Effect of HELLP syndrome on acute kidney injury in pregnancy and pregnancy outcomes: a systematic review and meta-analysis

CURRENT STATUS: POSTED

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DOI: 10.21203/rs.2.15750/v1

SUBJECT AREAS
Maternal & Fetal Medicine

KEYWORDS
HELPP syndrome, acute kidney injury, pregnancy outcomes, P-AKI
Abstract

Background

HELLP syndrome is a common complication during pregnancy, especially among those who with gestational hypertension. At present, the impact of HELLP syndrome on AKI (acute kidney injury) and maternal and infant outcomes is controversial. Thus, we conducted a meta-analysis to find out more about the relationship between HELLP syndrome and acute kidney injury during pregnancy and pregnancy outcomes.

Methods

We systematically searched PubMed, Embase and Cochrane Databases for cohort studies to assess the effect of HELLP syndrome on P-AKI (acute kidney injury in pregnancy) and maternal and infant outcomes. Using odds ratio (OR) with 95% confidence interval (CI) were pooled with a random- or fixed-effect models when appropriate.

Results

This meta-analysis included 11 cohort studies with a total of 6333 Participants, including 355 cases of pregnant women with HELLP syndrome and 5979 cases that without. HELLP syndrome has been associated with relatively higher risk of AKI during pregnancy [OR 4.87 95% CI 3.31–7.17 P < 0.001], fetal mortality [OR 1.56 95% CI 1.45–2.11 P < 0.001] and Maternal death [OR 3.70 95% CI 1.72–7.99 P < 0.001].

Conclusions

HELLP syndrome has been associated with relatively higher risk of P-AKI, fetal mortality and Maternal death.

Background

HELLP syndrome has been considered a serious complication of pre-eclampsia. It is characterized by the occurrence of hemolysis, elevated liver enzymes and thrombocytopenia. The effect of HELLP syndrome on pregnancy is enormous. A large number of studies have shown that HELLP syndrome is associated with acute kidney injury during pregnancy and pregnancy outcomes. Pregnant women with HELLP syndrome have a higher incidence of AKI and fetal mortality[1]. However, some studies have
opposite conclusions[2]. Therefore, a systemic analysis of the relationship between HELLP syndrome and acute kidney injury during pregnancy and pregnancy outcomes is necessary.

Methods
We have registered on PROSPERO and the code is CRD42018112333. We performed a systematic review of the literature based on the approach recommended by the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement for reporting meta-analysis[3]. Without language restrictions, the literature about Cohort studies or RCT that reported HELLP syndrome, AKI and pregnancy outcomes, from the inception to May 2019 was searched in PubMed, EMBASE and Cochrane. The following search terms were used: HELLP syndrome/pregnant women/AKI or P-AKI/Neonatal outcomes/Fetal outcomes/stillbirth/perinatal outcomes. Furthermore, we reviewed the reference lists in the retrieved articles and recent reviews to identify other potential relevant studies. We excluded studies that were cross-sectional, descriptive or case series/reports.

Data extraction and quality assessment
The following information was abstracted from all the included studies by using a standardized data collection form: study name (together with the first author’s name and publication year), study design, country, Definition of acute kidney injury, Definition of HELLP syndrome, Number of patients with HELLP syndrome, Number of patients without HELLP syndrome, Pregnancy outcomes, major clinical outcomes, and quantity score. We also checked the supplementary files, and contacted the authors for more detailed information when it’s necessary. The literature search, data extraction and quality assessment (Grading of Recommendations Assessment, Development and Evaluation system) were performed independently by two investigators (LQ and LGJ). Any discrepancy between the two investigators was adjudicated by a third reviewer (ZSQ). We assessed the authenticity and quality of the included studies by Newcastle-Ottawa scales (NOS)[4], 6 points or more is defined as high quality research.

Statistical analysis
The odds ratio (OR) and 95% confidence interval (CI) for each outcomes was calculated before pooling by the random-effects model. Heterogeneity across the included studies was analyzed using the I2 to
describe the percentage of variability (greater than 50% as evidence of a significant level)[5]. The appropriate pooling method was decided according to the value of the I^2 statistic: fixed-effects models for I^2 < 50% and random-effects models for I^2 ≥ 50%[5–7]. Subgroup analysis was conducted to assess the effect of adjustment for the key covariates. Potential publication bias was assessed with the Begg’s test and represented graphically with Begg funnel plots of the natural log of the OR versus its standard error (SE). A two-tailed P value less than 0.05 was considered statistically significant. All statistical analyses were performed using Stata 12.0.

Results
The literature search yielded 340 articles, with 11 studies identified according to the inclusion criteria (Fig.1).[1, 2, 8–16]. Table 1–2 summarized the characteristics of these included studies. These studies were performed between 1993 to 2011 with sample sizes ranging from 60 to 1099. The primary disease in all the studies was gestational hypertension, the patients were divided into HELLP syndrome group and no HELLP syndrome group and the study was conducted between the two groups. The study-design types were as follows: retrospective studies 9 items[1, 2, 8, 9, 11–13, 15, 16], and prospective studies 2 items[10, 14].

Kidney outcomes
8 studies reported 79 cases of AKI in 556 Pregnant women with HELLP syndrome and 58 cases of AKI in 1158 Pregnant women without HELLP syndrome, producing a 4.87 fold (95% CI 3.31 to 7.17, P = 0.000) higher likelihood in Pregnant women with HELLP syndrome compared with those without [1, 2, 8–13] with Very low evidence of heterogeneity (I^2 = 0%, P = 0.429 Fig. 2).

Pregnancy outcomes
4 studies reported 11 cases of Maternal death in 280 Pregnant women with HELLP syndrome and 32 cases of Maternal death in 1149 Pregnant women without HELLP syndrome, producing a 3.70 fold (95% CI 1.72 to 7.99, P = 0.001) higher likelihood in Pregnant women with HELLP syndrome compared with those without HELLP syndrome[1, 9–11] with Very low evidence of heterogeneity (I^2 = 0%, P = 0.616 Fig. 3). 8 studies reported 87 cases of stillbirth in 612 Pregnant women with HELLP syndrome and 163 cases of stillbirth in 1997 Pregnant women without HELLP syndrome[8–11, 13–16], producing
a 1.56 fold (95% CI 1.45 to 2.11, P = 0.005) higher likelihood in Pregnant women with HELLP syndrome compared with those without HELLP syndrome[14] with Very low evidence of heterogeneity (I² = 12.4%, P = 0.333 Fig. 4). There is not enough evidence that Pregnant women with HELLP syndrome are associated with an increased incidence of Neonatal death (OR, 1.41; 95% CI 0.94 to 2.13; P = 0.098 (Fig. 5). When a single study was removed in sequence, the heterogeneity did not decrease significantly and the conclusion did not change.

**Publication bias**

The Newcastle-Ottawa scales (NOS) evaluation indicated that The incidence rate of AKI had low-quality evidence (Table 1). Funnel plot of Begg’s test was used to show evidence of the publication bias, and found there were no bias in the incidence rate of AKI among the studies (Begg’s test, P = 0.38) (Figure 6).

**Discussion**

**Main findings**

HELLP syndrome has a significant impact on acute kidney injury during pregnancy and pregnancy outcomes. Unfortunately, the exact definition of HELLP syndrome and AKI employed in different studies didn’t reach a consensus. It is currently believed that the diagnosis of HELLP syndrome proposed by Sibai et al. is stricter and more widely used[17]. AKIN and RIFLE are currently widely used[18] in the assessment of acute kidney injury.

To the best of our knowledge, this is the first meta-analysis to explore the effect of HELLP syndrome on acute kidney injury during pregnancy and pregnancy outcomes. The analysis of the 11 included studies of 6333 pregnancies showed the relationship between HELLP syndrome during pregnancy and acute kidney injury and pregnancy outcomes. This study suggests that Pregnant women with HELLP syndrome was associated with higher risk of AKI (4.87 fold), stillbirth (3.70 fold), and Maternal death (1.56 fold). The effect of HELLP syndrome on neonatal mortality was not statistically significant in this study, but our data on this subject was less, an in-depth study with more data is necessary.

**Possible mechanism**

Traditionally, HELLP syndrome was considered to be a variant of preeclampsia, but it is, in fact, a
distinct disease, since 20% of pregnant women with HELLP syndrome do not have a history of hypertension or proteinuria [19, 20]. The pathogenesis of HELLP syndrome is not fully understood. Studies have shown that levels of anti-angiogenic factors (sFlt-1 and sEng) elevated and concentrations of pro-angiogenic mediators (PIGF) decreased in pregnant women with HELLP syndrome[21]. HELLP syndrome seems to be a TMA-like disorder, there are several clinical similarities between them: mechanical hemolysis, thrombocytopenia, and AKI[22]. A recent study suggests that there maybe a link between HELLP syndrome and complement dysregulation,[23]. In our study, the stillbirth rate of pregnant women with HELLP syndrome was 49.5%, which was higher than the stillbirth birth rate reported in the Serdar study(7.4–34%)[24]. Premature birth and placental abruption are the main causes of stillbirth. Moreover, the maternal mortality rate in our study was 2.5% higher than that in the Sibai (1%) literature[25].

Clinical implications and limitations

The strength of this systematic review and meta-analysis lies in the instruction significance for clinical question, large volume of data that included and rigorous methodology that used. However, our study had some limitations: Firstly, the number of cases in some studies is small, leading to the possibility of bias; Secondly, because there is no unified definition of AKI and HELLP syndrome in each study, some patients with AKI and HELLP syndrome may be missed.

Conclusion

HELLP syndrome during pregnancy has been associated with relatively higher risk of AKI, fetal mortality and Maternal death. Although some conclusions require more research to support, this study resolves the dispute.

Abbreviations

CC, indicates case–control; RC, retrospective cohort; PC prospective cohort; CV cardiovascular

The criteria of Sibai: hemolysis, elevated lactate dehydrogenase (LDH >600 IU/L), aspartate (AST > 40 IU/L), and/or alanine aminotransferase (ALT > 40 IU/L) and low platelet (Plt) count as class III (Plt:100–150×10^3 /mL), class II (Plt:50–99×10^3 /mL), and class I (Plt < 50×10^3 /mL).

AKI : Acute kidney injury.

Declarations
Ethics approval and consent to participate
Not applicable

Consent for Publication
Not applicable.

Availability of data and material
All data generated or analysed during this study are included in this published article. All literature reviewed in the study was publicly available.

Competing interests
Not applicable.

Funding
2018 Guangxi Zhuang Autonomous Region health and family planning committee project NO.:Z20180127. Qiang LIU is the head of the fund and is responsible for all expenditure items of the fund.

Authors’ contributions
LQ, and LGJ conceived the study, LQ, LGJ, ZSQ and ZWQ designed and planned the study, were involved in acquisition of data, carried out the literature search and data extraction. LQ, LGJ, CYJ and YJC analyzed the data. All authors drafted the manuscript, participated in the interpretation of the data and critical review of the manuscript, and approved the version to be published.

Acknowledgements
Not applicable

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Tables

Table 1

| Author, Year | Study Design | Country | HELLP was defined | AKI (ARF) was defined | Sample size of patients with AKI in patients with HELLP | Sample size of patients with AKI in patients without HELLP | Major clinical outcomes |
|--------------|--------------|---------|-------------------|-----------------------|-----------------------------------------------|-----------------------------------------------|------------------------|
| gul2004      | RC           | Turkey  | The criteria of Sibai | Creatinine level ≥1.2 mg/dL and/or oliguria <400 mL/24 hr | 132 (20/112) | 156 (10/146) | Kidney outcome |
| Zuberi1998   | RC           | Pakistan| The criteria of Sibai | Not clear | 38 (4/34) | 38 (1/37) | Kidney outcome | Fetal outcome |
| yildirim2011 | RC           | Turkey  | Not clear | Creatinine clearance ≤ 20 mL/min | 196 (21/175) | 903 (14/889) | Kidney outcome | Fetal outcome |
| Study          | Design | Country       | Criteria                                                                 | Outcome |
|---------------|--------|---------------|--------------------------------------------------------------------------|---------|
| F. Abroug 1992 | PC     | Tunisia       | Increased liver enzymes and thrombocytopenia                            | N/C     |
|               |        |               | Present with an elevated serum creatinine level ≥ 2 mg/dL               |         |
| haddad 2000   | RC     | USA           | The criteria of Sibai: oligouria or anuria in association with creatinine clearance ≤ 20 mL/min and an elevated serum creatinine level ≥ 2 mg/dL | Kidney outcome |
|               |        |               |                                                                          |         |
| liu 2006      | RC     | China Taiwan  | Hemolysis, increased liver enzymes, low platelet count                  |         |
|               |        |               | Severe reduction in renal function with elevated serum creatinine greater than 120 µmol/L (> 1.4 mg/dL) | Kidney outcome |
| martin 1993   | RC     | USA           | The presence of thrombocytopenia, hepatic dysfunction and haemolysis    |         |
|               |        |               | Not clear                                                                |         |
| Turgut 2010   | RC     | Turkey        | The presence of thrombocytopenia, hepatic dysfunction and haemolysis    |         |
|               |        |               | Creatinine clearance of ≤ 20 mL/min and an elevated serum creatinine level of ≥ 2 | Kidney outcome |
Abbreviations: CC, indicates case-control; RC, retrospective cohort; PC prospective cohort; CV cardiovascular

The criteria of Sibai: hemolysis, elevated lactate dehydrogenase (LDH > 600 IU/L), aspartate (AST > 40 IU/L), and/or alanine aminotransferase (ALT > 40 IU/L) and low platelet (Plt) count as class III (Plt: 100–150×10^3/mL), class II (Plt: 50–99×10^3/mL), and class I (Plt < 50×10^3/mL).

AKI: Acute kidney injury,

a Expressed as total number of patients (number in HELLP group/number in control group)

Table 2
Characteristics of the included studies

| Author, Year | Study Design | Country   | HELLP was defined | Sample size of patients with stillbirth in patients with HELLP | sample size of patients with stillbirth in patients without HELLP | Major clinical outcomes | Quality score |
|--------------|--------------|-----------|-------------------|---------------------------------------------------------------|---------------------------------------------------------------|------------------------|--------------|
| gul2005      | PC           | Turkey    | The criteria of  | 106                                                           | 261                                                            | Fetal outcome          | 6            |
|              |              |           | Sibai            | (11/95)                                                       | (12/249)                                                      |                        |              |
| abramovici   | RC           | Pakistan  | The criteria of  | 133                                                           | 141                                                            | Fetal outcome          | 6            |
| 1999         |              |           | Sibai            | (10/123)                                                      | (5/136)                                                       |                        |              |
| Osmanağaoğlu2004 | RC | Turkey    | Hemolysis, elevated liver enzymes, low platelet count | 51                                                            | 52                                                             | Fetal outcome          | 5            |
|              |              |           |                   | 27/24                                                         | 19/23                                                          |                        |              |

a: Expressed as total number of patients (number in PR-AKI group/number in control group)

Figures
Records identified through database searching (n=340)
  PubMed: 185
  Embase: 110
  Cochrane library: 45

281 of records after duplicates removed

281 of records screened

Records excluded (n=281), with reasons
  - animal experiment
  - in vitro study
  - case report
  - meeting abstract
  - review

Full texts assessed

Full texts excluded (n=41), with reasons
  - not RCT or CCT
Process for identifying studies eligible for the meta-analysis
Comparison of the incidence of AKI in pregnant women with HELLP syndrome and no HELLP syndrome
Comparison of the Maternal death in pregnant women with HELLP syndrome and no HELLP syndrome
Comparison of the stillbirth in pregnant women with HELLP syndrome and no HELLP syndrome
Figure 5

Comparison of Neonatal death in pregnant women with HELLP syndrome and no HELLP syndrome
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