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Pre-pregnancy body mass index and other risk factors for early- and late-onset hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome: A population-based retrospective cohort study.

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Title: Pre-pregnancy body mass index and other risk factors for early- and late-onset hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome: A population-based retrospective cohort study.

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Pre-pregnancy BMI and early- and late-onset HELLP syndrome

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Abstract

Background: Obesity increases risk of pre-eclampsia, but the association with hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome is understudied.

Objective: To examine the association between pre-pregnancy body-mass-index (BMI) and HELLP syndrome, including early- vs. late-onset disease.

Study Design: A retrospective cohort study, population-based data.

Setting: British Columbia (BC), Canada, 2008/09-2019/20.

Population: All pregnancies resulting in live births or stillbirths at ≥20 weeks' gestation.

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

Methods: BMI categories (kg/m^2) included: underweight (<18.5), normal (18.5-24.9), overweight (25.0-29.9), and obese (≥30.0). Rates of early- and late-onset HELLP syndrome (<34 vs. ≥34 weeks, respectively) were calculated per 1000 ongoing pregnancies at 20 and 34 weeks' gestation, respectively. Cox regression was used to assess the associations between risk factors (BMI and, e.g., maternal age, parity) and early- vs late-onset HELLP syndrome.

Main outcome measures: HELLP syndrome.

Results: The rates of HELLP syndrome per 1000 women were 2.8 overall (1,116 per 391,941 women), and 1.9, 2.5, 3.2 and 4.0 in underweight, normal BMI, overweight and obese categories, respectively. Overall, gestational age-specific rates increased with pre-pregnancy BMI. Adjusted hazard ratio [AHR] was 2.24 for early-onset (95% confidence interval [CI] 1.65-3.04) vs. AHR 1.48 (95% CI 1.23-1.80) for late-onset HELLP syndrome (p-value for interaction 0.025), compared with normal BMI as the reference group. Chronic hypertension, multiple gestation, bleeding (<20 weeks'

gestation and antepartum) also showed differing AHRs between early- vs. late-onset HELLP.

Conclusions: Pre-pregnancy BMI is positively associated with HELLP syndrome and the association is stronger with early-onset HELLP syndrome. Associations with early- and late-onset HELLP syndrome differed for some risk factors, suggesting possible differences in etiologic mechanisms.

Strengths and limitations of this study

- We were able to describe gestational age-specific incidence of HELLP syndrome, which requires population data on all pregnancies.
- Population-based design coupled with detailed information about demographic, behavioural and clinical factors that allowed for robust adjustment for possible confounding.
- We did not have detailed information on laboratory values used for the diagnosis of HELLP syndrome and therefore we were not able to estimate the severity of HELLP.

- We did not have information about race/ethnicity, socio-economic status (SES) and prior history of pregnancy with preeclampsia/eclampsia or HELLP syndrome.
- Pre-pregnancy BMI was largely self-reported. Approximately 25% of women had missing information about BMI, we used multiple imputation methods to address this limitation.

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Competing interests statement

The authors report no conflict of interest.

Key words

Hypertensive disorders of pregnancy, pregnancy complications, overweight, obesity, pre-pregnancy counseling, etiology, adverse pregnancy outcome, BMI, HELLP syndrome.

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Introduction

Hypertensive disorders of pregnancy, such as pre-eclampsia (PE), are among the leading causes of maternal morbidity and mortality, affecting 3-5% of pregnancies worldwide[1,2] and accounting for up to 14% of maternal deaths.[3] Early-onset PE at <34 weeks' gestation is often associated with placental insufficiency whereas late-onset PE is often associated with pre-existing maternal health conditions such as metabolic syndrome and obesity.[4] Early- vs late-onset PE differ in some risk factors, clinical management and rates of adverse perinatal outcomes.[5,6] Hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome occurs in 0.2-0.8% of pregnancies[7–9] and 10-20% of cases of severe PE.[10] Although HELLP syndrome has been

distinguished from PE as a separate disease,[11] it is still widely regarded as a form of severe PE.[9] While the distinction between early- and late-onset PE and the differences in the association with pre-pregnancy obesity has been established, these differences have not been studied in HELLP syndrome.

Pre-pregnancy obesity is a known modifiable risk factor for pre-eclampsia.[12–15] To date, the world prevalence of obesity has nearly tripled since 1975[16] and the proportion of pregnant women with obesity ranges from 1.8% to 25.3% globally.[17] The prevalence of pre-pregnancy obesity was 17.8% in 2012-2016 in Ontario, Canada[18] and 29.0% in 2019 in the United States.[19] Despite the large increases in obesity in high income countries, the association between maternal pre-pregnancy body-mass-index (BMI) and HELLP syndrome has not been adequately assessed in a large population-based study to date.

We carried out a population-based, retrospective cohort study to examine the association between maternal pre-pregnancy BMI and HELLP syndrome and to assess differences in this association in early- vs late-onset HELLP syndrome. We

hypothesized that maternal obesity is a risk factor for HELLP syndrome, and this relationship may be different in early- compared with late-onset disease. In additional analyses, we examined other risk factors for HELLP syndrome in terms of their association with early- vs late-onset HELLP syndrome.

Materials and Methods

Data sources and study population

The study included all live births and stillbirths at ≥20 weeks' gestation in British Columbia, Canada, between April 1, 2008 and March 31, 2020, with data obtained from the British Columbia Perinatal Database Registry (BCPDR).[20] The BCPDR includes information on >99% of births in BC, with detailed data on maternal demographic characteristics, prenatal care, pregnancy complications, labor and delivery characteristics and neonatal outcomes. Each record, abstracted from medical charts (or midwives' notes), includes also up to 25 ICD-10-CA (International Classification of Diseases, 10th Edition, Canada) codes for diagnoses related to delivery hospitalization and following hospital transfers if applicable. Chart abstraction is standardized and

conducted by trained personnel, and data quality is routinely assessed. Prior validation studies showed high accuracy of collected information on labor and delivery.[21]

Pre-pregnancy BMI and HELLP syndrome

Pre-pregnancy weight and height were based on maternal self-report or health care provider assessment at ≤11 weeks' gestation.[22] Body-mass-index (BMI) was classified as follows (in kg/m^2): underweight (<18.5), normal (18.5-24.9), overweight (25.0-29.9), and obese (≥30.0).[23] The primary outcome of this study was a physician diagnosis of HELLP syndrome in the medical chart, abstracted and recorded in the BCPDR. In Canada, HELLP syndrome is typically diagnosed by the following criteria: LDH ≥600 IU/l, liver transaminases (AST and ALT) elevated more than twice the upper limit of normal, and a platelet count <100,000/μl (10^9/l). Early- and late-onset HELLP syndrome were defined as HELLP syndrome with delivery at <34 weeks and ≥34 weeks' gestation, respectively. Early pregnancy ultrasound was used to ascertain gestational age, and last menstrual period was used for those with missing early pregnancy ultrasound.

Covariates

In addition to BMI, we examined the association between maternal age, nulliparity, pre-existing diabetes, chronic hypertension, *in vitro* fertilization (IVF) conception, multiple gestation, bleeding before 20 weeks, antepartum bleeding or hemorrhage, substance use and smoking during pregnancy and early- vs. late-onset HELLP syndrome. Alcohol use and prior adverse birth outcomes (prior stillbirth or neonatal death) were included as potential confounders; all these factors are known to be associated with HELLP syndrome.[24] Maternal age was categorized as <25, 25-34 and ≥35 years. All chronic conditions and pregnancy complications were identified using ICD-10 codes or data fields abstracted from medical charts to the BCPDR (Table A.1).

Statistical analyses

The rates of HELLP syndrome per 1000 deliveries were compared between women in each BMI category. Complete case analyses were performed for individuals with known BMI. The association between pre-pregnancy BMI and HELLP syndrome was

expressed using crude hazard ratios (HR) and 95% confidence intervals (CI), obtained from a Cox model without adjustment for other risk factors.

Gestational age-specific rates of HELLP syndrome were compared between women in the various BMI categories, using undelivered pregnancies at each gestational week as the denominator. These rates were plotted, and splines with 95% confidence intervals were fitted by the generalized additive model ("gam") smoothing method. Cox models with interaction terms between pre-pregnancy BMI categories and gestational age at HELLP onset (<34 vs ≥34 weeks' gestation) were used to obtain crude HRs and 95% CIs. This analysis was carried out to assess whether gestational age at onset modified the association between BMI and HELLP syndrome.

In multivariable analyses, Cox models were also used to adjust for covariates (listed above) and to also examine their associations with early- vs late-onset of HELLP syndrome using interaction terms. We did not assess early- vs late-onset of HELLP syndrome interactions with risk factors including alcohol use and prior adverse birth

outcomes due to a low number of women with HELLP in these categories, but adjusted for them in the model as potential confounders.

Sensitivity analyses included multiple imputations for missing BMI values based on a multiple imputation procedure using SAS statistical software (PROC MI).[25] Variables included in the imputation were those also included in the regression analyses. Ten imputed datasets were created, with the final results obtained using Rubin's rule.[26] All analyses were repeated with the imputed dataset and results were compared with the primary analyses.

All analyses were carried out using SAS version 9.4 (SAS Institute, Inc., Cary, NC) and R version 4.0.3.[27] Ethics approval was obtained from the University of British Columbia/Children's and Women's Hospital and Health Centre of British Columbia Research Ethics Board (#H20-03985).

Patient and Public Involvement

Patients or the public WERE NOT involved in the design, or conduct, or reporting, or dissemination plans of our research.

Results

Study population

Overall, 538,683 women had a live birth or stillbirth in British Columbia between April 1, 2008 and March 31, 2020 (Supplemental Figure 1). Records with missing gestational age or those with <20 weeks' gestation were excluded (n=14,206, 2.6%). The study population for the primary analyses included 391,941 pregnancies, after exclusion of women with missing BMI (n = 132,536; 24.6%). The overall incidence of HELLP syndrome was 2.85 (95% CI 2.68-3.01) per 1000 pregnancies (n = 1,116).

The proportion of women who were in underweight, normal BMI, overweight and obese categories prior to pregnancy was 5.7%, 59.1%, 21.4%, and 13.8%, respectively. Pre-existing diabetes, chronic hypertension, prior adverse pregnancy outcomes (stillbirth or neonatal death), multiple gestation, gestational hypertension, gestational diabetes, proteinuria, and alcohol use during pregnancy were more frequent in women with overweight and obesity compared with women with normal BMI (Table 1).

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

Nulliparity and ultrasound diagnosed fetal growth restriction were observed more frequently in the underweight group. Substance use and smoking during pregnancy were more frequent in underweight, overweight, and obese groups compared with women with normal BMI.

Unadjusted analyses for pre-pregnancy BMI

The rates of HELLP syndrome in women in underweight, normal, overweight, and obese categories were 1.9, 2.5, 3.2, and 4.0 per 1000 pregnancies, respectively (Table 2). Overall, crude HRs for HELLP syndrome in women who were in the overweight and obese categories were 1.29 (95% CI 1.12-1.49) and 1.62 (95% CI 1.39-1.90), respectively, compared with women who had normal BMI (Table A.2).

The rates of early- and late-onset HELLP syndrome were 0.7 (n=275) and 2.2 (n=841) per 1000 ongoing pregnancies at 20 weeks' and 34 weeks' gestation, respectively (Table A.3). Most cases of HELLP syndrome occurred at or after 34 weeks (75.4%; 841 out of total 1116 cases). Frequencies of overweight and obesity, older

maternal age (≥35), pre-existing diabetes, chronic hypertension, multiple gestation, bleeding before 20 weeks of gestation, antepartum bleeding/hemorrhage, substance use and smoking were higher among women with early-onset vs. late-onset HELLP syndrome. Frequencies of underweight, younger maternal age (<25 years), nulliparity, IVF conception, and alcohol use were higher among women with late-onset HELLP syndrome (Table A.3).

The rates of late-onset HELLP syndrome were higher than early-onset HELLP syndrome regardless of BMI category and maternal age group (Table 2). Nulliparous women, those with pre-existing diabetes, chronic hypertension, prior stillbirth/neonatal death, IVF conception, multiple gestation, alcohol use and substance use also had higher rates of late-onset than early-onset HELLP syndrome. Women with multiple gestation had highest rate of HELLP syndrome, followed by those with chronic hypertension.

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

Differences in gestational age-specific incidence rates of HELLP syndrome by BMI group are shown in Figure 1 (Panel A; Panel B shows log-transformed gestational-age specific rates).

Gestational age-specific rates of HELLP syndrome increased over the course of pregnancy, with higher rates at 36-37 weeks and a subsequent decline among women with pre-pregnancy BMI below or above normal values but not among those with normal BMI (Figure 1, Table A.4). Crude analyses showed that HRs for early-onset HELLP syndrome in women in overweight and obese groups were 1.62 (95% CI 1.21-2.16) and 2.37 (95% CI 1.77-3.18), respectively, compared with women with normal BMI. These HRs were 1.21 (95% CI 1.02-1.42) and 1.42 (95% CI 1.17-1.71) for late-onset HELLP syndrome, respectively (Table A.2).

Adjusted analyses

The associations did not change substantially after adjusting for other risk factors (Table 3). Gestational age at onset of HELLP syndrome modified the effect of maternal BMI on

HELLP syndrome, but only in the obese group. Specifically, obesity was more strongly associated with early-onset HELLP syndrome (AHR 2.24) than with late-onset HELLP syndrome (AHR 1.48, p-value for interaction = 0.025; Table 3).

Adjusted hazard ratios (AHR) for each risk factor calculated separately for early- vs late-onset HELLP syndrome are shown in Table 3. Risk factors significantly associated with HELLP syndrome included overweight, obesity, advanced maternal age (≥ 35 years), nulliparity, pre-existing diabetes, chronic hypertension, multiple gestation, and antepartum bleeding/hemorrhage. Smoking during pregnancy had an inverse association with HELLP syndrome. IVF conception was a risk factor for late-onset but not early-onset HELLP syndrome. Bleeding before 20 weeks and antepartum bleeding/hemorrhage were risk factors for early-onset but not late-onset HELLP syndrome. Obesity (p=0.025), chronic hypertension (p=0.041), multiple gestation (p=0.001), bleeding before 20 weeks (p=0.008) and antepartum bleeding/hemorrhage (p=0.011) differed significantly in their associations with early versus late-onset HELLP syndrome (p-values for interaction).

Sensitivity analyses

Women with missing BMI were not substantially different from women with known BMI (Table A.5); and the results were not appreciably changed after the analyses were repeated using imputed BMI values (Table A.6).

Discussion

Main findings

To our knowledge, this is the largest contemporary study examining the association between pre-pregnancy BMI and HELLP syndrome, including early- and late-onset disease. We showed that the majority of HELLP syndrome (75.4%) occurred at or after 34 weeks' gestation, with the rate of early-onset HELLP syndrome being substantially lower than that of late-onset HELLP syndrome. Women in overweight or obese groups were at elevated risk for developing HELLP syndrome. Obesity was more strongly associated with early-onset than late-onset HELLP syndrome. In addition to BMI, our study showed that chronic hypertension, bleeding before 20 weeks' gestation and

antepartum bleeding/hemorrhage were stronger risk factors for early-onset HELLP syndrome, whereas multiple gestation was a stronger risk factor for late-onset HELLP syndrome.

Interpretation in the context of scientific literature

The rate of HELLP syndrome in our study (2.8 per 1000 women) was similar to the previously reported rate of 2.5 per 1000 singleton pregnancies in Canada in 2012-2016.[24] Prior studies describing the association between pre-pregnancy obesity and HELLP syndrome are sparse and results vary. In a retrospective cohort study from a single tertiary hospital in the United States (n=434), Martin *et al.* found that maternal weight was not associated with HELLP syndrome.[28] Similarly, a case-control study (n= 129 cases and 476 controls) found no association between obesity and HELLP syndrome.[29] Furthermore, a retrospective case-control study (including n=687 cases and 601 controls) showed that pre-pregnancy BMI was associated with PE but not HELLP syndrome and suggested that PE and HELLP may have different pathophysiology.[12] In contrast, a population-based cohort study from Norway

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

(n=418,897) found that pre-pregnancy BMI ≥30kg/m^2 was associated with HELLP syndrome in the first but not the second pregnancy.[9] However, in that study, only 25% of women with a first pregnancy and 30% of women with their second pregnancy had information on BMI. More recently, a population-based study from Canada (n=1,078,323) showed that obesity documented in medical charts was a risk factor for HELLP syndrome,[30] however, obesity rates were underestimated and information on BMI was not available, precluding more detailed analyses.

While PE is typically recognized as early- vs late-onset disease (before vs ≥ 34 weeks gestation, respectively), this distinction is rarely made for HELLP syndrome. A prior population-based cohort study (n=96,861) showed that high pre-pregnancy BMI is a stronger risk factor for late-onset PE than early-onset PE.[15] That study also demonstrated a correlation between increased prevalence of maternal obesity in parallel with late-onset PE during the 18-year period, while the incidence of early-onset PE stayed relatively constant.[15] In contrast, our study shows a stronger association between overweight/obesity and early-onset HELLP syndrome compared with late-

onset HELLP syndrome. This suggests varying pathophysiological pathways between PE and HELLP syndrome or additional obesity-related pathophysiology associated with PE that leads to liver damage at earlier gestation, for instance, obesity-associated steatosis and non-alcoholic fatty liver disease.[31] We chose the same gestational age cut-off of 34 weeks for early- vs late-onset HELLP syndrome as in pre-eclampsia. However, our data suggest an increase in gestational age-specific rates after 28 weeks' gestation in women with obesity and after 30 weeks' gestation in women without obesity. A previous study showed a high proportion of HELLP syndrome cases occurring between 27 and 37 weeks[32] which indicates potential dissimilarities with early- vs late-onset PE. Chronic hypertension, however, was found to be a stronger risk factor for early-onset disease for both PE[6] and HELLP syndrome compared with late-onset disease. It is worth mentioning that the known inverse association between smoking and PE[6] was also observed in HELLP syndrome in our study, and this warrants further investigations.

Clinical and research implications

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

Our findings show that increases in gestational age-specific rates of HELLP syndrome vary by maternal pre-pregnancy BMI. The rates declined after 37 weeks' gestation in women who were in the underweight, overweight and obese categories, but continued increasing in women with normal BMI. This could be due to higher rates of medically indicated early-term deliveries in groups with low or high BMI, which has been shown to reduce maternal morbidity compared with expectant management.[33] It is possible that women whose pre-pregnancy BMI was below and above normal range were more likely to be considered at-risk (due to the abnormal BMI or associated co-morbidity) and delivered at early term (37-38 weeks) to prevent adverse maternal and infant outcomes. In addition to BMI, we also showed that chronic hypertension, bleeding before 20 weeks' gestation and antepartum bleeding/hemorrhage were more strongly associated with early- onset HELLP syndrome, while multiple gestation was more strongly associated with late-onset HELLP syndrome. These findings suggest that risk factors for HELLP syndrome have varied clinical relevance based on gestational age at onset of the disease.

Strengths and limitations

The strengths of this study include its population-based design coupled with detailed information about demographic, behavioural and clinical factors that allowed for robust adjustment for possible confounding. We had a large enough sample to provide precise estimates for associations with HELLP syndrome, a rare outcome.

This study also has several limitations. First, we did not have detailed information on laboratory values important for the diagnosis of HELLP syndrome and therefore we were not able to estimate the severity of HELLP. We assumed that the diagnosis of HELLP syndrome would lead to a prompt delivery to prevent worsening of maternal condition. However, in milder cases, expectant management with close observation may have led to a delay between the diagnosis and delivery, especially at very preterm gestation. As a result, incidence of early-onset HELLP syndrome may have been underestimated in our study. However, we do not expect a large inaccuracy in this regard because HELLP syndrome is considered a potentially life-threatening condition and delivery is typically not delayed. Second, we did not have information about

race/ethnicity, socio-economic status (SES) and prior history of pregnancy with PE/eclampsia or HELLP syndrome, which could have resulted in residual confounding in the assessments of the relation between BMI and HELLP syndrome. However, we adjusted for several possible confounders and did not observe changes in the association between BMI and HELLP syndrome, suggesting that our results are robust. Third, pre-pregnancy BMI was largely self-reported, which may have led to some misclassification. Several validation studies have shown relatively good accuracy of self-reported weight and height for epidemiological studies,[34–36] suggesting that a large misclassification bias is unlikely. A systematic review of BMI self-report misclassifications showed minimal influence on associations of BMI with pregnancy outcomes.[37]

Approximately 25% of women had missing information about BMI. These women were relatively similar to those with known BMI and sensitivity analyses using imputed BMI values yielded results almost identical to the main analyses. Lastly, the analyses

examining differences between early- and late-onset HELLP and risk factors other than BMI were exploratory, and further studies are required to confirm our findings.

Conclusions

Consistent with what is known about PE, pre-pregnancy BMI was found to be a risk factor for HELLP syndrome. However, contrary to the documented association between BMI and PE, with obesity being associated more strongly with late-onset than early-onset PE, our study showed that obesity was more strongly associated with early-onset than with late-onset HELLP syndrome. This information suggests different underlying pathophysiology of the various hypertensive disorders of pregnancy. Our findings can help maternity care providers with regard to pre-pregnancy counselling. Clinicians can better identify women who may benefit from obstetric intervention, as the risk of HELLP increases at late pre-term gestation in all women and continues to increase at term and post-term gestation in women with normal pre-pregnancy BMI. More research on the

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

gestational-age specific effects of pre-pregnancy BMI is needed to elucidate the underlying causes of HELLP syndrome.

Disclosure

The authors report no conflict of interest.

Disclaimer

All inferences, opinions, and conclusions drawn in this publication are those of the authors, and do not reflect the opinions or policies of Perinatal Services BC.

Author Statement/Contribution to Authorship

LW and SL were involved in the conception, planning, carrying out and analyzing data of the project. JNB, GMM, KSJ and NR provided helpful suggestions for the analysis. LW led the writing of the manuscript and received feedback from JNB, GMM, SL, KSJ, NR.

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Tables

Table 1. Maternal demographic and clinical characteristics by pre-pregnancy body-mass-index; British Columbia, 2008/09-2019/20[a]

	Underweight n = 22,392	Normal BMI n = 231,517	Overweight n = 83,864	Obese n = 54,168
Maternal age (years)				
< 25	4018 (17.9)	26332 (11.4)	9733 (11.6)	6947 (12.8)
25-34	14392 (64.3)	146790 (63.4)	52138 (62.2)	33948 (62.7)
≥ 35	3982 (17.8)	58395 (25.2)	21993 (26.2)	13273 (24.5)
Nullipara	12551 (56.1)	117740 (50.9)	37202 (44.4)	22020 (40.7)
Pre-existing diabetes	26 (0.1)	693 (0.3)	672 (0.8)	1006 (1.9)
Chronic hypertension	23 (0.1)	717 (0.3)	727 (0.8)	1380 (2.6)
Prior stillbirth /neonatal death	130 (0.6)	1894 (0.8)	979 (1.2)	791 (1.5)
IVF conception[b]	496 (2.2)	6835 (3.0)	2579 (3.1)	1639 (3.0)
Multiple gestation				
Twins	253 (1.1)	3318 (1.4)	1340 (1.6)	895 (1.7)
Triplets/Quadruplets[d]	<5 (0)	34 (0)	26 (0)	19 (0)
Bleeding < 20 weeks	483 (2.2)	4116 (1.8)	1572 (1.9)	1166 (2.2)
Antepartum bleeding/hemorrhage (≥ 20 weeks)	374 (1.7)	3352 (1.5)	1227 (1.5)	706 (1.3)
Intrauterine Growth Restriction[c]	987 (4.4)	5445 (2.4)	1472 (1.8)	953 (1.8)
Gestational Hypertension	547 (2.4)	8551 (3.7)	5694 (6.8)	6332 (11.7)
Gestational Diabetes	1680 (7.5)	19492 (8.4)	11548 (13.8)	11452 (21.1)

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

Proteinuria	161 (0.7)	2236 (1.0)	1267 (1.5)	1337 (2.5)
Alcohol use	192 (0.9)	2240 (1.0)	944 (1.1)	786 (1.5)
Substance use	1118 (5.0)	8099 (3.5)	3514 (4.2)	2970 (5.5)
Smoking	1727 (7.7)	12943 (5.6)	6155 (7.3)	5576 (10.3)
Gestational age at delivery (weeks)				
20-27	102 (0.5)	881 (0.4)	393 (0.5)	358 (0.7)
28-33	387 (1.7)	3423 (1.5)	1473 (1.8)	1158 (2.1)
34-36	1620 (7.2)	15119 (6.5)	6142 (7.3)	4680 (8.6)
37-41	20076 (89.7)	209831 (90.6)	75017 (89.5)	47448 (87.6)
≥ 42	207 (0.9)	2263 (1.0)	839 (1.0)	524 (1.0)

[a]Data shown as n(%)

[b]IVF = in vitro fertilization

[c]Ultrasound diagnosed intra-uterine growth restriction (IUGR)

[d]Information on cell numbers <5 was suppressed due to confidentiality reasons.

Table 2. Rates of early-onset and late-onset HELLP syndrome per 1000 ongoing pregnancies by maternal demographic and clinical characteristics; British Columbia, 2008/09-2019/20

	Early-onset HELLP syndrome	Late-onset HELLP syndrome	Overall
Pre-pregnancy BMI category			
Underweight	8 (0.4)	35 (1.6)	43 (1.9)
Normal weight	125 (0.5)	462 (2.0)	587 (2.5)
Overweight	73 (0.9)	199 (2.4)	272 (3.2)
Obese	69 (1.3)	145 (2.8)	214 (4.0)
Maternal age (years)			
< 25	30 (0.6)	97 (2.1)	127 (2.7)

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

25-34	158 (0.6)	512 (2.1)	670 (2.7)
≥ 35	87 (0.9)	232 (2.4)	319 (3.3)
Nullipara	188 (1.0)	629 (3.4)	817 (4.3)
Pre-existing diabetes	6 (2.5)	14 (6.3)	20 (8.3)
Chronic hypertension	19 (6.7)	20 (7.7)	39 (13.7)
Prior stillbirth /neonatal death[a]	<5 (<1.0)	<5 (<1.0)	5 (1.3)
IVF conception[b]	19 (1.6)	73 (6.7)	92 (8.0)
Multiple gestation	33 (5.6)	91 (19.3)	124 (21.1)
Bleeding (< 20 weeks)	12 (1.6)	10 (1.5)	22 (3.0)
Antepartum Bleeding/hemorrhage (≥ 20 weeks)	15 (2.7)	12 (2.5)	27 (4.8)
Alcohol use[a]	<5 (<1.0)	<11 (<2.7)	12 (2.9)
Substance use	14 (0.9)	25 (1.6)	39 (2.5)
Smoking	14 (0.5)	36 (1.4)	50 (1.9)

[a]Information on cell numbers <5 was suppressed due to confidentiality reasons. Other numbers were suppressed if needed to avoid back-calculation from the total

[b]IVF = in vitro fertilization

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

Table 3. Adjusted hazard ratios for early-onset and late-onset HELLP syndrome with 95% confidence intervals; British Columbia, 2008/09-2019/20

	Overall AHR (95% CI)[a]	Early-onset HELLP AHR (95% CI)	Late-onset HELLP AHR (95% CI)	P-value[b]
Pre-pregnancy BMI category				
Underweight	0.79 (0.58-1.07)	0.67 (0.33-1.38)	0.82 (0.58-1.16)	0.628
Normal weight	Ref	Ref	Ref	Ref
Overweight	1.34 (1.16-1.55)	1.63 (1.22-2.18)	1.26 (1.07-1.49)	0.129
Obese	1.65 (1.41-1.94)	2.24 (1.65-3.04)	1.48 (1.23-1.80)	0.025
Maternal age (years)				
< 25	0.92 (0.76-1.12)	0.92 (0.62-1.38)	0.92 (0.74-1.15)	0.998
25-34	Ref	Ref	Ref	Ref
⩾ 35	1.27 (1.11-1.47)	1.39 (1.06-1.83)	1.23 (1.05-1.45)	0.445
Nullipara	2.93 (2.56-3.36)	2.56 (1.97-3.33)	3.09 (2.63-3.63)	0.229
Pre-existing diabetes	2.40 (1.51-3.80)	1.64 (0.71-3.81)	2.88 (1.66-5.00)	0.273
Chronic hypertension	3.93 (2.80-5.51)	5.95 (3.62-9.79)	2.92 (1.83-4.66)	0.041
Prior stillbirth/neonatal death[c]	0.88 (0.36-2.13)	N/A	N/A	N/A
IVF conception[d]	1.21 (0.95-1.55)	0.83 (0.50-1.41)	1.37 (1.04-1.80)	0.101
Multiple gestation	13.66 (11.06-16.87)	8.31 (5.59-12.35)	17.81 (13.89-22.83)	0.001
Bleeding at < 20 weeks	0.95 (0.62-1.45)	1.89 (1.05-3.39)	0.60 (0.32-1.12)	0.008
Antepartum bleeding or hemorrhage (⩾ 20 weeks)	2.10 (1.43-3.08)	3.75 (2.22-6.35)	1.37 (0.77-2.43)	0.011
Alcohol use[c]	1.07 (0.60-1.90)	N/A	N/A	N/A
Substance use	0.98 (0.70-1.36)	1.38 (0.78-2.42)	0.84 (0.56-1.27)	0.166
Smoking	0.71 (0.53-0.96)	0.70 (0.40-1.23)	0.71 (0.50-1.01)	0.963

[a]AHR = adjusted hazard ratio, with 95% confidence interval in parentheses, unless otherwise specified

[b]p-value for interaction with early- vs late-onset HELLP syndrome.

[c]N/A = not applicable. We did not examine differences by early- vs late-onset for prior stillbirth/neonatal death or alcohol use due to small sample size.

[d]IVF = in vitro fertilization

Figure legend

Figure 1. Gestational-age specific rates of HELLP syndrome for each BMI category (Panel A); and log-transformed rates (Panel B). Rates from 40 to 45 weeks were combined. Splines with 95% confidence intervals were fitted by the generalized additive model ("gam") smoothing method.

Supplemental Figure 1. Flowchart of study sample selection.

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

Supplementary tables

Supplemental Table 1. Definitions and sources of variables

	Definition	Source
Maternal age (years)	Mother's age (in years) calculated at date of delivery.	BCPDR
Nullipara	Mother has never delivered a baby of at least 500 grams birth weight or at least 20 weeks gestation in a previous pregnancy.	BCPDR
Pre-existing diabetes	Pre-existing diabetes mellitus Type 1 or Type 2, insulin used.	BCPDR
	Pre-existing diabetes mellitus Type 1 or Type 2, insulin not used;	ICD-10
	or 'E10','E11', 'O245','O246','O247'	

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

Chronic hypertension	'O10','O11'	ICD-10
Prior stillbirth /neonatal death	Mother had at least one prior live born infant, who died within the first 28 days of life. Mother had at least one prior stillbirth or intrauterine death documented.	BCPDR
IVF conception	Mother had in-vitro fertilization to achieve the current pregnancy.	BCPDR
Multiple gestation	The incremental sequence number of babies born from the current pregnancy. Should be used with multiple_birth_count. Along with mother_id, required to link to MULTIPLE_LABOURS.	BCPDR
Antepartum bleeding		

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

< 20 weeks	Mother had any antepartum bleeding in pregnancy < 20 weeks gestation.	BCPDR
Antepartum bleeding or hemorrhage ≥ 20 weeks	Mother had any antepartum hemorrhage or bleeding in pregnancy ≥ 20 weeks gestation, including bleeding from cervical polyps.	BCPDR
Intrauterine Growth Restriction[a]	Health care provider identified intrauterine growth restriction (IUGR) during the antenatal period. Baby may or may not be appropriately grown at birth.	BCPDR
Gestational Hypertension	Care provider diagnosed mother with gestational hypertension during the current pregnancy.	BCPDR
Gestational Diabetes	Gestational diabetes, insulin dependent. Gestational diabetes, non-insulin dependent.	BCPDR

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

Proteinuria	Care provider diagnosed proteinuria (>+1g/L) during the current pregnancy.	BCPDR
Alcohol use	Care provider lists mother's use of alcohol as a risk factor in this pregnancy.	BCPDR
Substance use	Mother used any of the following substances at any time during the current pregnancy: heroin/opioids, cocaine, methadone, solvents, or marijuana; OR care provider lists use of prescription, 'other', or unknown other drug as a risk to the pregnancy.	BCPDR
Smoking	Mother smoked tobacco products during pregnancy.	BCPDR
Gestational age at delivery	Algorithm-based estimate of gestational age at delivery. Uses last menstrual period, first ultrasound (<20 weeks), clinical estimate from newborn exam, and documentation from maternal chart.	BCPDR

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

HELLP syndrome	Mother was diagnosed with HELLP Syndrome (H-hemolysis, EL-elevated liver enzymes, LP-low platelet count)	BCPDR

[a]Ultrasound diagnosed intra-uterine growth restriction (IUGR)

Supplemental Table 2. Rates of HELLP syndrome by Body-Mass-Index category and hazard ratios with 95% confidence intervals

	Underweight	Normal BMI	Overweight	Obese
All pregnancies				
N cases (rate per thousand)[a]	43 (1.9)	587 (2.5)	272 (3.2)	214 (4.0)
Crude HR[b]	0.78 (0.57-1.06)	Ref	1.29 (1.12-1.49)	1.62 (1.39-1.90)
Early-onset HELLP (< 34 wks)				
N cases (rate per thousand)[a]	8 (0.4)	125 (0.5)	73 (0.9)	69 (1.3)
Crude HR[b]	0.66 (0.32-1.35)	Ref	1.62 (1.21-2.16)	2.37 (1.77-3.18)

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

Late-onset HELLP (≥ 34 wks)				
N cases (rate per thousand)[a]	35 (1.6)	462 (2.0)	199 (2.4)	145 (2.8)
Crude HR[b]	0.81 (0.57-1.14)	Ref	1.21 (1.02-1.42)	1.42 (1.17-1.71)

[a]Rates are per 1000 ongoing pregnancies at 20 weeks (early-onset HELLP) and at 34 weeks gestation (late-onset HELLP).

[b]HR = hazard ratio, with 95% confidence interval in parentheses, unless otherwise specified

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

Supplemental Table 3. Maternal demographic and clinical characteristics by early- vs late-onset HELLP syndrome; British Columbia, 2008/09-2019/20[a]

	Early-onset HELLP n =275	Late-onset HELLP n = 841
Pre-pregnancy BMI category		
Underweight	8 (2.9)	35 (4.2)
Normal weight	125 (45.5)	462 (54.9)
Overweight	73 (26.6)	199 (23.7)
Obese	69 (25.1)	145 (17.2)
Maternal age (years)		
< 25	30 (10.9)	97 (11.5)
25-34	158 (57.5)	512 (60.9)
≥ 35	87 (31.6)	232 (27.6)

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

Nullipara	188 (68.4)	629 (74.8)
Chronic diabetes	6 (2.2)	14 (1.7)
Chronic hypertension	19 (6.9)	20 (2.4)
Prior stillbirth /neonatal death[b]	<5 (<1.8)	<5 (<0.5)
IVF conception[c]	19 (6.9)	73 (8.7)
Multiple gestation	33 (12.0)	91 (10.8)
Bleeding (< 20 weeks)	12 (4.4)	10 (1.2)
Antepartum bleeding/hemorrhage (≥ 20 weeks)	15 (5.5)	12 (1.4)
Alcohol use[b]	<5 (<1.8)	10 (1.2)
Substance use	14 (5.1)	25 (3.0)
Smoking	14 (5.1)	36 (4.3)

[a]Data shown as n(%)

[b]Information on cell numbers <5 was suppressed due to confidentiality reasons.

[c]IVF = in vitro fertilization

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

Supplemental Table 4. Cases of HELLP syndrome at each gestational age (rate per 1000 ongoing pregnancies)[a]

Gestational age (weeks)	Underweight n = 22,392	Normal BMI n = 231,517	Overweight n = 83,864	Obese n = 54,168
20-21	<5/22392 (<0.22)	<5/231517 (<0.02)	<5/83864 (<0.06)	<5/54168 (<0.09)
22-23	<5/22379 (<0.22)	<5/231351 (<0.02)	<5/83796 (<0.06)	<5/54108 (<0.09)
24-25	<5/22356 (<0.22)	6/231174 (0.03)	<5/83720 (<0.06)	5/54023 (0.09)
26-27	<5/22332 (<0.22)	14/230958 (0.06)	8/83609 (0.10)	6/53926 (0.11)
28-29	<5/22289 (0.04)	16/230635 (0.07)	14/83471 (0.17)	6/53810 (0.11)
30-31	<5/22232 (0.13)	22/230136 (0.10)	18/83269 (0.22)	23/53631 (0.43)

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

32-33	<5/22133 (0.14)	66/229249 (0.29)	29/82870 (0.35)	27/53303 (0.51)
34-35	10/21902 (0.46)	116/227212 (0.51)	58/81998 (0.71)	42/52652 (0.80)
36-37	13/21247 (0.61)	154/221075 (0.70)	70/79515 (0.88)	55/50825 (1.08)
38-39	11/17845 (0.62)	131/189757 (0.69)	56/66951 (0.84)	36/40911 (0.88)
≥ 40	<5/6278 (<0.80)	61/73662 (0.83)	15/26327 (0.57)	12/15135 (0.79)

[a]Information on cell numbers <5 was suppressed due to confidentiality reasons.

600

601

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

Supplemental Table 5. Demographic and clinical characteristics of women missing pre-pregnancy BMI, live births and stillbirths, British Columbia, 200/09-2019/20[a]

	BMI not missing n = 391,941	BMI missing n = 132,536
Maternal age (years)		
< 25	47030 (12.0)	20134 (15.2)
25-34	247268 (63.1)	78660 (59.4)
≥ 35	97643 (24.9)	33742 (25.5)
Nullipara	189513 (48.4)	53789 (40.6)
Pre-existing diabetes	2397 (0.6)	913 (0.7)
Chronic hypertension	2847 (0.7)	890 (0.7)
Prior stillbirth /neonatal death	3794 (1.0)	1734 (1.3)
IVF conception[b]	11549 (3.0)	3877 (2.9)
Multiple gestation		

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

Twins	5806 (1.5)	2478 (1.9)
Triplets/Quadruplets	82 (0)	27 (0)
Antepartum bleeding/hemorrhage		
< 20 weeks	7337 (1.9)	1813 (1.4)
≥ 20 weeks	5659 (1.4)	1496 (1.1)
Intrauterine Growth Restriction[c]	8857 (2.3)	2471 (1.9)
Gestational Hypertension	21124 (5.4)	6623 (5.0)
Gestational Diabetes	44172 (11.3)	13248 (10.0)
Proteinuria	21124 (5.4)	6623 (5.0)
Alcohol use	4162 (1.1)	1845 (1.4)
Substance use	15701 (4.0)	6758 (5.1)
Smoking	26401 (6.7)	10435 (7.9)
Second-hand smoke	26319 (6.7)	7565 (5.7)

[a]Data shown as n(%)

[b]IVF = in vitro fertilization

[c]Ultrasound diagnosed intra-uterine growth restriction (IUGR)

Supplemental Table 6. Hazard Ratios and 95% confidence intervals using imputed data for missing values of BMI

	Underweight	Normal BMI	Overweight	Obese
Early-onset HELLP (< 34 wks)				
N cases (rate per thousand)[a]	8 (0.4)	164 (0.5)	137 (0.9)	71 (1.3)
Adjusted HR[b]	0.76 (0.43-1.33)	Ref	1.54 (1.19-2.00)	2.06 (1.53-2.78)
Late-onset HELLP (≥ 34 wks)				
N cases (rate per thousand) [a]	35 (1.6)	572 (1.9)	376 (2.6)	148 (2.8)

60

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

Adjusted HR[b]	0.96 (0.51-1.8)	Ref	1.24 (0.92-1.66)	1.46 (1.03-2.08)

[a]Rates are per 1000 ongoing pregnancies at 20 weeks (early-onset HELLP syndrome) and at 34 weeks gestation (late-onset HELLP syndrome).

[b]HR = hazard ratio, with 95% confidence interval in parentheses, unless otherwise specified. Adjusted for nulliparity, maternal age, chronic diabetes, chronic hypertension, in vitro fertilization, antepartum bleeding/hemorrhage, gestational diabetes, alcohol, substance use, smoking during pregnancy, prior pregnancy outcomes, and multiple gestation.

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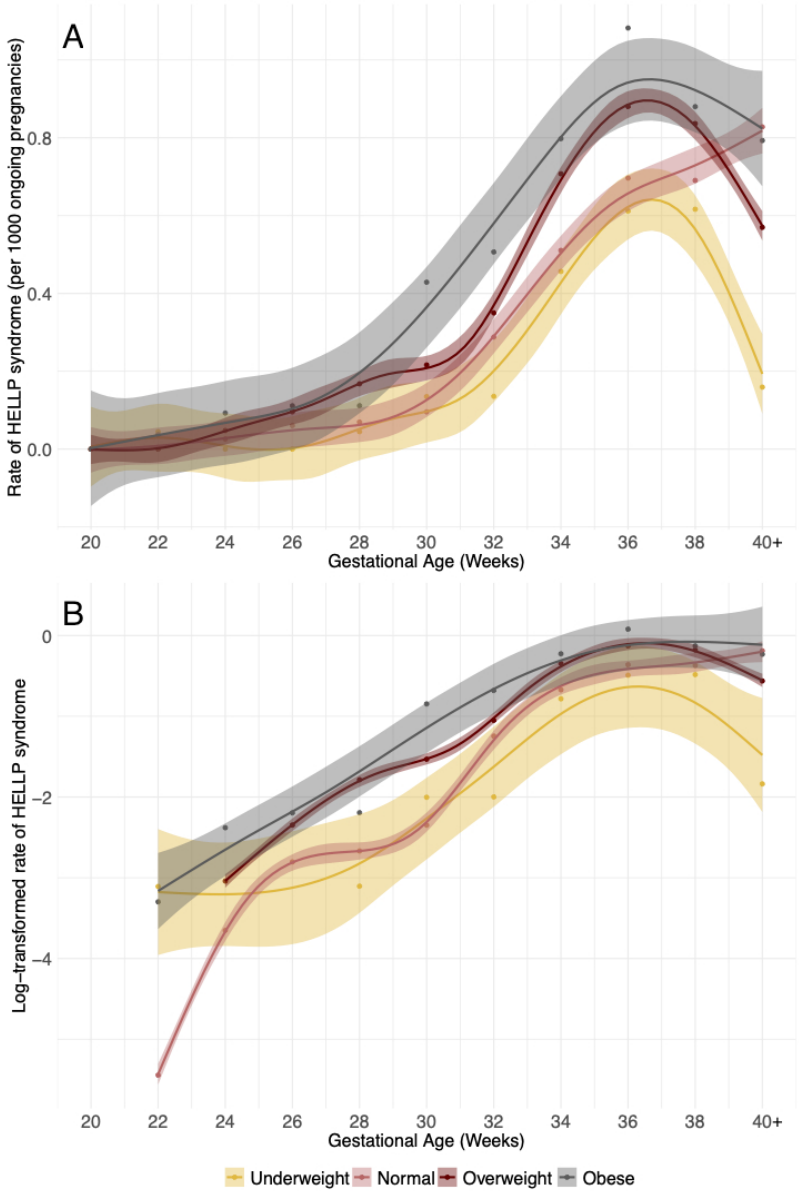

Figure 1. Gestational-age specific rates of HELLP syndrome for each BMI category (Panel A); and log-transformed rates (Panel B). Rates from 40 to 45 weeks were combined. Splines with 95% confidence intervals were fitted by the generalized additive model ("gam") smoothing method.

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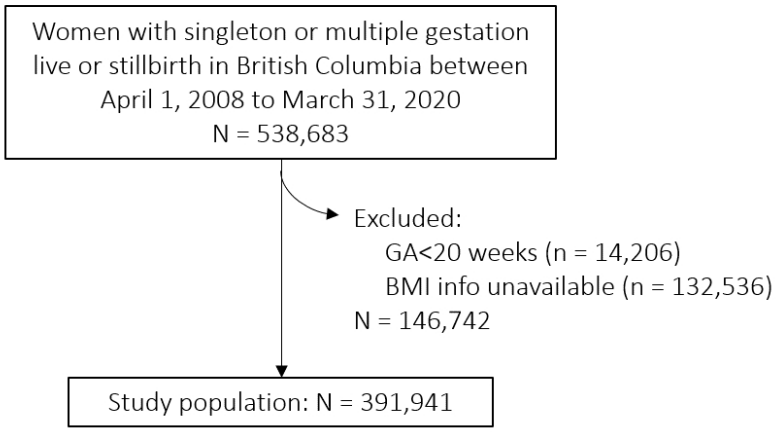

Supplemental Figure 1. Flowchart of study sample selection.

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title page	"Title: Pre-pregnancy body mass index and other risk factors for early- and late-onset hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome: A population-based retrospective cohort study."
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5	Lines 67-84
Objectives	3	State specific objectives, including any prespecified hypotheses	4-5	Lines 85-90
Methods				
Study design	4	Present key elements of study design early in the paper	5-6	Lines 92-122
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6	Lines 92-122
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5-6	Lines 92-122
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	N/A	N/A

Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-7	Lines 92-147
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*31*	Supplemental Table 1. Definitions and sources of variables
Bias	9	Describe any efforts to address potential sources of bias	6-7	Lines 123 - 147
Study size	10	Explain how the study size was arrived at	6-7	Lines 92-147

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7	Lines 123 - 147
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7	Lines 123 – 147
		(*b*) Describe any methods used to examine subgroups and interactions	6-7	Lines 123 – 147
		(*c*) Explain how missing data were addressed	6-7	Lines 123 - 147
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	N/A	
		(*e*) Describe any sensitivity analyses	6-7	Lines 123 - 147
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7-8	Lines 149-164
		(b) Give reasons for non-participation at each stage	7-8	Lines 149-164
		(c) Consider use of a flow diagram	29	Supplemental Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	22-23, 7-8	Table 1, Lines 149-164
		(b) Indicate number of participants with missing data for each variable of interest	7-8	Lines 149-155
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	7-8	Lines 149-155
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	7-8	Lines 149-164
		Case-control study—Report numbers in each exposure category, or summary measures of exposure		
		Cross-sectional study—Report numbers of outcome events or summary measures		
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-9	Lines 165-212
		(*b*) Report category boundaries when continuous variables were categorized	5	Lines 105-106
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A	

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10	Lines 213-216
Discussion				
Key results	18	Summarise key results with reference to study objectives	11	Lines 220-229
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13-23	Lines 280-307
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-13	Lines 230-279
Generalisability	21	Discuss the generalisability (external validity) of the study results	13-15	Lines 280-307
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Title page	

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Pre-pregnancy body mass index and other risk factors for early- and late-onset hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome: A population-based retrospective cohort study.

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Title: Pre-pregnancy body mass index and other risk factors for early- and late-onset hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome: A population-based retrospective cohort study.

Authors

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Pre-pregnancy BMI and early- and late-onset HELLP syndrome

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Abstract

Background: Obesity increases risk of pre-eclampsia, but the association with hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome is understudied.

Objective: To examine the association between pre-pregnancy body-mass-index (BMI) and HELLP syndrome, including early- vs. late-onset disease.

Study Design: A retrospective cohort study using population-based data.

Setting: British Columbia (BC), Canada, 2008/09-2019/20.

Population: All pregnancies resulting in live births or stillbirths at ≥20 weeks' gestation.

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

Methods: BMI categories (kg/m^2) included: underweight (<18.5), normal (18.5-24.9), overweight (25.0-29.9), and obese (≥30.0). Rates of early- and late-onset HELLP syndrome (<34 vs. ≥34 weeks, respectively) were calculated per 1000 ongoing pregnancies at 20 and 34 weeks' gestation, respectively. Cox regression was used to assess the associations between risk factors (e.g., BMI, maternal age and parity) and early- vs late-onset HELLP syndrome.

Main outcome measures: Early- and late-onset HELLP syndrome.

Results: The rates of HELLP syndrome per 1000 women were 2.8 overall (1,116 cases among 391,941 women), and 1.9, 2.5, 3.2 and 4.0 in underweight, normal BMI, overweight and obese categories, respectively. Overall, gestational age-specific rates of HELLP syndrome increased with pre-pregnancy BMI. Obesity (compared with normal BMI) was more strongly associated with early-onset HELLP syndrome (adjusted hazard ratio [AHR] 2.24, (95% confidence interval [CI] 1.65-3.04) than with late-onset HELLP syndrome (AHR 1.48, 95% CI 1.23-1.80) (p-value for interaction 0.025). Chronic

hypertension, multiple gestation, bleeding (<20 weeks' gestation and antepartum) also showed differing AHRs between early- vs. late-onset HELLP syndrome.

Conclusions: Pre-pregnancy BMI is positively associated with HELLP syndrome and the association is stronger with early-onset HELLP syndrome. Associations with early- and late-onset HELLP syndrome differed for some risk factors, suggesting possible differences in etiologic mechanisms.

Strengths and limitations of this study

- We were able to describe gestational age-specific incidence of HELLP syndrome, based on population data on all pregnancies.
- The population-based design coupled with detailed information about demographic, behavioural and clinical factors allowed robust adjustment for possible confounding.
- We did not have detailed information on laboratory values used for the diagnosis of HELLP syndrome and therefore we were not able to estimate the severity of HELLP syndrome.

- We did not have information about race/ethnicity, socio-economic status (SES) and prior history of pregnancy with preeclampsia/eclampsia or HELLP syndrome.
- Pre-pregnancy BMI was largely self-reported. Approximately 25% of women had missing information about BMI. We used multiple imputation methods to address this limitation.

Key words

Hypertensive disorders of pregnancy, pregnancy complications, overweight, obesity, pre-pregnancy counseling, etiology, adverse pregnancy outcome, BMI, HELLP syndrome.

Word count: 3036

Introduction

Hypertensive disorders of pregnancy, such as pre-eclampsia (PE), are among the leading causes of maternal morbidity and mortality, affecting 3-5% of pregnancies

worldwide(1,2) and accounting for up to 14% of maternal deaths.(3) Early-onset PE at <34 weeks' gestation is often associated with placental insufficiency whereas late-onset PE is often associated with pre-existing maternal health conditions such as metabolic syndrome and obesity.(4) Early- vs late-onset PE differ with regard to some risk factors, clinical management and rates of adverse perinatal outcomes.(5,6) A related condition, namely, hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome occurs in 0.2-0.8% of pregnancies(7–9) and 10-20% of cases of severe PE.(10) Although HELLP syndrome has been distinguished from PE as a separate disease,(11) it is still commonly viewed as a form of severe PE.(9) While the distinction between early- and late-onset PE and the difference in the associations between pre-pregnancy obesity and these conditions has been established, such differences have not been studied with regard to HELLP syndrome.

Pre-pregnancy obesity is a known modifiable risk factor for pre-eclampsia.(12–15) To date, the world prevalence of obesity has nearly tripled since 1975(16) and the proportion of pregnant women with obesity ranges from 1.8% to 25.3% globally.(17) The

prevalence of pre-pregnancy obesity was 17.8% in 2012-2016 in Ontario, Canada(18) and 29.0% in 2019 in the United States.(19) Despite the large increases in obesity in high income countries, the association between maternal pre-pregnancy body-mass-index (BMI) and HELLP syndrome has not been adequately assessed in a large population-based study to date.

We carried out a population-based, retrospective cohort study to examine the association between maternal pre-pregnancy BMI and HELLP syndrome and to assess differences in this association in early- vs late-onset HELLP syndrome. We hypothesized that maternal obesity is a risk factor for HELLP syndrome, and this relationship may be different in early- compared with late-onset disease. In additional analyses, we examined other risk factors for HELLP syndrome in terms of their association with early- vs late-onset HELLP syndrome.

Materials and Methods

Data sources and study population

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

The study included all live births and stillbirths at ≥20 weeks' gestation in British Columbia, Canada, between April 1, 2008 and March 31, 2020, with data obtained from the British Columbia Perinatal Database Registry (BCPDR).(20) The BCPDR includes information on >99% of births in BC, with detailed data on maternal demographic characteristics, prenatal care, pregnancy complications, labor and delivery characteristics and neonatal outcomes. Each record, abstracted from medical charts (or midwives' notes), includes up to 25 International Classification of Diseases, 10th Edition, Canadian version (ICD-10-CA) codes for diagnoses related to the delivery hospitalization. Chart abstraction is standardized and conducted by trained personnel, and data quality is routinely assessed. Prior validation studies showed high accuracy of collected information on labor and delivery.(21)

Pre-pregnancy BMI and HELLP syndrome

Pre-pregnancy weight and height were based on maternal self-report or health care provider assessment at ≤11 weeks' gestation.(22) BMI was classified as follows (in kg/m^2): underweight (<18.5), normal (18.5-24.9), overweight (25.0-29.9), and obese

(≥30.0).(23) The primary outcome of this study was a physician diagnosis of HELLP syndrome documented in the medical chart, and abstracted and recorded in the BCPDR. In Canada, HELLP syndrome is typically diagnosed using the Tennessee classification criteria, namely lactate dehydrogenase ⩾600 IU/l, liver transaminases (aspartate aminotransferase and alanine aminotransferase) elevated more than twice the upper limit of normal, and a platelet count <100,000/ μ l (109/l).(24) Early- and late-onset HELLP syndrome were defined as HELLP syndrome with delivery at <34 weeks and ≥34 weeks' gestation, respectively. Early pregnancy ultrasound was used to ascertain gestational age, and the last menstrual period estimate of gestational age was used for those without early pregnancy ultrasound information.

Covariates

In addition to BMI, we examined the association between maternal age, nulliparity, pre-existing diabetes, chronic hypertension, *in vitro* fertilization (IVF) conception, multiple gestation, bleeding before 20 weeks, antepartum bleeding or hemorrhage, substance use and smoking during pregnancy and early- vs. late-onset HELLP syndrome. Alcohol

use and prior adverse birth outcomes (prior stillbirth or neonatal death) were included as potential confounders; all these factors are known to be associated with HELLP syndrome.(25) Maternal age was categorized as <25, 25-34 and ≥35 years. All chronic conditions and pregnancy complications were identified using ICD-10 codes or data fields abstracted from medical charts to the BCPDR (Table A.1).

Statistical analyses

The rates of HELLP syndrome per 1000 deliveries were compared between women in each BMI category. Complete case analyses were performed for individuals with known BMI. The association between pre-pregnancy BMI and HELLP syndrome was first expressed using crude hazard ratios (HR) and 95% confidence intervals (CI), obtained from a Cox model without adjustment for other risk factors.

Gestational age-specific rates of HELLP syndrome were compared between women in the various BMI categories, using undelivered pregnancies at each gestational week as the denominator. These rates were plotted, and splines with 95% confidence intervals were fitted by the generalized additive model ("gam") smoothing

method. Cox models with interaction terms between pre-pregnancy BMI categories and gestational age at HELLP onset (<34 vs ≥34 weeks' gestation) were used to obtain crude HRs and 95% Cis. This analysis was carried out to assess whether gestational age at onset modified the association between BMI and HELLP syndrome.

In multivariable analyses, Cox models were also used to adjust for covariates (listed above) and to also examine their associations with early- vs late-onset of HELLP syndrome using interaction terms. We did not assess early- vs late-onset of HELLP syndrome interactions with risk factors including alcohol use and prior adverse birth outcomes due to a low number of women with HELLP syndrome in these categories, but adjusted for them in the model as potential confounders.

Sensitivity analyses included multiple imputations for missing BMI values based on a multiple imputation procedure using SAS statistical software (PROC MI).(26) Variables included in the imputation were those also included in the regression analyses. Ten imputed datasets were created, with the final results obtained using

Rubin's rule.(27) All analyses were repeated with the imputed dataset and results were compared with the primary analyses.

All analyses were carried out using SAS version 9.4 (SAS Institute, Inc., Cary, NC) and R version 4.0.3.(28) Ethics approval was obtained from the University of British Columbia/Children's and Women's Hospital and Health Centre of British Columbia Research Ethics Board (#H20-03985).

Patient and Public Involvement

Neither patients nor the public were involved in the design, or conduct, or reporting, or dissemination plans of our research.

Results

Study population

Overall, 538,683 women had a live birth or stillbirth in British Columbia between April 1, 2008 and March 31, 2020 (Supplemental Figure 1). Records with missing gestational age or those with <20 weeks' gestational duration were excluded (n=14,206, 2.6%). The

study population for the primary analyses included 391,941 pregnancies, after exclusion of women with missing BMI (n = 132,536; 24.6%). The overall incidence of HELLP syndrome was 2.85 (95% CI 2.68-3.01) per 1000 pregnancies (n = 1,116).

The proportion of women who were in underweight, normal BMI, overweight and obese categories prior to pregnancy was 5.7%, 59.1%, 21.4%, and 13.8%, respectively. Pre-existing diabetes, chronic hypertension, prior adverse pregnancy outcomes (stillbirth or neonatal death), multiple gestation, gestational hypertension, gestational diabetes, proteinuria, and alcohol use during pregnancy were more frequent in women with overweight and obesity compared with women with normal BMI (Table 1). Nulliparity and ultrasound diagnosed fetal growth restriction were observed more frequently in the underweight group. Substance use and smoking during pregnancy were more frequent in underweight, overweight, and obese groups compared with women with normal BMI.

Unadjusted analyses for pre-pregnancy BMI

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

The rates of HELLP syndrome in women in underweight, normal, overweight, and obese categories were 1.9, 2.5, 3.2, and 4.0 per 1000 pregnancies, respectively (Table 2). Overall, crude HRs for HELLP syndrome in women who were in the overweight and obese categories were 1.29 (95% CI 1.12-1.49) and 1.62 (95% CI 1.39-1.90), respectively, compared with women who had normal BMI (Table A.2).

The rates of early- and late-onset HELLP syndrome were 0.7 (n=275) and 2.2 (n=841) per 1000 ongoing pregnancies at 20 weeks' and 34 weeks' gestation, respectively (Table A.3). Most cases of HELLP syndrome occurred at or after 34 weeks (75.4%; 841 out of total 1116 cases). Frequencies of overweight and obesity, older maternal age (≥35), pre-existing diabetes, chronic hypertension, multiple gestation, bleeding before 20 weeks of gestation, antepartum bleeding/hemorrhage, substance use and smoking were higher among women with early-onset vs. late-onset HELLP syndrome. Frequencies of underweight, younger maternal age (<25 years), nulliparity, IVF conception, and alcohol use were higher among women with late-onset HELLP syndrome (Table A.3).

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

The rates of late-onset HELLP syndrome were higher than early-onset HELLP syndrome regardless of BMI category and maternal age group (Table 2). Nulliparous women, those with pre-existing diabetes, chronic hypertension, prior stillbirth/neonatal death, IVF conception, multiple gestation, alcohol use and substance use also had higher rates of late-onset than early-onset HELLP syndrome. Women with multiple gestation had highest rate of HELLP syndrome, followed by those with chronic hypertension.

Differences in gestational age-specific incidence rates of HELLP syndrome by BMI group are shown in Figure 1 (Panel A; Panel B shows log-transformed gestational-age specific rates).

Gestational age-specific rates of HELLP syndrome increased over the course of pregnancy, with higher rates at 36-37 weeks and a subsequent decline among women with pre-pregnancy BMI below or above normal values but not among those with normal BMI (Figure 1, Table A.4). Crude analyses showed that HRs for early-onset HELLP syndrome in women in overweight and obese groups were 1.62 (95% CI 1.21-2.16) and

2.37 (95% CI 1.77-3.18), respectively, compared with women with normal BMI. These HRs were 1.21 (95% CI 1.02-1.42) and 1.42 (95% CI 1.17-1.71) for late-onset HELLP syndrome, respectively (Table A.2).

Adjusted analyses

The associations did not change substantially after adjusting for other risk factors (Table 3). Gestational age at onset of HELLP syndrome modified the effect of maternal BMI on HELLP syndrome, but only in the obese group. Specifically, obesity was more strongly associated with early-onset HELLP syndrome (AHR 2.24) than with late-onset HELLP syndrome (AHR 1.48, p-value for interaction = 0.025; Table 3).

Adjusted hazard ratios (AHR) for each risk factor calculated separately for early- vs late-onset HELLP syndrome are shown in Table 3. Risk factors significantly associated with HELLP syndrome included overweight, obesity, advanced maternal age (≥ 35 years), nulliparity, pre-existing diabetes, chronic hypertension, multiple gestation, and antepartum bleeding/hemorrhage. Smoking during pregnancy had an inverse

association with HELLP syndrome. IVF conception was a risk factor for late-onset but not early-onset HELLP syndrome. Bleeding before 20 weeks and antepartum bleeding/hemorrhage were risk factors for early-onset but not late-onset HELLP syndrome. Obesity (p=0.025), chronic hypertension (p=0.041), multiple gestation (p=0.001), bleeding before 20 weeks (p=0.008) and antepartum bleeding/hemorrhage (p=0.011) differed significantly in their associations with early versus late-onset HELLP syndrome (p-values for interaction).

Sensitivity analyses

Women with missing BMI were not substantially different from women with known BMI (Table A.5); and the results were not appreciably changed after the analyses were repeated using imputed BMI values (Table A.6).

Discussion

Main findings

To our knowledge, this is the largest contemporary study examining the association between pre-pregnancy BMI and HELLP syndrome, including early- and late-onset disease. We showed that the majority of HELLP syndrome (75.4%) occurred at or after 34 weeks' gestation, with the rate of early-onset HELLP syndrome being substantially lower than that of late-onset HELLP syndrome. Women in overweight or obese groups were at elevated risk for developing HELLP syndrome. Obesity was more strongly associated with early-onset than late-onset HELLP syndrome. In addition to BMI, our study showed that chronic hypertension, bleeding before 20 weeks' gestation and antepartum bleeding/hemorrhage were stronger risk factors for early-onset HELLP syndrome, whereas multiple gestation was a stronger risk factor for late-onset HELLP syndrome.

Interpretation in the context of scientific literature

The rate of HELLP syndrome in our study (2.8 per 1000 women) was similar to the previously reported rate of 2.5 per 1000 singleton pregnancies in Canada in 2012-2016.(25) Prior studies describing the association between pre-pregnancy obesity and

HELLP syndrome are sparse and results vary. In a retrospective cohort study from a single tertiary hospital in the United States (n=434), Martin *et al.* found that maternal weight was not associated with HELLP syndrome.(29) Similarly, a case-control study (n= 129 cases and 476 controls) found no association between obesity and HELLP syndrome.(30) Furthermore, a retrospective case-control study (including n=687 cases and 601 controls) showed that pre-pregnancy BMI was associated with PE but not HELLP syndrome and suggested that PE and HELLP may have different pathophysiology.(12) In contrast, a population-based cohort study from Norway (n=418,897) found that pre-pregnancy BMI ≥30kg/m^2 was associated with HELLP syndrome in the first but not the second pregnancy.(9) However, in that study, only 25% of women with a first pregnancy and 30% of women with their second pregnancy had information on BMI. More recently, a population-based study from Canada (n=1,078,323) showed that obesity documented in medical charts was a risk factor for HELLP syndrome,(31) however, obesity rates were underestimated and information on BMI was not available, precluding more detailed analyses.

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

While PE is typically recognized as early- vs late-onset disease (before vs ≥ 34 weeks gestation, respectively), this distinction is rarely made for HELLP syndrome. A prior population-based cohort study (n=96,861) showed that high pre-pregnancy BMI is a stronger risk factor for late-onset PE than early-onset PE.(15) That study also demonstrated a correlation between increased prevalence of maternal obesity in parallel with late-onset PE during the 18-year period, while the incidence of early-onset PE stayed relatively constant.(15) In contrast, our study shows a stronger association between overweight/obesity and early-onset HELLP syndrome compared with late-onset HELLP syndrome. This suggests varying pathophysiological pathways between PE and HELLP syndrome or additional obesity-related pathophysiology associated with PE that leads to liver damage at earlier gestation, for instance, obesity-associated steatosis and non-alcoholic fatty liver disease.(32) We chose the same gestational age cut-off of 34 weeks for early- vs late-onset HELLP syndrome as in pre-eclampsia. However, our data suggest an increase in gestational age-specific rates after 28 weeks' gestation in women with obesity and after 30 weeks' gestation in women without

obesity. A previous study showed a high proportion of HELLP syndrome cases occurring between 27 and 37 weeks,(33) which indicates potential dissimilarities with early- vs late-onset PE. Chronic hypertension, however, was found to be a stronger risk factor for early-onset disease for both PE(6) and HELLP syndrome compared with late-onset disease. It is worth mentioning that the known inverse association between smoking and PE(6) was also observed in HELLP syndrome in our study, and this warrants further investigation.

Clinical and research implications

Our findings show that increases in gestational age-specific rates of HELLP syndrome vary by maternal pre-pregnancy BMI. The rates declined after 37 weeks' gestation in women who were in the underweight, overweight and obese categories, but continued increasing in women with normal BMI. This could be due to higher rates of medically indicated early-term deliveries in groups with low or high BMI, which has been shown to reduce maternal morbidity compared with expectant management.(34) It is possible that women whose pre-pregnancy BMI was below and above normal range were more likely

to be considered at-risk (due to the abnormal BMI or associated co-morbidity) and therefore delivered at early term (37-38 weeks) gestation to prevent adverse maternal and infant outcomes. However, further research in needed to confirm this hypothesis. In addition to BMI, we also showed that chronic hypertension, bleeding before 20 weeks' gestation and antepartum bleeding/hemorrhage were more strongly associated with early- onset HELLP syndrome, while multiple gestation was more strongly associated with late-onset HELLP syndrome. The association between bleeding at <20 weeks gestation and early-onset HELLP syndrome is novel. Such bleeding can be caused by abnormal placental conditions (e.g., abnormal implantation and associated bleeding), which may play a role in the development of HELLP syndrome. These findings are exploratory and require confirmation by other studies. However, they raise the intriguing possibility that determinants of HELLP syndrome (such as antepartum bleeding) have different associations with early and late onset HELLP syndrome depending on whether they occur at <20 weeks or at ⩾20 weeks' gestation. In our study, the association between antepartum bleeding at ⩾20 weeks' gestation and HELLP syndrome (which could

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

have been explained as being a consequence of HELLP syndrome causing placental abruption) was not significant in adjusted models.

Strengths and limitations

The strengths of this study include its population-based design coupled with detailed information about demographic, behavioural and clinical factors that allowed for robust adjustment for possible confounding. We had a large enough sample to provide precise estimates for associations with HELLP syndrome, a rare outcome.

This study also has several limitations. First, we did not have detailed information on laboratory values important for the diagnosis of HELLP syndrome and therefore we were not able to estimate the severity of HELLP. We assumed that the diagnosis of HELLP syndrome would lead to a prompt delivery to prevent worsening of maternal condition. However, in milder cases, expectant management with close observation may have led to a delay between the diagnosis and delivery, especially at very preterm gestation. As a result, incidence of early-onset HELLP syndrome may have been underestimated in our study. However, we do not expect a large inaccuracy in this

regard because HELLP syndrome is considered a potentially life-threatening condition and delivery is typically not delayed. Second, we did not have information about race/ethnicity, socio-economic status (SES) and prior history of pregnancy with PE/eclampsia or HELLP syndrome, which could have resulted in residual confounding in the assessments of the relation between BMI and HELLP syndrome. However, we adjusted for several possible confounders and did not observe changes in the association between BMI and HELLP syndrome, suggesting that our results are robust. Third, pre-pregnancy BMI was largely self-reported, which may have led to some misclassification. Several validation studies have shown relatively good accuracy of self-reported weight and height for epidemiological studies,(35–37) suggesting that a large misclassification bias is unlikely. A systematic review of BMI self-report misclassification showed minimal influence on associations between BMI and pregnancy outcomes.(38)

Approximately 25% of women had missing information about BMI. These women were relatively similar to those with known BMI and sensitivity analyses using imputed

BMI values yielded results almost identical to the main analyses. Lastly, the analyses examining differences between early- and late-onset HELLP and risk factors other than BMI were exploratory, and further studies are required to confirm our findings.

Conclusions

Consistent with what is known about PE, pre-pregnancy BMI was found to be a risk factor for HELLP syndrome. However, contrary to the documented association between BMI and PE, with obesity being associated more strongly with late-onset than early-onset PE, our study showed that obesity was more strongly associated with early-onset than with late-onset HELLP syndrome. This suggests potentially different underlying pathophysiology for the various hypertensive disorders of pregnancy. Our findings can help maternity care providers with regard to pre-pregnancy counselling. Clinicians can better identify women who may benefit from obstetric intervention, as the risk of HELLP increases at late pre-term gestation in all women and continues to increase at term and post-term gestation in women with normal pre-pregnancy BMI. More research on the

gestational-age specific effects of pre-pregnancy BMI is needed to elucidate the underlying causes of HELLP syndrome.

Disclosure

The authors report no conflict of interest.

Disclaimer

All inferences, opinions, and conclusions drawn in this publication are those of the authors, and do not reflect the opinions or policies of Perinatal Services BC.

Author Statement/Contribution to Authorship

LW and SL were involved in the conception, planning, carrying out and analyzing data of the project. JNB, GMM, KSJ and NR provided helpful suggestions for the analysis. LW led the writing of the manuscript and received feedback from JNB, GMM, SL, KSJ, NR.

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Competing interests statement

The authors report no conflict of interest.

Data availability

Data may be obtained from a third party and are not publicly available.

Ethics Approval Statement

Ethics approval was obtained from the University of British Columbia/Children's and Women's Hospital and Health Centre of British Columbia Research Ethics Board (#H20-03985).

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Pre-pregnancy BMI and early- and late-onset HELLP syndrome

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Tables

Table 1. Maternal demographic and clinical characteristics by pre-pregnancy body-mass-index; British Columbia, 2008/09-2019/20[a]

	Underweight n = 22,392	Normal BMI n = 231,517	Overweight n = 83,864	Obese n = 54,168
Maternal age (years)				
< 25	4018 (17.9)	26332 (11.4)	9733 (11.6)	6947 (12.8)
25-34	14392 (64.3)	146790 (63.4)	52138 (62.2)	33948 (62.7)
≥ 35	3982 (17.8)	58395 (25.2)	21993 (26.2)	13273 (24.5)
Nullipara	12551 (56.1)	117740 (50.9)	37202 (44.4)	22020 (40.7)
Pre-existing diabetes	26 (0.1)	693 (0.3)	672 (0.8)	1006 (1.9)
Chronic hypertension	23 (0.1)	717 (0.3)	727 (0.8)	1380 (2.6)
Prior stillbirth /neonatal death	130 (0.6)	1894 (0.8)	979 (1.2)	791 (1.5)
IVF conception[b]	496 (2.2)	6835 (3.0)	2579 (3.1)	1639 (3.0)
Multiple gestation				
Twins	253 (1.1)	3318 (1.4)	1340 (1.6)	895 (1.7)
Triplets/Quadruplets[d]	<5 (0)	34 (0)	26 (0)	19 (0)
Bleeding < 20 weeks	483 (2.2)	4116 (1.8)	1572 (1.9)	1166 (2.2)
Antepartum bleeding/hemorrhage (≥ 20 weeks)	374 (1.7)	3352 (1.5)	1227 (1.5)	706 (1.3)
Intrauterine Growth Restriction[c]	987 (4.4)	5445 (2.4)	1472 (1.8)	953 (1.8)
Gestational Hypertension	547 (2.4)	8551 (3.7)	5694 (6.8)	6332 (11.7)
Gestational Diabetes	1680 (7.5)	19492 (8.4)	11548 (13.8)	11452 (21.1)

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

Proteinuria	161 (0.7)	2236 (1.0)	1267 (1.5)	1337 (2.5)
Alcohol use	192 (0.9)	2240 (1.0)	944 (1.1)	786 (1.5)
Substance use	1118 (5.0)	8099 (3.5)	3514 (4.2)	2970 (5.5)
Smoking	1727 (7.7)	12943 (5.6)	6155 (7.3)	5576 (10.3)
Gestational age at delivery (weeks)				
20-27	102 (0.5)	881 (0.4)	393 (0.5)	358 (0.7)
28-33	387 (1.7)	3423 (1.5)	1473 (1.8)	1158 (2.1)
34-36	1620 (7.2)	15119 (6.5)	6142 (7.3)	4680 (8.6)
37-41	20076 (89.7)	209831 (90.6)	75017 (89.5)	47448 (87.6)
≥ 42	207 (0.9)	2263 (1.0)	839 (1.0)	524 (1.0)

[a]Data shown as n(%)

[b]IVF = in vitro fertilization

[c]Ultrasound diagnosed intra-uterine growth restriction (IUGR)

[d]Information on cell numbers <5 was suppressed due to confidentiality reasons.

Table 2. Rates of early-onset and late-onset HELLP syndrome per 1000 ongoing pregnancies by maternal demographic and clinical characteristics; British Columbia, 2008/09-2019/20

	Early-onset HELLP syndrome	Late-onset HELLP syndrome	Overall
Pre-pregnancy BMI category			
Underweight	8 (0.4)	35 (1.6)	43 (1.9)
Normal weight	125 (0.5)	462 (2.0)	587 (2.5)
Overweight	73 (0.9)	199 (2.4)	272 (3.2)
Obese	69 (1.3)	145 (2.8)	214 (4.0)
Maternal age (years)			
< 25	30 (0.6)	97 (2.1)	127 (2.7)

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

25-34	158 (0.6)	512 (2.1)	670 (2.7)
≥ 35	87 (0.9)	232 (2.4)	319 (3.3)
Nullipara	188 (1.0)	629 (3.4)	817 (4.3)
Pre-existing diabetes	6 (2.5)	14 (6.3)	20 (8.3)
Chronic hypertension	19 (6.7)	20 (7.7)	39 (13.7)
Prior stillbirth /neonatal death[a]	<5 (<1.0)	<5 (<1.0)	5 (1.3)
IVF conception[b]	19 (1.6)	73 (6.7)	92 (8.0)
Multiple gestation	33 (5.6)	91 (19.3)	124 (21.1)
Bleeding (< 20 weeks)	12 (1.6)	10 (1.5)	22 (3.0)
Antepartum Bleeding/hemorrhage (≥ 20 weeks)	15 (2.7)	12 (2.5)	27 (4.8)
Alcohol use[a]	<5 (<1.0)	<11 (<2.7)	12 (2.9)
Substance use	14 (0.9)	25 (1.6)	39 (2.5)
Smoking	14 (0.5)	36 (1.4)	50 (1.9)

[a]Information on cell numbers <5 was suppressed due to confidentiality reasons. Other numbers were suppressed if needed to avoid back-calculation from the total

[b]IVF = in vitro fertilization

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

Table 3. Adjusted hazard ratios for early-onset and late-onset HELLP syndrome with 95% confidence intervals; British Columbia, 2008/09-2019/20

	Overall AHR (95% CI)[a]	Early-onset HELLP AHR (95% CI)	Late-onset HELLP AHR (95% CI)	P-value[b]
Pre-pregnancy BMI category				
Underweight	0.79 (0.58-1.07)	0.67 (0.33-1.38)	0.82 (0.58-1.16)	0.628
Normal weight	Ref	Ref	Ref	Ref
Overweight	1.34 (1.16-1.55)	1.63 (1.22-2.18)	1.26 (1.07-1.49)	0.129
Obese	1.65 (1.41-1.94)	2.24 (1.65-3.04)	1.48 (1.23-1.80)	0.025
Maternal age (years)				
< 25	0.92 (0.76-1.12)	0.92 (0.62-1.38)	0.92 (0.74-1.15)	0.998
25-34	Ref	Ref	Ref	Ref
⩾ 35	1.27 (1.11-1.47)	1.39 (1.06-1.83)	1.23 (1.05-1.45)	0.445
Nullipara	2.93 (2.56-3.36)	2.56 (1.97-3.33)	3.09 (2.63-3.63)	0.229
Pre-existing diabetes	2.40 (1.51-3.80)	1.64 (0.71-3.81)	2.88 (1.66-5.00)	0.273
Chronic hypertension	3.93 (2.80-5.51)	5.95 (3.62-9.79)	2.92 (1.83-4.66)	0.041
Prior stillbirth/neonatal death[c]	0.88 (0.36-2.13)	N/A	N/A	N/A
IVF conception[d]	1.21 (0.95-1.55)	0.83 (0.50-1.41)	1.37 (1.04-1.80)	0.101
Multiple gestation	13.66 (11.06-16.87)	8.31 (5.59-12.35)	17.81 (13.89-22.83)	0.001
Bleeding at < 20 weeks	0.95 (0.62-1.45)	1.89 (1.05-3.39)	0.60 (0.32-1.12)	0.008
Antepartum bleeding or hemorrhage (⩾ 20 weeks)	2.10 (1.43-3.08)	3.75 (2.22-6.35)	1.37 (0.77-2.43)	0.011
Alcohol use[c]	1.07 (0.60-1.90)	N/A	N/A	N/A
Substance use	0.98 (0.70-1.36)	1.38 (0.78-2.42)	0.84 (0.56-1.27)	0.166
Smoking	0.71 (0.53-0.96)	0.70 (0.40-1.23)	0.71 (0.50-1.01)	0.963

[a]AHR = adjusted hazard ratio, with 95% confidence interval in parentheses, were obtained from the Cox model that included all variables in the table.

[b]p-value for interaction with early- vs late-onset HELLP syndrome.

[c]N/A = not applicable. We did not examine differences by early- vs late-onset for prior stillbirth/neonatal death or alcohol use due to small sample size.

[d]IVF = in vitro fertilization

Figure legend

Figure 1. Gestational-age specific rates of HELLP syndrome for each BMI category (Panel A); and log-transformed rates (Panel B). Rates from 40 to 45 weeks were combined. Splines with 95% confidence intervals were fitted by the generalized additive model ("gam") smoothing method.

Supplemental Figure 1. Flowchart of study sample selection.

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

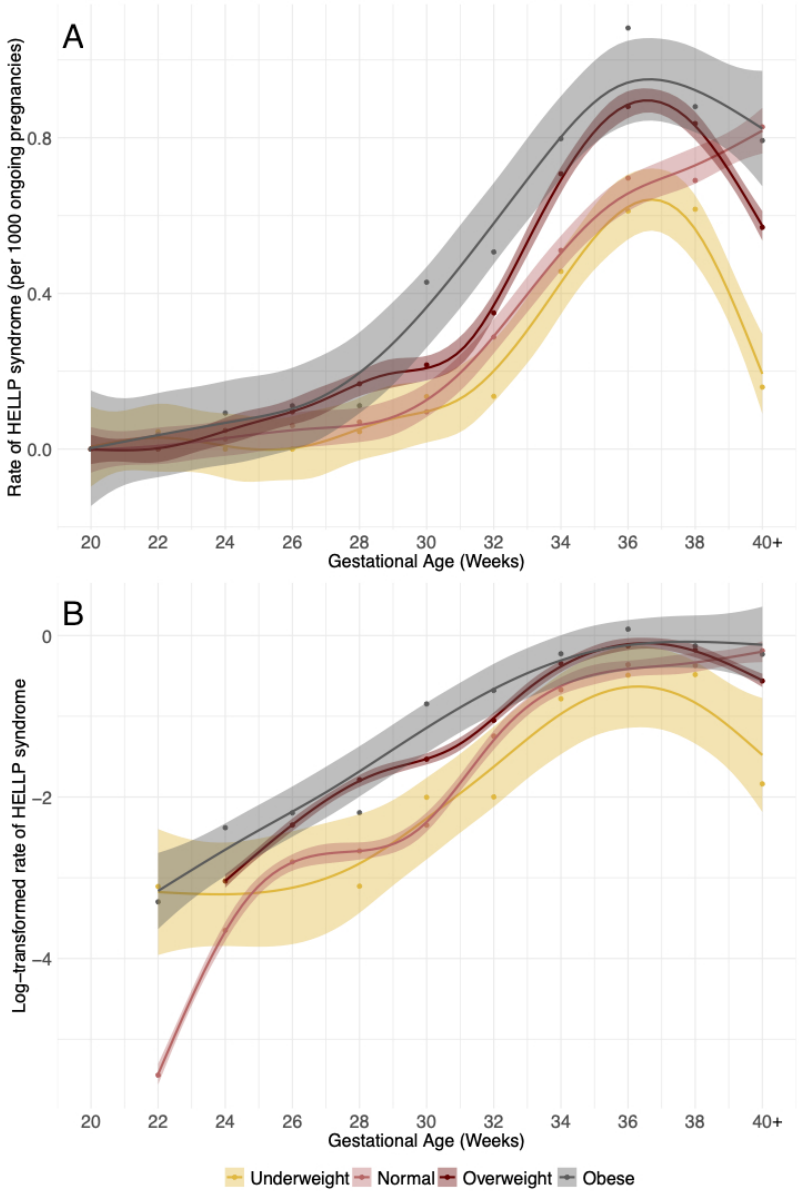

Figure 1. Gestational-age specific rates of HELLP syndrome for each BMI category (Panel A); and log-transformed rates (Panel B). Rates from 40 to 45 weeks were combined. Splines with 95% confidence intervals were fitted by the generalized additive model ("gam") smoothing method.

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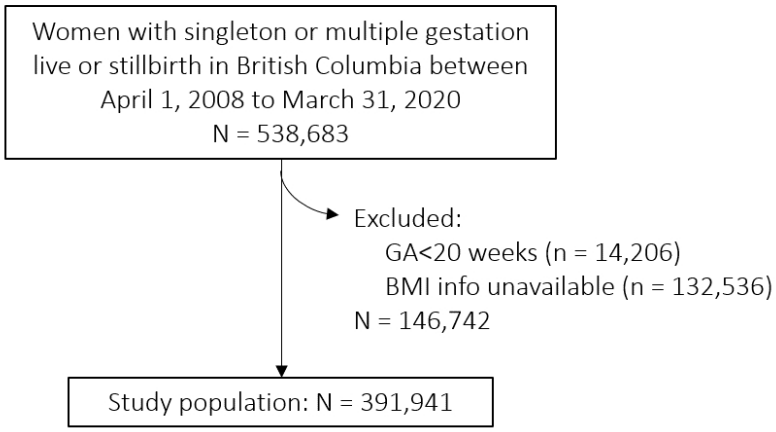

Supplemental Figure 1. Flowchart of study sample selection.

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Supplementary tables

Supplemental Table 1. Definitions and sources of variables

	Definition	Source
Maternal age (years)	Mother's age (in years) calculated at date of delivery.	BCPDR
Nullipara	Mother has never delivered a baby of at least 500 grams birth weight or at least 20 weeks gestation in a previous pregnancy.	BCPDR
Pre-existing diabetes	Pre-existing diabetes mellitus Type 1 or Type 2, insulin used. Pre-existing diabetes mellitus Type 1 or Type 2, insulin not used; or 'E10','E11', 'O245','O246','O247'	BCPDR ICD-10
Chronic hypertension	'O10','O11'	ICD-10
Prior stillbirth /neonatal death	Mother had at least one prior live born infant, who died within the first 28 days of life. Mother had at least one prior stillbirth or intrauterine death documented.	BCPDR
IVF conception	Mother had in-vitro fertilization to achieve the current pregnancy.	BCPDR
Multiple gestation	The incremental sequence number of babies born from the current pregnancy. Should be used with multiple_birth_count. Along with mother_id, required to link to MULTIPLE_LABOURS.	BCPDR

Antepartum bleeding < 20 weeks	Mother had any antepartum bleeding in pregnancy < 20 weeks gestation.	BCPDR
Antepartum bleeding or hemorrhage ≥ 20 weeks	Mother had any antepartum hemorrhage or bleeding in pregnancy ≥ 20 weeks gestation, including bleeding from cervical polyps.	BCPDR
Intrauterine Growth Restriction[a]	Health care provider identified intrauterine growth restriction (IUGR) during the antenatal period. Baby may or may not be appropriately grown at birth.	BCPDR
Gestational Hypertension	Care provider diagnosed mother with gestational hypertension during the current pregnancy.	BCPDR
Gestational Diabetes	Gestational diabetes, insulin dependent. Gestational diabetes, non-insulin dependent.	BCPDR
Proteinuria	Care provider diagnosed proteinuria (>+1g/L) during the current pregnancy.	BCPDR
Alcohol use	Care provider lists mother's use of alcohol as a risk factor in this pregnancy.	BCPDR

Substance use	Mother used any of the following substances at any time during the current pregnancy: heroin/opioids, cocaine, methadone, solvents, or marijuana; OR care provider lists use of prescription, 'other', or unknown other drug as a risk to the pregnancy.	BCPDR
Smoking	Mother smoked tobacco products during pregnancy.	BCPDR
Gestational age at delivery	Algorithm-based estimate of gestational age at delivery. Uses last menstrual period, first ultrasound (<20 weeks), clinical estimate from newborn exam, and documentation from maternal chart.	BCPDR
HELLP syndrome	Mother was diagnosed with HELLP Syndrome (H-hemolysis, EL-elevated liver enzymes, LP-low platelet count)	BCPDR

[a]Ultrasound diagnosed intra-uterine growth restriction (IUGR)

Supplemental Table 2. Rates of HELLP syndrome by Body-Mass-Index category and hazard ratios with 95% confidence intervals

	Underweight	Normal BMI	Overweight	Obese
All pregnancies				
N cases (rate per thousand)[a]	43 (1.9)	587 (2.5)	272 (3.2)	214 (4.0)
Crude HR[b]	0.78 (0.57-1.06)	Ref	1.29 (1.12-1.49)	1.62 (1.39-1.90)
Early-onset HELLP (< 34 wks)				
N cases (rate per thousand)[a]	8 (0.4)	125 (0.5)	73 (0.9)	69 (1.3)
Crude HR[b]	0.66 (0.32-1.35)	Ref	1.62 (1.21-2.16)	2.37 (1.77-3.18)
Late-onset HELLP (≥ 34 wks)				
N cases (rate per thousand)[a]	35 (1.6)	462 (2.0)	199 (2.4)	145 (2.8)
Crude HR[b]	0.81 (0.57-1.14)	Ref	1.21 (1.02-1.42)	1.42 (1.17-1.71)

[a]Rates are per 1000 ongoing pregnancies at 20 weeks (early-onset HELLP) and at 34 weeks gestation (late-onset HELLP).

[b]HR = hazard ratio, with 95% confidence interval in parentheses, unless otherwise specified

Supplemental Table 3. Maternal demographic and clinical characteristics by early- vs late-onset HELLP syndrome; British Columbia, 2008/09-2019/20[a]

	Early-onset HELLP n =275	Late-onset HELLP n = 841
Pre-pregnancy BMI category		
Underweight	8 (2.9)	35 (4.2)
Normal weight	125 (45.5)	462 (54.9)
Overweight	73 (26.6)	199 (23.7)
Obese	69 (25.1)	145 (17.2)
Maternal age (years)		
< 25	30 (10.9)	97 (11.5)
25-34	158 (57.5)	512 (60.9)
≥ 35	87 (31.6)	232 (27.6)
Nullipara	188 (68.4)	629 (74.8)
Chronic diabetes	6 (2.2)	14 (1.7)

Chronic hypertension	19 (6.9)	20 (2.4)
Prior stillbirth /neonatal death[b]	<5 (<1.8)	<5 (<0.5)
IVF conception[c]	19 (6.9)	73 (8.7)
Multiple gestation	33 (12.0)	91 (10.8)
Bleeding (< 20 weeks)	12 (4.4)	10 (1.2)
Antepartum bleeding/hemorrhage (≥ 20 weeks)	15 (5.5)	12 (1.4)
Alcohol use[b]	<5 (<1.8)	10 (1.2)
Substance use	14 (5.1)	25 (3.0)
Smoking	14 (5.1)	36 (4.3)

[a]Data shown as n(%)

[b]Information on cell numbers <5 was suppressed due to confidentiality reasons.

[c]IVF = in vitro fertilization

Supplemental Table 4. Cases of HELLP syndrome at each gestational age (rate per 1000 ongoing pregnancies)[a]

Gestational age (weeks)	Underweight n = 22,392	Normal BMI n = 231,517	Overweight n = 83,864	Obese n = 54,168
20-21	<5/22392 (<0.22)	<5/231517 (<0.02)	<5/83864 (<0.06)	<5/54168 (<0.09)
22-23	<5/22379 (<0.22)	<5/231351 (<0.02)	<5/83796 (<0.06)	<5/54108 (<0.09)
24-25	<5/22356 (<0.22)	6/231174 (0.03)	<5/83720 (<0.06)	5/54023 (0.09)
26-27	<5/22332 (<0.22)	14/230958 (0.06)	8/83609 (0.10)	6/53926 (0.11)
28-29	<5/22289 (0.04)	16/230635 (0.07)	14/83471 (0.17)	6/53810 (0.11)
30-31	<5/22232 (0.13)	22/230136 (0.10)	18/83269 (0.22)	23/53631 (0.43)
32-33	<5/22133 (0.14)	66/229249 (0.29)	29/82870 (0.35)	27/53303 (0.51)
34-35	10/21902 (0.46)	116/227212 (0.51)	58/81998 (0.71)	42/52652 (0.80)
36-37	13/21247 (0.61)	154/221075 (0.70)	70/79515 (0.88)	55/50825 (1.08)
38-39	11/17845 (0.62)	131/189757 (0.69)	56/66951 (0.84)	36/40911 (0.88)
≥ 40	<5/6278 (<0.80)	61/73662 (0.83)	15/26327 (0.57)	12/15135 (0.79)

[a]Information on cell numbers <5 was suppressed due to confidentiality reasons.

Supplemental Table 5. Demographic and clinical characteristics of women missing pre-pregnancy BMI, live births and stillbirths, British Columbia, 200/09-2019/20[a]

	BMI not missing n = 391,941	BMI missing n = 132,536
Maternal age (years)		
< 25	47030 (12.0)	20134 (15.2)
25-34	247268 (63.1)	78660 (59.4)
≥ 35	97643 (24.9)	33742 (25.5)
Nullipara	189513 (48.4)	53789 (40.6)
Pre-existing diabetes	2397 (0.6)	913 (0.7)
Chronic hypertension	2847 (0.7)	890 (0.7)
Prior stillbirth /neonatal death	3794 (1.0)	1734 (1.3)
IVF conception[b]	11549 (3.0)	3877 (2.9)
Multiple gestation		
Twins	5806 (1.5)	2478 (1.9)

Triplets/Quadruplets	82 (0)	27 (0)
Antepartum bleeding/hemorrhage		
< 20 weeks	7337 (1.9)	1813 (1.4)
≥ 20 weeks	5659 (1.4)	1496 (1.1)
Intrauterine Growth Restriction[c]	8857 (2.3)	2471 (1.9)
Gestational Hypertension	21124 (5.4)	6623 (5.0)
Gestational Diabetes	44172 (11.3)	13248 (10.0)
Proteinuria	21124 (5.4)	6623 (5.0)
Alcohol use	4162 (1.1)	1845 (1.4)
Substance use	15701 (4.0)	6758 (5.1)
Smoking	26401 (6.7)	10435 (7.9)
Second-hand smoke	26319 (6.7)	7565 (5.7)

[a]Data shown as n(%)

[b]IVF = in vitro fertilization

[c]Ultrasound diagnosed intra-uterine growth restriction (IUGR)

Supplemental Table 6. Hazard Ratios and 95% confidence intervals using imputed data for missing values of BMI

	Underweight	Normal BMI	Overweight	Obese
Early-onset HELLP (< 34 wks)				
N cases (rate per thousand)[a]	8 (0.4)	164 (0.5)	137 (0.9)	71 (1.3)
Adjusted HR[b]	0.76 (0.43-1.33)	Ref	1.54 (1.19-2.00)	2.06 (1.53-2.78)
Late-onset HELLP (≥ 34 wks)				
N cases (rate per thousand) [a]	35 (1.6)	572 (1.9)	376 (2.6)	148 (2.8)
Adjusted HR[b]	0.96 (0.51-1.8)	Ref	1.24 (0.92-1.66)	1.46 (1.03-2.08)

[a]Rates are per 1000 ongoing pregnancies at 20 weeks (early-onset HELLP syndrome) and at 34 weeks gestation (late-onset HELLP syndrome).

[b]HR = hazard ratio, with 95% confidence interval in parentheses, unless otherwise specified. Adjusted for nulliparity, maternal age, chronic diabetes, chronic hypertension, in vitro fertilization, antepartum bleeding/hemorrhage, gestational diabetes, alcohol, substance use, smoking during pregnancy, prior pregnancy outcomes, and multiple gestation.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title page	"Title: Pre-pregnancy body mass index and other risk factors for early- and late-onset hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome: A population-based retrospective cohort study."
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5	Lines 67-84
Objectives	3	State specific objectives, including any prespecified hypotheses	4-5	Lines 85-90
Methods				
Study design	4	Present key elements of study design early in the paper	5-6	Lines 92-122
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6	Lines 92-122
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5-6	Lines 92-122
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	N/A	N/A

Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-7	Lines 92-147
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*31*	Supplemental Table 1. Definitions and sources of variables
Bias	9	Describe any efforts to address potential sources of bias	6-7	Lines 123 - 147
Study size	10	Explain how the study size was arrived at	6-7	Lines 92-147

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7	Lines 123 - 147
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7	Lines 123 – 147
		(*b*) Describe any methods used to examine subgroups and interactions	6-7	Lines 123 – 147
		(*c*) Explain how missing data were addressed	6-7	Lines 123 - 147
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	N/A	
		(*e*) Describe any sensitivity analyses	6-7	Lines 123 - 147
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7-8	Lines 149-164
		(b) Give reasons for non-participation at each stage	7-8	Lines 149-164
		(c) Consider use of a flow diagram	29	Supplemental Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	22-23, 7-8	Table 1, Lines 149-164
		(b) Indicate number of participants with missing data for each variable of interest	7-8	Lines 149-155
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	7-8	Lines 149-155
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	7-8	Lines 149-164
		Case-control study—Report numbers in each exposure category, or summary measures of exposure		
		Cross-sectional study—Report numbers of outcome events or summary measures		
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-9	Lines 165-212
		(*b*) Report category boundaries when continuous variables were categorized	5	Lines 105-106
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A	

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10	Lines 213-216
Discussion				
Key results	18	Summarise key results with reference to study objectives	11	Lines 220-229
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13-23	Lines 280-307
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-13	Lines 230-279
Generalisability	21	Discuss the generalisability (external validity) of the study results	13-15	Lines 280-307
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Title page	

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Pre-pregnancy body mass index and other risk factors for early- and late-onset hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome: A population-based retrospective cohort study in British Columbia, Canada.

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Title: Pre-pregnancy body mass index and other risk factors for early- and late-onset hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome: A population-based retrospective cohort study in British Columbia, Canada.

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Pre-pregnancy BMI and early- and late-onset HELLP syndrome

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Abstract

Background: Obesity increases risk of pre-eclampsia, but the association with hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome is understudied.

Objective: To examine the association between pre-pregnancy body-mass-index (BMI) and HELLP syndrome, including early- vs. late-onset disease.

Study Design: A retrospective cohort study using population-based data.

Setting: British Columbia (BC), Canada, 2008/09-2019/20.

Population: All pregnancies resulting in live births or stillbirths at ≥20 weeks' gestation.

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

Methods: BMI categories (kg/m^2) included: underweight (<18.5), normal (18.5-24.9), overweight (25.0-29.9), and obese (≥30.0). Rates of early- and late-onset HELLP syndrome (<34 vs. ≥34 weeks, respectively) were calculated per 1000 ongoing pregnancies at 20 and 34 weeks' gestation, respectively. Cox regression was used to assess the associations between risk factors (e.g., BMI, maternal age and parity) and early- vs late-onset HELLP syndrome.

Main outcome measures: Early- and late-onset HELLP syndrome.

Results: The rates of HELLP syndrome per 1000 women were 2.8 overall (1,116 cases among 391,941 women), and 1.9, 2.5, 3.2 and 4.0 in underweight, normal BMI, overweight and obese categories, respectively. Overall, gestational age-specific rates of HELLP syndrome increased with pre-pregnancy BMI. Obesity (compared with normal BMI) was more strongly associated with early-onset HELLP syndrome (adjusted hazard ratio [AHR] 2.24, (95% confidence interval [CI] 1.65-3.04) than with late-onset HELLP syndrome (AHR 1.48, 95% CI 1.23-1.80) (p-value for interaction 0.025). Chronic

hypertension, multiple gestation, bleeding (<20 weeks' gestation and antepartum) also showed differing AHRs between early- vs. late-onset HELLP syndrome.

Conclusions: Pre-pregnancy BMI is positively associated with HELLP syndrome and the association is stronger with early-onset HELLP syndrome. Associations with early- and late-onset HELLP syndrome differed for some risk factors, suggesting possible differences in etiologic mechanisms.

Strengths and limitations of this study

- We were able to describe gestational age-specific incidence of HELLP syndrome, based on population data on all pregnancies.
- The population-based design coupled with detailed information about demographic, behavioural and clinical factors allowed robust adjustment for possible confounding.
- We did not have detailed information on laboratory values used for the diagnosis of HELLP syndrome and therefore we were not able to estimate the severity of HELLP syndrome.

- We did not have information about race/ethnicity, socio-economic status (SES) and prior history of pregnancy with preeclampsia/eclampsia or HELLP syndrome.
- Approximately 25% of women had missing information about BMI, and we used multiple imputation methods to address this limitation.

Key words

Hypertensive disorders of pregnancy, pregnancy complications, overweight, obesity, pre-pregnancy counseling, etiology, adverse pregnancy outcome, BMI, HELLP syndrome.

Word count: 3036

Introduction

Hypertensive disorders of pregnancy, such as pre-eclampsia (PE), are among the leading causes of maternal morbidity and mortality, affecting 3-5% of pregnancies worldwide(1,2) and accounting for up to 14% of maternal deaths.(3) Early-onset PE at <34 weeks' gestation is often associated with placental insufficiency whereas late-onset PE is often associated with pre-existing maternal health conditions such as metabolic syndrome and obesity.(4) Early- vs late-onset PE differ with regard to some risk factors, clinical management and rates of adverse perinatal outcomes.(5,6) A related condition, namely, hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome occurs in 0.2-0.8% of pregnancies(7–9) and 10-20% of cases of severe PE.(10) Although HELLP syndrome has been distinguished from PE as a separate disease,(11) it is still

commonly viewed as a form of severe PE.(9) While the distinction between early- and late-onset PE and the difference in the associations between pre-pregnancy obesity and these conditions has been established, such differences have not been studied with regard to HELLP syndrome.

Pre-pregnancy obesity is a known modifiable risk factor for pre-eclampsia.(12–15) To date, the world prevalence of obesity has nearly tripled since 1975(16) and the proportion of pregnant women with obesity ranges from 1.8% to 25.3% globally.(17) The prevalence of pre-pregnancy obesity was 17.8% in 2012-2016 in Ontario, Canada(18) and 29.0% in 2019 in the United States.(19) Despite the large increases in obesity in high income countries, the association between maternal pre-pregnancy body-mass-index (BMI) and HELLP syndrome has not been adequately assessed in a large population-based study to date.

We carried out a population-based, retrospective cohort study to examine the association between maternal pre-pregnancy BMI and HELLP syndrome and to assess differences in this association in early- vs late-onset HELLP syndrome. We

hypothesized that maternal obesity is a risk factor for HELLP syndrome, and this relationship may be different in early- compared with late-onset disease. In additional analyses, we examined other risk factors for HELLP syndrome in terms of their association with early- vs late-onset HELLP syndrome.

Materials and Methods

Data sources and study population

The study included all live births and stillbirths at ≥20 weeks' gestation in British Columbia, Canada, between April 1, 2008 and March 31, 2020, with data obtained from the British Columbia Perinatal Database Registry (BCPDR).(20) The BCPDR includes information on >99% of births in BC, with detailed data on maternal demographic characteristics, prenatal care, pregnancy complications, labor and delivery characteristics and neonatal outcomes. Each record, abstracted from medical charts (or midwives' notes), includes up to 25 International Classification of Diseases, 10th Edition, Canadian version (ICD-10-CA) codes for diagnoses related to the delivery hospitalization. Chart abstraction is standardized and conducted by trained personnel,

and data quality is routinely assessed. Prior validation studies showed high accuracy of collected information on labor and delivery.(21)

Pre-pregnancy BMI and HELLP syndrome

Pre-pregnancy weight and height were based on maternal self-report or health care provider assessment at ≤11 weeks' gestation.(22) BMI was classified as follows (in kg/m^2): underweight (<18.5), normal (18.5-24.9), overweight (25.0-29.9), and obese (≥30.0).(23) The primary outcome of this study was a physician diagnosis of HELLP syndrome documented in the medical chart, and abstracted and recorded in the BCPDR. In Canada, HELLP syndrome is typically diagnosed using the Tennessee classification criteria, namely lactate dehydrogenase⩾600 IU/l, liver transaminases (aspartate aminotransferase and alanine aminotransferase) elevated more than twice the upper limit of normal, and a platelet count <100,000/ μ l (109/l).(24) Early- and late-onset HELLP syndrome were defined as HELLP syndrome with delivery at <34 weeks and ≥34 weeks' gestation, respectively. Early pregnancy ultrasound was used to

ascertain gestational age, and the last menstrual period estimate of gestational age was used for those without early pregnancy ultrasound information.

Covariates

In addition to BMI, we examined the association between maternal age, nulliparity, pre-existing diabetes, chronic hypertension, *in vitro* fertilization (IVF) conception, multiple gestation, bleeding before 20 weeks, antepartum bleeding or hemorrhage, substance use and smoking during pregnancy and early- vs. late-onset HELLP syndrome. Alcohol use and prior adverse birth outcomes (prior stillbirth or neonatal death) were included as potential confounders; all these factors are known to be associated with HELLP syndrome.(25) Maternal age was categorized as <25, 25-34 and ≥35 years. All chronic conditions and pregnancy complications were identified using ICD-10 codes or data fields abstracted from medical charts to the BCPDR (Table A.1).

Statistical analyses

The rates of HELLP syndrome per 1000 deliveries were compared between women in each BMI category. Complete case analyses were performed for individuals with known

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

BMI. The association between pre-pregnancy BMI and HELLP syndrome was first expressed using crude hazard ratios (HR) and 95% confidence intervals (CI), obtained from a Cox model without adjustment for other risk factors.

Gestational age-specific rates of HELLP syndrome were compared between women in the various BMI categories, using undelivered pregnancies at each gestational week as the denominator. These rates were plotted, and splines with 95% confidence intervals were fitted by the generalized additive model ("gam") smoothing method. Cox models with interaction terms between pre-pregnancy BMI categories and gestational age at HELLP onset (<34 vs ≥34 weeks' gestation) were used to obtain crude HRs and 95% Confidence Intervals (CIs). This analysis was carried out to assess whether gestational age at onset modified the association between BMI and HELLP syndrome.

In multivariable analyses, Cox models were also used to adjust for covariates (listed above) and to also examine their associations with early- vs late-onset of HELLP syndrome using interaction terms. We did not assess early- vs late-onset of HELLP

syndrome interactions with risk factors including alcohol use and prior adverse birth outcomes due to a low number of women with HELLP syndrome in these categories, but adjusted for them in the model as potential confounders.

Sensitivity analyses included multiple imputations for missing BMI values based on a multiple imputation procedure using SAS statistical software (PROC MI).(26) Variables included in the imputation were those also included in the regression analyses. Ten imputed datasets were created, with the final results obtained using Rubin's rule.(27) All analyses were repeated with the imputed dataset and results were compared with the primary analyses.

All analyses were carried out using SAS version 9.4 (SAS Institute, Inc., Cary, NC) and R version 4.0.3.(28) Ethics approval was obtained from the University of British Columbia/Children's and Women's Hospital and Health Centre of British Columbia Research Ethics Board (#H20-03985).

Patient and Public Involvement

Neither patients nor the public were involved in the design, or conduct, or reporting, or dissemination plans of our research. We used only de-identified information and the need for patient's consent was waived.

Results

Study population

Overall, 538,683 women had a live birth or stillbirth in British Columbia between April 1, 2008 and March 31, 2020 (Supplemental Figure 1). Records with missing gestational age or those with <20 weeks' gestational duration were excluded (n=14,206, 2.6%). The study population for the primary analyses included 391,941 pregnancies, after exclusion of women with missing BMI (n = 132,536; 24.6%). The overall incidence of HELLP syndrome was 2.85 (95% CI 2.68-3.01) per 1000 pregnancies (n = 1,116).

The proportion of women who were in underweight, normal BMI, overweight and obese categories prior to pregnancy was 5.7%, 59.1%, 21.4%, and 13.8%, respectively. Pre-existing diabetes, chronic hypertension, prior adverse pregnancy outcomes

(stillbirth or neonatal death), multiple gestation, gestational hypertension, gestational diabetes, proteinuria, and alcohol use during pregnancy were more frequent in women with overweight and obesity compared with women with normal BMI (Table 1). Nulliparity and ultrasound diagnosed fetal growth restriction were observed more frequently in the underweight group. Substance use and smoking during pregnancy were more frequent in underweight, overweight, and obese groups compared with women with normal BMI.

Unadjusted analyses for pre-pregnancy BMI

The rates of HELLP syndrome in women in underweight, normal, overweight, and obese categories were 1.9, 2.5, 3.2, and 4.0 per 1000 pregnancies, respectively (Table 2). Overall, crude HRs for HELLP syndrome in women who were in the overweight and obese categories were 1.29 (95% CI 1.12-1.49) and 1.62 (95% CI 1.39-1.90), respectively, compared with women who had normal BMI (Table A.2).

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

The rates of early- and late-onset HELLP syndrome were 0.7 (n=275) and 2.2 (n=841) per 1000 ongoing pregnancies at 20 weeks' and 34 weeks' gestation, respectively (Table A.3). Most cases of HELLP syndrome occurred at or after 34 weeks (75.4%; 841 out of total 1116 cases). Frequencies of overweight and obesity, older maternal age (≥35), pre-existing diabetes, chronic hypertension, multiple gestation, bleeding before 20 weeks of gestation, antepartum bleeding/hemorrhage, substance use and smoking were higher among women with early-onset vs. late-onset HELLP syndrome. Frequencies of underweight, younger maternal age (<25 years), nulliparity, IVF conception, and alcohol use were higher among women with late-onset HELLP syndrome (Table A.3).

The rates of late-onset HELLP syndrome were higher than early-onset HELLP syndrome regardless of BMI category and maternal age group (Table 2). Nulliparous women, those with pre-existing diabetes, chronic hypertension, prior stillbirth/neonatal death, IVF conception, multiple gestation, alcohol use and substance use also had higher rates of late-onset than early-onset HELLP syndrome. Women with multiple

gestation had highest rate of HELLP syndrome, followed by those with chronic hypertension.

Differences in gestational age-specific incidence rates of HELLP syndrome by BMI group are shown in Figure 1 (Panel A; Panel B shows log-transformed gestational-age specific rates).

Gestational age-specific rates of HELLP syndrome increased over the course of pregnancy, with higher rates at 36-37 weeks and a subsequent decline among women with pre-pregnancy BMI below or above normal values but not among those with normal BMI (Figure 1, Table A.4). Crude analyses showed that HRs for early-onset HELLP syndrome in women in overweight and obese groups were 1.62 (95% CI 1.21-2.16) and 2.37 (95% CI 1.77-3.18), respectively, compared with women with normal BMI. These HRs were 1.21 (95% CI 1.02-1.42) and 1.42 (95% CI 1.17-1.71) for late-onset HELLP syndrome, respectively (Table A.2).

Adjusted analyses

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

The associations did not change substantially after adjusting for other risk factors (Table 3). Gestational age at onset of HELLP syndrome modified the effect of maternal BMI on HELLP syndrome, but only in the obese group. Specifically, obesity was more strongly associated with early-onset HELLP syndrome (AHR 2.24) than with late-onset HELLP syndrome (AHR 1.48, p-value for interaction = 0.025; Table 3).

Adjusted hazard ratios (AHR) for each risk factor calculated separately for early- vs late-onset HELLP syndrome are shown in Table 3. Risk factors significantly associated with HELLP syndrome included overweight, obesity, advanced maternal age (≥ 35 years), nulliparity, pre-existing diabetes, chronic hypertension, multiple gestation, and antepartum bleeding/hemorrhage. Smoking during pregnancy had an inverse association with HELLP syndrome. IVF conception was a risk factor for late-onset but not early-onset HELLP syndrome. Bleeding before 20 weeks and antepartum bleeding/hemorrhage were risk factors for early-onset but not late-onset HELLP syndrome. Obesity (p=0.025), chronic hypertension (p=0.041), multiple gestation (p=0.001), bleeding before 20 weeks (p=0.008) and antepartum bleeding/hemorrhage

(p=0.011) differed significantly in their associations with early versus late-onset HELLP syndrome (p-values for interaction).

Sensitivity analyses

Women with missing BMI were not substantially different from women with known BMI (Table A.5); and the results were not appreciably changed after the analyses were repeated using imputed BMI values (Table A.6).

Discussion

Main findings

To our knowledge, this is the largest contemporary study examining the association between pre-pregnancy BMI and HELLP syndrome, including early- and late-onset disease. We showed that the majority of HELLP syndrome (75.4%) occurred at or after 34 weeks' gestation, with the rate of early-onset HELLP syndrome being substantially lower than that of late-onset HELLP syndrome. Women in overweight or obese groups were at elevated risk for developing HELLP syndrome. Obesity was more strongly

associated with early-onset than late-onset HELLP syndrome. In addition to BMI, our study showed that chronic hypertension, bleeding before 20 weeks' gestation and antepartum bleeding/hemorrhage were stronger risk factors for early-onset HELLP syndrome, whereas multiple gestation was a stronger risk factor for late-onset HELLP syndrome.

Interpretation in the context of scientific literature

The rate of HELLP syndrome in our study (2.8 per 1000 women) was similar to the previously reported rate of 2.5 per 1000 singleton pregnancies in Canada in 2012-2016.(25) Prior studies describing the association between pre-pregnancy obesity and HELLP syndrome are sparse and results vary. In a retrospective cohort study from a single tertiary hospital in the United States (n=434), Martin *et al.* found that maternal weight was not associated with HELLP syndrome.(29) Similarly, a case-control study (n= 129 cases and 476 controls) found no association between obesity and HELLP syndrome.(30) Furthermore, a retrospective case-control study (including n=687 cases and 601 controls) showed that pre-pregnancy BMI was associated with PE but not

HELLP syndrome and suggested that PE and HELLP may have different pathophysiology.(12) In contrast, a population-based cohort study from Norway (n=418,897) found that pre-pregnancy BMI ≥30kg/m^2 was associated with HELLP syndrome in the first but not the second pregnancy.(9) However, in that study, only 25% of women with a first pregnancy and 30% of women with their second pregnancy had information on BMI. More recently, a population-based study from Canada (n=1,078,323) showed that obesity documented in medical charts was a risk factor for HELLP syndrome,(31) however, obesity rates were underestimated and information on BMI was not available, precluding more detailed analyses.

While PE is typically recognized as early- vs late-onset disease (before vs ≥ 34 weeks gestation, respectively), this distinction is rarely made for HELLP syndrome. A prior population-based cohort study (n=96,861) showed that high pre-pregnancy BMI is a stronger risk factor for late-onset PE than early-onset PE.(15) That study also demonstrated a correlation between increased prevalence of maternal obesity in parallel with late-onset PE during the 18-year period, while the incidence of early-onset

PE stayed relatively constant.(15) In contrast, our study shows a stronger association between overweight/obesity and early-onset HELLP syndrome compared with late-onset HELLP syndrome. This suggests varying pathophysiological pathways between PE and HELLP syndrome or additional obesity-related pathophysiology associated with PE that leads to liver damage at earlier gestation, for instance, obesity-associated steatosis and non-alcoholic fatty liver disease.(32) We chose the same gestational age cut-off of 34 weeks for early- vs late-onset HELLP syndrome as in pre-eclampsia. However, our data suggest an increase in gestational age-specific rates after 28 weeks' gestation in women with obesity and after 30 weeks' gestation in women without obesity. A previous study showed a high proportion of HELLP syndrome cases occurring between 27 and 37 weeks,(33) which indicates potential dissimilarities with early- vs late-onset PE. Chronic hypertension, however, was found to be a stronger risk factor for early-onset disease for both PE(6) and HELLP syndrome compared with late-onset disease. It is worth mentioning that the known inverse association between

smoking and PE(6) was also observed in HELLP syndrome in our study, and this warrants further investigation.

Clinical and research implications

Our findings show that increases in gestational age-specific rates of HELLP syndrome vary by maternal pre-pregnancy BMI. The rates declined after 37 weeks' gestation in women who were in the underweight, overweight and obese categories, but continued increasing in women with normal BMI. This could be due to higher rates of medically indicated early-term deliveries in groups with low or high BMI, which has been shown to reduce maternal morbidity compared with expectant management.(34) It is possible that women whose pre-pregnancy BMI was below and above normal range were more likely to be considered at-risk (due to the abnormal BMI or associated co-morbidity) and therefore delivered at early term (37-38 weeks) gestation to prevent adverse maternal and infant outcomes. However, further research is needed to confirm this hypothesis. In addition to BMI, we also showed that chronic hypertension, bleeding before 20 weeks' gestation and antepartum bleeding/hemorrhage were more strongly associated with

early- onset HELLP syndrome, while multiple gestation was more strongly associated with late-onset HELLP syndrome. The association between bleeding at <20 weeks gestation and early-onset HELLP syndrome is novel. Such bleeding can be caused by abnormal placental conditions (e.g., abnormal implantation and associated bleeding), which may play a role in the development of HELLP syndrome. These findings are exploratory and require confirmation by other studies. However, they raise the intriguing possibility that determinants of HELLP syndrome (such as antepartum bleeding) have different associations with early and late onset HELLP syndrome depending on whether they occur at <20 weeks or at ⩾20 weeks' gestation. In our study, the association between antepartum bleeding at ⩾20 weeks' gestation and HELLP syndrome (which could have been explained as being a consequence of HELLP syndrome causing placental abruption) was not significant in adjusted models.

Strengths and limitations

The strengths of this study include its population-based design coupled with detailed information about demographic, behavioural and clinical factors that allowed for robust

adjustment for possible confounding. We had a large enough sample to provide precise estimates for associations with HELLP syndrome, a rare outcome.

This study also has several limitations. First, we did not have detailed information on laboratory values important for the diagnosis of HELLP syndrome and therefore we were not able to estimate the severity of HELLP. We assumed that the diagnosis of HELLP syndrome would lead to a prompt delivery to prevent worsening of maternal condition. However, in milder cases, expectant management with close observation may have led to a delay between the diagnosis and delivery, especially at very preterm gestation. As a result, incidence of early-onset HELLP syndrome may have been underestimated in our study. However, we do not expect a large inaccuracy in this regard because HELLP syndrome is considered a potentially life-threatening condition and delivery is typically not delayed. Second, we did not have information about race/ethnicity, socio-economic status (SES) and prior history of pregnancy with PE/eclampsia or HELLP syndrome, which could have resulted in residual confounding in the assessments of the relation between BMI and HELLP syndrome. However, we

adjusted for several possible confounders and did not observe changes in the association between BMI and HELLP syndrome, suggesting that our results are robust. Third, pre-pregnancy BMI was largely self-reported, which may have led to some misclassification. Several validation studies have shown relatively good accuracy of self-reported weight and height for epidemiological studies,(35–37) suggesting that a large misclassification bias is unlikely. A systematic review of BMI self-report misclassification showed minimal influence on associations between BMI and pregnancy outcomes.(38)

Approximately 25% of women had missing information about BMI. These women were relatively similar to those with known BMI and sensitivity analyses using imputed BMI values yielded results almost identical to the main analyses. Lastly, the analyses examining differences between early- and late-onset HELLP and risk factors other than BMI were exploratory, and further studies are required to confirm our findings.

Conclusions

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

Consistent with what is known about PE, pre-pregnancy BMI was found to be a risk factor for HELLP syndrome. However, contrary to the documented association between BMI and PE, with obesity being associated more strongly with late-onset than early-onset PE, our study showed that obesity was more strongly associated with early-onset than with late-onset HELLP syndrome. This suggests potentially different underlying pathophysiology for the various hypertensive disorders of pregnancy. Our findings can help maternity care providers with regard to pre-pregnancy counselling. Clinicians can better identify women who may benefit from obstetric intervention, as the risk of HELLP increases at late pre-term gestation in all women and continues to increase at term and post-term gestation in women with normal pre-pregnancy BMI. More research on the gestational-age specific effects of pre-pregnancy BMI is needed to elucidate the underlying causes of HELLP syndrome.

Disclosure

The authors report no conflict of interest.

Disclaimer

All inferences, opinions, and conclusions drawn in this publication are those of the authors, and do not reflect the opinions or policies of Perinatal Services BC.

Author Statement/Contribution to Authorship

LW and SL were involved in the conception, planning, carrying out and analyzing data of the project. JNB, GMM, KSJ and NR provided helpful suggestions for the analysis. LW led the writing of the manuscript and received feedback from JNB, GMM, SL, KSJ, NR.

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Competing interests statement

The authors report no conflict of interest.

Data Sharing Statement

Data may be obtained from a third party and are not publicly available.

Ethics Approval Statement

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

Ethics approval was obtained from the University of British Columbia/Children's and Women's Hospital and Health Centre of British Columbia Research Ethics Board (#H20-03985).

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

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Pre-pregnancy BMI and early- and late-onset HELLP syndrome

547

548

Tables

Table 1. Maternal demographic and clinical characteristics by pre-pregnancy body-mass-index; British Columbia, 2008/09-2019/20[a]

	Underweight n = 22,392	Normal BMI n = 231,517	Overweight n = 83,864	Obese n = 54,168
Maternal age (years)				
< 25	4018 (17.9)	26332 (11.4)	9733 (11.6)	6947 (12.8)
25-34	14392 (64.3)	146790 (63.4)	52138 (62.2)	33948 (62.7)
≥ 35	3982 (17.8)	58395 (25.2)	21993 (26.2)	13273 (24.5)
Nullipara	12551 (56.1)	117740 (50.9)	37202 (44.4)	22020 (40.7)
Pre-existing diabetes	26 (0.1)	693 (0.3)	672 (0.8)	1006 (1.9)
Chronic hypertension	23 (0.1)	717 (0.3)	727 (0.8)	1380 (2.6)
Prior stillbirth /neonatal death	130 (0.6)	1894 (0.8)	979 (1.2)	791 (1.5)
IVF conception[b]	496 (2.2)	6835 (3.0)	2579 (3.1)	1639 (3.0)
Multiple gestation				
Twins	253 (1.1)	3318 (1.4)	1340 (1.6)	895 (1.7)
Triplets/Quadruplets[d]	<5 (0)	34 (0)	26 (0)	19 (0)
Bleeding < 20 weeks	483 (2.2)	4116 (1.8)	1572 (1.9)	1166 (2.2)
Antepartum bleeding/hemorrhage (≥ 20 weeks)	374 (1.7)	3352 (1.5)	1227 (1.5)	706 (1.3)
Intrauterine Growth Restriction[c]	987 (4.4)	5445 (2.4)	1472 (1.8)	953 (1.8)
Gestational Hypertension	547 (2.4)	8551 (3.7)	5694 (6.8)	6332 (11.7)
Gestational Diabetes	1680 (7.5)	19492 (8.4)	11548 (13.8)	11452 (21.1)

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

Proteinuria	161 (0.7)	2236 (1.0)	1267 (1.5)	1337 (2.5)
Alcohol use	192 (0.9)	2240 (1.0)	944 (1.1)	786 (1.5)
Substance use	1118 (5.0)	8099 (3.5)	3514 (4.2)	2970 (5.5)
Smoking	1727 (7.7)	12943 (5.6)	6155 (7.3)	5576 (10.3)
Gestational age at delivery (weeks)				
20-27	102 (0.5)	881 (0.4)	393 (0.5)	358 (0.7)
28-33	387 (1.7)	3423 (1.5)	1473 (1.8)	1158 (2.1)
34-36	1620 (7.2)	15119 (6.5)	6142 (7.3)	4680 (8.6)
37-41	20076 (89.7)	209831 (90.6)	75017 (89.5)	47448 (87.6)
≥ 42	207 (0.9)	2263 (1.0)	839 (1.0)	524 (1.0)

[a]Data shown as n(%)

[b]IVF = in vitro fertilization

[c]Ultrasound diagnosed intra-uterine growth restriction (IUGR)

[d]Information on cell numbers <5 was suppressed due to confidentiality reasons.

Table 2. Rates of early-onset and late-onset HELLP syndrome per 1000 ongoing pregnancies by maternal demographic and clinical characteristics; British Columbia, 2008/09-2019/20

	Early-onset HELLP syndrome	Late-onset HELLP syndrome	Overall
Pre-pregnancy BMI category			
Underweight	8 (0.4)	35 (1.6)	43 (1.9)
Normal weight	125 (0.5)	462 (2.0)	587 (2.5)
Overweight	73 (0.9)	199 (2.4)	272 (3.2)
Obese	69 (1.3)	145 (2.8)	214 (4.0)
Maternal age (years)			
< 25	30 (0.6)	97 (2.1)	127 (2.7)

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

25-34	158 (0.6)	512 (2.1)	670 (2.7)
≥ 35	87 (0.9)	232 (2.4)	319 (3.3)
Nullipara	188 (1.0)	629 (3.4)	817 (4.3)
Pre-existing diabetes	6 (2.5)	14 (6.3)	20 (8.3)
Chronic hypertension	19 (6.7)	20 (7.7)	39 (13.7)
Prior stillbirth /neonatal death[a]	<5 (<1.0)	<5 (<1.0)	5 (1.3)
IVF conception[b]	19 (1.6)	73 (6.7)	92 (8.0)
Multiple gestation	33 (5.6)	91 (19.3)	124 (21.1)
Bleeding (< 20 weeks)	12 (1.6)	10 (1.5)	22 (3.0)
Antepartum Bleeding/hemorrhage (≥ 20 weeks)	15 (2.7)	12 (2.5)	27 (4.8)
Alcohol use[a]	<5 (<1.0)	<11 (<2.7)	12 (2.9)
Substance use	14 (0.9)	25 (1.6)	39 (2.5)
Smoking	14 (0.5)	36 (1.4)	50 (1.9)

[a]Information on cell numbers <5 was suppressed due to confidentiality reasons. Other numbers were suppressed if needed to avoid back-calculation from the total

[b]IVF = in vitro fertilization

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

Table 3. Adjusted hazard ratios for early-onset and late-onset HELLP syndrome with 95% confidence intervals; British Columbia, 2008/09-2019/20

	Overall AHR (95% CI)[a]	Early-onset HELLP AHR (95% CI)	Late-onset HELLP AHR (95% CI)	P-value[b]
Pre-pregnancy BMI category				
Underweight	0.79 (0.58-1.07)	0.67 (0.33-1.38)	0.82 (0.58-1.16)	0.628
Normal weight	Ref	Ref	Ref	Ref
Overweight	1.34 (1.16-1.55)	1.63 (1.22-2.18)	1.26 (1.07-1.49)	0.129
Obese	1.65 (1.41-1.94)	2.24 (1.65-3.04)	1.48 (1.23-1.80)	0.025
Maternal age (years)				
< 25	0.92 (0.76-1.12)	0.92 (0.62-1.38)	0.92 (0.74-1.15)	0.998
25-34	Ref	Ref	Ref	Ref
⩾ 35	1.27 (1.11-1.47)	1.39 (1.06-1.83)	1.23 (1.05-1.45)	0.445
Nullipara	2.93 (2.56-3.36)	2.56 (1.97-3.33)	3.09 (2.63-3.63)	0.229
Pre-existing diabetes	2.40 (1.51-3.80)	1.64 (0.71-3.81)	2.88 (1.66-5.00)	0.273
Chronic hypertension	3.93 (2.80-5.51)	5.95 (3.62-9.79)	2.92 (1.83-4.66)	0.041
Prior stillbirth/neonatal death[c]	0.88 (0.36-2.13)	N/A	N/A	N/A
IVF conception[d]	1.21 (0.95-1.55)	0.83 (0.50-1.41)	1.37 (1.04-1.80)	0.101
Multiple gestation	13.66 (11.06-16.87)	8.31 (5.59-12.35)	17.81 (13.89-22.83)	0.001
Bleeding at < 20 weeks	0.95 (0.62-1.45)	1.89 (1.05-3.39)	0.60 (0.32-1.12)	0.008
Antepartum bleeding or hemorrhage (⩾ 20 weeks)	2.10 (1.43-3.08)	3.75 (2.22-6.35)	1.37 (0.77-2.43)	0.011
Alcohol use[c]	1.07 (0.60-1.90)	N/A	N/A	N/A
Substance use	0.98 (0.70-1.36)	1.38 (0.78-2.42)	0.84 (0.56-1.27)	0.166
Smoking	0.71 (0.53-0.96)	0.70 (0.40-1.23)	0.71 (0.50-1.01)	0.963

[a]AHR = adjusted hazard ratio, with 95% confidence interval in parentheses, were obtained from the Cox model that included all variables in the table.

[b]p-value for interaction with early- vs late-onset HELLP syndrome.

[c]N/A = not applicable. We did not examine differences by early- vs late-onset for prior stillbirth/neonatal death or alcohol use due to small sample size.

[d]IVF = in vitro fertilization

Figure legend

Figure 1. Gestational-age specific rates of HELLP syndrome for each BMI category (Panel A); and log-transformed rates (Panel B). Rates from 40 to 45 weeks were combined. Splines with 95% confidence intervals were fitted by the generalized additive model ("gam") smoothing method.

Supplemental Figure 1. Flowchart of study sample selection.

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

Pre-pregnancy BMI and early- and late-onset HELLP syndrome

599

600

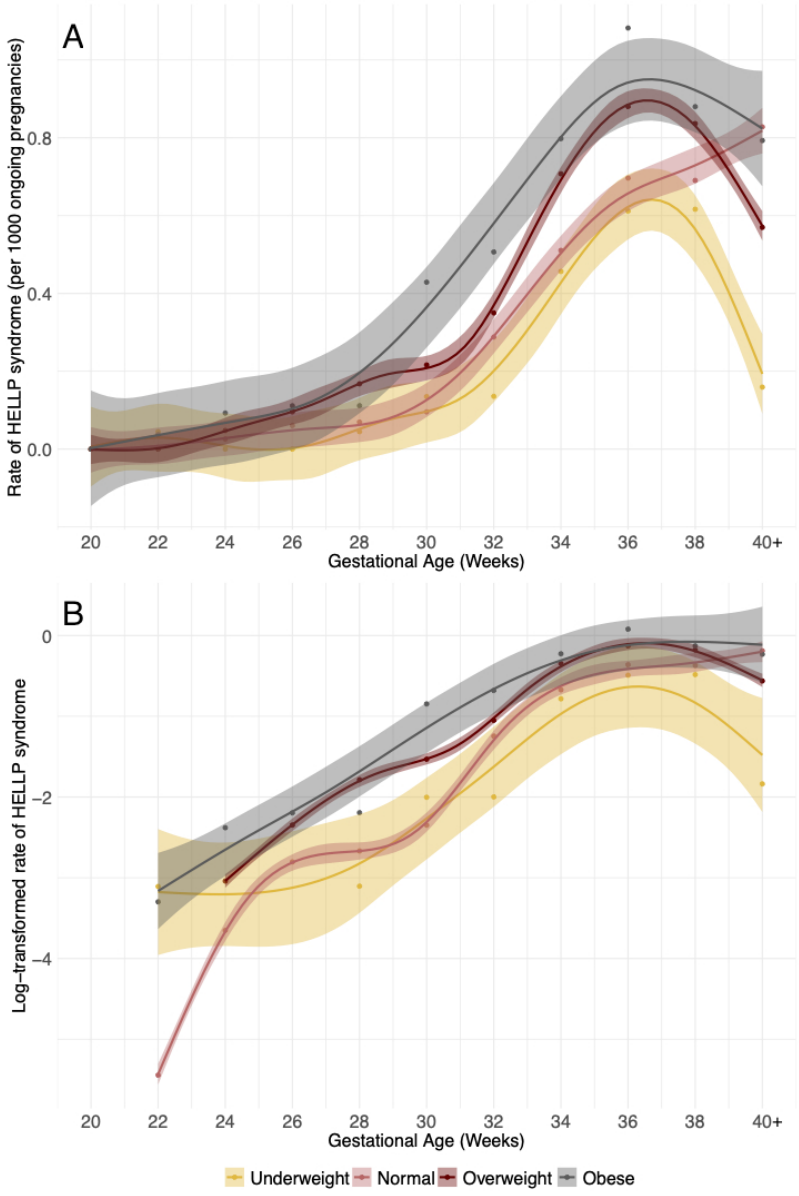

Figure 1. Gestational-age specific rates of HELLP syndrome for each BMI category (Panel A); and log-transformed rates (Panel B). Rates from 40 to 45 weeks were combined. Splines with 95% confidence intervals were fitted by the generalized additive model ("gam") smoothing method.

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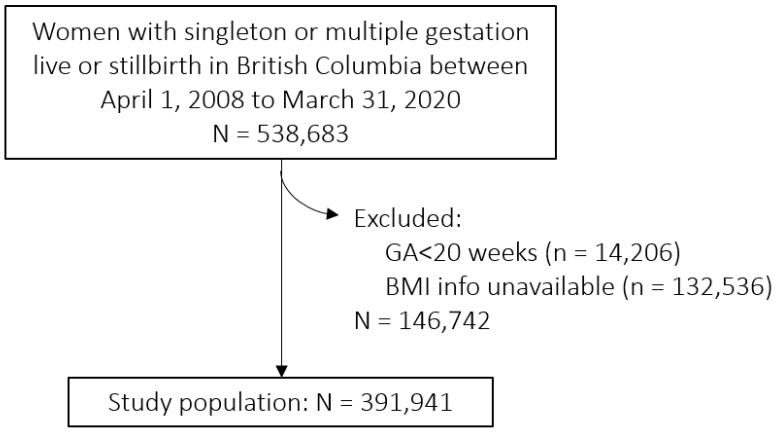

Supplemental Figure 1. Flowchart of study sample selection.

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Supplementary tables

Supplemental Table 1. Definitions and sources of variables

	Definition	Source
Maternal age (years)	Mother's age (in years) calculated at date of delivery.	BCPDR
Nullipara	Mother has never delivered a baby of at least 500 grams birth weight or at least 20 weeks gestation in a previous pregnancy.	BCPDR
Pre-existing diabetes	Pre-existing diabetes mellitus Type 1 or Type 2, insulin used. Pre-existing diabetes mellitus Type 1 or Type 2, insulin not used; or 'E10','E11', 'O245','O246','O247'	BCPDR ICD-10
Chronic hypertension	'O10','O11'	ICD-10
Prior stillbirth /neonatal death	Mother had at least one prior live born infant, who died within the first 28 days of life. Mother had at least one prior stillbirth or intrauterine death documented.	BCPDR
IVF conception	Mother had in-vitro fertilization to achieve the current pregnancy.	BCPDR
Multiple gestation	The incremental sequence number of babies born from the current pregnancy. Should be used with multiple_birth_count. Along with mother_id, required to link to MULTIPLE_LABOURS.	BCPDR

Antepartum bleeding < 20 weeks	Mother had any antepartum bleeding in pregnancy < 20 weeks gestation.	BCPDR
Antepartum bleeding or hemorrhage ≥ 20 weeks	Mother had any antepartum hemorrhage or bleeding in pregnancy ≥ 20 weeks gestation, including bleeding from cervical polyps.	BCPDR
Intrauterine Growth Restriction[a]	Health care provider identified intrauterine growth restriction (IUGR) during the antenatal period. Baby may or may not be appropriately grown at birth.	BCPDR
Gestational Hypertension	Care provider diagnosed mother with gestational hypertension during the current pregnancy.	BCPDR
Gestational Diabetes	Gestational diabetes, insulin dependent. Gestational diabetes, non-insulin dependent.	BCPDR
Proteinuria	Care provider diagnosed proteinuria (>+1g/L) during the current pregnancy.	BCPDR
Alcohol use	Care provider lists mother's use of alcohol as a risk factor in this pregnancy.	BCPDR

Substance use	Mother used any of the following substances at any time during the current pregnancy: heroin/opioids, cocaine, methadone, solvents, or marijuana; OR care provider lists use of prescription, 'other', or unknown other drug as a risk to the pregnancy.	BCPDR
Smoking	Mother smoked tobacco products during pregnancy.	BCPDR
Gestational age at delivery	Algorithm-based estimate of gestational age at delivery. Uses last menstrual period, first ultrasound (<20 weeks), clinical estimate from newborn exam, and documentation from maternal chart.	BCPDR
HELLP syndrome	Mother was diagnosed with HELLP Syndrome (H-hemolysis, EL-elevated liver enzymes, LP-low platelet count)	BCPDR

[a]Ultrasound diagnosed intra-uterine growth restriction (IUGR)

Supplemental Table 2. Rates of HELLP syndrome by Body-Mass-Index category and hazard ratios with 95% confidence intervals

	Underweight	Normal BMI	Overweight	Obese
All pregnancies				
N cases (rate per thousand)[a]	43 (1.9)	587 (2.5)	272 (3.2)	214 (4.0)
Crude HR[b]	0.78 (0.57-1.06)	Ref	1.29 (1.12-1.49)	1.62 (1.39-1.90)
Early-onset HELLP (< 34 wks)				
N cases (rate per thousand)[a]	8 (0.4)	125 (0.5)	73 (0.9)	69 (1.3)
Crude HR[b]	0.66 (0.32-1.35)	Ref	1.62 (1.21-2.16)	2.37 (1.77-3.18)
Late-onset HELLP (≥ 34 wks)				
N cases (rate per thousand)[a]	35 (1.6)	462 (2.0)	199 (2.4)	145 (2.8)
Crude HR[b]	0.81 (0.57-1.14)	Ref	1.21 (1.02-1.42)	1.42 (1.17-1.71)

[a]Rates are per 1000 ongoing pregnancies at 20 weeks (early-onset HELLP) and at 34 weeks gestation (late-onset HELLP).

[b]HR = hazard ratio, with 95% confidence interval in parentheses, unless otherwise specified

Supplemental Table 3. Maternal demographic and clinical characteristics by early- vs late-onset HELLP syndrome; British Columbia, 2008/09-2019/20[a]

	Early-onset HELLP n =275	Late-onset HELLP n = 841
Pre-pregnancy BMI category		
Underweight	8 (2.9)	35 (4.2)
Normal weight	125 (45.5)	462 (54.9)
Overweight	73 (26.6)	199 (23.7)
Obese	69 (25.1)	145 (17.2)
Maternal age (years)		
< 25	30 (10.9)	97 (11.5)
25-34	158 (57.5)	512 (60.9)
≥ 35	87 (31.6)	232 (27.6)
Nullipara	188 (68.4)	629 (74.8)
Chronic diabetes	6 (2.2)	14 (1.7)

Chronic hypertension	19 (6.9)	20 (2.4)
Prior stillbirth /neonatal death[b]	<5 (<1.8)	<5 (<0.5)
IVF conception[c]	19 (6.9)	73 (8.7)
Multiple gestation	33 (12.0)	91 (10.8)
Bleeding (< 20 weeks)	12 (4.4)	10 (1.2)
Antepartum bleeding/hemorrhage (≥ 20 weeks)	15 (5.5)	12 (1.4)
Alcohol use[b]	<5 (<1.8)	10 (1.2)
Substance use	14 (5.1)	25 (3.0)
Smoking	14 (5.1)	36 (4.3)

[a]Data shown as n(%)

[b]Information on cell numbers <5 was suppressed due to confidentiality reasons.

[c]IVF = in vitro fertilization

Supplemental Table 4. Cases of HELLP syndrome at each gestational age (rate per 1000 ongoing pregnancies)[a]

Gestational age (weeks)	Underweight n = 22,392	Normal BMI n = 231,517	Overweight n = 83,864	Obese n = 54,168
20-21	<5/22392 (<0.22)	<5/231517 (<0.02)	<5/83864 (<0.06)	<5/54168 (<0.09)
22-23	<5/22379 (<0.22)	<5/231351 (<0.02)	<5/83796 (<0.06)	<5/54108 (<0.09)
24-25	<5/22356 (<0.22)	6/231174 (0.03)	<5/83720 (<0.06)	5/54023 (0.09)
26-27	<5/22332 (<0.22)	14/230958 (0.06)	8/83609 (0.10)	6/53926 (0.11)
28-29	<5/22289 (0.04)	16/230635 (0.07)	14/83471 (0.17)	6/53810 (0.11)
30-31	<5/22232 (0.13)	22/230136 (0.10)	18/83269 (0.22)	23/53631 (0.43)
32-33	<5/22133 (0.14)	66/229249 (0.29)	29/82870 (0.35)	27/53303 (0.51)
34-35	10/21902 (0.46)	116/227212 (0.51)	58/81998 (0.71)	42/52652 (0.80)
36-37	13/21247 (0.61)	154/221075 (0.70)	70/79515 (0.88)	55/50825 (1.08)
38-39	11/17845 (0.62)	131/189757 (0.69)	56/66951 (0.84)	36/40911 (0.88)
≥ 40	<5/6278 (<0.80)	61/73662 (0.83)	15/26327 (0.57)	12/15135 (0.79)

[a]Information on cell numbers <5 was suppressed due to confidentiality reasons.

Supplemental Table 5. Demographic and clinical characteristics of women missing pre-pregnancy BMI, live births and stillbirths, British Columbia, 200/09-2019/20[a]

	BMI not missing n = 391,941	BMI missing n = 132,536
Maternal age (years)		
< 25	47030 (12.0)	20134 (15.2)
25-34	247268 (63.1)	78660 (59.4)
≥ 35	97643 (24.9)	33742 (25.5)
Nullipara	189513 (48.4)	53789 (40.6)
Pre-existing diabetes	2397 (0.6)	913 (0.7)
Chronic hypertension	2847 (0.7)	890 (0.7)
Prior stillbirth /neonatal death	3794 (1.0)	1734 (1.3)
IVF conception[b]	11549 (3.0)	3877 (2.9)
Multiple gestation		
Twins	5806 (1.5)	2478 (1.9)

Triplets/Quadruplets	82 (0)	27 (0)
Antepartum bleeding/hemorrhage		
< 20 weeks	7337 (1.9)	1813 (1.4)
≥ 20 weeks	5659 (1.4)	1496 (1.1)
Intrauterine Growth Restriction[c]	8857 (2.3)	2471 (1.9)
Gestational Hypertension	21124 (5.4)	6623 (5.0)
Gestational Diabetes	44172 (11.3)	13248 (10.0)
Proteinuria	21124 (5.4)	6623 (5.0)
Alcohol use	4162 (1.1)	1845 (1.4)
Substance use	15701 (4.0)	6758 (5.1)
Smoking	26401 (6.7)	10435 (7.9)
Second-hand smoke	26319 (6.7)	7565 (5.7)

[a]Data shown as n(%)

[b]IVF = in vitro fertilization

[c]Ultrasound diagnosed intra-uterine growth restriction (IUGR)

Supplemental Table 6. Hazard Ratios and 95% confidence intervals using imputed data for missing values of BMI

	Underweight	Normal BMI	Overweight	Obese
Early-onset HELLP (< 34 wks)				
N cases (rate per thousand)[a]	8 (0.4)	164 (0.5)	137 (0.9)	71 (1.3)
Adjusted HR[b]	0.76 (0.43-1.33)	Ref	1.54 (1.19-2.00)	2.06 (1.53-2.78)
Late-onset HELLP (≥ 34 wks)				
N cases (rate per thousand) [a]	35 (1.6)	572 (1.9)	376 (2.6)	148 (2.8)
Adjusted HR[b]	0.96 (0.51-1.8)	Ref	1.24 (0.92-1.66)	1.46 (1.03-2.08)

[a]Rates are per 1000 ongoing pregnancies at 20 weeks (early-onset HELLP syndrome) and at 34 weeks gestation (late-onset HELLP syndrome).

[b]HR = hazard ratio, with 95% confidence interval in parentheses, unless otherwise specified. Adjusted for nulliparity, maternal age, chronic diabetes, chronic hypertension, in vitro fertilization, antepartum bleeding/hemorrhage, gestational diabetes, alcohol, substance use, smoking during pregnancy, prior pregnancy outcomes, and multiple gestation.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title page	"Title: Pre-pregnancy body mass index and other risk factors for early- and late-onset hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome: A population-based retrospective cohort study."
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5	Lines 67-84
Objectives	3	State specific objectives, including any prespecified hypotheses	4-5	Lines 85-90
Methods				
Study design	4	Present key elements of study design early in the paper	5-6	Lines 92-122
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6	Lines 92-122
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5-6	Lines 92-122
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	N/A	N/A

Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-7	Lines 92-147
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*31*	Supplemental Table 1. Definitions and sources of variables
Bias	9	Describe any efforts to address potential sources of bias	6-7	Lines 123 - 147
Study size	10	Explain how the study size was arrived at	6-7	Lines 92-147

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7	Lines 123 - 147
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7	Lines 123 – 147
		(*b*) Describe any methods used to examine subgroups and interactions	6-7	Lines 123 – 147
		(*c*) Explain how missing data were addressed	6-7	Lines 123 - 147
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	N/A	
		(*e*) Describe any sensitivity analyses	6-7	Lines 123 - 147
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7-8	Lines 149-164
		(b) Give reasons for non-participation at each stage	7-8	Lines 149-164
		(c) Consider use of a flow diagram	29	Supplemental Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	22-23, 7-8	Table 1, Lines 149-164
		(b) Indicate number of participants with missing data for each variable of interest	7-8	Lines 149-155
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	7-8	Lines 149-155
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	7-8	Lines 149-164
		Case-control study—Report numbers in each exposure category, or summary measures of exposure		
		Cross-sectional study—Report numbers of outcome events or summary measures		
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-9	Lines 165-212
		(*b*) Report category boundaries when continuous variables were categorized	5	Lines 105-106
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A	

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10	Lines 213-216
Discussion				
Key results	18	Summarise key results with reference to study objectives	11	Lines 220-229
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13-23	Lines 280-307
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-13	Lines 230-279
Generalisability	21	Discuss the generalisability (external validity) of the study results	13-15	Lines 280-307
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Title page	

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.