Serum LDH values in hypertensive disorders of pregnancy and their association with maternal and neonatal morbidity: a meta-analysis

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Abstract

Objectives: Serum lactate dehydrogenase has been extensively studied in hypertensive disorders of pregnancy. However, to date, its clinical usefulness in the field remains unknown. The present meta-analysis has been designed to evaluate differences in serum LDH values among patients with hypertensive disorders of pregnancy and to help determine its diagnostic accuracy as well its predictive accuracy in determining adverse pregnancy outcomes. Methods: We searched Medline, Scopus, Clinicaltrials.gov, EMBASE, Cochrane Central Register of Controlled Trials CENTRAL and Google Scholar databases from their inception till March 18, 2021. Meta-analysis was performed using the meta and metafor functions in Rstudio. Pooled mean differences (MD) were calculated with the Hartung-Knapp-Sidik-Jonkman. Meta-regression analyses, publication bias assessment and Trim and Fill function were also performed. The adequacy of the sample size was evaluated with Trial Sequential Analysis. Results: Fifty-two articles were included that comprised 5,340 women with hypertensive disorders of pregnancy and 2,890 healthy controls. The meta-analysis revealed significant differences among patients with preeclampsia (either mild or severe) compared to controls, as well as among patients with mild and severe preeclampsia. Significant asymmetry was noted after examining funnel plots, however, and the trim and fill analysis revealed that differences were significant only among cases with severe preeclampsia and healthy controls. Morbidity outcomes increased with LDH levels $>$ 600 IU/L and particularly when these exceeded 800 IU/L. However, confidence and prediction intervals indicated an underpowered sample size for the accurate determination of the odds of developing maternal morbidity. Conclusions: Despite the extensive research in the field of hypertensive disorders of pregnancy, there is still lack of evidence concerning the diagnostic performance of serum LDH in clinical practice; hence, research should expand in this direction to evaluate its clinical utility.

Introduction

Preeclampsia is a multisystem progressive disorder characterized by the new onset of hypertension and proteinuria or the new onset of hypertension and significant end-organ dysfunction with or without proteinuria in the last half of pregnancy or postpartum [1]. It is estimated to complicate approximately 4.6% of pregnancies worldwide [2]. Its pathophysiology is complex and not fully understood yet. Both maternal and placental factors are involved. Abnormal placentation and remodeling of spiral arteries may lead to placental hypo-perfusion, hypoxia, ischemia and the release of various antiangiogenic factors into the maternal circulation, causing systemic endothelial dysfunction [3]. In addition, immunological and genetic factors have been proposed.

Preeclampsia can be characterized as early onset (<34 weeks of gestation) and late onset ([?]34 weeks of gestation). Early-onset disease is associated with worse prognosis and poorer maternal and fetal outcomes, such as fetal growth restriction and preterm birth [4, 5].

Severe preeclampsia (or preeclampsia with severe features) is diagnosed when there is severe hypertension

(systolic BP [?]160 mmHg or diastolic BP [?]110 mmHg) and/or specific signs or symptoms of significant end-organ dysfunction: thrombocytopenia (< 100,000 platelets/microL), impaired liver function that is not accounted for by alternative diagnoses and as indicated by abnormally elevated blood concentrations of liver enzymes (to more than twice the upper limit normal concentrations), or by severe persistent right upper quadrant or epigastric pain unresponsive to medications, renal insufficiency (serum creatinine > 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease), pulmonary edema, new-onset headache unresponsive to medication and not accounted for by alternative diagnoses, visual disturbances [1].

Preeclampsia is associated with an increased risk for life-threatening obstetric or medical complications, intrauterine growth restriction, oligohydramnios and preterm labor. It is estimated that 10-15% of direct maternal deaths are associated with preeclampsia and eclampsia [6]. Therefore, it is essential to estimate the risk of preeclampsia early in pregnancy and identify high risk women that need frequent surveillance and prophylactic administration of low-dose aspirin. Although various laboratory and imaging tests have been proposed for preeclampsia prediction, the optimal screening model to be widely used in clinical practice remains a matter of debate [7].

Lactate dehydrogenase (LDH) is a cytoplasmic enzyme that catalyzes the interconversion of pyruvate and lactate acid and is present in tissues throughout the body. It is released into circulation following cellular death and tissue injury. LDH is a highly sensitive marker for tissue breakdown, but it is nonspecific as it is also elevated in many clinical disorders. It is a marker of hemolysis, liver dysfunction and has been used as a marker of myocardial infarction as well as a biomarker of inflammation [8-10]. Several studies have associated serum LDH levels with severity of preeclampsia, adverse maternal and perinatal outcomes [11-13].

The aim of this systematic review is to assess the usefulness of LDH as a prognostic biomarker in preeclampsia, as well as to provide a summary effect estimate concerning its effectiveness in predicting preeclampsia complications and adverse maternal and neonatal outcomes.

Protocol and registration

The present meta-analysis was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [14]. The study was based in aggregated data that have been already published in the international literature. Patient consent and institutional review board approval were not retrieved as they are not required in this type of studies. The study‘s protocol was published in open science framework, prior to the conduct of this review (Registration DOI: 10.17605/OSF.IO/UGWT6).

Types of studies and patients

The eligibility criteria for the inclusion of studies were predetermined. Observational studies that assessed differences in serum LDH levels among women with hypertensive disorders of pregnancy (gestational hypertension, preeclampsia, eclampsia, HELLP syndrome) and healthy controls were considered eligible for inclusion. Small case series (<10 patients), case reports, conference proceedings and animal studies were excluded from the present systematic review. Studies that involved pregnant women with comorbidities were excluded from the present systematic review. The control group consisted of healthy pregnant women, without evidence of any gestational complication. Studies were not excluded based on preeclampsia definition, since no date restrictions were applied.

Information sources and search methods

Two authors (V.P and M.P.) searched Medline (1966–2021), Scopus (2004–2021), Clinicaltrials.gov (2008–2021), EMBASE (1980-2021), Cochrane Central Register of Controlled Trials CENTRAL (1999-2021) and Google Scholar (2004-2021) along with the reference lists of electronically retrieved full-text papers. The date of the last search was set at March 18, 2021. The search strategy included the text words “lactate dehydrogenase; LDH; preeclampsia; gestational hypertension; HELLP” and is presented in brief in **Supplemental Figure 1** .

Studies were selected in three consecutive stages. Following deduplication, the titles and abstracts of all electronic articles were independently screened by three authors (MP, VP and SS) to assess their eligibility. The decision for inclusion of studies in the present meta-analysis was taken after retrieving and reviewing the full version of articles that were considered potentially eligible. Discrepancies that arose in this latter stage were resolved by consensus from all authors.

Predefined outcomes

Outcome measures were predefined during the design of the present systematic review. Data extraction was performed using a modified data form that was based in Cochrane's data collection form for intervention reviews for RCTs and non-RCTs [15]. Investigated outcomes were predetermined based in our previous systematic review that examined the role of serum uric acid as a predictive factor of preeclampsia [16]. Briefly, the main outcome of interest was the comparison of serum LDH levels among preeclamptic and healthy pregnant women in all gestational trimesters.

The prognostic role of uric acid was planned to be evaluated by comparing its levels among women with mild and severe preeclampsia, as well as with eclampsia and HELLP (hemolysis, elevated liver enzymes and low platelet count) syndrome. The diagnostic accuracy of serum uric acid in terms of predicting adverse perinatal outcomes (rate of cesarean section, fetal growth restriction, low birth weight, preterm birth, 5' Apgar score <7, fetal or neonatal death) was also evaluated.

Assessment of risk of bias and quality of evidence

The methodological quality of the included studies was assessed by two independent reviewers (A.P and S.S..) using the Newcastle Ottawa scale. The scale incorporates domains that include assessment of selection of study groups, comparability of groups and methods ascertainment of the outcome of interest. A point is awarded in a 9-point based system. For the purposes of the present systematic review the two points that are awarded for comparability of groups refer to differences in baseline gestational age at assessment of serum LDH and in maternal age.

Quality of evidence was evaluated under the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework, ranging from very low to high. More specifically, credibility of evidence was assessed by taking into account the following domains: study limitations, directness, consistency, precision and publication bias. In particular, study limitations were evaluated based on risk of bias assessments (NOS score), while directness was judged using the PICOS (population, intervention, comparison, outcome, study type) approach. To assess consistency and precision, clinically important effects were defined as serum LDH differences of [?]100 U/L, indicating a range of equivalence from -50 to 50 U/L. In this context, consistency referred to the agreement of 95% confidence and prediction intervals for each outcome in relation to clinically relevant effects, while precision assessment was made by taking into account whether 95% CI extended into the range of equivalence.

Statistical analysis

Statistical meta-analysis was performed with RStudio using the*meta and metafor* functions (RStudio Team (2015). RStudio: Integrated Development for R. RStudio, Inc., Boston, MA URL http://www.rstudio.com/). Statistical heterogeneity was not considered during the evaluation of the appropriate model of statistical analysis as the anticipated methodological heterogeneity of included studies did not leave space for assumption of comparable effect sizes among studies included in the meta-analysis [17]. Confidence intervals were set at 95%. We calculated pooled mean differences (MD) and 95% confidence intervals (CI) with the Hartung-Knapp-Sidik-Jonkman instead of the traditional Dersimonian-Laird random effects model analysis (REM). The decision to proceed with this type of analysis was taken after taking into consideration recent reports that support its superiority compared to the Dersimonian-Laird model when comparing studies of varying sample sizes and between-study heterogeneity [18]. When variables where expressed as median (range), median (interquartile range) or interquartile range and sample size transformation where performed to acquire the mean and standard deviation to include the studies in the meta-analysis [19].

Subgroup analysis was planned to be conducted on the basis of pregnancy trimester (1st, 2nd or 3rd), preeclampsia onset (early or late), severity (mild or severe) and complications (eclampsia and HELLP syndrome). Residual heterogeneity was planned to be explored by conducting meta-regression analysis taking into account the following parameters: year of publication, sample size (using a cut-off of 100 patients in at least one arm of the analysis), region (stratified in North America, Europe and other countries), Newcastle-Ottawa Scale score, study design, type of sample and definition of preeclampsia. Meta-regression was not performed for covariate levels with <3 studies. Publication bias was assessed by examining the possibility of small-study effects through the visual inspection of funnel plots. The asymmetry of funnel plots was statistically evaluated using the Egger's regression and Begg-Mazumdar's rank correlation tests. The Trim and Fill function was also used to evaluate potential differences in summary estimates after correction of asymmetry. Publication bias was evaluated by examining the potential presence of small-study effects through the visual inspection of contour enhanced and traditional funnel plots. Contour enhanced funnel plots permit the assessment of statistical significance of observed study estimates and may help differentiate if asymmetry arises from publication bias or other variables such as study quality.

Prediction intervals

Prediction intervals (PI) were also calculated, using the *meta*function in RStudio, to evaluate the estimated effect that is expected to be seen by future studies in the field. The estimation of prediction intervals takes into account the inter-study variation of the results and express the existing heterogeneity at the same scale as the examined outcome.

Trial sequential analysis

To evaluate the information size, we performed trial sequential analysis (TSA) which permits investigation of the type I error in the aggregated result of meta-analyses performed for primary outcomes that were predefined in the present meta-analysis. A minimum of 3 studies was considered as appropriate to perform the analysis. Repeated significance testing increases the risk of type I error in meta-analyses and TSA has the ability to re-adjust the desired significance level by using the O‘ Brien-Flemming a-spending function. Therefore, during TSA sequential interim analyses are performed that permit investigation of the impact of each study in the overall findings of the meta-analysis. The risk for type I errors was set at 5% and for type II errors at 20%. The TSA analysis was performed using the TSA v. 0.9.5.10 Beta software (http://www.ctu.dk/tsa/).

Results

Overall, 52 studies were included in this meta-analysis (references presented in the **Appendix**). A summary of their methodological characteristics is presented in the **Appendix** . Most of the studies included pregnant women at the third trimester of pregnancy. The actual gestational age at assessment was particularly heterogeneous as several studies included populations at gestational ages that covered both the early and late preterm period. The Newcastle - Ottawa revealed that the methodological quality of included studies ranged from moderate to inferior. The quality of evidence following evaluation of the GRADE framework revealed moderate study limitations and significant inconsistency (**Table 1**).

Primary outcomes

Significant differences were noted in serum LDH levels of women diagnosed with preeclampsia compared to controls (**Figure 2**). Significant asymmetry was observed following assessment of the forest plot with the majority of assessed studies falling into the level of higher statistical significance (p<.01); thus, suggesting that it might be attributed to other reasons than publication bias. The trim and fill function included 11 simulated studies and the overall effect following their addition was not significant (MD -334.42, 95%CI -334.42, 58.81, *p=.162*). The meta-regression function did not reveal a significant effect of the NOS score and publication year on the outcomes of the meta-analysis. Trial sequential analysis revealed that the required sample size was reached to ensure the adequacy of findings. Prediction intervals did not reach statistical significance (-385.82, 744.45 IU/L).

Similarly, differences among mild preeclampsia cases and controls were also noted. Significant asymmetry was observed that was also attributed to other reasons than publication bias as the majority of studies fell into the level of high statistical significance (p<.01). The trim and fill function included 7 simulated studies and the overall effect following their addition was not significant (MD 68.85, 95%CI -22.75, 160.45). The meta-regression analysis revealed that the effect was significantly skewed by the parameters of NOS and publication year; thus, denoting that the asymmetry might be the result of these parameters. The required information was exceeded with the first fraction of studies as denoted by the trial sequential analysis results. Prediction intervals fell into the non-significant level (-101.47, 453.74).

Severe preeclampsia cases had more pronounced differences compared to control women (MD 371.86, 95% CI 258.76, 484.97 IU/L). Funnel plot analysis revealed significant asymmetry that was not attributed to publication bias. The trim and fill function included 7 simulated studies and the overall effect following their addition maintained statistical significance (MD 175.68, 95%CI 18.53, 332.83). Meta-regression analysis revealed that both the NOS and publication year influenced the results of the primary analysis; thus, denoting that the asymmetry might be the result of these factors. Sample size was adequate to support this finding.

Direct comparison of cases with mild with those that had severe preeclampsia revealed that women with mild preeclampsia had significantly lower levels of LDH (MD -162.04, 95% CI -217.18, -106.80 IU/L) (**Figure 3**). Ten simulated studies were added with the trim and fill function which resulted in non-significant differences among the two groups (MD -51.25, 95%CI -125.18, 22.67). As in the case of the previous comparisons, funnel plot analysis revealed that asymmetry was not attributed to publication bias, but meta-regression analysis failed to reveal a significant effect of the quality of included studies or of the year of publication to these findings. Sample size was adequate to support the result of the meta-analysis.

Secondary outcomes

The results of the meta-analysis of investigated secondary variables is summarized in **Table 2** . Briefly, significant increased levels of LDH were observed among cases with HELLP compared to cases with preeclampsia and cases with eclampsia. Early onset preeclampsia cases had also significantly increased levels of LDH compared to controls. The remaining differences were not significant.

The diagnostic accuracy of LDH in predicting preeclampsia could not be explored; instead, odds ratios of developing maternal morbidity and perinatal fetal/neonatal death outcomes were determined. Specifically, we observed that the odds of developing HELLP, renal failure, disseminated intravascular coagulation (DIC) and pulmonary edema were increased when serum LDH levels exceeded 600 IU/L and particularly when these increased more than 800 IU/L (**Appendix & Table 3**). Perinatal fetal/neonatal mortality was also more likely to occur.

Qualitative analysis

The sensitivity of LDH in predicting preeclampsia was reported in four articles that were particularly heterogeneous due to the quite heterogeneous optimal cut-off values that were evaluated; thus, precluding analysis of results. Specifically, Duan et al reported an area under the curve (AUC) that reached 0.899 and a sensitivity of 92.5% using a cut-off value of 183.5 U/L [20]. Similarly, Khalil observed that LDH could help differentiate severe preeclampsia from healthy controls as well as patients with proteinuria, gestational hypertension and mild preeclampsia using a cut-off value of 208 U/L (sensitivity 100%, AUC 71.2%) [21]. On the other hand, Fazal et al reported that the accuracy of LDH in detecting preeclampsia was limited (sensitivity 50% at an optimal cut-off of 525 U/L) [22]; however, their sample size was particularly small to establish definitive conclusions. Kasraeian et al used a cut-off of 336 U/L and observed that the specificity was also low (59%) [23].

Discussion

The findings of our meta-analysis suggest that the existing literature supports the existence of significant differences in serum LDH levels among patients with preeclampsia compared to healthy controls. This finding is more predominant in women with severe preeclampsia, compare to those with mild features of the

disease. However, at this point it should be noted that these findings are particularly skewed and seem to be attributed to the poor methodological quality of included studies, as well other potential factors (described in the materials and methods), that we could not investigate, due to the lack of substantial differences among the included studies. Of specific importance is the lack of available evidence in the field of the diagnostic accuracy of this biomarker as the vast majority of studies failed to evaluate its sensitivity and specificity. Moreover, we observed a complete lack of data concerning the predictive accuracy of serum LDH on determining adverse maternal and neonatal outcomes in studies enlisted in our systematic review.

However, this does not mean that there is no data to support the potential use of this enzyme in the field of obstetrics as there are scarce data that evaluate its predictive accuracy in the presence of hemolysis. Specifically, the most recent and largest in sample size study in the field suggests that LDH levels >400 IU/L are associated with severe maternal and neonatal complications in the presence of hemolysis [13]. However, a standardized cut-off value has not been established yet as there seem to be large discrepancies among the few studies that exist in the field [24, 25].

Several other diseases may trigger the increase of serum LDH as well, including pregnancy-associated thrombotic thrombocytopenic purpura, diseases of the liver etc [26]. It remains relatively unknown whether increases are comparable, however, current research suggests that the use of combined examinations of LDH with other biomarkers such as liver enzymes may help establish an accurate diagnosis [27].

Limitations and strengths

Our study is limited by the methodological quality of included studies and by the presence of significant inconsistency and publication bias that was observed among studies that presented data that were used for the analysis of investigated primary outcomes. However, we believe that with the use of sensitivity and meta-regression analysis we were able to fill the gaps in current research, and underline that the differences in serum LDH values among the various groups of pregnancy associated disorders are minimal and do not need further investigation. A significant limitation of our study is also the lack of a diagnostic and predictive accuracy analysis that would help determine the actual value of serum LDH in detecting preeclampsia and differentiating patients at risk of developing adverse effects (maternal or neonatal).

Implications for current clinical practice and future research

The findings of this meta-analysis suggest that serum LDH differences are minimal among the various forms of hypertensive disorders of pregnancy. The only potential group that might benefit from the addition of serum LDH in standard preclinical evaluation is that of patients with severe preeclampsia. Maternal morbidity outcomes as well as perinatal mortality of the fetus/neonate were found increased among patients with an increased LDH value and particularly among those with LDH that exceeded 800 IU/L. However, the observed confidence intervals as well as prediction intervals indicated a wide range of the effect size; thus, indicating that the actual power of this biomarker was low in determining these adverse outcomes. Given this information we believe that it is difficult to determine the actual levels that may help discriminate patients at risk of experiencing adverse maternal or neonatal outcomes as current evidence is scarce and reports particularly heterogeneous optimal cut-off values.

Taking this into consideration, we believe that future research should focus in patients with severe preeclampsia and incorporate a predictive accuracy analysis that will help discriminate patients at risk of severe morbidity at specific cut-off points. Taking in mind that the increase of LDH might precede more severe adverse effects, such as acute hemolysis, kidney injury, pulmonary oedema, admission to the ICU and NICU it would be prudent to evaluate the optimal interval to delivery of patients with unaffected blood parameters (including platelets, creatinine, liver enzymes) that firstly develop an increase in serum LDH. In order to do so, future research should firstly establish an ideal cut-off value that is associated with increased specificity (and if possible, sensitivity) for developing severe morbidity. Following that, evaluation of the optimal interval to deliver will become possible.

Conclusion

The findings of the present meta-analysis do not support a significant increase of serum LDH in hypertensive disorders of pregnancy with the exception of patients with that develop severe preeclampsia. Even in this latter group, however, the actual diagnostic accuracy of the enzyme seems to be limited by the scarce available evidence. Its predictive accuracy in determining adverse maternal and neonatal outcomes is extremely limited and is mainly based in pregnant women that develop hemolysis. Future research should expand in this field, rather than assessing differences in serum LDH values among the various subgroups of hypertensive disorders of pregnancy.

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Figure legends

Figure 1. Search plot diagram.

Figure 2. Forest plot and contour enhanced funnel plot (preeclampsia vs control). Forest plot: Vertical line = "no difference" point between the two groups. Green squares = risk ratios; Diamonds = pooled mean differences and 95 confidence intervals for all studies; Horizontal black lines = 95% CI; Horizontal red line = 95% prediction intervals. Contour enhnanced funnel plot: 95% CI per level of statistical significance, white color: $p>.05$, navy blue: $p<.05$, blue: $p<.025$, light blue:$p<.01$).

Figure 3. Forest plot and contour enhanced funnel plot (mild preeclampsia vs severe preeclampsia). Forest plot: Vertical line = "no difference" point between the two groups. Green squares = risk ratios; Diamonds = pooled mean differences and 95 confidence intervals for all studies; Horizontal black lines = 95% CI; Horizontal red line = 95% prediction intervals. Contour enhnanced funnel plot: 95% CI per level of statistical significance, white color: $p>.05$,navy blue: $p<.05$, blue: $p<.025$, light blue: $p<.01$).

Table captions

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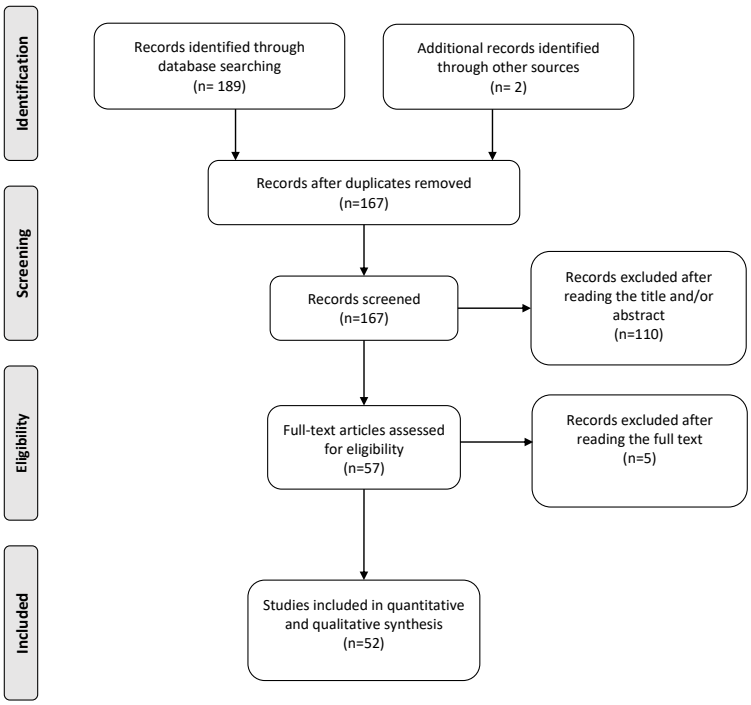
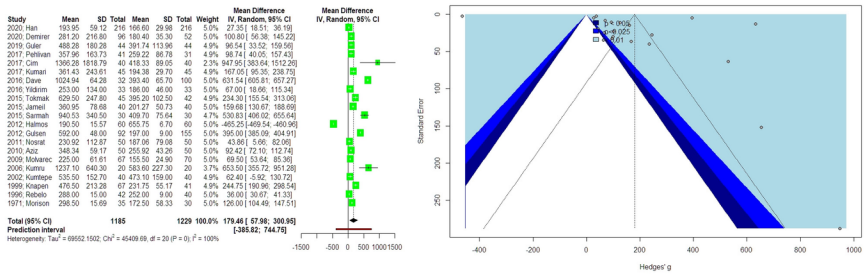
Table 3. Summary of maternal and neonatal morbidity. OR: odds ratio; CI: confidence intervals; PI; prediction intervals





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