DESCRIPTIVE ANALYSIS OF WOMEN MANAGED AS HELLP SYNDROME AT CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

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DECLARATION

I, Sauad Sahal Mohamed Salem, declare that this research is my own work. It is being submitted to the Faculty of Health Sciences at the University of the Witwatersrand in partial fulfilment for the degree of Master of Medicine in Obstetrics and Gynaecology.

It has not been submitted before for any other degree, part of degree or examination at this or any other university.

Signed

Date: 12/09/2018

DEDICATION

I dedicate my research to my beloved husband Fawzi for supporting, encouraging and pushing me further than I thought I could go. To my father who taught me to believe in myself. To my mother who has been the source of my positive inspiration in my academic journey. To give a special thanks to my loving daughter Faudwa for her patience. I will always appreciate my siblings for helping me and never leaving my side.

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ABSTRACT

Background

The acronym HELLP syndrome (haemolysis, elevated liver enzymes, and low platelets) is a serious complication of preeclampsia. It occurs in 0.5 to 0.9% of all pregnancies, it complicates 10-20% of pregnancies with severe pre-eclampsia or eclampsia and is associated with significant maternal and perinatal morbidity and mortality.

Objectives

To describe the demographic characteristics, haematological and biochemical findings and the risk factors in women with HELLP syndrome. We also describe the maternal complications and the perinatal outcomes in women with HELLP syndrome.

Methods

The present study is a retrospective, cross-sectional study of women with HELLP syndrome who delivered at Chris Hani Baragwanath Academic Hospital (CHBAH) between 01/052017 and 30/09/2017. The CHBAH is a tertiary and regional hospital performing approximately 19300 total deliveries and approximately 7718 caesarean sections (C/S) per annum. Women presenting with HELLP syndrome are assessed and managed according to the University of the Witwatersrand obstetrics protocol.

Results

The total number of deliveries at Chris Hani Baragwanath Academic Hospital during the study period was 9095. Fifty-eight women had HELLP syndrome and were included in the study. The incidence of HELLP syndrome in the present study was 0.67%. Most women were multiparous. Acute kidney injury was found in 36.2%, disseminated intravascular coagulation in 6.8%, 22.4% needed blood transfusions, abruptio placenta occurred in 15.5% and eclampsia in 12%. There were 5.1% in need of ICU admission and caesarean section was performed in 81%. The maternal mortality rate was 2.9 per 100 000 live births. The perinatal mortality rate was 39.7 per 1000 live births.

Conclusion

The HELLP syndrome carries significant morbidity and mortality for the mother and fetus. An early diagnosis in women with preeclampsia might improve the prognosis in pregnant or post-partum women with pre-eclampsia.

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AFLP	Acute fatty liver of pregnancy
AKI	Acute kidney injury
ALT	Alanine aminotransferase
AMA	Advanced maternal age
APLS	Antiphospholipid syndrome
ARDS	Acute respiratory distress syndrome
AST	Aspartate transaminase
BMI	Body mass index
BP	Blood pressure
CHBAH	Chris Hani Baragwanath Academic Hospital
CTG	Cardiotocography
DBP	Diastolic Blood Pressure
DIC	Disseminated intravascular coagulation
EFW	Estimated fetal weight
FBC	Full blood count
FDP	Fibrin degradation products
Hb	Haemoglobin
HELLP	Haemolysis, elevated liver enzymes, low platelets.
HIV	Human immunodeficiency virus
HUS	Haemolytic-uremic syndrome
ICU	Intensive care unit
INR	International normalized ratio
IUGR	Intrauterine growth restriction
LCHAD	Long-chain 3-hydroxyacyl-CoA dehydrogenase
LDH	Lactate dehydrogenase
MAP	Mean Arterial Pressure
$MgSO_4$	Magnesium sulphate
NICU	Neonatal intensive care unit
NST	Non-stress test
NVD	Normal vaginal delivery

PCR	Protein creatinine ratio
PlGF	Placental growth factor
PRES	Posterior reversible encephalopathy syndrome
RCT	Randomised controlled trial
SBP	Systolic Blood Pressure
sFlt-1	Soluble fms-like tyrosine kinase-1
sVEGFR-1	Soluble vascular endothelial growth factor receptor-1
TTP	Thrombotic thrombocytopenic purpura
UA	Umbilical artery Doppler
U&E	Urea and electrolytes
VEGF	Vascular endothelial growth factor
WCC	White cell count

1 LITERATURE REVIEW

1.1 Introduction

HELLP syndrome is a severe form of hypertensive disease in pregnancy. The acronym HELLP is an abbreviation for the three major features of the syndrome, namely, haemolysis (H), elevated liver enzymes (EL), and low platelet count (LP).

The different facets of HELLP syndrome have been described individually since the early 1900s. However, in 1954 it was Pritchard et al. who were the first to report a series of three women who presented with the three laboratory abnormalities, namely intravascular haemolysis, elevated liver enzymes and low platelet levels.[1] Over the latter part of the twentieth century, numerous authors published reports on increasing numbers of women that had been identified with similar laboratory finding over and above severe pre-eclampsia. It was not until 1982 that Louis Weinstein established the term HELLP syndrome based on the three predominant laboratory features.[1]

The World Health Organization (WHO) estimates that approximately 12% of maternal deaths in low to middle-income countries (LMIC) are due to hypertensive diseases in pregnancy .[2] According to the Saving Mothers report for 2014-2016, 14% of all maternal deaths in South Africa were due to hypertensive complications of pregnancy.[3] Most of the cases, 52.5%, were due to eclampsia with 12.9% being attributed to HELLP syndrome.[3]

The HELLP syndrome can develop during pregnancy or during the postpartum period.[4] The development and progression of the disease can often be particularly rapid.[4] For this reason, continued observation for 48 hours is advisable and up to 7 days after delivery in certain cases.[4]

1.2 Epidemiology of HELLP syndrome

The incidence of HELLP syndrome ranges from 0.2 to 0.8% of all pregnancies and complicates 10 to 20% of pregnancies with severe pre-eclampsia or eclampsia.[1] Its incidence is lower in developed countries. In Germany, a study done by Hagen et al. found an incidence of 0.32%.[5] Compared to low-income countries, a study done by Adu Bonsaffoh in Ghana demonstrated an incidence of 0.8%.[6] and Buga, et al. in South Africa found an incidence of 1.2%.[7] The incidence is significantly higher in Caucasian women.[8,9]

The HELLP syndrome typically occurs after 27 weeks of gestation with approximately 50% of the cases occuring in the third trimester.[4] However 15% of women may present before 27 weeks gestation with the remaining cases occurring in the immediate postpartum period.[4]

1.3 Pathophysiology of HELLP syndrome

The HELLP syndrome is characterised by thrombocytopenia, haemolytic anaemia, and liver dysfunction resulting from microvascular endothelial activation and cell injury.[10] Many hypotheses have attempted to define the pathogenesis of HELLP syndrome, but the true pathology remains unclear.[11] Some theories have suggested that HELLP syndrome is a variant of severe pre-eclampsia and the pathophysiology arises from a common source.[12] In pre-eclampsia, defective placental vascular remodelling results in inadequate placental perfusion.[9], specifically, during weeks 16 to 22 of pregnancy with absent or defective second wave of trophoblastic invasion into the decidua.[9] The hypoxic placenta then releases various placental factors such as soluble vascular endothelial growth factor receptor (sVEGFR1).[13,14] This sVEGFR-1 binds to Vascular endothelial growth factor (VEGF) and placental growth factor (PlGF) and prevents binding to endothelial cell receptors resulting in endothelial cell and placental dysfunction.[13,14] The end result is hypertension, proteinuria, and increased platelet activation and aggregation.[14] Additionally, Maynard et al. confirmed that excess circulating placental soluble fms-like tyrosine kinase 1 (sFlt1) and soluble endoglin lead to endothelial dysfunction by antagonizing circulating VEGF and PlGF.[15]

In addition, activation of the coagulation cascade causes consumption of platelets due to adhesion onto the damaged endothelium.[16] Microangiopathic haemolysis also occurs due to shearing of erythrocytes as they travel through capillaries laden with platelet-fibrin deposits.[16]

An alternative hypothesis that proposes acute maternal immune rejection can result in endothelial dysfunction, platelet activation and aggregation, and arterial hypertension.[17] It is thought that immunocompetent maternal cells come into contact with the genetically distinct fetus altering the maternal-fetal immune balance.[17]

1.4 Risk factors for HELLP syndrome

1.4.1 Maternal age

Women over the age of 35 years tend to have additional risk factors such as chronic hypertension and diabetes mellitus, which predispose them to developing HELLP syndrome.[18] Women with HELLP syndrome usually tend to be older than 25 years of age

compared with women with pre-eclampsia who are more often younger than 20 years old or older than 45 years.[18]

1.4.2 Parity

A study done in 2002 by Williams et al. aimed to determine the effect of parity on the occurrence of HELLP syndrome.[19] They demonstrated the incidence of HELLP syndrome and severe pre-eclampsia in three groups of women: primigravid primiparous, multigravid primiparous; and multiparous women. The incidence of HELLP syndrome in the two groups of primiparous women was similar but significantly higher than in the multiparous group.[19] The incidence of complications in hypertensive pregnant women varied by parity but not by gravidity.[19]

1.4.3 Previous hypertensive disorders

Studies have found that hypertensive complications in previous pregnancies are risk factors for recurrence in a later pregnancy.[20,21] Although HELLP syndrome is considered a disease of the first pregnancy, the risk of developing recurrent HELLP syndrome is increased among parous women who have had pre-eclampsia and/ or HELLP syndrome in a previous pregnancy.[22] Sep et al. reported recurrence rates varying from zero to 31% for pre-eclampsia in a cohort of pregnant women and from 3-7% for HELLP syndrome.[23] Fortunately, the majority of women with a history of pre-eclampsia or HELLP syndrome have uncomplicated subsequent pregnancies.[24] Sisters and children of women who had HELLP syndrome also have increased risks of developing hypertensive disorders in pregnancy.[25]

1.4.4 Multiple pregnancies

Due to the increased amount of placental tissue, multiple pregnancy is a risk factor for hypertensive disorders of pregnancy.[26] There is an incidence of between 13 and 37% of hypertensive disorders in women with twin pregnancies.[27] This is a 2-3 fold increase in the reported incidence for women with singleton pregnancies.[26,27] The increased placental weight correlates with increased levels of soluble fms-like tyrosine kinase-1 (sFlt-1) and an increased risk of pre-eclampsia and HELLP syndrome.[28] In twin pregnancies, circulating sFlt-1 levels as well as the ratio of sFlt-1 levels: PlGF be twice as high as those in singleton pregnancies.[24]

1.4.5 Racial origin

Williams et al. in 1997, evaluated ethnic variations in HELLP syndrome in a population with hypertensive disease in pregnancy.[29] In this study, Caucasian and Chinese women were more likely than East Indian women to develop HELLP syndrome.[29]

1.4.6 Body mass index

According to the World Health Organization and the Institute of Medicine, definitions of overweight is: BMI ≥25 and <30 kg/m^2 and obesity: BMI ≥30 kg/m^2, [30] Obesity is an epidemic in South African women. Sixty-eight percent of South African women are overweight or obese; one in five women has a BMI more than 35.[30] In a study by Leeners, et al. body mass index (BMI) was investigated as a risk factor in the development of HELLP syndrome.[31] They found that a BMI greater than 26 kg/m^2 had no effect on the risk of HELLP syndrome.[31] Increased BMI appears to correlate with the risk of developing preeclampsia but not HELLP syndrome.[31]

1.4.7 Medical disorders

Preexisting diabetes is a risk factor for pre-eclampsia and therefore HELLP syndrome.[32] There is a relatively low incidence of pre-eclampsia, between 2-7%, in non-diabetic women, compared with 15 to 20% and 10-14% of pregnancies in women with Type1 and Type 2 diabetes respectively.[32,33]

Women with essential hypertension who have been treated before pregnancy are at increased risk of superimposed pre-eclampsia.[32] A study by Lecarpentier et al. found the rate of superimposed pre-eclampsia was 23.2%, and all women who developed HELLP syndrome had pre-eclampsia.[34] Approximately 3.9% of women with eclampsia developed HELLP syndrome in the study done by Onuh et al.[35]

1.4.8 Autoimmune disease

Women with antiphospholipid syndrome (APLS) are at a significant risk of developing preeclampsia or HELLP syndrome during pregnancy.[36] The actual connection between HELLP syndrome and APLS is unclear.[36] However, a retrospective study by Thuong et al. showed that HELLP syndrome occurs at an earlier stage of gestation in women with APLS than those without APLS.[36] In some women, HELLP syndrome may be the presenting manifestation of antiphospholipid syndrome.[37] Another retrospective series of 75 pregnant

women with HELLP syndrome, showed that 10.5% were found to have antiphospholipid syndrome.[37]

1.5 Presentation of HELLP syndrome

Signs and symptoms of HELLP syndrome are dependent on the stage and severity at which the woman presents.[38] Typical clinical symptoms include right upper quadrant, abdomen or epigastric pain in 30 to 90% of women, associated with nausea and vomiting or flu-like symptoms.[18,39] This may be accompanied by a headache, in 30 to 60% of women, and visual disturbances in 20%.[39] The onset of HELLP syndrome is rapid, variable and sometimes atypical, therefore the diagnosis is often delayed for up to seven days.[40,41,42] Due to the nonspecific nature of symptoms, many women are misdiagnosed with disorders such as cholecystitis, oesophagitis, gastritis, hepatitis, viral fever or idiopathic thrombocytopenia.[43]

Women with HELLP syndrome may present with hypertension, tachycardia, tachypnea, and right upper quadrant tenderness.[44] Proteinuria is present in over 85% of women and hypertension in 80%.[44] Hepatomegaly can sometimes occur, while jaundice is evident in five percent of women.[45] Fifty-five to 67% of women present with nondependent edema, which can be periorbital or in the upper or lower extremities.[45] Pulmonary findings may include crackles secondary to noncardiogenic pulmonary edema. HELLP syndrome is characterized by worsening of signs and symptoms during the night and recovery during the day.[46]

1.6 Prognosis of women with HELLP syndrome

Maternal mortality of women with HELLP syndrome ranges from one to three percent. A study by Ellison et al. showed the maternal mortality rate was 2.5 per 100 000 live births.[47] The perinatal mortality rate may be as high as 34% among babies born to women with HELLP syndrome.[48] These estimates are dependent on the access to and quality of healthcare and therefore may vary geographically.[46] The majority of women with HELLP syndrome will stabilize within 24 to 48 hours post-delivery, with a more prolonged postpartum recovery time in women with very severe disease.[44]

In future pregnancies, women are at increased risk of pre-eclampsia or pregnancy-induced hypertension as well as preterm delivery, fetal growth restriction, and placental abruption.[49]

There is an estimated recurrence rate for HELLP syndrome of between 2 and 27% for subsequent pregnancies.[22]

Women who develop HELLP syndrome during pregnancy are at increased risk of developing hypertension and cardiovascular disease in later life.[49]

1.7 Criteria for diagnosis of HELLP syndrome

There are two major classification systems in the diagnosis of HELLP syndrome based on the three key diagnostic features of the syndrome (Table 1.1). These include the Mississippi-Triple Class System and the Tennessee Classification System (Table 1.2).[4]
The intravascular haemolysis is microangiopathic in nature and typically diagnosed by the presence of schistocytes or fragments on a peripheral blood smear following a decrease in haemoglobin without blood loss.[4] An increased serum bilirubin (≥ 1.2 mg/dl); an increased unconjugated bilirubin level; or low serum haptoglobin levels of < 0.10 mg/dl may also be used to diagnose the presence of haemolysis.[4] The elevated lactate dehydrogenase (LDH) levels are usually as a result of ruptured red cells together with liver ischaemia and the elevated LDH level > 600 U/L indicates the severity of haemolysis.[4,39,50]

In the Mississippi-Triple Class System, the maternal platelet count as a primary, indicator of the severity of the disease.[38] Class 1 indicates the most severe disease with a platelet count of less than 50 $x10^9$/L. Class 1 and Class 2 require an LDH > 600 U/L and AST >70 U/L, while Class 3 requires LDH > 600 U/L and AST ≥ 70 U/L in addition to the specific platelet count.[38]

Table 1.1 Criteria for the diagnosis of HELLP syndrome.[51]

Haemolysis
Abnormal peripheral blood smear (burr cell, schistocytes, echinocytes, triangular cells).
Increase bilirubin level > 1.2mg/dl.
Low serum haptoglobin level.
A significant drop in haemoglobin levels unrelated to blood loss.
Elevated liver enzymes
Elevated aspartate transaminase > 70U/L.
Elevated alanine transaminase >70U/L.
Increased lactate dehydrogenase > 600U/L.
Low platelet count (<150 x 10^3 /mm^3)

The Tennessee classification system, created by Sibai, classified women into true/complete HELLP syndrome compared with partial/incomplete HELLP syndrome.[4] The diagnosis of complete HELLP syndrome requires all three major features to be present.[4] Whereas, incomplete HELLP syndrome may consist of only one or two elements (H or EL or LP).[4] A percentage of published reports may include women who had no evidence of haemolysis.[4] These women are then referred to as having as ELLP syndrome (elevated liver enzymes and low platelets).[46]

Table 1.2 Classification of HELLP syndrome.[39]

Mississippi classification	**Tennessee classification**
Class 1 **Platelet count <50 x 10^9/L** **AST or ALT > 70 IU/L** **LDH > 600 IU/L**	True or complete Platelet count< 100 x 10^9/L AST>70 IU/L LDH>600 IU/L
Class 2 **Platelet count = 50-100 x 10^9/L** **AST or ALT > 70 IU/L** **LDH > 600 IU/L**	Partial or incomplete (Severe pre-eclampsia with any one of the following: ELLP, HEL, EL, LP) *
Class 3 **Platelet = 100-150 x 10^9/L** **AST or ALT > 70 IU/L** **LDH > 600 IU/L**	

* ELLP-Absent of haemolysis, EL-elevated liver function, LP-low platelets.

Diagnosis post-delivery is still possible as laboratory abnormalities often take a short period to return to normal. There is often a transient worsening in the condition within the first 2448 hours after delivery.[52] However, there should be an improvement in platelet count and a downward trend in LDH and liver transaminases by the fourth day postpartum.[52]

1.8 Differential diagnosis of HELLP syndrome

The HELLP syndrome can often be confused with other causes of microangiopathic anaemia including disseminated intravascular coagulopathy, acute fatty liver (AFL), haemolytic-uraemic syndrome, and thrombotic thrombocytopenic purpura (TTP). Some of differential diagnosis of HELLP syndrome is shown in (Table 1.3).[53]

Acute fatty liver of pregnancy and HELLP syndrome share several clinical features and can occur concurrently. This makes them difficult to distinguish clinically.[53] An increased prothrombin time and activated partial thromboplastin time together with hypoglycaemia and raised serum creatinine concentrations are more common with AFLP. Although liver biopsy is the gold standard for diagnosing AFLP, it is not a common practice as the performance of this procedure may increase the incidence of bleeding at the biopsy site depending on the severity of coagulopathy and thrombocytopaenia.[53]

Thrombotic thrombocytopenic purpura (TTP) and haemolytic uraemic syndrome (HUS) are also differential diagnosis of HELLP syndrome. Thrombocytopenia, microangiopathic haemolytic anaemia, and renal failure are seen in both TTP-HUS as well as HELLP syndrome.[10] Also, high LDH concentration levels >2000 IU/L suggests that TTP or HUS is a more likely diagnosis than HELLP syndrome.[54]

Table1.3 1 Differential diagnosis of the HELLP syndrome.[53]

1. Diseases related to pregnancy Benign thrombocytopenia of pregnancy
   Acute fatty liver of pregnancy (AFLP)

2. Infectious and inflammatory diseases not specifically related to pregnancy: Virus hepatitis
   Cholangitis
   Cholecystitis
   Upper urinary tract infection
   Gastritis
   Gastric ulcer
   Acute pancreatitis

3. Thrombocytopaenia
   Immunologic thrombocytopenia (ITP)
   Folate deficiency
   Systemic lupus erythematosus (SLE)
   Antiphospholipid syndrome (APS)

4. Rare diseases that may mimic HELLP syndrome
   Thrombotic thrombocytopenic purpura (TTP)
   Haemolytic uremic syndrome (HUS)

1.9 Human immunodeficiency virus and HELLP syndrome

The overall HIV prevalence is 29.7% amongst women who present for antenatal clinic staterun facilities in South Africa.[55]

The association between HIV and hypertensive diseases in pregnancy has been thought to both increase or decrease the risk.[56] The immunosuppressive effects of HIV may reduce the hyper-inflammation associated with pre-eclampsia.[57] In contrast, an increased risk for preeclampsia may arise from chronic arterial dysfunction with endothelial damage, which has been previously associated with HIV.[57]
Recent systematic reviews and meta-analysis show no significant association between HIV positivity and hypertensive disorders in pregnancy.[58]

The HIV infection and pre-eclampsia are accompanied by endothelial dysfunction and inflammation.[59] The HIV-1 envelope proteins augment endothelial damage.[60] Previous reports demonstrate a reduction in the pro-angiogenic factors in HIV-uninfected pregnancies, therefore influencing placentation and vascularization.[61] Govender et al. compared the placental expression of VEGFR-1 (Flt-1) and sFlt-1 in HIV positive and HIV negative pre-eclamptic and normotensive pregnant Black African women.[62] They found elevated Flt-1 and sFlt-1 levels in placentae of pre-eclamptic women but no difference in the Flt-1 and sFlt-1 immuno-expression between HIV negative and positive pregnancies.[62]

1.10 Management

Definitive management of HELLP syndrome depends on the gestational age and the condition of the women.[63] If the women are unstable, with severe thrombocytopenia, renal or liver dysfunction, or if the gestational age is more than 34 weeks or less than 24 weeks, then immediate delivery is preferable.[63]

For women between 27and 34 weeks, delivery within 48 hours of evaluating and stabilizing the maternal condition as well as administering corticosteroids treatment for fetal lung maturity, is advocated.[39] Delivery should be accomplished within 24 hours following the last dose of steroids.[39]

However, there is disagreement regarding the management of a group of women, where there are mild to moderate blood test abnormalities and a reassuring fetal condition, consideration has been given to the inevitable fetal lung immaturity prior 34 weeks.[39]There is literature to support prolonging pregnancy until 34 weeks of gestation or until the

development of maternal or fetal indications for delivery, however the controversy lies in balance the risk between maternal and perinatal morbidity and mortality.[39,48,64]

The use of corticosteroids in the management of HELLP syndrome remains controversial. In a prospective randomised controlled study by Magann et al. the effect of antepartum corticosteroids in preterm pregnancies with HELLP syndrome was evaluated.[65] The study included 25 women, 13 of which were controls.[65] The treatment group had a mean gestational age of 30.7 weeks.[65] In the treatment arm, women were given dexamethasone (10 mg) intravenously every 12 hours until delivery.[65] Women were delivered if there was any deterioration in maternal or fetal condition, gestational age of 34 weeks, or a platelet count of less than 50 x 10^3/ml.[65] The authors found that the women who received dexamethasone had significantly increased urinary output, platelet counts and reduced ALT and LDH levels over time in comparison to the untreated group.[65] They also had a longer interval from initiation to delivery than the control group (41 versus 15 hours).[65] The authors concluded that steroids treatment stabilised disease in HELLP syndrome, but that effect was temporary.[65]

In contrast, in a Cochrane review of randomised controlled trials comparing corticosteroid treatment with placebo, no treatment or other drug, showed there was no difference in the risk of maternal death, severe maternal morbidity or perinatal morbidity or mortality.[66] The only clear effect was improved platelet count.[66]

For women between 24 and 26 weeks gestation, expectant management is advised with the use of antihypertensive agents to control blood pressure provided there is no deterioration in the maternal or fetal condition.[39,64]

1.11 Complications of HELLP syndrome

1.11.1 Maternal complications

Disseminated intravascular coagulopathy

The HELLP syndrome may progress to disseminated intravascular coagulopathy in 8% of women.[67] Disseminated intravascular coagulopathy is most often related to abruptio placentae and associated with thrombocytopenia, increased prothrombin time, increased international normalized ratio (INR), increased fibrin degradation products and low serum fibrinogen concentration.[40]

Placental abruption

According to Rakshit et al., placental abruption occurs in 36% of women with complete HELLP syndrome, and 12.5% of women with partial HELLP syndrome.[68] Abruptio placentae should be suspected in cases of vaginal bleeding, abdominal pain, and nonreassuring fetal status. Abruptio placentae associated with the HELLP syndrome increases the risk of DIC substantially as well as the risk of pulmonary oedema, renal failure and the need for blood transfusion.[39,69,70]

Acute renal failure

In 2005 Eser et al. found an incidence of acute renal failure of 17.2% in 26 women with HELLP syndrome. In their study, two women had permanent renal injury, one of whom later underwent peritoneal dialysis.[71] The incidence of AKI can be as high as 36% in women with HELLP syndrome.[72] In women with onset of post-partum HELLP syndrome, the risk of renal failure and pulmonary oedema is significantly increased compared to those with an antenatal onset.[73]

Women with HELLP syndrome often progress to endovascular thrombosis, lumen occlusion and hypoperfusion with a reduction in glomerular filtration, resulting in acute renal failure in seven to 36%.[74,75] The majority of women with HELLP syndrome-related AKI progress to acute tubular necrosis, however, with adequate supportive care, they will have a near complete reversal of renal function.[76,77]

Pulmonary edema

Pulmonary edema is a life-threatening event that occurs in 10% of pregnant women.[69] It should be suspected when the woman complains of shortness of breath, chest pain, or difficulty breathing. Signs may include decreased oxygen saturation, tachypnea, and basal crackles on auscultation. The risk of developing pulmonary edema is more than doubled for women with class 1 HELLP syndrome compared with class 2 and 3.[78] Women with Class 1 HELLP syndrome are more likely to experience acute lung injury or acute respiratory distress syndrome (ARDS) and require continuous positive airway pressure or mechanical ventilation than women in Class 2 or 3.[78]

Liver haematoma

Hepatic haemorrhage and rupture occurs in an estimated 1% of women with class 1 or 2 HELLP syndrome.[79] A study by Barton reported 34 women having HELLP syndrome with a subcapsular haematoma in 38% women, 3% with hepatic infarction and hepatic rupture in up to 12%.[80] According to Wicke et al. at least one out of five women with liver rupture caused by HELLP syndrome had early subcapsular liver haematoma formation compatible with class 3 disease.[81]

Eclampsia

Martin et al. found the incidence of eclampsia significantly higher in nulliparous than in parous mothers (10.2% vs. 5.5%, p=0.012). However, associated major maternal morbidity occurred significantly more often in parous women (50% vs. 26%, p=0.043).[82]

Women with class 1 or 2 HELLP syndrome are 3.5 times more likely to have significant central nervous system morbidity compared with class 3 HELLP syndrome or non-HELLP severe pre-eclampsia.[38] This includes stroke, mental status changes or coma.[83,84] Visual complications including retinal detachment, haemorrhage, and cortical blindness are infrequent in proportion to disease severity (1.4% in class 1 and 2).[38] These are usually short-lived with full recovery within one to six months, except when cerebral haemorrhage or stroke is the cause.[38,85]

Caesarean section

A study by Martin et al. reported that caesarean delivery is performed more often for women with class 1 HELLP syndrome (61%) than class 2 (57%), class 3 (53%), or non-HELLP severe pre-eclampsia (48%).[82] On the contrary, Matchaba et al. reported that the incidence of caesarean section does not increase with the severity of HELLP syndrome.[86] Caesarean section can cause severe maternal morbidity in women with HELLP syndrome.[87]

Puerperal sepsis

Women with HELLP syndrome are twice as likely to develop infectious morbidity than those with without HELLP syndrome severe pre-eclampsia.[88] This is might be due to emergency caesarean section intervention or wound haematoma.

Intensive care unit admission

HELLP syndrome is a common cause of intensive care unit admission among hypertensive women because it is a life-threatening and has a high maternal mortality rate. In an unpublished study by Bryant et al. eight women (11%) admitted to CHBAH for hypertensive diseases in pregnancy, found that more than half (62%) had been diagnosed with HELLP syndrome.[89] A study by Osmanagaoglu et al. in Turkey, found 30% of women with HELLP syndrome were admitted to ICU.[69]

1.11.2 Fetal complications

Perinatal morbidity and mortality are dependent on prematurity or nature of the disease. Several studies have shown that perinatal morbidity is higher in women with HELLP syndrome than in those with hypertension only.[90] However, there are also studies showing that gestational age was more important than the maternal disease for perinatal outcomes.[91]

Fetal Growth Restriction and oligohydramnios

However, imbalance in angiogenic regulators leading to placental bed hypoxia and a subsequent endothelial dysfunction may have ultimately resulted in IUGR. A retrospective study was published in 2003 by Roelofsen et al. on the outcome of infants born after pregnancies complicated by HELLP or ELLP syndrome. The gestational age was 29.9 weeks in the HELLP group and 30.3 weeks in the ELLP group. Sixty-four percent were born before 32 weeks of gestation.[92] In 2011, a retrospective study by Yucesoy et al. concluded that, among 44 women with HELLP syndrome, there were (20.5%) cases with oligohydramnios.[93]

Preterm delivery

In 2001, Murray et al. published the outcomes of 20 women with HELLP syndrome over a 5year period. Eighty-five percent were delivered by caesarean section within 24 hours of diagnosis.[94] Of these, 65% were preterm pregnancies with the mean gestation at delivery of 33.5 weeks and the mean birth weight of 1923 grams.[94] Forty percent of the neonates developed respiratory distress syndrome.[94]

In 2018, a study conducted by Kongwattanakul et al. investigated the perinatal outcomes between non-severe pre-eclampsia versus pre-eclampsia with HELLP syndrome.[95] Neonatal complications were significantly higher in the pre-eclampsia with HELLP syndrome group low birth weight (35.1% versus 74.3%, p=0.001), birth asphyxia (4.4% versus 18.2%,

p=0.001), neonatal intensive care unit admission (7.0% versus 30.9%, p=0.001). However, stillbirths only occurred in cases of pre-eclampsia with HELLP syndrome (1.4%).[95]

1.12 Prevention of HELLP syndrome

No studies have been done specifically on the prevention of HELLP syndrome. Several studies have demonstrated a prevention of pre-eclampsia which in turn would presumably reduce the incidence of HELLP syndrome.[96] A meta-analysis of by Bujold et al. reported that low-dose aspirin started at or before 16 weeks of pregnancy was associated with a 50% reduction in the overall risk for pre-eclampsia and an 80% reduction in preterm preeclampsia.[96] The results of a recent randomised controlled trial by Duley et al. including more than 30 000 women, showed a 17% reduction in the risk of pre-eclampsia associated 7with the use of antiplatelet agents.[97] Low-dose aspirin should not be routinely prescribed for pre-eclampsia prevention, however, it should be considered in women with previous early pre-eclampsia at less than 34 weeks.[98] The ASPRE trial demonstrated that administration of 150 mg aspirin, compared with placebo, result in a 62% reduction in the incidence of preterm PE but had no significant effect on the incidence of term PE.[99] Randomised trials of magnesium, zinc, vitamin C, vitamin E, or fish oil supplementation have demonstrated no benefit.[100] Inherited thrombophilias have not been established as a cause of placentamediated pregnancy complications, including pre-eclampsia, and anticoagulation of women with an inherited thrombophilia to prevent pre-eclampsia is not recommended outside clinical trials.[101]

A Cochrane study by Hofmeyr et al. showed that high-dose calcium supplementation, of more than one gram per day, is associated with a significant reduction in the risk of preeclampsia, particularly in women with low calcium diets.[102] It also reduced the risk of preterm birth and maternal death or serious morbidity, but it was thought to increase the risk of HELLP syndrome.[102]

2 AIM OF THE STUDY

2.1 Problem statement

Maternal deaths secondary to complications of hypertensive disorders of pregnancy are a significant problem in South Africa. The 2014 to 2016 Saving Mothers report on maternal deaths in South Africa showed that hypertensive disease contributed to 14% of maternal deaths.[3] This equates to 661 maternal deaths due to eclampsia, severe hypertension, HELLP syndrome, and liver rupture. As a tertiary facility, there is a high incidence of hypertensive disorders in pregnancy managed in the maternity unit of Chris Hani Baragwanath Academic Hospital. Despite this, there is a paucity of literature regarding HELLP syndrome, its outcomes, and complications, in this and similar settings.

2.2 Objectives

2.2.1 To describe the following:

a) Demographic characteristics of women with HELLP syndrome.
b) Haematological and biochemical findings in women with HELLP syndrome.
c) The presence of risk factors in women with HELLP syndrome.

2.2.2 To describe the maternal complications and outcomes in women with HELLP syndrome.

2.2.3 To describe the perinatal outcomes in women with HELLP syndrome.

3 METHODS

3.1 Study design

This was a retrospective cross-sectional study of women with HELLP syndrome delivered at Chris Hani Baragwanath Academic Hospital between 01/05/2017 and 30/09/2017.

3.2 Study setting

The current study was conducted in the maternal unit at the CHBAH which the third largest hospital in the world. It was in the Soweto area of Johannesburg and is a central hospital that provides tertiary care. Chris Hani Baragwanath Hospital is an academic hospital affiliated with the University of the Witwatersrand, therefore, women presenting with HELLP syndrome are assessed and managed according to the University of the Witwatersrand Obstetrics protocol reflected in Figure 3.1 below.[103]

University of the Witwatersrand obstetric protocol for management of women admitted with HELLP syndrome

1. Arrange for transfer to a high care area.
2. Insert a urinary catheter and monitor urine output hourly.
3. Take blood for FBC, U&E, AST, and INR.
4. Assess gestational age and fetal weight by ultrasound, with umbilical artery Doppler studies at <32 weeks.
5. Do CTG if the fetus is viable (≥26 weeks).
6. Treat the high BP
7. In women <34 weeks, plan for delivery within 24-48 hours to allow betamethasone to take effect.
8. Deliver as soon as possible if <26 weeks or ≥34 weeks.
9. If platelet count is <50/mm^3 and caesarean section is planned, give platelet transfusion 1 megaunit at operation.
10. Arrange for delivery and notify paediatricians if the baby is expected to weigh <1500 g.

Figure 3.1 University of the Witwatersrand Obstetrics protocol.

In the year 2016, there were approximately 19 300 deliveries, with 7 718 caesarean sections. In the first ten months of 2016, there were 10 132 antenatal referrals from the surrounding clinics in addition to 31 001 antenatal follow-up visits. Whilst pre-eclampsia constituted eight to ten percent of women requiring antenatal care.

Women admitted from the antenatal clinic or obstetric admissions area are transferred to the maternity unit high care area or high care extension in the labour ward. Once HELLP syndrome is diagnosed, women are delivered in either the labour ward, high care area or theatre and are then transferred back to the high care area or high care extension in labour ward for an eight-hour observation period.

3.3 Study population

The study population included all women delivered at the CHBAH who were treated for HELLP syndrome.

3.3.1 Inclusion criteria

All pregnant women with HELLP syndrome regardless of age, maternal or pregnancy outcome admitted to the maternity unit high care area or high care area extension in CHBAH.

3.3.2 Exclusion Criteria

All pregnant women known with prior hepatic diseases, platelets disorders, or haemolytic anaemia were excluded. The medical records of all women in whom the medical records could not be located were also not included in the study.

3.4 Data collection

Data were collected from women files with the use of a data sheet (Appendix A). Cases were identified from the high care area, extended high care area and intensive care unit registers. The records of these women were then reviewed, and the relevant data captured.

For the present study, the following definitions were used.

Table 3.1 Definitions and parameters used hypertensive disorders of pregnancy

Variable	Definition
Hypertension	A systolic BP ≥140 mmHg or a diastolic BP ≥90 mmHg, on 2 occasions more than 4 hours apart, or a single BP ≥160/110 mmHg.
Chronic hypertension	Hypertension diagnosed before 20 weeks of pregnancy.
Chronic renal disease	Proteinuria or chronic renal disease diagnosed before 20 weeks of pregnancy
Gestational hypertension	Hypertension detected after 20 weeks without any features of pre-eclampsia
Pre-eclampsia	Hypertension detected after 20 weeks with the presence of 1 of the following: 1. Proteinuria. 2. End-organ dysfunction (abnormal renal, hepatic, haematological dysfunction ,pulmonary edema, or neurological involvement). 3.Intrauterine growth restriction (confirmed on ultrasound).
Severe Preeclampsia	Pre-eclampsia one of the following: 1. Systolic BP ≥160 mmHg or a diastolic BP ≥110 mmHg measured on 2 occasions more than 4 hours apart or 2. Diastolic BP ≥120 mmHg 3. Organ dysfunction irrespective of the level of BP, e.g. renal dysfunction, raised liver enzymes or thrombocytopenia.
Eclampsia	Generalized tonic-clonic seizures after 20 weeks of pregnancy and within 7 days after delivery, associated with hypertension and proteinuria, in the absence of other causes of convulsions.
Imminent eclampsia	Symptoms and signs that develop in a pre-eclamptic woman: a severe headache, visual disturbances, epigastric pain hyperreflexia, dizziness, and fainting, vomiting.

HELLP syndrome	**Haemolysis** Abnormal peripheral blood smear (burr cell, schistocytes) Elevated bilirubin >1.2mg/dl Low serum haptoglobin A significant drop in haemoglobin levels unrelated to blood loss. **Elevated liver enzymes** Elevated aspartate transaminase or alanine transaminase >2 x the upper limit of normal Increased lactate dehydrogenase >2 x the upper limit of normal. **Low platelet count (<150000/mm^3).**
Proteinuria	Presence of ≥1+ protein on reagent strip (dipstick) testing on 2 clean catch urine specimens taken ≥4 hours apart, or protein excretion >300 mg in a 24-hour specimen of urine or >0.03g/dL on a spot protein sample of urine
Low Apgar score	Apgar less than 7 at 1 minute and /or 5 minutes
Intrauterine growth restriction	A sonographic estimated fetal weight that measures less than 5th percentile on for gestational age with an umbilical artery Doppler more than the 95th percentile for gestation or a decline or plateau in fetal growth.
Birth asphyxia	A temporary interruption of oxygen availability that implies a risky metabolic challenge, even when the insult does not lead to a fatal outcome
Haemoglobin (Hb) levels	Normal Hb >10g/dL; Anaemia Hb <10g/Dl
Platelet count	Normal if > 150 x10^9 platelets/L, thrombocytopenia if <150 x10^{9}platelets/L, Class1 thrombocytopenia < 50 x10^{9}platelets/L, Class 2 thrombocytopenia 50- 100 x10^{9}platelets/L, Class 3 100- 150 x10^{9}platelets/L
Urea	Raised if > 4.5μmol/L
Creatinine	Raised > 90 μmol/L
LDH	Normal < 600 U/L, Raised >600U/L
INR	Raised >1
Raised AST/ALT	>40IU
Haptoglobin	Haemolysis present if< 0.01mg/dl

3.5 Data Analysis

Data was captured using a data capture sheet (Appendix A) and transferred into a Microsoft Excel spreadsheet. The data were then analyzed by a statistician with the aid of the

STATISTICA® program. Frequencies were expressed as percentages with 95% confidence intervals, means expressed with standard deviations and medians with ranges. Comparisons of frequencies were done using the Chi–squared and Fisher's exact tests. Frequency distributions were compared using the Student's t-test for parametric data and the MannWhitney test for non-parametric data. A p-value of <0.05 was used to determine statistical significance.

3.6 Ethics

The research protocol was submitted and approved by the University of Witwatersrand's Human Research Ethics Committee (M170978) (Appendix B) and institutional approval was obtained from the CEO of CHBAH. This study was registered with the National Research Database.

3.7 Funding

Costs of the study were minimal as it was a retrospective study. The costs included stationery and printing which were covered by the principal investigator.

4 RESULTS

There were 9095 deliveries during the study period, 61 (0.67%) of whom were treated for HELLP syndrome. The records of three women could not be obtained and these were excluded from the analysis.

4.1 Demographic and antenatal characteristics

Table 4.1 describes the demographic details of women who had HELLP syndrome. The median age was 29 years ranging from 16 to 44 years, 9 (15.5%) women were > 35 years of age and most women were more than 25 years of age (69%). The weight was recorded in 39 women. The median weight was 64 kilograms, ranging between 46 and 126 kilograms. The heights were recorded for 30 women. The median BMI was found to be 26.7 kg/m^2 with a range of 19.8 kg/m^2 to 46.4 kg/m^2. Eight women (26.7%) had a BMI of more than 30kg/m^2. There were no women with cardiac disease and there was one woman with diabetes.

Table 4.1 Demographics and antenatal characteristics

Variable		**Median (range) Number (%) n= 58**
Age (years)		29 (16-44)
Black race		57 (98.3)
Parity		1 (0-4)
Gravity		2 (1-5)
Primigravida		17 (29.3)
Multiparity		41 (70.7)
Gestational age at diagnosis		31 (21-41)
	< 28 weeks	18 (31)
	29- 32 weeks	14 (24.2)
	33- 36 weeks	18 (31)
	>37 weeks	8 (13.8)
New partner n=36		12 (33.3)
Family history of hypertension n=52		11 (21.2)
Smoker n=55		8 (14.5)
Alcohol consumption n=55		1 (1.8)
Calcium supplementation		14 (24.1)
Co-morbidity n=47	Chronic hypertension	13 (27.7)
	Diabetic	1 (2.1)
	None	33 (70.2)
Weight (kg) n=39		64 (46-126)
Body mass index (kg/m^2) n=30		26.7 (19.8-46.4)
Gestational age in weeks at booking		22 (9-33)
Ultrasound <24 weeks (1^{st} ultrasound)		15 (25.8)

Ultrasound >24 weeks (1st ultrasound)		49 (84.4)
Booking haemoglobin (g/dL)		12.4 (8-15)
HIV seropositive		12 (20.6)
Multiple pregnancies		2 (3.4)
Doppler at diagnosis n=55	IUGR	26 (47.2)
	Umbilical artery Doppler (RI)	0.89 (0.7-0.9)

IUGR= Intrauterine Growth Restriction, RI= resistance index, HIV= Human immunodeficiency virus.

4.2 Diagnosis at admission

Fifty-five (94.8%) women were diagnosed with pre-eclampsia of which 22 (37.9%) were diagnosed with imminent eclampsia developed HELLP syndrome. Twenty-seven (46.5%) were diagnosed with HELLP syndrome. The diagnosis at admission is shown in Table 4.2 below.

Table 4.2 Admission diagnosis

Variable	**Median (range) Number (%) n=58**
Pre-eclampsia	55 (94.8)
Gestational hypertension	3 (5.1)
Eclampsia	4 (6.8)
Chronic hypertension	13 (22.4)
HELLP syndrome	27 (46.5)
Imminent eclampsia	22 (37.9)

HELLP= Haemolysis, Elevated liver enzymes, Low platelet.

4.3 Results of investigation at admission

On admission, the blood pressures were recorded using automated machines. The median systolic blood pressure (SBP) was 181 mmHg while the median diastolic blood pressure was 112 mmHg and the median mean arterial pressure (MAP) was 121 mmHg. The median estimated fetal weight at admission on ultrasound was 1510 g and ranged from 343 g to 3593g. Eighteen (31%) had umbilical artery Dopplers > 95th percentile for gestation. The admission procedures are described in Table 4.3 below. **Table 4.3 Results of investigations at admission**

Variable		**Median (range) Number (%) n=58**
Blood pressure	SBP	181 (142-228)
	DBP	112 (98-158)
	MAP	121 (82-128)
NST	Normal	11 (18.9)

	Suspicious		16 (27.5)
	Pathological		8 (13.7)
	Not done/ unavailable		23 (39.6)
Ultrasound finding	EFW in grams		1510 (343-3593)
	Doppler studies	Not done	28 (48.3)
		Normal	12 (20.6)
		UA>95th percentile	18 (31)

NST = Non-stress test, EFW= Estimated fetal weight, UA=Umbilical artery Doppler

4.4 Antihypertensive treatments and MgSO4 used in women with HELLP syndrome

Fifty-five women received a loading dose of $MgSO_4$ which contained 4 grams of $MgSO_4$ intravenously. Fifty-one women received a maintenance dose of $MgSO_4$ of 1gram per hour intravenously for 24 hours. The median of magnesium sulphate maintenance was 24 hours with a range of (10-24) hours and it was stopped in 8 women because they developed oliguria. Antihypertensive therapies are reflected in Table 4.4 below.

Table 4.4 Antihypertensive treatments and $MgSO_4$ used in women with HELLP syndrome

Variable		**Median (range) Number (%) n=58**
Antihypertensive agents	Amlodipine	58 (100)
	Methyldopa	58 (100)
	Labetalol	7 (12)
$MgSO_4$	$MgSO_4$ loading dose	55 (94.8)
	$MgSO_4$ maintenance dose	51 (87.9)

MgSO4 = Magnesium sulphate.

4.5 Results of blood tests at admission and at diagnosis

There was a statistically significant decrease in haemoglobin and platelet levels. Twentyfour-hour urine collection for proteinuria quantification was performed in two women. The comparison between results of tests at admission and diagnosis is reflected in Table 4.5 below.

Table 4.5 Comparison between results of tests at admission and at diagnosis

Variable		Admission Median (range) Number (%) n=58	Diagnosis Median (range) Number (%) n=58	P- value
WCC x 10^9/L		11.64 (4.4-23.7)	11.95 (4.7-29)	0.090
Hb in g/dl		13.1 (8.2-15.5)	12.2 (6.9-15.5)	<0.001
Platelet count x 10^9/L		114 (45-298)	93 (36-147)	<0.001
Urea in mmol/L		3.8 (1.8-9.6)	4.4 (1.9-23)	0.004
Creatinine in µmol/L		69 (43-210)	70 (35-683)	0.090
ALT in U/L		69 (7-646)	86 (17-646)	0.002
AST in U/L		94 (14-1036)	120 (42-1036)	0.012
LDH in U/L		788 (378-1790)	669.5 (324-1896)	0.314
INR		1.095 (0.93-1.77)	1.03 (0.85-2.64)	0.364
PTT in sec		31 (22.2-52.2)	30.25 (22-112.6)	0.158
Smear Red cell Fragmentation	Mild	10 (55.5)	13 (56.6)	0.376
	Moderate	2 (11.1)	5 (21.7)	0.218
	Marked	6 (33.3)	5 (21.7)	0.7729
Proteinuria*	1	17 (29.3)	17 (29.3)	1.00
	2	28 (48.3)	29 (50)	0.853
	3	13 (22.4)	12 (20.7)	0.821

WCC= white cell count; Hb= haemoglobin; ALT= alanine transaminase; AST= aspartate transaminase; LDH=lactate dehydrogenase; INR= international normalized ratio; PTT= partial thromboplastin time; PCR= protein creatinine ratio; * Proteinuria documented from dipstick as 1+ (0.3 g/l), 2+ (1 g/l) or 3+ (3 g/l).

4.6 Comparison between blood results at diagnosis and worst blood result after diagnosis

Table 4.6 describes the percentage deterioration between results obtained at diagnosis of HELLP syndrome and the worst documented results after diagnosis. Seventeen women, after diagnosis of HELLP syndrome, had no further deterioration in their platelet count.

Table 4.6 Comparison between results at diagnosis and worst result after diagnosis

Variable	Diagnosis Median (range) Number (%) n=58	Worst Result Median (range) Number (%) n=58	Percentage Difference*	P-value	Time from diagnosis to worst results in hours
Platelet count x 10^9/L	93 (36-147)	73.5 (19-146)	20.9	<0.05	46 (16-74)
Urea (mmol/L)	4.4 (1.9-23)	5.45 (2.1-36.3)	23.8	<0.05	33 (18-65)
Creatinine (µmol/L)	70 (35-683)	81 (48-695)	14.2	<0.05	33 (18-65)
ALT (U/L)	86 (17-646)	96 (17-646)	11.6	<0.05	40 (18-71)
AST (U/L)	120 (42-1036)	139 (621269)	15.8	<0.05	40 (18-71)

ALT= alanine transaminase, AST= aspartate transaminase. * Percentage difference between the variable at diagnosis and worst value after diagnosis.

4.7 Delivery characteristics

Eleven women (18.9%) had normal vaginal deliveries. Two (18.2%) babies born via vaginal delivery were live neonates and nine (81.8%) had demised, two were fresh stillbirth (FSB) and seven were macerated stillbirth (MSB). The caesarean section rate for all women admitted to CHBAH during the study period was 42.6%. Forty-seven women (81%) had caesarean section deliveries with 33 (56.9%) live neonates and 14 (24.1%) demised fetuses (four FSB, six MSB) early neonatal death 4(8.5%). The delivery characteristics are shown in Table 4.7 below.

Table 4.7 Delivery characteristics of women diagnosed with HELLP syndrome

Variable		Median (range) Number (%) n=58
Induction of labour (n=14)	Oral misoprostol Number of doses	2 (3.4) 6.5 (4-9)
	Vaginal misoprostol Doses	10 (17.2) 3 (1-4)
	Catheter bulb Duration in hours	2 (3.4) 19 (15-23)
NVD n=11	Live infant	2 (18.2)
	Stillbirths	9 (81.8)
Caesarean section n=47	Live infant	33 (70.2)
	Stillbirths	10 (21.1)
	Early neonatal death	4 (8.5)
	Pfannenstiel incision	37 (78.7)

	Midline incision	10 (21.3)
	Lower uterine segment incision	41 (87.2)
	Classical incision	6 (12.8)

4.8 Maternal complications

Table 4.8 below, reflects the antenatal and postnatal maternal complications in women with HELLP syndrome. The platelet count obtained at diagnosis of HELLP syndrome was used to classify the severity of thrombocytopenia. Four (6.8%) women had Class 1 thrombocytopenia at diagnosis. One of these women died after having a caesarean section from developing puerperal sepsis, DIC, pulmonary oedema, multiorgan dysfunction, and Posterior reversible encephalopathy syndrome (PRES). She was HIV seropositive, had a relook laparotomy for sepsis and was admitted to ICU for ventilatory and inotrope support. Three (5.1%) women were admitted to the ICU, 1 for continuous veno-venous haemodialysis (CVVHD) and two for ventilatory support as they had developed metabolic acidosis postcaesarean section. One woman had a caesarean section for abruptio placenta and required ventilatory and inotrope support during blood transfusion and correction of metabolic acidosis. She was ventilated in the maternity high care area and had intermittent dialysis as there were no ICU beds available during her admission. The third woman requiring inotrope support developed a postpartum haemorrhage at caesarean section, had a subtotal hysterectomy and was one of the women admitted to ICU for ventilatory support. Three women required blood transfusions of more than four units of packed cells.

Table 4.8 Maternal complications stratified by platelet count

Variable	**Total Number (%) n=58**	**Platelet count**		**P value***
		< 100 x 10^9/L Number (%) n=30	**≥ 100 x 10^9/L Number (%) n=28**	
Eclampsia	7 (12)	5	2	0.24
Abruptio placenta	9 (15.5)	3	6	0.03
AKI	21 (36.2)	10	11	0.42
Dialysis	3 (5.1)	2	1	0.52
Caesarean section	47 (81)	26	21	0.21
Relook laparotomy	2 (3.4)	1	1	0.73
Blood transfusion	13 (22.4)	7	6	0.55
DIC	4 (6.8)	3	1	0.61
ICU admission	3 (5.1)	2	1	0.52
Ventilatory support	3 (5.1)	2	1	0.52
Inotrope use	3 (5.1)	1	2	0.47

*Fischer exact test, AKI=acute kidney injury, DIC= disseminated intravascular coagulopathy, ICU= intensive care unit.

4.9 Fetal and neonatal complications

There were 13 (22.4%) MSBs, 6 (10.3%) FSBs. Four (6.9%) resulted in early neonatal deaths. There were 35 (60.3%) neonates with intrauterine growth restriction, and 10 (17.2%) were born with low Apgar scores. Nineteen (32.7%) babies were admitted to the neonatal intensive care unit, most of them due to extremely low birth weight or respiratory distress syndrome. The fetal and neonatal complications are shown in table 4.9 below.

Table 4.9 Fetal and neonatal complications

Variable		**Median (range) Number (%) n=58**
IUGR		35 (60.3)
Oligohydramnios		42 (72.4)
Preterm delivery	< 28 weeks gestation	18 (31)
	29-32 weeks gestation	14(24)
	33-36 weeks gestation	18(31)
LBW		20 (34.5)
VLBW		13 (22.4)
ELBW		14 (24.1)
APGAR score <7 at 1 minute		10 (17.2)
NICU admission		19 (32.7)
Demised fetuses n= 23	MSB	13 (22.4)
	FSB	6 (10.3)
	ENND	4 (6.9)

IUGR= Intrauterine growth restriction, NICU= Neonatal intensive care unit, LBW=Low birth weight,VLBW= very low birth weight, ELBW= extremely low birth weight, MSB =macerated still birth, FSB = fresh stillbirth, ENND = early neonatal death

4.10 Post-delivery organ system involvement

The woman who demised had PRESS and pulmonary oedema after massive blood transfusion and developed puerperal sepsis. Two (3.4%) women had persistently elevated liver enzymes and there were no cases of subcapsular liver haematoma or liver rupture, 6 (10.3%) women had anaemia and needed blood transfusions. Post-delivery organ system involvement is shown in table 4.10 below.

Table 4.10 Post-delivery organ systems involvement

Variable	**Median (range) Number (%) n=58**
Central nervous system	1 (1.7)
Respiratory	1 (1.7)
Cardiovascular system	4 (6.8)

Liver	2 (3.4)
Renal	5 (8.6)
Haematological	6 (10.3)

5 DISCUSSION

The incidence of HELLP syndrome ranges from 0.5 to 0.9% of all pregnancies and complicates 10 to 20% of pregnancies in women with severe pre-eclampsia or eclampsia.[5,6] The incidence of HELLP syndrome in the present study was 0.67% of the women delivered at CHBAH. Bearing in mind that this is a predominantly high-risk population, this may or may not be reflective of a high incidence of HELLP syndrome in either a Sowetan or predominantly black population. In 1999, a study by Buga et al. found an incidence of 1.2% in women in the Eastern Cape.[7] These figures are well within the estimated incidence, however, the incidence in the present study and Eastern Cape are comparatively higher than the incidence in high-income countries.[7] For example, in 2001 Hagen et al. in Germany, reported that HELLP syndrome occurred in roughly 1 in 310 births or 0.32%.[5] The incidence also appears to be higher in African countries. In 2014, Adu Bonsaffoh et al. in Ghana, found an incidence of 0.8% for HELLP syndrome.[6] The incidence of HELLP syndrome has decreased over the last two decades.

5.1 Demographic characteristics

Most women were older than 25 years old (69%) which is in keeping with the findings described by Sibai et al.[18] A study by Williams et al. found that multiparous women were more likely to be diagnosed with HELLP syndrome.[19] This is similar to the findings of the current study were multiparous women had double the risk of HELLP syndrome compared to nulliparous women.

The HIV prevalence in this study was 20.6%, which is lower than the background incidence of 30.8% of HIV in women attending antenatal care nationally.[55] This may be due to the immunosuppressive effects of HIV preventing the development of hyper-inflammation associated with pre-eclampsia or our study had a relatively small sample size to draw any conclusions from.

The percentage of women with obesity in the present study was 26.7%, which is almost five times higher than the percentage of obese women (5.6%) in a study done by Leeners et al.[31] This is probably because of the high prevalence of obesity among South African women. In

South Africa 1 in 5 women has a BMI of more than 35, 68% of South African women are overweight or obese.[30] Obesity is a risk factor for chronic hypertension which may result in hypertension and pre-eclampsia and may hence contribute to increasing the incidence of HELLP syndrome. However, the number of women in our study is small compared to the study by Leeners et al. (58 women versus 323 women). Only 5.1% of women in the present study was diagnosed with gestational hypertension prior to complicating with HELLP syndrome. This is a much lower percentage than 27% found by Williams et al.[19] In addition, 6.8% of women who developed HELLP syndrome were diagnosed with eclampsia on admission. This is incidence is higher than that of the study done by Onuh et al. (3.9%) in Nigeria.[35] This may reflect late presentation or may also be indicative of a greater number of Sowetan women with co-existing eclampsia and HELLP syndrome.

In 2014, a Cochrane review of calcium supplementation as a method of preventing preeclampsia, showed a paradoxical increase in the risk of developing HELLP syndrome as a result of calcium supplementation (RR 2.67, 95% CI 1.05 - 6.82).[102] Women in Soweto are routinely given calcium as a supplement during the antenatal period at a dose of 1 g/day. However, in this study, only 24.1% of women were documented to have received calcium supplements. This may be due to a discrepancy in the documentation of supplement prescription antenatally or un-booked women.

Thirty-three percent of women did not receive antenatal care, while 67% of women were booked for antenatal care. Despite early booking and antenatal care, 25.8% of booked cases also developed HELLP syndrome. Thirty-three were un-booked women. This may be reflective of the lack of transport amongst various other factors and represented a population of women who would have benefited from early diagnosis and treatment.

5.2 Haematological and biochemical findings in women with HELLP syndrome

In the present study, there was a statistically significant decrease in the haemoglobin concentrations, platelet count, and elevation of liver transaminases. This is expected, as they are criteria for diagnosis.[51] A high serum level of LDH was shown to have a high predictive value for significant maternal morbidity in various studies analyzed by Martin et al.[45] However, there were no statistically significant differences between LDH levels at admission and at diagnosis in this study. Markedly raised LDH > 2000 IU/L suggests that TTP or HUS which was not found in any woman in our study.[54] Despite hepatic dysfunction, most of these women did not develop any abnormalities in their international normalized ratio (INR).

Fragmentation noted on smear was an important criterion when considering a differential diagnosis of HUS and TTP, where fragmentation is marked in the latter two conditions. There was no significant difference in fragmentation in the present study, however, six women had marked fragmentation in their blood smear which resolved upon treatment of HELLP syndrome.

Although urinary protein determination was by the dipstick method, it is not surprising that all women with HELLP syndrome registered 1+ or more proteinuria, which contributes to the diagnosis of pre-eclampsia.

There is no literature exploring the percentage difference between the variables at diagnosis and worst values after diagnosis. The present study analysed the percentage difference in the median platelet count between the diagnosis and worst results was 20.8%, whereas; the percentage difference in urea was 23.3%; creatinine: 14.2%; ALT: 11.6% and AST: 15.8%.

In our study, there were significant maternal and perinatal complications in women who had a platelet count less than 50 x 10^9/L. This is in keeping with Martin et al. in Mississippi, who found approximately half of the number of pregnancies complicated by class 1 HELLP syndrome, exhibited significant maternal morbidity, specifically with hepatic and renal morbidity, caesarean section incidence of 61% and high perinatal mortality rate of 119 per 1000 births.[38] In the present study 53% of women with class 1 HELLP syndrome had AKI, 53% had blood transfusions and 92% had delivery by caesarean section.

5.3 Maternal complications and outcomes in women with HELLP syndrome

5.3.1 Maternal mortality

The global maternal mortality ratio is 216 per 100 000.[104] Ellison et al. found the maternal mortality was 2.5 per 100 000 live birth which is similar with our study of 2.86 per 100 000 live births.[47] One woman died after having a caesarean section and developing puerperal sepsis, DIC, pulmonary oedema, multiorgan dysfunction, and PRESS. She was HIV seropositive, was admitted to ICU.

5.3.2 Delivery characteristics

In the index study, most women (57%) who underwent induction of labour with either oral misoprostol, vaginal misoprostol or catheter bulb was successful. The rest of the women had caesarean delivery for worsening platelet levels or failed induction of labour.

Caesarean delivery was performed in 81.1% of women in this study which was similar with the findings of Murray et al. In Ireland, where 85% of women with HELLP syndrome were delivered by caesarean section.[93]An explanation for the high caesarean section rate is that most women presented with HELLP syndrome at 36 weeks gestation with unfavorable cervical conditions. It has been reported by Matchaba et al. that the incidence of caesarean section did not increase with the severity of HELLP syndrome.[86] In 2014 a prospective study by Amorim, et al. viewed maternal outcomes according to mode of delivery in women with severe pre-eclampsia and found that the risk of severe maternal morbidity was significantly greater in women submitted to caesarean section (54% versus 32.7%).[87] Factors that continued to be associated with severe maternal morbidity were a diagnosis of HELLP syndrome after delivery (OR = 3.73; 95% CI: 1.55–9.88) and having a caesarean section (OR = 1.91; 95% CI: 1.52–4.57).[87] In our study, immediate delivery by the caesarean route did not prevent death for one woman who had a primary postpartum haemorrhage and developed DIC, had a massive blood transfusion as a result of blood loss and subsequently developed sepsis. Two (3.4%) women underwent abdominal hysterectomy, which is comparatively lower than in the study of Eser et al. (8.6%).[71]

Haddad et al. described DIC in 8% of women with HELLP syndrome.[67] This finding is similar to the present study, where 6.8% of women with HELLP syndrome had an increased INR. However, the leading cause of an increased INR in three women was due to HELLP syndrome, and in one additional woman, an increased INR was due to a placental abruption.
5.3.3 Eclampsia, placental abruption and acute kidney injury

In the index study, seven (12%) women with HELLP syndrome complicated with eclampsia, which is considerably lower than the 52.9% in the study conducted by Martin et al.[64] However, this discrepancy may be due to the relatively small sample size. Socolov et al. found that placental abruption occurs in 16% of women with HELLP syndrome, comparable to our study where they constituted 15.5%.[72] The incidence of acute kidney failure was 36.2% and found to be similar to the finding by Socolov D, et al. where the incidence was 36% which in the index study was independent of abruptio placentae.[72] The risk of requiring dialysis was highest among women with worsening creatinine level or oligouria.[72] The increased incidence of eclampsia may be explained by the discontinuation or no use of magnesium sulphate maintenance therapy in women who were anuric or those who had oligouria.

5.3.4 Intensive care unit admission findings

In an unpublished retrospective study by Bryant et al. women admitted to CHBAH ICU with obstetric conditions were reviewed over a period of one year.[89] Of the eight women (11%) admitted for hypertensive diseases in pregnancy, more than half (62%) had been diagnosed with HELLP syndrome.[89] All these women made a full recovery.[89] In our study 4.9% of women with HELLP syndrome were admitted to ICU for mechanical ventilation, inotrope support or severe acidosis. One (33%) of women with HELLP syndrome who was admitted to CHBAH ICU died. This mortality rate in ICU is in keeping with the study done by Osmanagaoglu et al. (30%).[69] Although the study population is too small to make a conclusively comparison.

5.4 Perinatal outcomes in babies born to women with HELLP syndrome.

5.4.1 Perinatal mortality

The increased incidence of perinatal morbidity and mortality seen in pregnancies complicated by HELLP syndrome is likely due to the need for premature delivery together with chronic uteroplacental vascular lesions resulting in a compromised in uteroplacental blood supply.[105] In 2005 Gul et al. reported perinatal mortality as 34% before 32 weeks gestation and 8% after 32 weeks gestation in women with preeclampsia and HELLP syndrome.[48] In our study, the perinatal mortality rate was 25.9% before 32 weeks gestation which is lower than Gul's study.[48] This might reflect the highly trained staff in NICU, the beneficial effects of steroids and magnesium sulphate antenatally or the decision to deliver via caesarean section. But the perinatal mortality rate was 13.8% after 32 weeks which is higher than Gul's study. This may be due to the delay in the diagnosis of HELLP syndrome, late antenatal booking or more stillbirths at presentation. More than half of the women who had a stillbirth in this study were antenatally unbooked. Poor perinatal outcomes may be preventable by early booking for antenatal care and for staff to realise those at risk and early referral for tertiary care.

5.4.2 Preterm delivery

Intuitively, the primary goal of care is maternal survival and reduction in maternal mortality whilst attempting to balance fetal outcomes. Aggressive treatment with maternal stabilisation and delivery have been advocated to prevent maternal mortality even at an early gestational age as delivery is considered the primary management of HELLP syndrome. This might explain the high rate of preterm delivery in this study. A third of the women with HELLP

syndrome were between 33 and 36 weeks gestation, with 31% equal to and less than 28 weeks, 24.2% between 29 and 32 weeks and 13.8% equal to and more than 37 weeks. A study by Sibai, et al. found 41.2% of women less than 28 weeks, 40.4% were between 31 and 36 weeks and 18.4% at more than 36 weeks.[40]

Socolov et al. found that in 88% of women delivered by caesarean section the most prevalent indication was acute fetal distress.[72]These findings are comparable with our study, where 81% of women had caesarean sections, more than half of which were due to fetal compromise.

5.4.3 Low birth weight and IUGR

The mean birth weight found by Socolov et al. was 1632 g ± 824 grams.[72] It is comparable with this study in which the median birth weight was 1510 grams (343- 3593g). However, in the index trial most of the babies weighed less than 1500 grams which may have a socioeconomic implication or reflect an earlier presentation.

Many of the babies born had evidence of IUGR (60.3%), this is far higher than the finding by Sibai et al. (31.6%), which is an expected complication associated with pre-eclampsia.[40]

5.4.4 Low APGAR and NICU admission

In the index study, 17.2% of newborns had an initial Apgar score of less than 7. They required oxygen therapy and the correction of biological deficits including acidosis, hypoglycemia, and hypocalcemia. In our study 32.7% of neonates were born to women with HELLP syndrome were admitted to NICU. This is far lower rate than the finding by Kim et al. in Korea, who found 85.7% of babies born to women with HELLP syndrome required NICU admission.[106] The lower rate of NICU admission in the index study may be explained by lack of neonatal intensive care beds.

This study shows that neonatal morbidity is increased in pregnant women complicated by HELLP syndrome. Thus, management and delivery of women with HELLP syndrome and infants should be performed at tertiary hospitals, where highly trained neonatal intensive care unit personnel and facilities are available, to improve both the maternal and neonatal outcomes. Consideration should be given to in-utero transfer as opposed to transferring postdelivery as these babies are often premature.

7 STRENGTH AND LIMITATIONS

The study was retrospective which may have impacted on the quality of data available. Some files were not found, and so women had to be excluded from the study. Another limitation may be the relatively small sample size. Most women were of African ethnicity, which reflects the population served by the hospital. However, the limited contribution from other racial groups affected the interpretation of race as a risk factor for HELLP syndrome but may be more reflective of findings akin to the Sowetan community. The incidence of HELLP syndrome in this study may be higher as data was gathered from a tertiary care referral centre. In addition, the lack of information regarding the incidence rate for HELLP syndrome in the general South African population may limit the application of the results to other settings in the country.

6 CONCLUSIONS

The rate of serious maternal and fetal adverse outcomes increases in women with HELLP syndrome. Therefore, regular antenatal care, early diagnosis of pre-eclampsia, and optimal management are essential. Early detection of complications with timely intervention may assist in minimising maternal and fetal morbidity and mortality.

Percentage difference between the results at diagnosis and the worst laboratory results is a new finding reflecting a range of 11 to 20% worsening in the results dependent on the laboratory variable being used. Reduced perinatal mortality in the index study reflected the need for tertiary centre for women with HELLP syndrome. The need for ICU is underestimated and not currently addressed by limited ICU facilities in this institution.

At this time, increasing hypertension and diabetes in the community may lead to further increase in the incidence of pre-eclampsia with a progressive rise in HELLP syndrome.

Further studies with a larger sample size may address gaps in knowledge regarding these issues.

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APPENDEX A

Appendix 1: Data Sheet

Study number

N=No (0) Y=Yes (1) Not documented =Blank space

Demographics and History

Age					
Race	A (1)	C (2)	I (3)	W (4)	O (5)
Parity					
Gravity					
Gestation					
Partner	Same (1)		Different (0)		
Family history	Y (1)		N (0)		
Habits	Smoker	Y (1)		N (0)	
	Alcohol	Y (1)		N (0)	
calcium supplementation	Y (1		N (0)		
Comorbidity	Cardiac (1)	Chronic hypertension (2)	Diabetes (3)	APLS (4)	Others (5/6/7/8)

Antenatal booking

Booking Gestation			
Weight when booking			
BMI			
Booking HB			
RPR	N (0)	Y (1)	
RVD	N (0)	Y (1)	
CD4			
PMTCT	N (0)		
ARV	N (0)	Y (1)	
	FDC	Y (1)	N (0)
	3TC	Y (1)	N (0)
	AZT	Y (1)	N (0)
	EFV	Y (1)	N (0)
	TDF	Y (1)	N (0)

	D4T	Y (1)	N (0)
	NVP	Y (1)	N (0)
Sonar			
Early Sonar (< 24weeks)	Y (1)	N (0)	
Latest Sonar (> 24 weeks)	Y (1)	N (0)	
Multiple pregnancy	Y (1)	N (0)	
IUGR	Y (1)	N (0)	
Umbilical artery doppler	Y (1)	N (0)	
MCA doppler	Y (1)	N (0)	

Diagnosis at admission

1	Pre-Eclampsia	N	Y
2	Gestational HPT	N	Y
3	Chronic HPT	N	Y
4	Eclampsia	N	Y
5	HELLP syndrome	N	Y
6	Imminent eclampsia	N	Y
7	Other	N	Y
	Specify		

Admission procedures

NST	N	Y
	Always Normal (0) Ever Suspicious (1) Ever Pathological (2)	
Sonar done	N	Y
	EFW	
	Doppler	Not done (0) Normal (1) Abnormal (2)
Antihypertensive agents within 48 hours of diagnosis of HELLP	Nifedipine Y/N	
	Amlodipine Y/N	
	Methyldopa Y/N	
	Cardura Y/N	
	Labetalol Y/N	
	MgSO4 Y/N	Duration in hours

Investigations at admission

Laboratory data	Results at admission	Results at diagnosis
WBC		
FBC		
HB		
PLT		
Urea		
Creatinine		
ALT		
AST		
LDH		
INR		
PTT		
Haptoglobin		
Smear	Fragments	Mild
		Moderate
		Marked
Urine dipstick	1+ 2+	3+
Urine PCR		
Total protein in 24hrs urine		

Worst laboratory results

Platelet count	
Urea	
Creatinine	
ALT	
AST	

Mode of delivery			**Duration/dose**
Induction of labour	N / Y		
	Oral Misoprostol	N/Y	Doses (1-12)
	Vaginal Misoprostol	N/Y	mg 1 /2/3/4 Repeats
	Catheter bulb	N/Y	
	Syntocinon	N/Y	Hours
Vaginal delivery		N/Y	
	Normal vaginal	N/Y	
	Assisted vaginal	N/Y	
Caesarean section		N/Y	

Complcations

Complications	N	Y			
Maternal					
Eclampsia	0	1			
Sub capsular hematoma	0	1			
Abruptio placentae	0	1			
Acute kidney injury	0	1			
Dialysis	0	1	Intermittent	0	1
			Continuous	0	1
Caesarean section	0	1	Lower segment	0	1
			Hysterotomy	0-	1
Relook laparotomy	0	1			
Blood transfusion	0	1	PackedCells	Units	
			Platelets	Units	
			FFPs	Units	
			Cryoprecipitate		
DIC	0	1			
PRES	0	1			
Cerebrovascular accident	0	1			
Intracranial hemorrhage	0	1			
ICU admission	0	1			
Ventilation	0	1	Duration in days		
Inotropes	0	1	Duration in hours		
Death	0	1			
Fetal/neonatal					
IUGR	0	1			
Apgar<7	0	1			
Birth asphyxia	0	1			
Preterm delivery	0	1			
NICU admission	0	1			
Still birth	0	1			
Oligohydramnios	0	1			
IUFD	0	1			

Post delivery organ system involvement/complication (Tick relevant organ system)

CNS (1)	**Respiratory(2)**	**CVS (3)**	**Liver(4)**	**Renal(5)**
Muskuloskeletal (6)	**GIT (7)**	**Haematology (8)**	**Endocrine (9)**	

On discharge

Proteinuria	Y	N
Urea	Y	N
Creatinine	Y	N
Readmission	Y	N
Reason for readmission		

APPENDEX B

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R14/49 Dr S Salem

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M170978

NAME: (Principal Investigator)	Dr S Salem
DEPARTMENT:	School of Clinical Medicine Department of Obstetrics and Gynaecology Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Descriptive analysis of women managed as HELLP syndrome at Chris Hani Baragwanath Academic Hospital
DATE CONSIDERED:	29/09/2017
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr P Naidoo
APPROVED BY:	Professor PE Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	15/12/2017

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on 3rd floor, Phillip V Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.
I/We fully understand the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to resubmit to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. in this case, the study was initially reviewed in **September** and will therefore be due in the month of **September** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature _____ Date _____

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDEX C

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