAP* score for neonatal acute physiology, *OR* odds ratio, *CI* confidence interval.
[a]Adjusted for maternal age, antenatal steroid use, smoking, GA, sex, c-section, out born, SNAPII>20, twin growth discordance.
[b]Composite Outcome = any of mortality, BPD, severe IVH/PVL, severe ROP, NEC, nosocomial infection.

confidence in our results. Using a population-based cohort allowed us to make inferences at a population level.

However, our study is not without limitations. Our data has not made distinctions between the various subtypes of HDP, which may prove to be an important contributing factor to the subsequent development of ROP, although current evidence suggests that subcategorization is not necessary and may increase error due to variations in reporting between centres.[49] Our data also does not differentiate between mono and dichorionic twin pregnancies. However, the incidence of HDP and weight discordance is similar between mono and dichorionic twins.[34] There is also a risk of selection intervention bias in our data, as mothers identified as having HDP and being at a greater risk of negative outcomes may have had closer surveillance throughout the pregnancy.

In summary, our study demonstrates increased odds of severe ROP and increased odds of mortality in twin infants <29 weeks gestation born of hypertensive pregnancies compared to normotensive pregnancies. Our data can be used to identify infants at increased risk of ROP and can be used to counsel parents of HDP pregnancies.

Data disclosure

The data generated for the current study are not publicly available due data transfer agreements and approvals that specifically indicate that the data will not be distributed outside the coordinating site of the Canadian Neonatal Network.

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AUTHOR CONTRIBUTIONS

K.Y.: Concept and design, supervised and revised the proposal, drafting of the manuscript, revision of the manuscript. K.Y.: Wrote the proposal, interpreted data, drafting of manuscript, revision of the manuscript. B.A.: Reviewed proposal, interpreted data, revision and critical appraisal of the manuscript. S.H.: Reviewed proposal, interpreted data, revision, and critical appraisal of the manuscript. D.L.: Interpreted data, revision, and critical appraisal of the manuscript. J.E.: Interpreted data, revision, and critical appraisal of the manuscript. M.C.: Interpreted data, revision, and critical appraisal of the manuscript. M.B.: Revision and critical appraisal of the manuscript, acquisition and analysis of data. P.S.S.: Revision and critical appraisal of the manuscript, acquisition, and analysis of data. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity are appropriately investigated and resolved.

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COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

A retrospective cohort study using anonymized data form a large data base. The study was approved by the Conjoint Health Research Ethics Board University of Calgary.

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Correspondence and requests for materials should be addressed to Kamran Yusuf.

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