PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	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.
AUTHORS	Wang, Li Qing; Bone, Jeffrey; Muraca, Giulia M; Razaz, Neda; Joseph, K.S.; Lisonkova, Sarka

VERSION 1 – REVIEW

REVIEWER	Nasa, Prashant NMC Healthcare LLC, Critical Care Medicine
REVIEW RETURNED	05-Dec-2023

GENERAL COMMENTS	Thank you for this nice work. The authors tried to evaluate the association of obesity with HELLP syndrome in a large retrospective population cohort. I have few comments: 1. Antepartum bleeding and bleeding before 20 weeks has been associated with an increased risk of HELLP syndrome in the analysis. However, it is unclear whether the bleeding precedes the HELLP syndrome or was associated with HELLP syndrome. Can you explain the pathophysiology for this association and risk factor? 2. The diagnostic criteria of HELLP syndrome used in the study needs a reference. 3. Adjusted cohort: what all factors were adjusted? 4. The hypothesis that underweight and overweight had less incidence of HELLP with increased age because of early delivery needs validation with secondary analysis of the cohort. This overarching statements need to be checked in the cohort. There are few typos in the manuscript that need attention 1. Results: chronic hypertensionprior adverse outcome (space between hypertension and prior) 2. Discussion: However in that study, only 25% of women 3. continue to increase at term

VERSION 1 – AUTHOR RESPONSE

Response to Reviewers
Thank you for your thoughtful comments.

1. Antepartum bleeding and bleeding before 20 weeks has been associated with an increased risk of HELLP syndrome in the analysis. However, it is unclear whether the bleeding precedes the HELLP

syndrome or was associated with HELLP syndrome. Can you explain the pathophysiology for this association and risk factor?
Response:
Bleeding before 20 weeks' gestation preceded the occurrence of HELLP syndrome as all cases of HELLP syndrome were diagnosed at ≥20 weeks. Causes of such bleeding can include those due to placental complications e.g., implantation bleeding. Although the mechanism underlying the association between bleeding <20 weeks gestation and HELLP syndrome is unclear, implantations and placental complications are thought to play a role in development of HELLP syndrome. However, it is important to note that associations do not imply causation, and more research is needed in this area.
The association between antepartum bleeding ≥20 weeks and HELLP syndrome could also have been due to placental complications such as placental abruption. However, this association was not significant in the adjusted models.
We made the following changes:
Line 320: "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 a consequence of HELLP syndrome causing placental abruption) was not significant in adjusted models."

2. The diagnostic criteria of HELLP syndrome used in the study needs a reference.
Response: We clarified the sentence and added a reference.
Line 140: "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/μl (109/l).24"
"Khalid F, Mahendraker N, Tonismae T. HELLP Syndrome. [Updated 2023 Jul 29]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan. PMID: 32809450. Available from: https://www.ncbi.nlm.nih.gov/books/NBK560615/

3. Adjusted cohort: what all factors were adjusted?
Response: All variables in Table 3 were included in Cox regression model (i.e., maternal age, parity, pre-existing diabetes, chronic hypertension, prior stillbirth/neonatal death, IVF conception, multiple gestation, bleeding at < 20 weeks, antepartum bleeding, antepartum hemorrhage (≥ 20 weeks), alcohol use, substance use, smoking during pregnancy).
We have clarified this in the footnote to Table 3.

4. The hypothesis that underweight and overweight had less incidence of HELLP with increased age because of early delivery needs validation with secondary analysis of the cohort. This overarching statements need to be checked in the cohort.
Response: This potential explanation for our findings was our hypothesis. Even though this hypothesis is quite plausible, it requires further research. We made this clearer in the Discussion as follows:
Line 313: "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."

5. There are few typos in the manuscript that need attention
5.1. Results: chronic hypertensionprior adverse outcome (space between hypertension and prior)
Response: we did not find this typo, it may have occurred during the file merges and transfer. The sentence in the discussion is currently as follows:
"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."

5.2. Discussion: However in that study, only 25% of women
Response: In the revised manuscript, the sentence reads as follows:
"However, in that study, only 25% of women with a first pregnancy and 30% of women with their second pregnancy had information on BMI."

5.3. continue to increase at term
Response: In the revised manuscript, the sentence reads as follows:
"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."

VERSION 2 – REVIEW

REVIEWER	Nasa, Prashant NMC Healthcare LLC, Critical Care Medicine
REVIEW RETURNED	13-Feb-2024

GENERAL COMMENTS	The authors have done a wonderful job with succinct presentation. The discussion will add new information related to late-onset HELLP syndrome. The hypothesis of obese pregnant are considered high–risk and treated early is an exploratory hypothesis and needs prospective validation. Minor correction: Line 153: Cis change to 95% Confidence Intervals (CIs).

VERSION 2 – AUTHOR RESPONSE

The authors have done a wonderful job with succinct presentation. The discussion will add new information related to late-onset HELLP syndrome. The hypothesis of obese pregnant are considered high–risk and treated early is an exploratory hypothesis and needs prospective validation.

Response: This has now been mentioned in the Discussion section.

6. Minor correction: Line 153: Cis change to 95% Confidence Intervals (CIs).

Response: The sentence now reads as follows: 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).