Thesis

The Spectrum of HELLP Syndrome

A retrospective study of cases from 2005 - 2020

submitted by

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Declaration of Academic Integrity

I hereby confirm that the present diploma thesis is the result of my own independent scholarly work. I also confirm that in all cases, where material from the work of others (in books, articles, essays, dissertations, and on the internet) is acknowledged, quotations and paraphrases are clearly indicated. No material other than that cited in the reference list has been used. I have read and understood the Medical University's regulations and procedures concerning plagiarism.

Graz,07.05.2024 *Julia Barbara Ebmeyer eh.*

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Zusammenfassung

Hintergrund: Das HELLP-Syndrom ist eine Schwangerschaftskomplikation, die erstmals vor fast vier Jahrzehnten beschrieben wurde. Seitdem haben Forscher*innen und Kliniker*innen nicht nur die Definition des HELLP-Syndroms präzisiert, sondern auch neuere Laborgrenzwerte für die Diagnose festgelegt. Es verwundert daher nicht, dass das HELLP-Syndrom nach wie vor eine der größten ungelösten Herausforderungen im Bereich der Geburtshilfe darstellt.

Zielsetzung: Untersuchung des Facettenreichtums des HELLP-Syndroms mit besonderem Schwerpunkt auf seiner Manifestation, Klassifizierung, dem Schweregrad der Morbidität, dem mütterlichen Outcome und den neonatalen Implikationen.

Methodik: In einer retrospektiven Studie an einem Universitätsklinikum wurden 163 Patientinnen identifiziert, die zwischen 2005 und 2020 an ein HELLP-Syndrom erkrankten. Es wurde eine detaillierte statistische Analyse der demografischen, klinischen und Laborparameter durchgeführt. Die Studienpopulation wurde je einer Untergruppe zugeteilt, abhängig vom Zeitpunkt des Auftretens des HELLP-Syndroms, prä- und postpartal (genannt PRE und POST). Die gesamte Studienpopulation wurde dann noch einmal in eine separate Untergruppe aufgeteilt, auf der Grundlage des Schweregrads der Morbidität (klinische Manifestation und Komplikation), SEVERE und LOW. Die Untergruppen wurden mittels Mann-Whitney-U-Tests und t-Tests verglichen. Der Chi-Quadrat-Test wurde verwendet, um die Beziehung zwischen kategorischen Variablen zu bestimmen. Ein p-Wert von $< .05$ wurde als statistisch signifikant definiert.

Ergebnisse: Die statistische Analyse ergab, dass ein HELLP-Syndrom, das zu einer schweren mütterlichen Morbidität führt (Gruppe SEVERE), mit einer niedrigen Thrombozytenzahl (<60.000), einer erhöhten AST (>300 U/L), einer hohen LDH (>550 U/L) und einem hohen Blutdruck (systolisch >170 mmHg, diastolisch >100 mmHg oder mittlerer arterieller Druck >120 mmHg) korreliert. Die Anwendung der Endpunkte auf die Untergruppen PRE und POST ergab keine statistisch signifikanten Unterschiede zwischen den beiden Gruppen in allen Kategorien ($p > 0,05$), außer bei den Laborwerten ($p <0,01$). Hier hat die PRE-Untergruppe signifikant schlechtere Laborwerte als die POST-Gruppe, obwohl dies keinen signifikanten Einfluss auf die Dauer des Krankenhausaufenthalts ($p=3,1$) oder die Morbidität hatte. Darüber hinaus weist eine vom HELLP-Syndrom

betroffene Frau in unserer Studie charakteristische Merkmale auf ($p>0,05$): Alter (31 Jahre), BMI (23), Schwangerschaftsdauer (34 Wochen), Symptome (Oberbauchschmerzen, Kopfschmerzen, Übelkeit) und voraussichtliche Art der Entbindung (Kaiserschnitt).

Diskussion: Trotz der Identifizierung signifikanter Marker für schwere Morbidität wichen paradoxerweise einige Fälle von diesem Muster ab, was die Unvorhersehbarkeit und Komplexität dieses Syndroms verdeutlicht. Patientinnen mit diesen Markern müssen engmaschig überwacht werden, und die Geburt sollte eingeleitet oder geplant werden, sofern die Patientin noch schwanger ist. Der Vergleich unserer Ergebnisse mit grundlegenden Studien ergab Parallelen und Unterschiede in Bezug auf den Beginn, den Schweregrad und die Folgen des HELLP-Syndroms in verschiedenen Populationen. Während bei der Symptomatik konstante Tendenzen beobachtet wurden, weisen Abweichungen beim Alter der Mutter, bei den Entbindungsmethoden und bei der mütterlichen Sterblichkeitsrate auf die Notwendigkeit weiterer Untersuchungen zu möglichen Einflussfaktoren auf die Manifestation und den Schweregrad des Syndroms hin.

Schlussfolgerungen und zukünftige Perspektiven: Die vorgestellten Daten ergaben statistisch signifikante Parameter für schwere Morbidität beim HELLP-Syndrom, die möglicherweise als prädiktive Marker verwendet werden könnten. Darüber hinaus bieten die Daten Einblicke in die prä- und postpartale Manifestation, die mütterlichen Outcomes und die neonatalen Implikationen. Insbesondere die weiterhin vorherrschende Frühgeburtlichkeit bei HELLP-Syndrom-Fällen verdeutlicht die anhaltenden Herausforderungen bei der Behandlung dieser Erkrankung. Der Bedarf an weiteren multizentrischen Studien, die verschiedene Bevölkerungsgruppen einbeziehen, ist notwendig, insbesondere angesichts der Komplexität dieses Syndroms, einschließlich des potenziell fatalen Ausgangs für Mutter und Kind.

Abstract

Background: HELLP Syndrome is a pregnancy complication that was first identified almost four decades ago. Since then, researchers and clinicians continue to refine not only its definition, but also newer laboratory cut off values for diagnostic purposes. Unsurprisingly, HELLP syndrome continues to be one of the most unresolved challenges in the field of obstetrics.

Aims: To examine the multifaceted nature of HELLP syndrome, with a special emphasis on its manifestation, classification, severity of morbidity, maternal outcome, and neonatal implications.

Methodology: A retrospective single center study identified 163 patients diagnosed with HELLP syndrome between 2005 and 2020. A detailed statistical analysis of demographic, clinical, and laboratory parameters was conducted. The study population was divided into a subgroup based on the timing of occurrence of HELLP, pre- and postpartum (PRE and POST). The entire study population was then also divided into a separate subgroup based on the severity of morbidity (clinical manifestation and complication), SEVERE and LOW. Subgroups were compared using Mann- Whitney- U Tests and t-Test. The Chi-square test was used to determine the relationship between categorical variables. A p value of $< .05$ was defined as statistically significant.

Results: Statistical analysis revealed that a HELLP syndrome leading to severe maternal morbidity (SEVERE group) correlates with low platelet counts (<60,000), elevated AST (>300 U/L), high LDH (>550 U/L), and high blood pressure (systolic >170 mmHg, diastolic >100 mmHg, or mean arterial pressure >120 mmHg). Applying the endpoints to the subgroups PRE and POST showed no statistically significant dissimilarity between the two across all categories ($p > 0.05$), except the laboratory values ($p < 0.01$). Here, the PRE subgroup has significantly worse laboratory values than the POST group, though it had no significant effect on the length of hospitalization (p=3.1) or morbidity. In addition, a woman affected by HELLP syndrome in our study exhibits characteristic features (p>0,05): age (31 years), BMI (23), gestational period (34 weeks), symptoms (upper abdominal pain, headache, nausea), and expected mode of delivery (caesarean section).

Discussion: Despite the identification of significant markers for severe morbidity, paradoxically, some cases deviated from this pattern, showcasing the unpredictability and complexity inherent in this syndrome. Patients presenting with these markers must be closely monitored, and delivery should be induced or planned if the woman is still pregnant. Comparison of our results with seminal studies revealed parallels and variations in the onset, severity, and outcomes of HELLP syndrome across different populations. While consistent trends in symptomatology were observed, deviations in maternal age, delivery methods, and maternal mortality rates indicate the need for further research into potential influences on syndrome manifestation and severity.

Conclusions and future directions: The presented data revealed statistically significant parameters for severe morbidity in HELLP Syndrome, that could potentially be used as predictive markers. In addition, the data offer insights into its pre- and postpartum manifestation, maternal outcomes, and neonatal implications. Especially the continued predominance of preterm deliveries in HELLP syndrome cases, highlight the persistent challenges in managing this condition. The need for further multi-centric studies incorporating diverse populations is warranted, especially due to the complexity of this syndrome, including the potentially fatal outcome of mother and child.

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Abbreviation

AFLP	Acute Fatty Liver Of Pregnancy
aHUS	Atypical Pregnancy-Related Hemolytic-Uremic Syndrome
ALT	Alanine Aminotransferase
APS	Antiphospholipid Syndrome
ASA	Acetylsalicylic Acid
AST	Aspartate Aminotransferase
BMI	Body Mass Index
BP	Blood Pressure
BPD	Bronchopulmonary Dysplasia
C- Section	Cesarean Section
CI	Confidence Interval
CS	Cesarean Section
CTG	Cardiotocograph
DGGG	Deutsche Gesellschaft Für Gynäkologie Und Geburtshilfe (German Board of Gynecology and Obstetrics)
Dia	Diastolic
HDP	Hypertensive Disorders During Pregnancy
HELLP	Hemolysis, Elevated Liver Enzymes, Low Platelets
ICD - 10	International Statistical Classification of Diseases and Related Health Problems
ICU	Intensive Care Unit
IUGR	Inter Uterine Growth Restriction
LDH	Lactate Dehydrogenase
LKH	Landes Krankenhaus (State Hospital)
LM	Lung Maturation
MAP	Mean Arterial Pressure
MBU	Micro Blood Analysis For Fetal Blood Ph
OEGGG	Österreichische Gesellschaft Für Gynäkologie Und Geburtshilfe (Austrian Board of Gynecology and Obstetrics)
PE	Preeclampsia
RDS	Respiratory Distress Syndrome
SGA	Small For Gestational Age
SLE	Systemic Lupus Erythematosus

Sys	Systolic
TMA	Thrombotic Microangiopathies
TTP	Thrombotic Thrombocytopenic Purpura
VE	Vacuum Extraction

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1 Introduction

1.1 Hypertensive Disorders during Pregnancy

Hypertensive disorders during pregnancy (HDP) are very common, occurring in up to eight % of pregnancies (1). As such, they are a leading cause of maternal and fetal morbidity and mortality worldwide (2). HDP is characterized by elevated blood pressure (≧140/90 mmHg) and can manifest during pregnancy, at childbirth, or in the postpartum period (3). The American College of Obstetricians and Gynecologists classifies five major types of HPD (3, 4):

1. Gestational hypertension: High blood pressure which develops during pregnancy but normalizes after delivery.
2. Chronic hypertension: High blood pressure that antecedes pregnancy or develops in the first trimester without signs or symptoms of preeclampsia.
3. Preeclampsia: new onset of hypertension and symptoms of significant end organ dysfunction, with or without proteinuria, after 20 weeks of gestation.
4. Eclampsia: grand mal seizures as a manifestation of severe preeclampsia in the absence of other neurological causes.
5. Hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome: A severe form of preeclampsia that can occur during pregnancy or postpartum with or without hypertension.

Table 1 details the differences and similarities between the five different types of hypertensive disorders:

Table 1: Hypertensive Pregnancy Disorders and their Characteristics, modified according to the ACOG Practice Bulletin, Number 222 (4)

	Normotension before Pregnancy	Hypertension during Pregnancy	Proteinuria	Other identifying features
Gestational Hypertension	Yes	Yes	No	Normotension after birth
Chronic Hypertension	No	Yes	Rarely	Hypertension for at least 12 weeks postpartum
Preeclampsia	Yes	Yes	Mostly	At least one new end organ dysfunction
Eclampsia	Yes	Yes	Variable	new-onset tonic-clonic, focal, or multifocal seizures
HELLP Syndrome	Variable	Up to 80% of patients	Mostly	Low platelet count, elevated LDH, elevated AST/ ALT

AST, aspertate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase

Despite decades of intensive research, the underlying mechanism, by which pregnancy induces or worsens hypertension, remains elusive.

1.2 The HELLP Syndrome

This research dissertation centers on HELLP syndrome, a relatively rare condition affecting 0.1 to 0.2 % of pregnant individuals. Coined by Dr. Louis Weinstein in 1982, HELLP is an acronym representing hemolysis, elevated liver enzymes, and low platelets (5). While HELLP is classified as a form of severe preeclampsia (PE), in accordance with the ICD 10 classification, only a small proportion, approximately 5-20% of cases, exhibit specific signs of severe PE (6).

Typically, symptoms manifest between the 27th and 37th weeks of gestation, with an additional 10-30% occurring within the immediate post-partum period, up to 72 hours after delivery.

The syndrome not only affects the outcome of the mothers, but also the mortality and morbidity their children. Up to 70% of infants born to mothers with HELLP syndrome experience preterm birth and face an increased risk of perinatal mortality and significant morbidity, including bronchopulmonary dysplasia (BPD), respiratory distress syndrome (RDS), and non-traumatic intracranial hemorrhage (7-9). However, it is noteworthy that HELLP syndrome does not directly cause neonatal thrombocytopenia (10).

1.2.1 Pathophysiology

Histopathologic findings of the liver in patients with HELLP Syndrome revealed intravascular fibrin deposits, which could cause hepatic sinusoidal obstruction, intrahepatic vascular congestion, and higher intrahepatic pressure, leading to hepatic necrosis, hemorrhage within the parenchyma and subcapsular area, and ultimately capsular rupture (11). These patients also share similarities with those who have Preeclampsia, including endothelial injury, heightened levels of inflammatory cytokines, an imbalance in angiogenesis, increased angiotensin II type 1 autoantibody, intravascular fibrin deposition, and elevated platelet activation and consumption (6, 12).

The thrombocytopenia in HELLP patients is believed to be the result of platelet activation and adherence to damaged vascular endothelial cells. (13)

A new study by Jiménez et al. identified five sequence variants that generated premature stop codons in genes playing an essential role in placental physiology and six variants that lead to a destabilization of protein structures, adding insight to the molecular origin of the syndrome and polygenetic nature (14). Findings such as these can lead to the development of a clinical biomarker for diagnostic purposes.

Unfortunately, the precise pathophysiological mechanisms underlying HELLP syndrome largely elude complete comprehension, leaving a realm of uncertainty concerning its affected population and the remarkable variation in symptom severity.

1.2.2 Risk Factors

A recent study by Lisonkova et al. concluded that risk factors for HELLP include age ≥35 years, rural residence, nulliparity, parity ≥ 4, chronic and gestational hypertension, diabetes, assisted reproduction, chronic cardiac conditions, systemic lupus erythematosus, obesity, chronic hepatic conditions, placental disorders (e.g. feto-maternal transfusion syndrome), and congenital anomalies (7). There seems to also be a yet unidentified genetic link, as women whose sisters or mothers suffered from HELLP are more likely to develop the syndrome (15).

A Norwegian population-based cohort study, including all women who delivered their first or second child from 1999 to 2014 (n = 1006), was able to show that, body mass index ≥30 kg/m^2 and diabetes were associated with HELLP syndrome in first, but not in second pregnancy. Chronic hypertension and multiparity were risk factors both in the first and second pregnancy. The strongest risk factors during the second pregnancy were a history of HELLP syndrome or preterm preeclampsia in the first pregnancy, which inversely correlated with gestational age at first delivery (16).

1.2.3 Clinical Presentation and Diagnosis

Typical presenting signs and symptoms are abdominal pain in the right upper quadrant or epigastric pain, elevated blood pressure, nausea and vomiting, blurred vision, and headaches (6). The abdomen can be tender upon examination and the pain is often described as colicky. More severe complications can be present at the initial diagnosis or develop shortly thereafter. These include placental abruption, acute kidney injury, pulmonary edema, subcapsular or intraparenchymal liver hematoma, retinal detachment, and seizures (17).
The diagnosis is confirmed through laboratory findings of low platelet count, elevated liver enzymes, and hemolysis markers. In contrast to Preeclampsia, elevated blood pressure of > 140/90 mmHg, proteinuria > 300 mg/day, or a spot urine protein: creatinine ratio of > 30 mg/mmol, is not compulsory for a diagnosis (1).

1.2.4 Classification Systems

There are currently two major classifications systems for the diagnosis of HELLP. The Mississippi classification classifies the syndrome based on disease severity into 3 levels. It

also allows for a partial HELLP syndrome when 2 of the 3 laboratory parameters are satisfied and severe PE or Eclampsia is present. The laboratory parameters are platelet count, Aspartate aminotransferase (AST), Alanine aminotransferase (ALT) and Lactate dehydrogenase (LDH) (18).

The Tennessee classification system is a more simplified version of Mississippi. Its cut off values are low platelets (< $100 \cdot 10^9$/L), increased AST or ALT (≥ 70 U/L), and increased LDH (> 600 U/L), without any levels of disease severity (5).
Table 2 is a summary of the specific laboratory values utilized in classifying HELLP Syndrome according to the above described classification systems.

Table 2: Mississippi and Tennessee Classification of HELLP Syndrome, according to Wallace et al. (6)

	HELLP Class	Platelets ($x10^9$)	AST or ALT (U/L)	LDH (U/L)
Mississippi	1	≤50	≥70	≥600
	2	≤100 to ≥50	≥70	≥600
	3	≤150 to ≥100	≥40	≥600
	Partial HELLP	Presence of 2 of the 3 above laboratory abnormalities along with evidence of sever Preeclampsia or Eclampsia		
Tennessee		≤100	≥70	≥600

There is still a lack of consensus on the laboratory findings and especially their cut off values to diagnose HELLP syndrome (19). This makes the comparison of data on the incidence, course, and management of the syndrome especially difficult. Hohlagschwandtner et al. compared the diagnostic criteria for HELLP syndrome among the nine most cited research studies on the disorder.

Table 3: Comparison of Diagnostic Criteria for HELLP Syndrome, based on Hohlagschwandtner et al. (20)

	Platelets ($x10^9$)	AST (U/L)	ALT (U/L)	LDH (U/L)
Weinstein	<100	Abnormal	Abnormal	-
Sibai	<100	>70	-	>600
Harms et al.	<150	>15	>19	>240
De Boer et al.	<100	-	>50	>180
Visser and Wallenburg	<100	>30	>30	-
Neiger et al.	<150	>60	-	-
Hamm et al.	<150	>16	>20	-
Schwerk et al.	<150	>15	>17	>240
Martin et al.	<150	≥40	≥40	≥600

AST, aspertate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase

1.2.5 Treatment and Management

As of today, there is no curative treatment for HELLP syndrome. The most effective treatment to alleviate symptoms and reduce mortality is immediate delivery after stabilization of the mother (1). Because complications can develop rapidly and most infants are born preterm, patients with HELLP should be treated in a tertiary care center with access to maternal and neonatal intensive care units. In accordance with national and international guidelines, the following course of treatment is recommended (3, 4, 21):

Conservative Management for 48 Hours: Between the 24th and 34th week of gestation, conservative management can be considered, if the benefit for the child is certain and severe complications for the mother can be avoided under continuous monitoring. The monitoring includes daily blood work, regular blood pressure measurements (if hypertension is present) and fetal heartrate (CTG) monitoring. Part of the conservative management is antihypertensive medication, such as urapidil or nifedipine, as well as magnesium sulphate to prevent maternal seizures and for fetal neuroprotection. The glucocorticoid Betamethasone is administered to pregnant women when there is a high likelihood of preterm birth, typically between 24 and 34 weeks of gestation, to promote functional lung maturity of the fetus. The aim is to reduce life-threatening neonatal disorders that increase the risk of chronic disease (22). It is usually given as two injections, 24 hours apart, and reaches its peak effect around 48 hours after the first dose.
The benefits are as follows (23-26):

1. Stimulating Surfactant Production: Betamethasone helps stimulate the production of surfactant, a complex mixture of lipids (~90%) and proteins (~10%) that line the lung's alveoli. Surfactant reduces surface tension in the alveoli, making it easier for the lungs to inflate and preventing their collapse during exhalation (27).
2. Preventing Respiratory Distress Syndrome: The primary benefit of this treatment is the reduction in the risk of respiratory distress syndrome. RDS is primarily caused by deficiency of pulmonary surfactant in a premature lung. It is characterized by tachypnea, retractions, flaring, grunting, and/ or cyanosis.
3. Enhancing Neonatal Outcomes: The use of betamethasone is associated with improved neonatal outcomes, including a reduced need for mechanical ventilation and a decreased risk of intraventricular hemorrhage (IVH), necrotizing enterocolitis, and neonatal mortality.

In case of severe complications, fetal demise, pregnancies without a reasonable chance of extrauterine survival (such as gestational age under 23 weeks), and placental abruptions, immediate delivery via caesarean birth is the best course of action.

Delivery: After 48 hours of conservative management, the risk of severe complications outweighs the benefits of continuing the pregnancy Unless there are specific indications for a caesarean birth, such as breech position, previous caesarean births, non-reassuring fetal status, vaginal delivery is the preferred method. For patients with HELLP syndrome and a favorable cervix, labor is induced with a prostaglandin E1 or E1 or with oxytocin, regardless of gestational age. However, if the cervix is unfavorable, signs of fetal compromise are present, or the induction fails, caesarean birth is the only option.

Additional Medications and Treatments: Depending on the thrombocyte count, a platelet transfusion can help stabilize the mothers and prevent excessive bleeding during birth. The threshold for prophylactic transfusion is seen as controversial and should mainly be considered when a caesarean birth is planned. Consensus of the OEGGG is the use of thrombocyte transfusions to a achieve a concentration of ≥ 70-100 Gpt/L for blood loss >1500mL (3).

Corticosteroids – Dexamethasone and Prednisolone:

The use of corticosteroids is the most controversial approach to treat HELLP. When dexamethasone was first used in clinical trials in the 1990s, the hope was to ameliorate and stabilize the patients in the antepartum period and accelerate recovery after delivery (28).
The University Hospital Graz has routinely used corticosteroids to treat HELLP over the past decades. This treatment regimen involves the administration of one to three intravenous infusions of high-dose Prednisolone (ranging from 0.5g to 1g). The rationale behind this approach lies in countering the potential immunological aspect of the syndrome, akin to the management of anaphylactic shock, to attempt to prolong the pregnancy. Prednisolone distinguishes itself from other corticosteroids due to its predominant placental inactivation through 11beta-hydroxysteroid-dehydrogenase 2 (11beta-HSD2) enzyme and its relatively short half-life, thereby primarily exerting its therapeutic effects on the mother rather than the fetus (29).

Over the past 30 years, studies have been contradictory, demonstrating benefits as well as lack of effectiveness of corticosteroid treatment.
There was no evidence for a benefit from dexamethasone in the two largest randomized, double-blind, placebo-controlled studies to date (30, 31). Fonseca et al. found that the hospitalization duration of patients who received dexamethasone therapy was observed to

be shorter than that of the placebo group, with a mean of 6.5 days compared to 8.2 days, but this difference did not attain statistical significance (P = .37). The study found no significant differences in the time taken for platelet counts to recover (hazard ratio, 1.2; 95% CI, 0.8-1.8), for LDH (hazard ratio, 0.9; 95% CI, 0.5-1.5) and AST (hazard ratio, 0.6; 95% CI, 0.4-1.1) to reach normal levels, or in the development of complications, among both pregnant and postpartum women (31).

However, earlier observational studies and small randomized trials suggested a speedier improvement in maternal laboratory values, especially concerning platelet count after corticosteroid administration (32, 33). Isler et al. recommend the use of Dexamethasone for maternal and fetal indication, as it can pass the placenta blood barrier and accelerate fetal lung maturity in preterm women (32). Halting the disease progression would allow for more time for cervical ripening and thereby reduce the need for caesarean delivery (33). Van Runnard Heimel et al. found that for women with HELLP syndrome early in their pregnancy benefit from prolonged administration of prednisolone as a preventative measure for recurring symptoms, thereby prolonging their pregnancy. Their platelet counts also recovered significantly faster compared to the placebo group (1.7 days vs 6.2 days respectively) (34).
The strength of these conclusions must be weighed against the fact that these studies only consisted of small number of women, were observational or retrospective, included mild forms of HELLP syndrome and varied greatly in their definition of HELLP. Nonetheless, it is reasonable to conclude that corticosteroids should be considered when treating HELLP as it has potentially positive therapeutic effects and few risks.

1.2.6 Differential Diagnoses

For patients presumptively diagnosed with HELLP, who experience a lack of response to aggressive corticosteroid therapy and the persistence of symptoms for over seven days post-partum, a concurrent disorder or a HELLP imitator must be considered as the cause. The major disorders that have to be ruled out are acute fatty liver of pregnancy (AFLP), thrombotic thrombocytopenic purpura (TTP), atypical pregnancy-related hemolytic-uremic syndrome (aHUS), systemic lupus erythematosus (SLE), and Antiphospholipid syndrome (APS) (35). Depending on the school of thought, severe Preeclampsia also must be

considered. Due to the similarities in clinical and histologic features, it may be challenging to establish a definitive diagnosis, and it is possible for HELLP to occur simultaneously with any of these disorders (35, 38).

Characterized by maternal liver dysfunction or failure, AFLP is an obstetric emergency that requires imminent delivery and supportive care. TTP and HUS are thrombotic microangiopathies (TMA). TMAs have a characteristic triad of hemolytic anemia, thrombocytopenia, and an organ dysfunction, typically placenta or kidney. TTP is caused by a Willebrand factor-cleaving protease ADAMTS13 activity reduction, with laboratory findings very similar to HELLP. aHUS is the result of an uncontrolled activation of the complement system and usually occurs postpartum. As a multisystem disease, SLE flares can closely imitate severe PE/ HELLP, especially in patients with lupus hepatitis or lupus nephritis. APS is an autoimmune disorder caused by antiphospholipid antibodies resulting in Hypertension, proteinuria, thrombocytopenia. (35, 36)

The Covid-pandemic has shown that infections with SARS-CoV-2 during pregnancy are linked to a significant increase in the likelihood of severe preeclampsia, eclampsia, and HELLP syndrome. Diagnosis of HELLP in infected patients may be difficult due to the overlapping laboratory abnormalities of COVID-19 and HELLP (37).

Bergmann et al. summarized the similarities and differences of the most important differential diagnoses as well as their management (Table 4) (38). The visual representation of the homogeneity of symptoms underlines just how difficult it is to find the correct diagnosis, further compounded by the pressure of responsibility for two life’s at the same time.

Table 4: Differential Diagnoses of HELLP Syndrome, modified according to Bergmann et al (30)

	PE	HELLP	TTP	aHUS	AFLP	APS	SLE
Hypertension	+++	+++	+	++	+	+/-	++
Proteinuria	+++	+++	+/-	+++	+/-	+/-	+++
Upper abdominal pain	+/-	+++	+/-	+/-	++	+/-	+/-
Neurologic deficits	+	+	++	+/-	+	+	+
Thrombocytopenia	+	+++	+++	+++	+	+	+
Hemolysis	+/-	+++	+++	+++	+	+/-	+
Renal Dysfunction	+/-	+	+	+++	++	+/-	++
Elevated transaminases	+	+++	+/-	+/-	+++	+/-	+
Disseminated intravascular coagulation	+/-	+	+/-	+/-	+++	+/-	+/-
Peak incidence	3rd Trimester	3rd Trimester, post-partum	2nd/ 3rd Trimester	Post-partum	3rd Trimester	At any time	At any time
Management	If severe: rapid delivery	Rapid delivery	Plasma exchange	Plasma exchange/ infusion Ecuzulimab	Supportive delivery	ASA, low-molecular-weight heparin	Hydroxychloro-quine, corticosteroids, other immune suppressants

PE; Preeclampsia, TTP; thrombocytopenic purpura, aHUS; atypical pregnancy-related hemolytic-uremic syndrome, AFLP; acute fatty liver of pregnancy, APS; Antiphospholipid syndrome, SLE; systemic lupus erythematosus

1.2.7 Long Term Prognosis

Although most women, who have had pregnancies complicated by HELLP syndrome, recover in the first week after delivery, some can develop long-term health problems (6). In subsequent pregnancies, they face a higher risk of developing HELLP syndrome (14-24%), Preeclampsia (22-28%), and small for gestational age infants (5.9%) (39-42). Furthermore, women who were previously normotensive but developed HELLP syndrome are more prone to hypertension, which can raise their risk of cardiovascular disease (40, 41). Studies have also suggested that HELLP syndrome may cause permanent neurological damage, just like cardiovascular disease, suggesting that vascular endothelial damage occurs during the disease process (43). Women with HELLP syndrome are at risk to suffer from postpartum depression, increased anxiety, and associative memory impairment for up to five years after delivery. Experiencing a severe illness along with an unforeseen caesarean delivery, especially of a premature baby, can be an immense physical and psychological burden to endure (44-46).

A meta-analysis study conducted by Davis et al. found that in utero exposure to HDP is associated with an increase of 2.39 mmHg in systolic pressure, 1.35 mmHg in diastolic pressure, and an 0.32 kg/m^2 increase in body mass index in the children (4–30 years old) (47). However, other studies have also shown that the long-term outcome of children born to HELLP mothers are far better than has been previously assumed (48)

2 Methodology

2.1 Study Design

This single center retrospective study received approval from the Ethics Committee of the Medical University of Graz, Nr. 33-430 ex 20/21. The need for informed consent was waived, because of the study design. The data collection and analysis were conducted according to the principals of the Declaration of Helsinki.
A retrospective study design was chosen to include as many patients as possible, since HELLP Syndrome is a very rare disease.

2.2 Inclusion and Exclusion Criteria

Eligibility for the study was defined as women diagnosed with HELLP Syndrome between 01.01.2005 and 31.12.2020, who were treated at the University Hospital Graz (LKH Graz).

Inclusion criteria:

- Diagnosis and Treatment of HELLP Syndrome
- At least one thrombocyte count of $\leq 100 \times 10^9$ /L
- Over 18 years old

Exclusion criteria was:

- Severe fetal abnormalities
- Pre-existing or active maternal morbidities that can severely impact the pregnancy, such as heart defects, cerebral insults, or trauma.
- Premature rupture of the membranes or early onset labor that negatively impacted the outcome of the mother or child.
- Gemini or multiple pregnancies

2.3 Data Collection

The study population was identified first through their laboratory findings. All pregnant women between 01.01.2005 and 31.12.2020 with a thrombocyte count of $\leq 100 \times 10^9$ /L were extracted from the electronic patient database openMedocs, (Steiermärkischen Krankenanstaltengesellschaft m.b.H) of the Department of Obstetrics and Gynecology,

Medical University Graz, identifying 888 women. Each patients' records were crosschecked for the diagnosis of HELLP Syndrome and whether all inclusion or exclusion criteria were met. Ultimately, 163 women were included in the study population.
The data was collected through the electronic patient record system PIA (ViewPoint, GE Healthcare, UK), openMedocs, patient records, discharge papers, laboratory findings, midwife documentation, and ICU documentation. Ultimately, 120 data points were recorded for every patient.
Each patient was assigned a random number to ensure anonymity and their data was collected in a Microsoft Excel spreadsheet. The regulations of the data protection act (DSG 2000) were followed.

2.4 Data Analysis

All data was analyzed using Microsoft Excel and IBM SPSS Statistics 28.
The study collective was first described using descriptive statistical analysis, focusing on mean, standard deviation, minimum and maximum values, as well as percentages. Subgroups were compared using Mann- Whitney- U Tests and t-Test. The Chi-square test was used to determine the relationship between categorical variables.
A p value of $< .05$ was defined as statistically significant.

2.5 Study Groups

To facilitate comparative analysis and discern dissimilarities and similarities, the study population was divided into two independent subpopulations, which were further split into two subgroups based on predefined variables. For each subpopulation, the entire study population was used.
The first subpopulation differentiated the patients based on the timing of occurrence of HELLP syndrome pre- or postpartum. This created the two subgroups named PRE and POST.
The second subpopulation separated the population according to the severity of morbidity experienced. The subgroups were named SEVERE and LOW. Severe morbidity was defined as the presence of pneumological, cerebral, or renal complications, instances of severe haemorrhage requiring blood, platelet, or plasma transfusions, the occurrence of Eclampsia, the requirement for revision surgery, severe infections and sepsis, intensive care unit (ICU)

treatment involving prolonged intubation, dependency on vasopressors, and the need for hemofiltration.

3 Results

3.1 Demographics

A total of 163 women were included in the retrospective study. Table 5 summarizes the demographic parameters that were collected. The data showed that on average the women were 31 years old, the youngest recorded age was 18, the oldest 47. 68% of patients were pregnant for the first time. The highest documented gravitas was 13, with 8 resulting in live births. Five (3%) of the 163 pregnancies were conceived using invitro fertilization.

Table 5: Demographic Characteristics of the Study Population

	n	$\bar{x}$	SD	Min	Max
Age (years)	163	31.73	5.01	18	47
BMI (kg/m^2) (preconception)	154	23.43	4.89	45.4	16.9
Gravitas	163	1 (Mode)	1.27	1	13
Parity	163	0 (Mode)	0.91	0	8

Data is given as mean +/- standard deviation and minimum and maximum values.

Only six women reported suffering from HELLP Syndrome during a prior pregnancy. Seventeen (10%) women had a preexisting hypertensive disorder, while an additional 79 (49%) women developed pregnancy-induced hypertension.

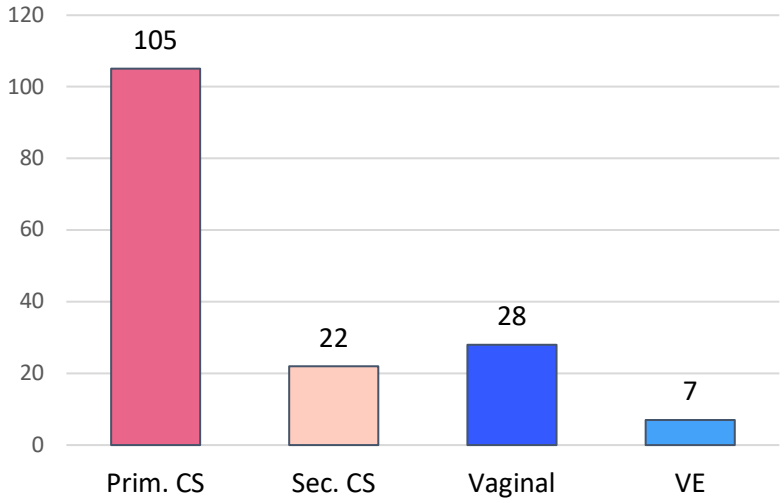
3.2 Birth

Labor was induced 46 times, using Dinoproston (Propess©), synthetic Oxytocin (Syntocinon©), Misoprostol (Cyprostol©) and/or Foleys Catheter Balloon. The methods of delivery included 28 natural vaginal births, seven vacuum extractions (VE), 105 primary cesarean- sections and 22 secondary cesarean sections, due to failure of advancement in induction or fetal distress. Figure 1 depicts the absolute count of distribution of delivery modes.

Combined, Cesarean-Sections (primary and secondary) were performed in 79% of all births,

56 cases with spinal anesthesia and 70 under general anesthesia.

Figure 1: Distribution of Birth Mode



Data is given in absolute numbers.
Prim. CS, primary Cesarean Section; Sec. CS, secondary Cesarean section; VE, Vacuum Extraction

The majority of patients (88%) were admitted in their third trimester and two women arrived post-partum from a secondary hospital to receive treatment for HELLP Syndrome. The data shows, that because of the inherent inability to cure HELLP syndrome and thereby prolong the pregnancy, 65.5% of children were born prematurely (<37 week), with the earliest recorded surviving gestational age of 23+2 weeks. This is reflected by the low birthweight, both in absolute gram values and when assessed within percentile distributions (Table 6).

Table 6: Parameters of Delivery

	n	$\bar{x}$	SD	MIN	MAX
Gestation at Admittance (weeks +days)	161	34+0	4+5	19+4	40+6
Gestation at Birth (weeks +days)	163	34+2	4+3	20+0	40+6
Time from Admittance until Delivery (hours)	163	44:07	82:49	0:56	606:55
Length of Hospitalization (days)	163	8.17	5.45	1.53	40.92

Data is given as mean +/- standard deviation and minimum and maximum values.

The average time admittance until delivery of 44 hours and 07 minutes underscores that the majority of pregnancies required a rapid delivery. Only a small number of pregnancies (7) could be prolonged by at least five days. The delivery time was calculated with the time laps between admittance to the hospital and delivery of the baby.
The average length of hospitalization was 8.17 days. The shortest was 1.53 and the longest 40.92. Standard procedure in Graz is a hospital stay of four to five days after a cesarean section.

3.3 Children

During the 15-year timespan of this study, 160 children were delivered at the LKH Graz, two were delivered at secondary hospitals and one medically necessary interruption was performed. Unfortunately, the death of five children (3%) had to be recorded. Tables 7, 8, and 9 show the parameters which were collected for the children.

Table 7: Prepartum Parameters of the Children

	N	n	%
LM	162	59	36
CTG Pathological	162	39	26
MBU	162	7	4
SGA/ IUGR	162	42	26
Gender	162		
Female		73	46
Male		89	54

Data is given as absolute numbers and percentage of total study population.
LM= lung maturation, CTG = cardiotocograph, SGA= small for gestational age, IUGR= inter uterine growth restriction, MBU= micro blood analysis for fetal blood pH

The glucocorticoid Betamethasone was administered to 59 (36%) fetuses to promote lung maturation before delivery. CTG monitoring during delivery is standard practice in Graz. 39 pathological CTG curves were recorded, triggering seven MBUs. Ultrasound controls upon admittance showed that 42 (26%) fetuses were either small for gestational age or had a inter uterine growth restriction.

The parameters for the children shown in Table 8 were all taken immediately after delivery. It is notable that the prematurity of the children tended to consistently place them in the lowest quartile when assessed in both absolute weight in grams and weight as a percentage. The lowest recorded weight was 308g and the highest 3930g. The weight data, both in percentile and grams, show a wide dispersion and substantial variability.

On the other hand, the umbilical blood pH data for both arterial and venous categories have less variability. The average arterial and venous pH levels in the umbilical cord of the newborns fell within the normal range.

Table 8: Postpartum Parameters of the Children

	n	$\bar{x}$	SD	MIN	MAX
Weight percentile	162	27.03	20.813	< 3	90
Weight in grams	162	2128.01	883.83	308	3930
pH Arterial	146	7.29	0.0656	6.99	7.39
pH Venous	127	7.33	0.0622	7.04	7.45

Data is given as mean +/- standard deviation and minimum and maximum values.

The 5- minute APGAR score was chosen as a predictive marker for infant outcome (Table 9). Current literature has shown that a score of below seven at five minutes increases the relative risk of cerebral palsy, as high as 20- to 100-fold compared to children with higher scores (49-52). The inverse also holds true- for children with an APGAR score of seven or greater, it is unlikely, that peripartum ischemia caused neonatal encephalopathy. Large population studies have repeatedly and reassuringly shown that a low APGAR is not the only factor with a causality to cerebral palsy. In fact, most children with a low APGAR score will not develop the neurological disease (53).

Table 9: Special Outcome Parameters Children

	n	%
APGAR 5 < 7	10	6.12
Arterial pH < 7	1	0.07
<10th Percentile Weight	39	24.07

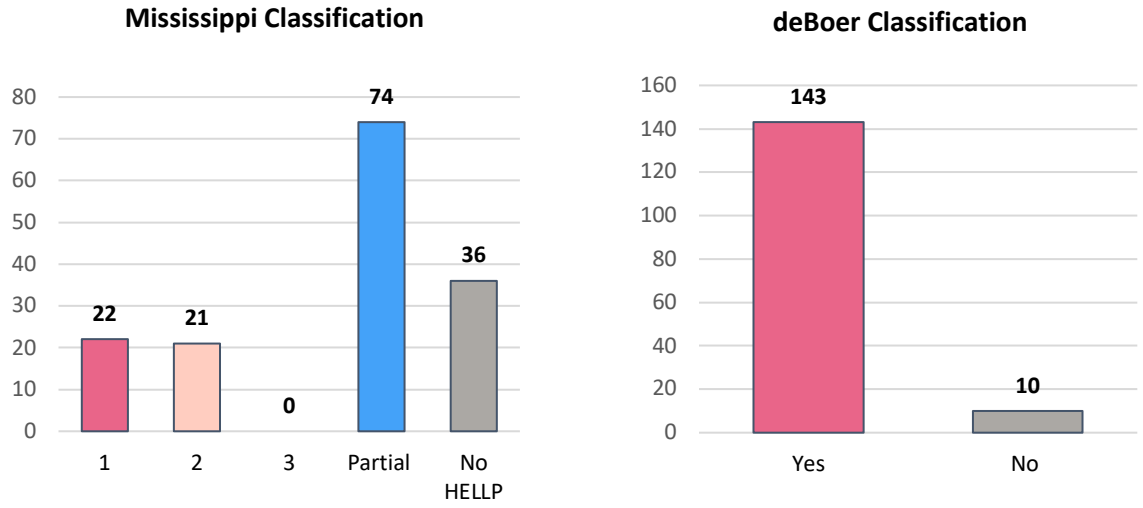
Data is given as absolute numbers and percentage of total study population.

A birth weight of less than 10th percentile for gestational age is categorized as Small for Gestational Age (54). In a normal population the distribution follows 10% of newborns are below this value and 90% above. For our study population over twice as many (24.07%) newborns were below this threshold. Perinatal mortality and morbidity are greatly increased compared to infants with appropriate weight for gestational age and complications can arise throughout childhood and beyond (55-57).

3.4 HELLP Classification

All women included in the study were subjected to categorization based on both the Mississippi Classification and the DeBoer criteria. However, in the case of 10 women, certain laboratory values necessary for classification were unavailable, resulting in a total of 153 women eligible for categorization. When solely employing the parameters defined by the Mississippi Classification, 117 women were diagnosed with HELLP Syndrome. In contrast, using the cut off values proposed by DeBoer, 143 women were positively identified.

Figure 2: Distribution of HELLP Syndrome Classification



Data is given as absolute numbers.

Because of the limitations of the aforementioned classification systems (as described in chapter 1.2.3), this retrospective study encompassed a cohort of 163 women, carefully selected based on the distinctive clinical manifestations of HELLP, the progressive

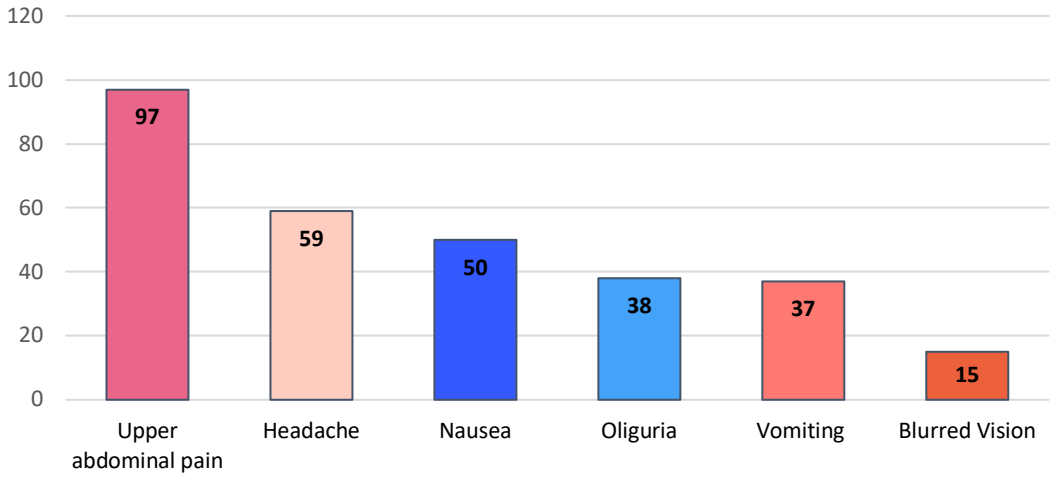
deterioration of the pertinent laboratory parameters, and the official diagnosis with HELLP by the treating physician at the time.

Of the 163 women, 108 (66%) developed HELLP Syndrome before delivery and 55 (34%) after delivery, forming the subgroups further analyzed in chapter 3.9.

3.5 Symptoms

The most common symptoms of HELLP Syndrome were recorded and summarized in Figure 4, multiple answers possible. 28 women showed none of the characteristic signs or symptoms of HELLP syndrome. Their diagnosis was a chance finding as part of routine blood work.

Figure 3: Distribution of Symptoms



Data is given as absolute numbers; multiple answers were possible.

Even though HELLP Syndrome is classified as a hypertensive pregnancy disorder and a severe form of preeclampsia, not every patient suffered from hypertension. The blood pressure of seventeen patients stayed below 140/90 mmHg during their hospital stay. Nevertheless, the vital parameters of the women admitted were closely monitored. Table 9 showcases both the initial blood pressure readings upon admission to the hospital and the subsequent highest recorded blood pressure values (systolic, diastolic and mean arterial blood pressure). 94 (57%) women presented with a blood pressure of >140/90 mmHg upon admittance and 146 (89%) proceeded to develop a blood pressure exceeding the threshold.

Notably, sixteen women suffered from hypertension before their pregnancy, 79 (48%) women developed pregnancy induced hypertension.

Table 10: Blood Pressure Recordings in mmHg

	N	$\bar{x}$	SD	MIN	MAX
BP Sys admittance	161	146.39	22	71	214
BP Dia admittance	161	90.60	14.26	53	123
MAP admittance	161	109.03	15.66	58.94	147.68
BP Sys max	163	166.24	22.62	111	223
BP Dia max	163	98.90	16.77	11	142
MAP max	163	121.14	16.89	63.47	167.41

Data is given as mean +/- standard deviation and minimum and maximum values.
BP, blood pressure; Dia, diastolic; Sys, Systolic; MAP, mean arterial pressure;

The data shows deviations in blood pressure across all measurements, with relatively high standard deviations, implying substantial variability within each metric.

3.6 Lab values

The hallmark features of hemolysis, elevated liver enzymes and low platelets of HELLP syndrome were assessed using the laboratory values platelet count, AST, ALT and LDH. Table 11 summaries the finding for final blood workup before delivery and Table 12 summarizes the most severe laboratory values recorded during the hospitalization period.

Table 11: Maternal Laboratory Values before Delivery

	n	$\bar{x}$	SD	MIN	MAX
Platelets x10^9	161	99.55	44.48	13	263
AST (U/L)	157	193.03	224.65	13	1152
ALT (U/L)	158	184.97	188.01	9	888
LDH (U/L)	151	396.68	250.65	110	1454

Data is given as mean +/- standard deviation and minimum and maximum values.
AST, aspertate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase.

Table 12: Most Severe Maternal Laboratory Values

	n	$\bar{x}$	SD	MIN	MAX
Platelets (U/L)	162	64.83	20.49	13	132
AST (U/L)	158	264.20	305.25	19	2369
ALT (U/L)	158	231.19	220.87	16	1617
LDH (U/L)	153	495.41	355.46	126	3624

Data is given as mean +/- standard deviation and minimum and maximum values.
AST, aspertate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase.

Before birth 142 (88%) women had thrombocytopenia, 130 (83%) showed elevated AST and 129 (82%) showed elevated ALT levels, and 104 (68%) shoed heightened LDH levels. The worst labs showed that every patient developed a thrombocytopenia of <150 units/L, with the highest count being 132 and the lowest 13. 156 (98%) and 150 (94%) women showed increased AST and ALT levels and 150 (98%) had elevated LDH levels.

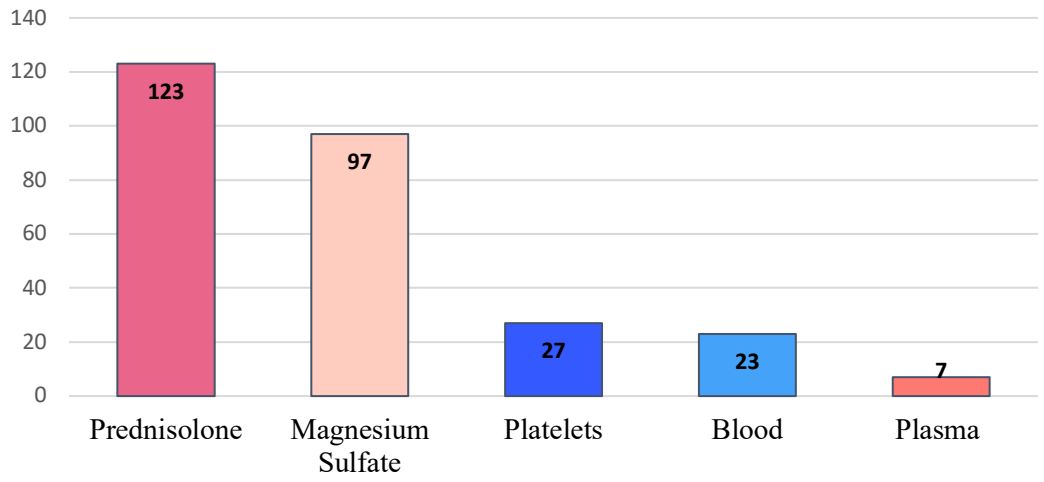
3.7 Intravenous Treatments

During the hospitalization of diagnosed women, several intravenous medications and blood products are used to combat the symptoms of HELLP syndrome. Figure 4 summarizes how many women received these interventions; multiple answers possible. The platelets, blood, and plasma transfusions were given both pre- and post-surgery, functioning to stabilize patients undergoing medical interventions, and additionally serve as critical indicators of severe morbidity as further analyzed in chapter 3.10. The glucocorticoid Prednisolone was administered as an intervention aimed at prolonging gestation and elevating/ stabilizing thrombocyte counts. Additionally, the use of magnesium sulphate was employed as a preventive measure against maternal seizures and for fetal neuroprotection.

Prednisolone was administered to 123 (75%) patients. Of those, 33 patients received a second dose and ten a third. The total dosage varied between 0,25g and 3g. Magnesium sulfate was given to 97 (59%) patients. Infusions of platelets, blood products and plasma were given to 57 patients.

All patients with an elevated blood pressure of above 140/90 mmHg received at least one dose of urapidil or nifedipine.

Figure 4: Intravenous Treatments during Hospitalization



Data is given as absolute numbers; multiple answers were possible.

3.8 Intensive Care Unit Stay

A total of 40 women were treated in the intensive care unit. The average age was 33 years compared to 31 years for the entire study population. The average length of stay was 53.9 hours, with the longest duration being 563.1 hours and the shortest being 7 hours. Only one woman was admitted to the ICU prepartum; all others were treated postpartum. The primary reasons for intensive care were high blood pressure/ hypertensive crisis and severe blood loss during delivery, attributed to low platelet counts. Other indications were intercranial bleeding with hemiparesis, polyureic kidney failure, eclamptic seizures, paralytic ileus, and sepsis. The woman who stayed the longest suffered a cardiac arrest caused by a posterior cardiac infarction postpartum but was successfully resuscitated.

Unfortunately, one woman died postpartum in the ICU due to complications associated with HELLP syndrome.

3.9 HELLP Pre- vs. Post-Partum

As outlined in chapter 2.5, the study population was subclassified into two subgroups: HELLP syndrome manifestation prepartum PRE and postpartum POST. The Group PRE included 108 women; the group POST included 56. A Mann-Whitney U test was employed to investigate potential differences between these two groups, denoted as Group PRE and Group POST. The examination encompassed eleven variables: patient age, patient BMI before pregnancy, length of pregnancy, length of hospitalization, systolic blood pressure, MAP, platelet count, ALT levels, AST levels, LDH levels, and child weight. The results are summarized by Table 13. The results revealed no statistically significant dissimilarity between the two groups across all categories ($p > 0.05$), except the laboratory values ($p < .001$). Here, the PRE subgroup has significantly worse laboratory values than the POST group, though it had no significant effect on the length of hospitalization.

Table 13: Comparison of the Subgroups PRE and POST

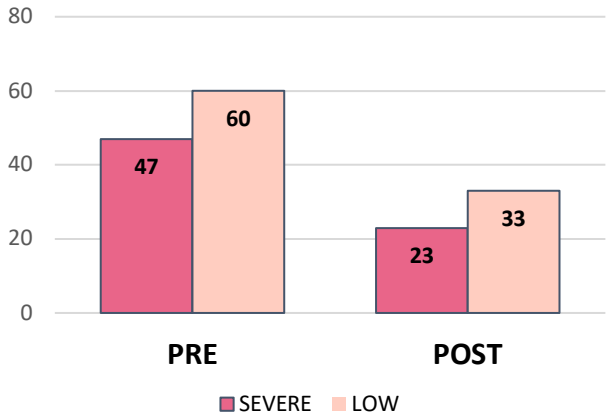
	PRE n= 108 (66%)			POST n= 56 (34%)			
	Mean	SD	Median	Mean	SD	Median	p
Age (years)	31.66	5.41		31.86	4.31		.110
BMI (before Pregnancy)	23,92	5.39		22,65	4.67		.065
Length of Pregnancy (days)	237.33	32.73		244.43	30.16		.282
Length of Hospitalization (days)	7.95	5.24		8.57	5.88		.307
Systolic BP Max (mmHg)	165	22.25		168	23.34		.323
MAP Max (mmHg)	120.88	16.59		121.62	15.51		.203
Platelets $x10^9$ (U/L)	64.76	20.61	64	64.96	42.96	68,5	.018
AST (U/L)	256.74	236.12	153	278.18	186.24	159	<.001
ALT (U/L)	236.94	194.56	164	220.42	165.77	159	<.001
LDH (U/L)	465.72	252.32	351	549.83	242.44	496,5	<.001
Weight Child (gram)	2118.00	896.53		2146.96	889.97		.092

Data is given as mean and standard deviation. Laboratory values include median.
BMI, Body Mass Index; BP, Blood Pressure; MAP, Mean Arterial Pressure; AST, Aspartate Aminotransferase; ALT, Alanine Aminotransferase; LDH, Lactate dehydrogenase; U/L, Units per Litre

Although fewer women in the POST group were admitted to the ICU for further observation – 20% vs 27% –, they stayed almost twice as long, with a median duration of 51:45 hours compared to 27:00 hours.

The chi-squared test was conducted to assess the association between severe morbidity and pre- and postpartum HELLP Syndrome. The observed frequencies were compared to the expected frequencies under the assumption of independence.

Figure 5: Comparison of severe Morbidity for the Subgroups PRE and POST



Data is given in absolute numbers.

The calculated chi-squared was χ^2= 0.122, $p = -.027$, $\varphi = 0.27$, with 1 degree of freedom. Comparing this to the critical chi-squared value of 3.841 for a significant alpha level of α = 0.05, the calculated chi-squared value is below the critical value. Therefore, the results of the chi-squared test indicate no statistically significant association between morbidity and the timing of occurrence (pre/post partum). In other words, severe and low morbidity are unrelated to when HELLP syndrome occurs.

A second chi squared test was performed to assess the role of nullipara (0 births) and multipara (≥1 births) in the development of HELLP syndrome pre- or postpartum The result, chi-squared value χ^2= 0.749, $p = -.068$, $\varphi = 0.68$, showed no statistically significant difference in the observed and expected frequency of parity in the subgroups. This suggests that there is no correlation between the timing of HELLP Syndrome and the number of pregnancies.

3.10 Severe Morbidity vs. low Morbidity

The total study population was further categorized according to the severity of maternal morbidity. The criteria for the allocation to the SEVERE group was pneumological, cerebral, or renal complications, instances of severe haemorrhage requiring blood, platelet, or plasma

transfusions, the occurrence of Eclampsia, the need for revision surgery, severe infections and sepsis, intensive care unit (ICU) treatment involving prolonged intubation, dependency on vasopressors, and the need for hemofiltration. The remaining women were assigned to the LOW group, who exhibited little to no morbidity. The group SEVERE included 70 patients and the group LOW encompassed 93.

The same set of eleven variables (patient age, patient BMI before pregnancy, length of pregnancy, length of hospitalization, systolic blood pressure, MAP, platelet count, ALT levels, AST levels, LDH levels, and child weight), previously applied to the PRE and POST subgroups, was utilized to compare these two subgroups, as. The results of the statistical analysis are summarized in Table 14. Employing the Mann-Whitney U test, this study revealed no significant difference ($p > 0.05$) between the two groups concerning patient age, length of pregnancy, hospitalization duration, ALT levels, and child weight. However, significant differences were noted in the variables maximum systolic blood pressure, maximum mean arterial pressure, platelet count, AST levels, and LDH levels.

Across all eleven variables, the LOW group appeared marginally more favorable in terms of patient health compared to the SEVERE group. For instance, the length of pregnancy was longer by three days, discharge from the hospital occurred two days earlier, and their laboratory values overall were better.

Table 14: Comparison of the Subgroups SEVERE and LOW

	SEVERE n= 70 (43%)			LOW n= 93(57%)			p
	$\bar{x}$	SD	Median	$\bar{x}$	SD	Median	
Age (years)	31.54	5.19		31.87	4.89		.670
BMI (before Pregnancy)	23.19	3.81		23.61	5.60		.618
Length of Pregnancy (days)	238.89	33,05		241.27	30.31		.765
Length of Hospitalization (days)	9.25	6.72		7.36	4.12		.090
Systolic BP Max (mmHg)	171.63	21.16		162.18	22.95		.012
MAP Max (mmHg)	125.44	13.24		117.90	18.61		.006
Platelets $x10^9$ (U/L)	57,10	20.95	59	70.57	18.23	74	<.001
AST (U/L)	333.97	387,03	187.5	211.49	212.32	145	.036
ALT (U/L)	269,87	269,85	161.5	201.97	170.96	162	.319
LDH (U/L)	580,36	458,06	483.5	434.31	242.91	346	.003
Weight Child (gram)	2125,78	903,93		2129.67	873.54		.937

Data is given as mean and standard deviation. Laboratory values include median.
BMI, Body Mass Index; BP, Blood Pressure; MAP, Mean Arterial Pressure; AST, Aspartate Aminotransferase; ALT, Alanine Aminotransferase; LDH, Lactate dehydrogenase: U/L, Units per Litre

The data shows, that a HELLP syndrome leading to severe maternal morbidity seems to correlates with low platelet counts (<60,000), elevated AST (>300 U/L), high LDH (>550 U/L), and high blood pressure (systolic >170 mmHg, diastolic >100 mmHg, or mean arterial pressure >120 mmHg).

Just like with the PRE and POST groups, a chi- squared test was preformed to analyse the role of nullipara and multipara in the development of HELLP syndrome in combination with severe and low morbidity. The calculated χ^2 value of 0.188 is less than the critical value 3.841 with $\alpha = 0.05$ significance level, with concludes that there is no significant difference

between the observed and expected frequencies of parity in the data. Thereby we can conclude that severe and low morbidity is unrelated to parity of the patient.

4 Discussion

This retrospective single centre study focused on 163 patients diagnosed with HELLP syndrome between 2005 and 2020. Demographic characteristics, laboratory parameters and outcomes of patients and their children were collected and statistically analysed.

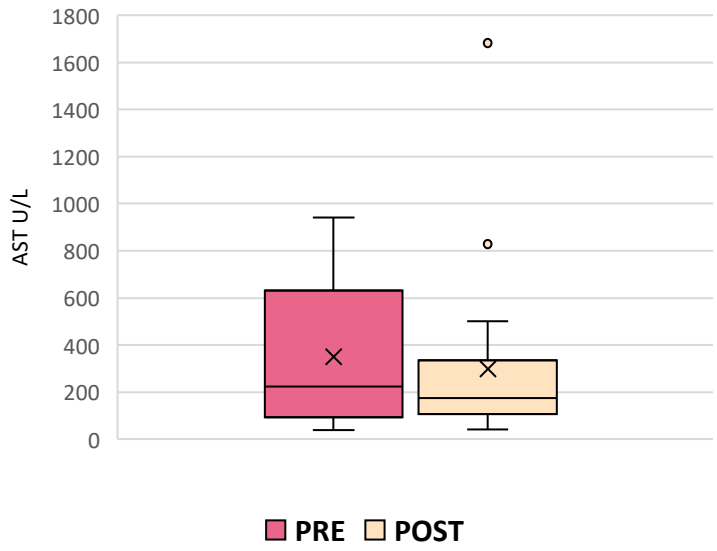
Pooling together all the gathered data points provided a clear profile of the typical woman affected by HELLP syndrome within our study cohort: she is 31 years old, with a normal BMI of 23. It is her first known pregnancy, and she is at 34 weeks of gestation. She contacts the obstetric hospital ward because she suffers from worsening upper abdominal pain, headaches, and nausea. A blood workup will show low platelets (<70,000) and elevated liver enzymes and LDH levels. Her delivery is most likely going to be by caesarean section, and the infant's size is expected to be relatively small, around the 27th percentile.

Two systems of classification were utilized to identify HELLP syndrome: the officially recognized Mississippi Classification and the de Boer Classification, informally used by scholars and clinicians globally. The latter system identified 26 additional women due to the lower threshold concerning the LDH levels. Ten additional women were included in the study, who did not meet the classification threshold of a singular value in Mississippi and de Boer systems but showed all the characteristic signs and symptoms of HELLP syndrome and were treated as such. Further ten women were included even though their laboratory workups were incomplete or unusable due to hemolysis of the sample. However, all other data points were recorded, and they were treated for HELLP syndrome during their hospitalization. The decision to include these 20 women was made based on the principle that a classification system for a multifaceted disease such as this one should be a diagnostic tool and not an infallible mandate.

The manifestation of HELLP syndrome was divided into prepartum and postpartum. Subsequently two groups were formed: PRE and POST. The only parameters where the two groups statistically diverged from another are the laboratory parameters platelet count, AST, ALT and LDH. Although, when comparing the mean and median directly, the difference is minimal. The laboratory values for AST are used as an example of this in Figure 7.
When combining these results with the chi squared test from chapter 3.9, showing that there was no significant difference between severe and low morbidity occurrence between the two

groups, it becomes clear, that postpartum HELLP syndrome should not be underestimated. It can result in just as severe morbidities as prepartum HELLP can.

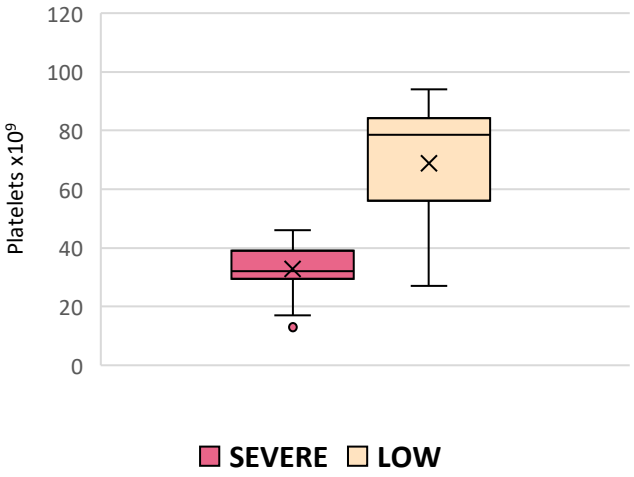
Figure 6: Comparison of AST Levels for PRE and POST Subgroups



The patients were further divided into two groups as follows: suffering from severe morbidity (SEVERE) and showing little to no morbidity (LOW). The two groups were compared using the same eleven variables as the PRE and POST group. The findings indicated that demographic parameters such as age, BMI, and parity have no discernible impact on morbidity in our study population. Additionally, the duration of pregnancy and the infant's weight showed a high degree of similarity.

The two groups diverged significantly in the variables systolic blood pressure, platelet count, AST, ALT, and LDH. Figure 8 serves as an exemplar illustrating the difference in platelet counts between the two groups.

Figure 7: Comparison of Platelet Count for the Subgroups SEVERE and LOW



Summarizing our results (Table 14), a HELLP syndrome leading to severe maternal morbidity correlates with low platelet counts (<60,000), elevated AST (>300 U/L), high LDH (>550 U/L), and high blood pressure (systolic >170 mmHg, diastolic >100 mmHg, or mean arterial pressure >120 mmHg). Patients presenting with these parameters must be closely monitored and treated accordingly.

Counterintuitively and in contrast with the statistical results mentioned above, the comparison between these two subgroups on an individual patient level also showed that pathological laboratory values and elevated blood pressure do not always go hand in hand with severe symptoms and morbidity. For example, patient nr. 34 was a 37-year-old primipara with a normal pregestational BMI of 20. She was admitted to the delivery ward at 39 + 4 week pregnant with upper abdominal pain. Her status at admission was as follows: blood pressure 202/116 mmHg, platelet count 47,000, AST 133 U/L, ALT 90 U/L, LDH 372 U/L. She delivered a healthy infant with 3660g by C- Section and was released without complications after 5 days. During her hospitalization, she experienced zero complications, that would be expected with her clinical presentation – such as headaches, severe bleeding, or placental dysfunction. Cases such as this show just how unpredictable HELLP syndrome can be.

4.1 Comparison to current Scientific Literature

These following passages will review and assess the findings of this retrospective study within the existing literature on HELLP syndrome. By comparing our results and observations with those described in prior studies, we aim to gain a better understanding of the varied manifestations and implications of HELLP syndrome for both mother and child.

A study conducted in 1990 by Sibai et al. (58) examining 304 diagnosed HELLP syndrome cases, found that 209 (69%) presented with prepartum HELLP and 95 (31%) were postpartum manifestations. Similarly, our study found that among the 163 patients, 108 (66%) developed HELLP Syndrome before delivery and 55 (34%) after. Notably, in the prepartum group, 75% of Sibai's patients developed HELLP after the 26th week of gestation compared to 90% in this study.

In 1993 Sibai et al. (17) published a subsequent single center study looking at the maternal morbidity of 442 HELLP pregnancies in Memphis, Tennessee. They found 309 (70%) prepartum cases and 133 (30%) postpartum cases. The converging findings on the onset of the syndrome in all three studies not only show a consistent trend, but also underscore the importance of recognizing HELLP as not only a prepartum disorder but also postpartum.

Our study ventured a step further by analyzing whether there exists a difference in the severity of morbidity between pre- and postpartum HELLP Syndrome cases. The rate of severe morbidity was lower postpartum than prepartum, 32% vs. 68% respectively, but a chi squared test showed that these results were not statistically significant. Deruelle et al. also found no influence of the time of onset of HELLP syndrome and the severity of symptoms (59). There are however differences in the inclusion criteria of severe morbidity, which necessitates careful consideration when comparing the results.

As part of our study, we created a composite morbidity score to identify the women with high morbidity and compared this SEVERE group to the LOW group, women without notable morbidity. There are no comparative studies in the current literature. From other studies dealing with the topic of preeclampsia and HELLP syndrome, similar results regarding morbidity were reported. Abdulkadir et al. compared pre-eclampsia cases with HELLP syndrome cases and found a significantly higher morbidity in the HELLP group.

The morbidity in his study compared to our study is similar, except for a longer hospital stay in his study of 13.2 vs. 8.5 days in our study (60).

Another study by Martin et al, showed that about 44-50 % of cases of HELLP syndrome are associated with maternal morbidity, if the platelet counts dropped < 50.000 cells /µL (19). Similar results were found in our study with an association of low platelets and higher morbidity.
Since HELLP syndrome can often be relapsing remitting, a drop in platelets around the 50,000 mark should be considered as a warning, and delivery should be considered at this time at the latest.

The reported maternal mortality rate for Sibai et al. was 1.1%, involving five patients, whilst only one (0.6%) mortality occurred in Graz. This difference could also be attributed to the advancements in medical diagnostics and care.
A difference is also notable in the age of the women. Whilst the average age for Sibai et al. was 24.4 ± 5.6 years, the women in our study were almost 7 years older with 31.73 ± 5.01 years. Additionally, both studies identified upper abdominal pain, headaches, and nausea as the most common symptoms. Despite this consistency in symptomatology, the disparities in age demographics raise questions about potential age-related effects on HELLP syndrome incidence and severity across different populations, especially when taking the motherly mortality into account. The age gap can also be attributed to the rising maternal age of first pregnancies over the past decades.
Another major difference between the two studies is the method of delivery. In Graz, 79% of HELLP cases were delivered via cesarean section compared to only 42%. While Sibai's findings indicated that postpartum HELLP syndrome cases were more likely to have delivered at term ($p < 0.002$), this trend could not be shown in our study. This is most likely due to variations in clinical practices and differences in disease progression between the studied populations.

Several studies (7, 16) have identified a Body Mass Index over 30 before pregnancy to be a risk factor for HELLP Syndrome. This was not observed in the population of this study, which had an average BMI of 23.42 ± 4.89. Merely 13(8%) of women reported a BMI of >30 before their pregnancy. However, it has to be taken into account, that the weight of the women was based on self-reporting and thereby a recollection bias as to be considered.

The 1998 retrospective study by Kändler et al. compared the outcomes of newborns from mothers with HELLP syndrome in Erlangen, Germany (48). Over the course of five years, 68 newborns were identified, and their outcome evaluated. Among this cohort, 53 (78%) were premature births and were treated in the neonatal intensive care unit. The mean age of gestation was 33.91 weeks ± 3.26 at birth with a recorded mean birth weight of 1671g ± 623. The Graz study found congruent data on the newborns with a prematurity rate of 65.5%, at the mean age of 34.01 ± 4.71 with a slightly higher birth weight of 2128,01g ± 883,83. Because of the inability to cure HELLP syndrome and the potential onset in the second trimester, the frequency of preterm deliveries remains high, even decades after the first publications on the disease. The mean duration of gestation and weight determined in this study does not differ considerably from the observations of other publications (10, 48, 61, 62).

A discernable difference between our study and other research findings concerning the children's outcome is the mortality rate. It is below the rate of comparatives studies shown by Table 15 (10, 48, 62, 63). This observation could potentially be attributed to advancements in neonatal care, as the comparative studies are from the 1990s, and the successful interdisciplinary care for mother and child in Graz.

Table 15: Comparison of the Mortality Rate of the delivered Child

	Graz	Deruelle et al.	Kändler et al	Harms et al.	Eeltink et al.	Sibai et al.
Mortality rate in %	3.08	3.5	3.8	8.4	9.9	17.4

4.2 Limitations

As HELLP syndrome has such a low incidence rate, the most economical way to gather a large study population is to look at the past.

In the medical field, retrospective studies, while contributing valuable information, are inherently prone to certain limitations. One critical limitation involves the reliance on pre-existing data, leading to issues related to data quality and completeness. Such is the case in this study. The data was collected from archived medical records and databases where data collection was often inconsistent or incomplete due to varying recording practices over the 15-year timespan. Inaccuracies in the recording of patient information, missing data points, and inconsistent documentation can significantly compromise the reliability and validity of findings, potentially introducing bias into the study. Especially high stress environments, such as the labor and delivery ward, are vulnerable to this. To counteract this limitation, multiple data sources were used to create a more complete and reliable data set.

Another significant limitation of retrospective studies lies in their susceptibility to confounding variables and bias. The inability to control or account for all potential confounders or variables of interest at the time of data collection poses a considerable challenge. Confounding factors, such as unmeasured variables or differences in treatment protocols over time, may influence the observed associations between variables, leading to erroneous conclusions (64). Over the timespan of this study, new research results and technology changed how patients were medically treated and how efficient the care was. For example, better diagnostic tools have made the distinction between the differential diagnosis of HELLP Syndrome much easier.
Lastly, because of the 15-year timespan and the nature of hospital shift work, the women received care from multiple physicians, midwives, and nurses, each of whom had a subjective understanding of disease prevalence, symptom presentation, and treatment options. This is evident in the variation within many of the data points, including delivery methods and medication administration.

The study population of 163 women is large compared to many other research papers. However, to find further valuable insight into the syndrome, a much larger multicenter study with structured data collection is essential.

The division of the study population into subgroups based on morbidity was based on clinical routine and experience and not on scientifically substantiated data. The inclusion criteria contained all factors that would complicate and/ or prolong the hospitalization of the women compared to a normal birthing process.

Because of this, the comparison to other studies is increasingly complex, as every author has a different approach to the definition of severe morbidity.

5 Conclusion

HELLP Syndrome is a pregnancy complication that was classified for the first time in 1982 by Dr. Weinstein. Since then, numerous researchers and physicians have continued to focus on understanding the quintessence of the syndrome by refining the definition, suggesting new laboratory cut off values, and identifying differential diagnosis. The perplexity surrounding HELLP syndrome persists, making the disease one of the most compelling and unresolved challenges in the field of obstetrics.

In this retrospective dissertation focusing on 163 patients diagnosed with HELLP syndrome, a detailed analysis of demographic, clinical, and laboratory parameters was conducted. The study provided insights into the multifaceted nature of HELLP syndrome, with a special emphasis on its manifestation, classification, severity of morbidity, maternal outcome, and neonatal implications.

Through statistical analysis, it was determined that a woman affected by HELLP syndrome in our study exhibits characteristic features, including age, BMI, gestational period, symptoms, and expected mode of delivery. Notably, none of these factors are distinct enough to aid in early detection of HELLP syndrome.

The use of two classification systems, Mississippi and DeBoer, revealed discrepancies in identifying affected women, emphasizing the need for a more inclusive diagnostic approach, that is not solely based on laboratory values. To capture all potential cases accurately, one must look at the patient as a whole and not and not base clinical decisions only on her blood work. Nevertheless, we found that a HELLP syndrome leading to severe maternal morbidity correlates with low platelet counts (<60,000), elevated AST (>300 U/L), high LDH (>550 U/L), and high blood pressure (systolic >170 mmHg, diastolic >100 mmHg, or mean arterial pressure >120 mmHg). Patients presenting with these parameters must be closely monitored and if the woman is still pregnant delivery should be induced or planed.

Our study described the distinction between prepartum and postpartum manifestations of HELLP syndrome, highlighting that both forms can lead to severe maternal morbidities.

Postpartum manifestation should not be overlooked or underestimated, as it has comparable risks and can lead to severe complications.

The identifying markers of HELLP syndrome —low platelet count, elevated liver enzymes (AST, ALT), high LDH levels, as well as increased blood pressure — are statistically significant indicators for severe morbidity in affected patients. Paradoxically, some cases deviated from this pattern, showcasing the unpredictability and complexity inherent in this syndrome.

The comparison of our results with seminal studies revealed parallels and variations in the onset, severity, and outcomes of HELLP syndrome across different populations. While consistent trends in symptomatology were observed, deviations in maternal age, delivery methods, and maternal mortality rates indicate further need for the research into potential influences on syndrome manifestation and severity.

In line with the current literature, our findings underscore the continued predominance of preterm deliveries in HELLP syndrome cases, highlighting the persistent challenges in managing this condition and its implications for neonatal health. The low child mortality rate in our study is attributed to excellent interdisciplinary care and advancements in neonatology.

In conclusion, this research dissertation of HELLP syndrome offers insights into its pre- and postpartum manifestation, severity of morbidity, maternal outcomes, and neonatal implications. The need for further multi-centric studies incorporating diverse populations is warranted due to the complexity of this syndrome, including the potentially fatal outcome of mother and child. Our results contribute to the understanding of HELLP syndrome and underscore the importance of individualized management strategies to mitigate its impact on maternal and neonatal health.

6 References

1. Gillon TE, Pels A, von Dadelszen P, MacDonell K, Magee LA. Hypertensive disorders of pregnancy: a systematic review of international clinical practice guidelines. PLoS One. 2014;9(12):e113715.
2. Olson-Chen C, Seligman NS. Hypertensive Emergencies in Pregnancy. Crit Care Clin. 2016;32(1):29-41.
3. DGGG O, SGGG. S2k-Leitlinie Hypertensive Schwangerschaftserkrankungen: Diagnostik und Therapie 2019 [1.1:[Available from: https://register.awmf.org/assets/guidelines/015-018l_S2k_Diagnostik_Therapie_hypertensiver_Schwangerschaftserkrankungen_2019-07.pdf
.
4. Gestational Hypertension and Preeclampsia: ACOG Practice Bulletin, Number 222. Obstet Gynecol. 2020;135(6):e237-e60.
5. Weinstein L. Syndrome of hemolysis, elevated liver enzymes, and low platelet count: a severe consequence of hypertension in pregnancy. Am J Obstet Gynecol. 1982;142(2):159-67.
6. Wallace K, Harris S, Addison A, Bean C. HELLP Syndrome: Pathophysiology and Current Therapies. Curr Pharm Biotechnol. 2018;19(10):816-26.
7. Lisonkova S, Razaz N, Sabr Y, Muraca GM, Boutin A, Mayer C, et al. Maternal risk factors and adverse birth outcomes associated with HELLP syndrome: a population-based study. BJOG. 2020;127(10):1189-98.
8. Mao M, Chen C. Corticosteroid Therapy for Management of Hemolysis, Elevated Liver Enzymes, and Low Platelet Count (HELLP) Syndrome: A Meta-Analysis. Med Sci Monit. 2015;21:3777-83.
9. Abramovici D, Friedman SA, Mercer BM, Audibert F, Kao L, Sibai BM. Neonatal outcome in severe preeclampsia at 24 to 36 weeks' gestation: does the HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome matter? Am J Obstet Gynecol. 1999;180(1 Pt 1):221-5.
10. Harms K, Rath W, Herting E, Kuhn W. Maternal hemolysis, elevated liver enzymes, low platelet count, and neonatal outcome. Am J Perinatol. 1995;12(1):1-6.
11. Dusse LM, Alpoim PN, Silva JT, Rios DR, Brandao AH, Cabral AC. Revisiting HELLP syndrome. Clin Chim Acta. 2015;451(Pt B):117-20.
12. Chaiworapongsa T, Chaemsaithong P, Yeo L, Romero R. Pre-eclampsia part 1: current understanding of its pathophysiology. Nat Rev Nephrol. 2014;10(8):466-80.
13. Stubbs TM, Lazarchick J, Van Dorsten JP, Cox J, Loadholt CB. Evidence of accelerated platelet production and consumption in nonthrombocytopenic preeclampsia. Am J Obstet Gynecol. 1986;155(2):263-5.
14. Jimenez KM, Morel A, Parada-Nino L, Alejandra Gonzalez-Rodriguez M, Florez S, Bolivar-Salazar D, et al. Identifying new potential genetic biomarkers for HELLP syndrome using massive parallel sequencing. Pregnancy Hypertens. 2020;22:181-90.
15. Jebbink J, Wolters A, Fernando F, Afink G, van der Post J, Ris-Stalpers C. Molecular genetics of preeclampsia and HELLP syndrome - a review. Biochim Biophys Acta. 2012;1822(12):1960-9.
16. Malmstrom O, Morken NH. HELLP syndrome, risk factors in first and second pregnancy: a population-based cohort study. Acta Obstet Gynecol Scand. 2018;97(6):709-16.

17. Sibai BM, Ramadan MK, Usta I, Salama M, Mercer BM, Friedman SA. Maternal morbidity and mortality in 442 pregnancies with hemolysis, elevated liver enzymes, and low platelets (HELLP syndrome). Am J Obstet Gynecol. 1993;169(4):1000-6.
18. Martin JN, Jr., Rose CH, Briery CM. Understanding and managing HELLP syndrome: the integral role of aggressive glucocorticoids for mother and child. Am J Obstet Gynecol. 2006;195(4):914-34.
19. Martin JN, Jr., Rinehart BK, May WL, Magann EF, Terrone DA, Blake PG. The spectrum of severe preeclampsia: comparative analysis by HELLP (hemolysis, elevated liver enzyme levels, and low platelet count) syndrome classification. Am J Obstet Gynecol. 1999;180(6 Pt 1):1373-84.
20. Hohlagschwandtner M, Bancher-Todesca D, Strohmer H. HELLP (hemolysis, elevated liver enzymes, and low platelets) needs help. Am J Obstet Gynecol. 2000;182(5):1271.
21. Sibai BM. Diagnosis, controversies, and management of the syndrome of hemolysis, elevated liver enzymes, and low platelet count. Obstet Gynecol. 2004;103(5 Pt 1):981-91.
22. Hallman M, Peltoniemi O, Kari MA. Enhancing functional maturity before preterm birth. Neonatology. 2010;97(4):373-8.
23. Roberts D, Brown J, Medley N, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev. 2017;3(3):CD004454.
24. Gyamfi-Bannerman C, Thom EA, Blackwell SC, Tita AT, Reddy UM, Saade GR, et al. Antenatal Betamethasone for Women at Risk for Late Preterm Delivery. N Engl J Med. 2016;374(14):1311-20.
25. Crowley P, Chalmers I, Keirse MJ. The effects of corticosteroid administration before preterm delivery: an overview of the evidence from controlled trials. Br J Obstet Gynaecol. 1990;97(1):11-25.
26. Liggins GC, Howie RN. A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants. Pediatrics. 1972;50(4):515-25.
27. Jobe AH, Ikegami M. Biology of surfactant. Clin Perinatol. 2001;28(3):655-69, vii-viii.
28. Magann EF, Martin RW, Isaacs JD, Blake PG, Morrison JC, Martin JN, Jr. Corticosteroids for the enhancement of fetal lung maturity: impact on the gravida with preeclampsia and the HELLP syndrome. Aust N Z J Obstet Gynaecol. 1993;33(2):127-31.
29. van Runnard Heimel PJ, Schobben AF, Huisjes AJ, Franx A, Bruinse HW. The transplacental passage of prednisolone in pregnancies complicated by early-onset HELLP syndrome. Placenta. 2005;26(10):842-5.
30. Katz L, de Amorim MM, Figueiroa JN, Pinto e Silva JL. Postpartum dexamethasone for women with hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome: a double-blind, placebo-controlled, randomized clinical trial. Am J Obstet Gynecol. 2008;198(3):283 e1-8.
31. Fonseca JE, Mendez F, Catano C, Arias F. Dexamethasone treatment does not improve the outcome of women with HELLP syndrome: a double-blind, placebo-controlled, randomized clinical trial. Am J Obstet Gynecol. 2005;193(5):1591-8.
32. Martin JN, Jr., Thigpen BD, Rose CH, Cushman J, Moore A, May WL. Maternal benefit of high-dose intravenous corticosteroid therapy for HELLP syndrome. Am J Obstet Gynecol. 2003;189(3):830-4.
33. Isler CM, Barrilleaux PS, Magann EF, Bass JD, Martin JN, Jr. A prospective, randomized trial comparing the efficacy of dexamethasone and betamethasone for the

treatment of antepartum HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome. Am J Obstet Gynecol. 2001;184(7):1332-7; discussion 7-9.
34. van Runnard Heimel PJ, Huisjes AJ, Franx A, Koopman C, Bots ML, Bruinse HW. A randomised placebo-controlled trial of prolonged prednisolone administration to patients with HELLP syndrome remote from term. Eur J Obstet Gynecol Reprod Biol. 2006;128(1-2):187-93.
35. Morton A. Imitators of preeclampsia: A review. Pregnancy Hypertens. 2016;6(1):1-9.
36. Tran TT, Ahn J, Reau NS. ACG Clinical Guideline: Liver Disease and Pregnancy. Am J Gastroenterol. 2016;111(2):176-94; quiz 96.
37. Conde-Agudelo A, Romero R. SARS-CoV-2 infection during pregnancy and risk of preeclampsia: a systematic review and meta-analysis. Am J Obstet Gynecol. 2022;226(1):68-89 e3.
38. Bergmann F, Rath W. The Differential Diagnosis of Thrombocytopenia in Pregnancy. Dtsch Arztebl Int. 2015;112(47):795-802.
39. Sullivan CA, Magann EF, Perry KG, Jr., Roberts WE, Blake PG, Martin JN, Jr. The recurrence risk of the syndrome of hemolysis, elevated liver enzymes, and low platelets (HELLP) in subsequent gestations. Am J Obstet Gynecol. 1994;171(4):940-3.
40. Sibai BM, Ramadan MK, Chari RS, Friedman SA. Pregnancies complicated by HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets): subsequent pregnancy outcome and long-term prognosis. Am J Obstet Gynecol. 1995;172(1 Pt 1):125-9.
41. Habli M, Eftekhari N, Wiebracht E, Bombrys A, Khabbaz M, How H, et al. Long-term maternal and subsequent pregnancy outcomes 5 years after hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome. Am J Obstet Gynecol. 2009;201(4):385 e1-5.
42. van Oostwaard MF, Langenveld J, Schuit E, Papatsonis DN, Brown MA, Byaruhanga RN, et al. Recurrence of hypertensive disorders of pregnancy: an individual patient data metaanalysis. Am J Obstet Gynecol. 2015;212(5):624 e1-17.
43. Amaral LM, Cunningham MW, Jr., Cornelius DC, LaMarca B. Preeclampsia: long-term consequences for vascular health. Vasc Health Risk Manag. 2015;11:403-15.
44. van Pampus MG, Wolf H, Weijmar Schultz WC, Neeleman J, Aarnoudse JG. Posttraumatic stress disorder following preeclampsia and HELLP syndrome. J Psychosom Obstet Gynaecol. 2004;25(3-4):183-7.
45. Delahaije DH, Dirksen CD, Peeters LL, Smits LJ. Anxiety and depression following preeclampsia or hemolysis, elevated liver enzymes, and low platelets syndrome. A systematic review. Acta Obstet Gynecol Scand. 2013;92(7):746-61.
46. Brusse I, Duvekot J, Jongerling J, Steegers E, De Koning I. Impaired maternal cognitive functioning after pregnancies complicated by severe pre-eclampsia: a pilot case-control study. Acta Obstet Gynecol Scand. 2008;87(4):408-12.
47. Davis EF, Lazdam M, Lewandowski AJ, Worton SA, Kelly B, Kenworthy Y, et al. Cardiovascular risk factors in children and young adults born to preeclamptic pregnancies: a systematic review. Pediatrics. 2012;129(6):e1552-61.
48. Kandler C, Kevekordes B, Zenker M, Kandler M, Beinder E, Lang N, et al. Prognosis of children born to mothers with HELLP-syndrome. J Perinat Med. 1998;26(6):486-90.
49. Ehrenstein V. Association of Apgar scores with death and neurologic disability. Clin Epidemiol. 2009;1:45-53.

50. Lopriore E, van Burk GF, Walther FJ, de Beaufort AJ. Correct use of the Apgar score for resuscitated and intubated newborn babies: questionnaire study. BMJ. 2004;329(7458):143-4.
51. Lie KK, Groholt EK, Eskild A. Association of cerebral palsy with Apgar score in low and normal birthweight infants: population based cohort study. BMJ. 2010;341:c4990.
52. Nelson KB, Ellenberg JH. Apgar scores as predictors of chronic neurologic disability. Pediatrics. 1981;68(1):36-44.
53. American Academy Of Pediatrics Committee On F, Newborn, American College Of O, Gynecologists Committee On Obstetric P. The Apgar Score. Pediatrics. 2015;136(4):819-22.
54. Battaglia FC, Lubchenco LO. A practical classification of newborn infants by weight and gestational age. J Pediatr. 1967;71(2):159-63.
55. De Jesus LC, Pappas A, Shankaran S, Li L, Das A, Bell EF, et al. Outcomes of small for gestational age infants born at <27 weeks' gestation. J Pediatr. 2013;163(1):55-60 e1-3.
56. Guellec I, Lapillonne A, Renolleau S, Charlaluk ML, Roze JC, Marret S, et al. Neurologic outcomes at school age in very preterm infants born with severe or mild growth restriction. Pediatrics. 2011;127(4):e883-91.
57. Ray JG, Park AL, Fell DB. Mortality in Infants Affected by Preterm Birth and Severe Small-for-Gestational Age Birth Weight. Pediatrics. 2017;140(6).
58. Sibai BM. The HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets): much ado about nothing? Am J Obstet Gynecol. 1990;162(2):311-6.
59. Deruelle P, Coudoux E, Ego A, Houfflin-Debarge V, Codaccioni X, Subtil D. Risk factors for post-partum complications occurring after preeclampsia and HELLP syndrome. A study in 453 consecutive pregnancies. Eur J Obstet Gynecol Reprod Biol. 2006;125(1):59-65.
60. Turgut A, Demirci O, Demirci E, Uludogan M. Comparison of maternal and neonatal outcomes in women with HELLP syndrome and women with severe preeclampsia without HELLP syndrome. J Prenat Med. 2010;4(3):51-8.
61. Dotsch J, Hohmann M, Kuhl PG. Neonatal morbidity and mortality associated with maternal haemolysis elevated liver enzymes and low platelets syndrome. Eur J Pediatr. 1997;156(5):389-91.
62. Eeltink CM, van Lingen RA, Aarnoudse JG, Derks JB, Okken A. Maternal haemolysis, elevated liver enzymes and low platelets syndrome: specific problems in the newborn. Eur J Pediatr. 1993;152(2):160-3.
63. Sibai BM, Taslimi MM, el-Nazer A, Amon E, Mabie BC, Ryan GM. Maternal-perinatal outcome associated with the syndrome of hemolysis, elevated liver enzymes, and low platelets in severe preeclampsia-eclampsia. Am J Obstet Gynecol. 1986;155(3):501-9.
64. Talari K, Goyal M. Retrospective studies - utility and caveats. J R Coll Physicians Edinb. 2020;50(4):398-402.