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Review article

HELLP syndrome and COVID-19: A minor revision of a possible new "COVID-19-linked HELLP-like syndrome"

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ABSTRACT

To report the characteristics described in the literature on a possible new "COVID-19-linked HELLP-like syndrome" in pregnant women with COVID-19: its association with the severity; prevalence; clinical; laboratory; pathophysiological and therapeutic management differences from the classic HELLP syndrome and their impact on outcomes. Observational, cohort, case-control, case-series and case-report studies were included. Data were extracted independently by the authors of the study, to ensure accuracy, consistency and performed the quality assessment. The database search resulted in 77 references, of which two satisfied the eligibility criteria. In these 2 studies we found a possible "COVID-19-linked HELLP-like syndrome", associated with severe COVID-19. There is a high possibility of the existence of "COVID-19-linked HELLP-like syndrome" and its association with severe COVID-19 in pregnant women, with a prevalence of 28,6%. Some characteristics of "COVID-19-linked HELLP-like syndrome" and the classic HELLP syndrome are similar. Differential diagnosis indicated two different types of therapeutic management: conservative for "COVID-19-linked HELLP-like syndrome" and delivery for the HELLP syndrome. HELLP clinical management is mandatory for both.

Pregnant women are considered to be at risk for COVID-19 disease. They have higher rates of admission to intensive care units (ICUs), a greater need for mechanical ventilation and higher mortality rates [1]. During gestation, COVID-19 is associated with increased premature-birth rates, higher perinatal morbidity and mortality, a higher incidence of preeclampsia (PE) [2] and an inflammatory syndrome similar to HELLP syndrome, which we denominate "COVID-19-linked HELLP-like syndrome" (CLHLS), as well as more severe manifestations of this inflammation (Fig. 1).

Preeclampsia is a multisystemic, multifactorial, hypertensive disorder of pregnancy mediated by the placenta with an unknown etiology and an incidence of approximately 5 % which is considered a clinical manifestation of maternal endothelial dysfunction [8]. Clinically, PE presents as hypertension (BP $\geq$ 140/90 mmHg) and proteinuria ($\geq$ ++ of protein in a dipstick urinalysis or $\geq$ 300 mg in 24 h or $\geq$ 30 mg/mol proteinuria/creatinuria ratio) and manifests after the 20th week of gestation in previously normotensive pregnant women [19]. As gestation progresses, PE can develop into more severe conditions, such as eclampsia [7], hemorrhagic stroke and a syndrome with hemolysis associated with elevated liver enzymes and a low platelet count (HELLP syndrome), leading to kidney failure, acute pulmonary edema and death [9]. The condition is considered to be preeclampsia when, even in the absence of proteinuria, maternal target organ dysfunction (thrombocytopenia, liver dysfunction, kidney failure, acute pulmonary edema, imminent eclampsia) and eclampsia [7] (convulsive tonic-clonic seizures resulting from cerebral edema) are present.

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In pregnant women and women in the puerperium with severe inflammatory forms of COVID-19, there has been shown to be a greater prevalence of PE [2] with severe findings (2 to 3 × greater), and many of these cases developed into HELLP syndrome. In light of these findings, it was necessary to determine whether this clinical picture occurs in any gestation or whether there is an association with severe cases of COVID-19, which is also more prevalent in pregnant women. However, it was difficult to establish the differential diagnosis between CLHLS (the possible new syndrome similar to PE with severe findings found in some pregnancies which imitates HELLP) and the classic HELLP syndrome as they are similar, with overlap occurring between the two syndromes [3,4,5,10,12].

Clinical, laboratory and microvascular pathophysiological similarities between the classic HELLP syndrome and CLHLS have been observed. These changes may be related to endothelial dysfunction, intravascular inflammation with locoregional onset (respiratory tract) and increased helper T cells and B cells that secrete autoantibodies against angiotensin-II type-1 receptors and are associated with COVID-19 [6]. The condition then becomes systemic, with poor placental perfusion, thrombin activation and arterial hypertension, which are fundamental characteristics of the pathophysiology of the PE/HELLP syndrome and are mediated by the placenta and of unknown etiology [7,9].

Because of the importance of CLHLS, this article sought to demonstrate the characteristics and prevalence of this possible new form of the HELLP syndrome in pregnant women with COVID-19 described in the literature. We also sought to describe the pathophysiological, clinical and laboratory differences between the two conditions and to determine whether the appearance of CLHLS is associated with different degrees of COVID-19 severity. Finally, to demonstrate the differences in management for each condition and its impact on outcomes.

The terms used in the search strategy were defined through the research question and the acronym PICO, where P = Pregnant women, I = COVID-19 OR severe COVID-19; C = HELLP syndrome and pre-eclampsia OR eclampsia; O = Conservative management for the HELLP-like syndrome. Carrying out delivery for the classic HELLP syndrome. The Descriptors in Health Sciences (DeCS) and Medical Subject Heading (MeSH) and Emtree (Embase/Elsevier) terms were evaluated together where AND: looks for one term associated with another, OR: similarity and "" delimits. (child-bearing OR gravidity OR intrauterine pregnancy OR labor presentation OR pregnancy maintenance OR pregnancy trimesters AND HELLP-like syndrome and COVID-linked AND Pre-eclampsia OR Eclampsia OR HELLP Syndrome AND COVID-19 OR SARS-CoV-2 OR severe acute respiratory syndrome coronavirus 2019 infection OR severe COVID-19 OR severe COVID (Table 1).

The following bibliographic sources were searched: MEDLINE/PubMed, EMBASE (Elsevier), BVS (BIREME) and CINAHL (EBSCO). The following multidisciplinary databases were also searched: Web of Science (Main Collection Clarivate Analytics) and SCOPUS (Elsevier). Gray literature: Database: OpenGrey, up to November 30th, 2022. No language restriction was used. The PROSPERO protocol was registered under number - CDR 42022380465.

The database search resulted in 77 references, of which 33 were duplicates. The titles and abstracts of the 44 articles were read, and 42 articles were excluded because they were reviews its focus only in the subject or part of it. The two studies that met the eligibility criteria were selected. These covered the period up to November 30th, 2022. The first objective of the articles was limited to determining whether there is an association between the severity of COVID-19 and CLHLS.

Studies in populations of pregnant women with COVID-19 have shown that there are certain clinical, laboratory and pathophysiological characteristics [4,12,14] that support the possible existence of a new syndrome similar to the HELLP syndrome. While these characteristics do not constitute the HELLP syndrome, they can lead to greater maternal and perinatal morbidity and mortality [2]. After reviewing the studies identified, we propose the term "COVID-19-linked HELLP-like syndrome" to better define this syndrome. In the two studies, the new syndrome was associated with severe COVID-19 and had a prevalence of 28.6 % (10/35 cases) [3,4] (Table 2). In our service, we had 1 case of CLHLS in pregnant women with mild COVID-19 and we did not find this description in the analyzed studies. An important demonstration that this syndrome is not only associated with severe COVID-19, as described in the literature.

Because of the close similarity between CLHLS and the classic HELLP syndrome in pregnant women with severe COVID-19, it proved very difficult to establish a differential diagnosis, both in view of the clinical

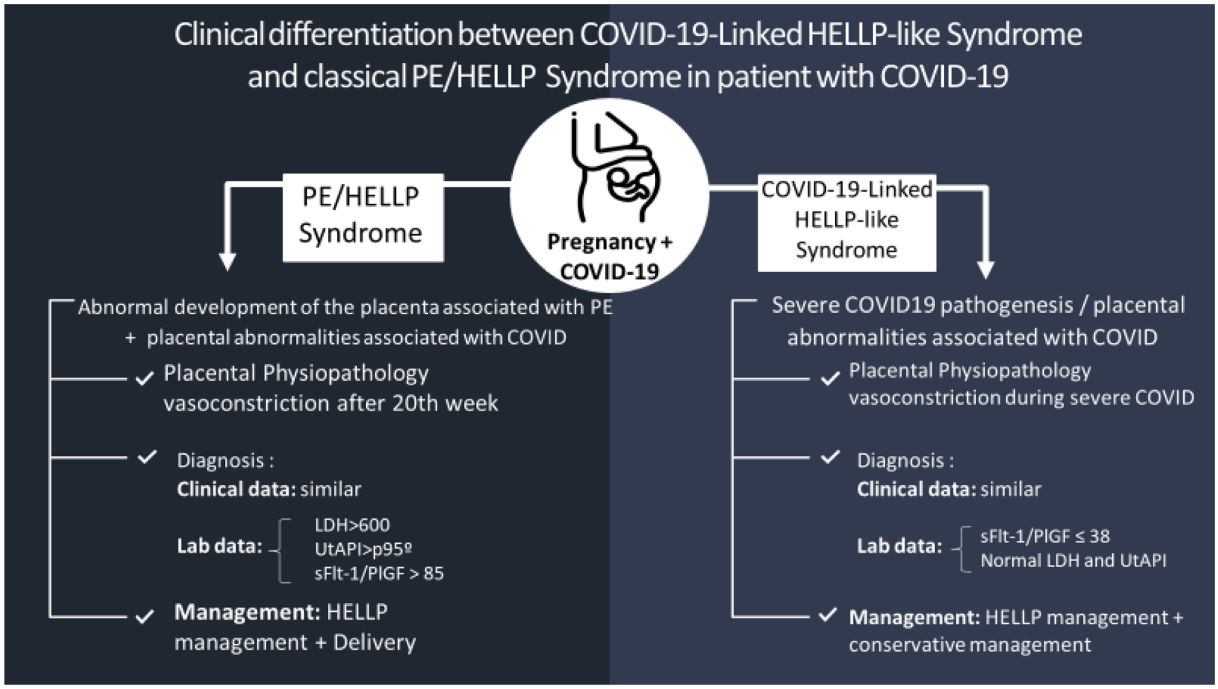

Fig. 1. DESCRIPTION OF "COVID-19-Linked HELLP-like syndrome". SOBIERAY NLEC et al., 2022.

Table 1
DESCRIPTORS: DeCS/MeSH and EMTREE.

Keywords	Descriptors DeCS/MESH and EMTREE	Synonyms
Pregnant Women	Gestation OR Pregnancy	Child bearing OR gravidity OR intrauterine pregnancy OR labor presentation OR pregnancy maintenance OR pregnancy trimesters
'HELLP-like syndrome and COVID-linked'	'HELLP-like syndrome and COVID-linked'	HELLP-like syndrome and COVID-linked
Eclampsia and Preeclampsia OR HELLP SYNDROME	Preeclampsia OR Eclampsia	Preeclampsia like OR eclampsia OR pre eclampsia OR pre- eclampsia OR pre-eclamptic toxaemia OR preclampsia OR preeclamptic toxaemia OR preeclamptic toxemia OR toxaemia, preeclamptic OR toxemia, preeclamptic OR HELLP Syndrome
COVID-19 / severe COVID	COVID-19 OR sars-cov-2 OR ncov 2019 OR severe acute respiratory syndrome coronavirus 2019 infection OR severe COVID-19 OR severe COVID	2019 novel coronavirus disease OR 2019 novel coronavirus epidemic OR 2019 novel coronavirus infection OR 2019-ncov disease OR 2019-ncov infection OR covid OR covid 19 OR covid 19 induced pneumonia OR covid 2019 OR covid-19 OR covid-19 induced pneumonia OR covid-19 pneumonia OR covid19 OR sars coronavirus 2 infection OR sars coronavirus 2 pneumonia OR sars- cov-2 disease OR sars-cov-2 infection OR sars-cov-2 pneumonia OR sars-cov2 disease OR sars- cov2 infection OR sarscov2 disease OR sarscov2 infection OR coronavirus disease 2019 OR coronavirus disease 2019 pneumonia OR coronavirus disease-19 OR coronavirus infection 2019 OR ncov 2019 disease OR ncov 2019 infection OR new coronavirus pneumonia OR novel coronavirus 2019 disease OR novel coronavirus 2019 infection OR novel coronavirus disease 2019 OR novel coronavirus infected pneumonia OR novel coronavirus infection 2019 OR novel coronavirus pneumonia OR paucisymptomatic coronavirus disease 2019 OR severe acute respiratory syndrome 2 OR severe acute respiratory syndrome 2 pneumonia OR severe acute respiratory syndrome cov-2 infection OR severe acute respiratory syndrome coronavirus 2 infection OR severe acute respiratory syndrome coronavirus 2019 infection OR severe covid-19 OR covid severe OR severe covid.

Table 2
Prevalence of COVID-19-linked hellp-like syndrome in pregnant women with mild and severe COVID-19.

AUTHORS (YEAR)	Diagnosis	COVID-19		Study Design
		Mild n (%)	Severe n (%)	
Figueras, F. et al (2020)	HELLP-like syndrome	–	6/27 (22.2 %)	Case series
Mendoza, M. et al (2020)	PE-like syndrome	0/34 (0.0 %)	4/08 (50 %)	Cohort
		Total: 0/34 (0,0%)	10/35 (28.6%)	

Notes:
PE-like syndrome – Preeclampsia-like syndrome.
HELLP syndrome – Hemolysis, elevated liver enzymes and low platelet count syndrome.

characteristics of the severe flu symptoms common to both (fever, cough, headache, sore throat, dyspnea and hypoxia) and the same clinical characteristics of PE/HELLP syndrome (high blood pressure, proteinuria, elevated liver enzymes and a low platelet count) in both conditions. The laboratory parameters LDH, sFlt-1:PlGF ratio and UtAPI do not change in cases of CLHLS; if these are normal, they therefore exclude the HELLP syndrome [4,11]. The clinical characteristics of the HELLP syndrome disappear in cases of CLHLS after the viral infection and inflammation have ceased. In the classic HELLP syndrome this spontaneous regression of the clinical and laboratory parameters does not occur [3,4] (Fig. 1).

For the differential diagnosis laboratory findings such as LDH $>$ 600 UI/L and results of imaging tests such as uterine artery Doppler (UtAPI $>$ p95) were used to diagnose PE/HELLP syndrome [3,4]. Some authors used an imbalance in antiangiogenic and angiogenic biomarkers (sFlt-1: PlGF $>$ 85) as predictive of a diagnosis of PE/HEELP syndrome within four weeks, with a positive predictive value (PPV) of 36.7 %. A value of sFlt-1:PlGF $<$ 38 excluded a diagnosis of PE/HELLP syndrome in the next seven days, with a negative predictive value (NPV) of 99.3 %, and confirms the diagnosis of CLHLS [4,11] (Table 3), respecting the thresholds of these biomarkers (sFlt-1 and PlGF) according to gestational age.

Abnormal placental development was present in both conditions. In PE/classic HELLP syndrome, alterations resulting from vasoconstriction

Table 3
Differential diagnosis between COVID-19-linked hellp-like syndrome and classic hellp syndrome in pregnant women with COVID-19.

Differential Diagnosis	HELLP Syndrome + COVID-19	COVID-Linked HELLP-like Syndrome
Placenta	Abnormal development of the placenta associated with vasoconstriction in PE is observed after 20th week + placental abnormalities associated with COVID-19	Severe COVID-19 pathogenesis and placental abnormalities associated with COVID-19 + vasoconstriction during severe COVID-19
Clinical data	Similar Remain after COVID-19	Similar, Disappear after COVID-19
Lab. Data	sFlt-1/PLGF $>$ 85 LDH $>$ 600 UI/L UtAPI $>$ p95°	sFlt-1/PlGF $\leq$ 38 Normal LDH and UtAPI
Management	HELLP management + delivery	HELLP management + Conservative Management

Notes:
PE: Preeclampsia.
HELLP Syndrome: Hemolysis, Elevated Liver enzymes and Low Platelet count syndrome.
COVID-19: Coronavirus disease-2019.
LDH: Lactate dehydrogenase.
sFlt-1/PLGF ratio: soluble fms-like tyrosine kinase-1/placental growth factor.
UtAPI: Uterine artery pulsatility index.

(low perfusion and infarctions) characteristic of the pathophysiology of PE which appear after the 20th week of gestation were observed together with placental abnormalities characteristic of infection with COVID-19. In contrast, in CLHLS only placental abnormalities characteristic of the viral infection and inflammatory reaction during the severe form of COVID-19 were observed, and these were accompanied by vascular changes (poor perfusion), fibrin deposition and chronic histiocytic intervillositis [4,12,13] (Table 3).

In institutions where biomarker tests were not available to determine the s-Flt-1:PlGF ratio suggested by many authors or only the PlGF [14], LDH and uterine artery Doppler measurements (UtAPI) were used for the differential diagnosis [3,4]. Conservative management was chosen until the viral infection and inflammatory storm disappeared when the results for LDH, UtAPI and placental function were normal, a characteristic of CLHLS. Essential initial management of HELLP was performed, allowing gestation to continue and the mother's clinical condition to improve [3,4] (Table 3).

Some authors suggest that COVID-19 during gestation is a risk factor for development of PE/HELLP syndrome [15] or a cause of PE [16]. Other authors have noted the similarity between their pathophysiologies [4,12,14], such as endothelial dysfunction [8], intravascular inflammation, proteinuria [17], high blood pressure, changes in the complement system [18] and activation of the coagulation cascade in more severe forms of COVID-19. Acetylsalicylic acid (ASA) in low doses has been recommended by some authors for pregnant women who contract SARS-CoV-2 before the 28th week of gestation to prevent PE/HELLP syndrome [15]. Earlier studies, however, indicated low doses of ASA before the 16th week of gestation to prevent PE/HELLP syndrome when there is at least one major risk factor or two moderate risk factors [19].

The strong association between the severe form of COVID-19 and CLHLS was shown in two studies (one cohort and one case series): two Spanish studies [3,4], with a prevalence of 28.6 % (10/35 cases) of severe cases admitted to ICUs and no cases of CLHLS in mild cases of COVID-19 in pregnant women (0/34 cases). These data brings a hypothesis that CLHLS is linked with severity of COVID-19. Although we observed in our service, the CLHLS associated with 1 case of mild COVID-19 (1/104 cases). Many recent studies, also suggest the possible existence of the new imitator of preeclampsia and HELLP syndrome in pregnant women with COVID-19, and that could delay the diagnosis and thus increasing maternal morbidity and mortality [20–22].

The main reason for making a differential diagnosis between PE/HELLP syndrome and CLHLS is to determine the management to be adopted, which is very different in the two situations. In the classic HELLP syndrome, delivery is indicated, but in the case of CLHLS this could lead to a worsening of the COVID-19. Conservative management is recommended for CLHLS to avoid needless interventions or iatrogenic preterm birth in this group of pregnant patients. The inflammatory condition should be controlled in an attempt to improve the outcome and allow gestation to continue so that increased maternal morbidity is avoided [4]. HELLP clinical management was performed in both situations [3,4] and was considered mandatory at the beginning of the treatment.

Our review of the literature revealed the high possibility of the existence of "COVID-19-linked HELLP-like syndrome" in pregnant women with severe COVID-19, with a prevalence of 28.6 % in the severe COVID-19 cases. Some clinical, laboratory and pathophysiological characteristics were found to be similar in CLHLS and the classic HELLP syndrome. Our study has shown that CLHLS is closely associated with more severe cases of COVID-19 in pregnant women. The importance of differential diagnosis to determine the management to be adopted should be highlighted and is based on the sFlt-1:PlGF ratio, UtAPI and LDH levels, which confirm CLHLS when the results are unremarkable and exclude HELLP syndrome. Conservative management is recommended for CLHLS, and the viral infection and inflammatory condition should be allowed to resolve spontaneously and gestation to continue, thereby preventing the mother's condition worsening and avoiding iatrogenic preterm birth. In contrast, in the classic HELLP syndrome the clinical changes, such as high blood pressure, changes in laboratory findings, such as proteinuria, and organ dysfunction and changes in placental function remain even after the viral infection has regressed, indicating the need for delivery to resolve the condition. Initial HELLP clinical management was performed in a similar fashion in both situations and was considered indispensable in both.

Authors' contributions

MZ, CFK and NLECS were involved in the conception and planning of the minor revision.

NLECS, SLP and NSC carried out the search, extracted data, performed the quality assessment and drafted the manuscript.

MZ, SLP, NLECS, NSC and CFK idealized the figure.

All authors seen and approved the final version of the manuscript.

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Background

Severe COVID-19 during pregnancy is associated with a higher incidence of preeclampsia and a possible new inflammatory syndrome, which we suggesting a denomination of "COVID-19-linked HELLP-like syndrome".

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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