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# Frequency and severity of liver involvement in hypertensive disorders of pregnancy

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**ABSTRACT – Background –** Pre-eclampsia (PE) and eclampsia (E) are among the leading causes of maternal and fetal morbidity and mortality. Both are associated with an evolving spectrum of liver disorders. **Objective** – The aim of this study was to evaluate the frequency and severity of liver involvement in pregnant women admitted to an intensive care unit with PE/E and to assess its influence on adverse maternal and fetal outcomes. **Methods –** All subjects, hospitalized between January 2012 and March 2019, were retrospectively evaluated for clinical and biochemical liver-related abnormalities and their frequencies were subsequently correlated with maternal-fetal outcomes. **Results –** A total of 210 women (mean age 31±6.4 years, mean gestational age 33.8±4.1 weeks) with PE/E were included in the study. Most of them had severe hypertension (n=184) and symptoms of abdominal pain (48%) and headache (40%). Liver enzymes abnormalities were seen in 49% of the subjects, usually less than five times the upper limit of normal. Subcapsular hemorrhage and spontaneous hepatic rupture were identified in one woman who died. No patient had definitive diagnosis for acute fatty liver of pregnancy, neither acute liver failure. A total of 62% of deliveries occurred before 37 weeks. Fetal mortality was observed in 6 (3%) cases. There was no correlation between mean levels of liver enzymes and maternal and fetal outcomes. **Conclusion –** Biochemical abnormalities of liver enzymes are frequently seen in women with PE/E, but outside the spectrum of HELLP syndrome, they are not associated with adverse maternal and fetal outcomes. Liver-related complications are rare but can be life-threatening.

**Keywords –** Pregnancy; liver; hypertensive disorders; pre-eclampsia; eclampsia.

## INTRODUCTION

Hypertensive disorders are a common complication of pregnancy that encompasses chronic hypertension, transient gestational hypertension, pre-eclampsia/eclampsia (PE/E)[1-3] and preeclampsia superimposed on chronic hypertension[3,4].

Women with PE may develop life-threatening complications such as eclampsia, characterized by the development of coma and seizures; stroke; pulmonary edema; heart failure; renal failure; coagulopathy, usually heralded by hemolysis, elevated liver enzymes, and low platelet counts (HELLP) syndrome; acute liver failure, due to superimposed acute fatty liver of pregnancy (AFLP); subcapsular hepatic and splenic hematomas; hepatic infarction and hepatic and splenic rupture[2,5-8]. Pre-eclampsia was previously classified as mild or severe. However, now it is well acknowledged that even mild PE cases can evolve rapidly to eclampsia and severe organ dysfunction. Thus, it is of utmost importance to closely follow-up this group of pregnant women for early signs of clinical deterioration in order to improve maternal and fetal outcomes[2,5].

Liver enzymes are frequently abnormal in up to 1/3 of the subjects with PE/E[6-8], even in those not evolving to HELLP syndrome[9-11]. There is a paucity of data regarding the spectrum of liver involvement in PE/E, including the frequency and outcomes of life-threatening events such as AFLP, hepatic hematoma and liver rupture. It is also unknown whether abnormal liver enzymes at baseline could predict adverse maternal-fetal outcomes and a higher frequency of liver-related complications in those patients.

The present study aimed to analyze the frequency and severity of liver involvement in pregnant women admitted to an ICU due to PE/E and to assess its impact on maternal-fetal morbidity and mortality.

## METHODS

The study was conducted in a tertiary hospital, with a total of 21.406 deliveries between January 2012 and March 2019. All pregnant women admitted to the ICU of Gastroenterology and Hepatology of the Portuguese Hospital of Salvador, Bahia, Brazil who fulfilled the diagnosis of PE/E and superimposed PE/E[2] were retrospectively evaluated. This ICU is the reference unit in the Hospital for critically ill obstetric patients. All were followed according to a predefined institutional protocol based on the International Society's recommendations for the Study of Hypertension in Pregnancy[2], under the obstetric team's supervision for optimal maternal and fetal supportive care and management.

Women who had chronic hypertension without established

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criteria for PE[2] were excluded from the study. Data at admission regarding demographics, clinical and laboratory parameters were collected in all subjects. Prior history and family history of PE/E, chronic hypertension, diabetes, and pregnancy characteristics including twin pregnancy, previous pregnancies, and gestational age at admission were elicited in every woman. Early-onset PE/E was considered when a diagnosis was established before 34 weeks of pregnancy and late-onset PE/E when diagnosed after that.

Data on maternal outcomes included the development of eclampsia, HELLP syndrome, stroke, pulmonary edema, heart failure, acute kidney injury, as well as liver-related complications, such as AFLP, acute liver failure (ALF), hepatic hematoma, hepatic infarction or rupture, and death. In this context, acute kidney injury was defined arbitrarily as creatinine levels higher or equal to 1.2 mg/dL and/or oliguria with urine output less than 500 mL in 24 hours[5]. HELLP syndrome was defined using the Tennessee classification system, considering the following criteria: hemolysis with increased lactate dehydrogenase (LDH) equal or higher than 600 U/L, increased aspartate aminotransferase (AST) levels equal or higher than 70 U/L and platelet count below 100.000 $mm^3$. Complete HELLP syndrome was considered when all three variables were present, partial HELLP syndrome in the presence of two of them. The Mississippi triple-class HELLP System was also used to diagnose and classify the syndrome's severity[10]. Whenever suspected, AFLP was screened using the Swansea criteria[11]. Acute liver failure was diagnosed according to international guidelines[12]. Investigation for other liver-related complications such as subcapsular and/or hepatic hematoma and hepatic rupture was carried out by computed tomography (CT) scan or magnetic resonance imaging (MRI) at the attending physician's discretion. Data on fetal outcomes included prematurity and death. Prematurity was defined as birth before 37 weeks of pregnancy.

The study was approved by the Ethics Committee in Research of the Portuguese Hospital of Salvador, Bahia. The study was registered on Plataforma Brasil – CAAE nº 42462721.5.0000.5029.

### Statistical analysis

Descriptive analysis was performed. Continuous variables were expressed as mean ± SD and categorical variables as proportions. Univariate analysis was tested using $X^2$ test or the Fisher exact probability test when appropriate. Continuous variables were compared using the *t*-test. *P* values ≤0.05 were considered significant. 95% confidence intervals were reported when appropriate. All statistical analysis was performed using SPSS version 22.0 for Windows (SPSS Inc, Chicago, IL, United States).

## RESULTS

Two hundred and ten pregnant women (mean age 31±6years, mean gestational age 34±4 weeks) with PE/E (n=171) or with superimposed PE/E (n=39) were included in the study. Early PE/E was observed in 85 (40%) women and late PE/E in the other 125 (60%) subjects. Clinical and laboratory data of those subjects are depicted in TABLE 1. Briefly, most pregnancies were in the third trimester with a mean gestational age of 33.8±4.1 weeks. Only one patient was diagnosed with PE after delivery. Family history of PE/E and previous history of pre-eclampsia, as well as twin pregnancies were present in a minority of cases. Chronic hypertension and diabetes were reported in 19% and 5% of the subjects. (TABLE 1). At admission, the most common symptoms were abdominal pain, either epigastric or in the right upper quadrant (48%), and headache (40%). Most of the patients had severe hypertension defined as either systolic blood pressures ≥160 mmHg and/or diastolic blood pressures ≥110 mmHg. Most of them had proteinuria and one-third had thrombocytopenia (TABLE 1).

**TABLE 1**. Clinical and laboratory features of pregnant women admitted with PE/E at admission or in the first 24 hours (n=210).

| | |
|---|---|
| Age (years) | 31±6 |
| Age ≥35 years | 57 (27%) |
| Gestational age (weeks) | 34±4 |
| Second trimester of pregnancy | 22 (10%) |
| Third trimester of pregnancy | 188 (90%) |
| Family history of PE/E | 1 (0.5%) |
| Nulliparity | 12 (6%) |
| Previous history of PE/E | 16 (8%) |
| Twin pregnancy | 3 (1%) |
| Previous pregnancy (ies) | |
| One pregnancy | 121 (58%) |
| Two pregnancies | 75 (38%) |
| Chronic hypertension | 39 (19%) |
| Previous diabetes mellitus | 11 (5%) |
| Signs and symptoms at admission | |
| Abdominal pain | 100 (48%) |
| Headache | 83 (40%) |
| Photophobia | 30 (14%) |
| Mental confusion | 5 (2%) |
| Severe hypertension* | 184 (87.6%) |
| Laboratory results# | |
| Platelets ($mm^3$) | 168.000±59.000 |
| Low platelet counts | 75 (35.7%) |
| Schizocytes on peripheral smear | 31 (14.8%) |
| Peak bilirubin levels (mg/dL) | 0.6±1.17 |
| Peak LDH level (U/L) | 861±627 |
| Peak AST level (U/L) | 98±199 |
| Peak ALT level (U/L) | 90±163 |
| Peak uric acid (mg/dL) | 6.5±1.7 |
| Proteinuria (mg/24 h urine) | 1789.6±3553 |
| Proteinuria (>300mg/24 h urine) | 192 (91.4%) |

PE/E: pre-eclampsia or eclampsia. *Systolic BP ≥160 and/or diastolic BP ≥110 mmHg; #in the first 24 hours.

The development of full-blown HELLP syndrome varied from 10% to 21%, depending on diagnosis criteria. Twenty patients fulfilled the criteria for complete HELLP syndrome according to Tennessee classification, and 39 others were diagnosed with partial HELLP syndrome, with low platelet counts and abnormal LDH (n=9) or abnormal AST and LDH (n=30). Using the Mississippi classification, 45 patients evolved to HELLP syndrome with 5 (2%), 16 (8%) and 24 (11%) categorized as class 1, 2 and 3, respectively. Eclampsia was observed in just 6 (3%) patients (TABLE 2). Liver involvement expressed by abnormal levels of AST and/or ALT was seen in 49% of the subjects, with most fluctuations below five times the upper limit of normal. Few women (n=12) had marked (more than 5-fold) elevations of liver enzymes. None of the patients fulfilled criteria for AFLP or ALF. Subcapsular and parenchymal liver hemorrhage and spontaneous hepatic rupture were identified in one patient who died of hemorrhagic shock. This woman was 44 years old with multiple previous pregnancies. She was admitted with PE, with right upper quadrant abdominal pain, platelet count of 73.000 $mm^3$, LDH of 3.666 U/L, total bilirubin of 2.8 mg/dL, AST of 1.361 U/L and schizocytes in peripheral smear fulfilling criteria for HELLP syndrome, rapidly evolving after delivery to hemorrhagic shock due hepatic rupture disclosed by CT scan. No more fatalities were observed and maternal death was 0.5%.

**TABLE 2.** Maternal and fetal outcomes in women admitted to the intensive care unit with PE/E (n=210).

| | |
|---|---|
| Complete HELLP syndrome (Tennessee criteria) | 20 (10%) |
| Partial HELLP syndrome (Tennessee criteria) | 39 (19%) |
| HELLP syndrome (Mississippi criteria) | 45 (21%) |
| Class 1 | 5 (2%) |
| Class 2 | 16 (8%) |
| Class 3 | 24 (11%) |
| Eclampsia | 6 (3%) |
| Acute kidney injury | 12 (6%) |
| Pulmonary edema | 2 (1%) |
| Liver involvement | |
| Abnormal ALT and/or ALT levels | 103 (49%) |
| Between 1.1 to 5 x ULN | 91 (43%) |
| Between 5.1–10 x ULN | 4 (2%) |
| Above 10.1 x ULN | 8 (4%) |
| Length of hospital stay (days) | 5.2±4.2 |
| Fetal mortality | 6 (3%) |
| Maternal mortality | 1 (0.5%) |

HELLP: Hemolysis;,elevated liver enzymes and low platelet counts; PE/E: pre-eclampsia or eclampsia.

Regarding fetal outcomes, prematurity and extreme prematurity were observed in 113 (53%) and 22 (11%) newborns. Fetal mortality was observed in 6 (3%).

Liver enzymes abnormalities were not associated with eclampsia development; HELLP syndrome defined either by Tennessee or Mississippi criteria, and maternal and fetal outcomes (data not shown).

## DISCUSSION

In the present paper, the authors have retrospectively evaluated 210 women with PE/E admitted to the ICU with a particular interest in liver involvement manifested either by liver enzymes abnormalities or liver related complications. The results of this study show that derangement of liver tests are frequent in patients with PE/E, forming a spectrum of disease that range from mild manifestations to occurrence of more serious events.

Liver involvement was reported to occur in 3.2% of all pregnancies, mainly due to pregnancy-specific disorders, particularly PE/E[13]. The incidence of PE/E varies from 2.2%–4.6%[4,14] worldwide and is associated with an array of liver disorders ranging from modest to severe elevations of AST and/or ALT, described in approximately 30% of patients[7], which may or may not be related to the development of HELLP syndrome or other life-threatening liver-related disorders[6-8,15-17]. In the present study, abnormalities of AST and/or ALT were observed in half of the patients. Most of them had slight elevations of liver enzymes up to five times the upper limit of normal, but 12% showed modest to severe fluctuations of AST and/or ALT. Those elevations were not within the spectrum of HELLP syndrome in more than half of the cases, and their magnitude was not significantly related to the development of HELLP syndrome or to adverse maternal and fetal outcomes. None of the patients in the present cohort developed criteria for AFLP and ALF. Even though patients with AFLP usually have overlapping HELLP syndrome features and PE/E, none of our subjects had criteria for diagnosing AFLP or ALF[6-8]. One of the pregnancies was complicated by a fatal subcapsular hemorrhage associated with a hepatic hematoma and spontaneous hepatic rupture leading to hemorrhagic shock after delivery. The occurrence of those complications in PE/E is anecdotal. It has been observed in 0.5% to 1.6% of those women with HELLP syndrome, usually associated with high mortality rates[9,18]. HELLP syndrome, on the other hand, was reported to occur in the literature in 0.2–0.6% of all pregnancies and in 10% to 20% of those cases of PE/E[8,15,16]. The frequency of HELLP syndrome superimposed in PE/E in the present study was similar, ranging from 10% to 21% depending on the employed criteria. The frequency of prematurity, maternal and fetal deaths were similar to previously published reports[4,14].

Abnormal liver tests are thought to reflect liver dysfunction resulting from a combination of factors considering the context of a multisystem disorder. The aetiology of PE/E is incompletely understood. It is postulated that various pathways and mechanisms are interlinked. Recent studies have identified the importance of immunological factors, an increased maternal inflammatory response to trofoblasts, increases in inflamatory cytokines and endothelial dysfunction[8]. Vasospasm may be a contributor to liver injury, which can involve fibrin deposition, periportal hemorrage, necrosis or infarction of hepatocytes.

In this study, we observed low mortality rates. Mortality rate for

both mother and baby has been reduced due to earlier recognition of hypertensive disorders of pregnancy, fetal monitoring and fetal and maternal supportive care. The implementation of standardised measures and multidisciplinary approach with interaction between the teams of hepatology and obstetrics can improve maternal and perinatal outcomes.

## CONCLUSION

In conclusion, biochemical abnormalities of liver enzymes are frequently observed in pregnant women with PE/E. Elevated liver enzymes should be monitored with caution since they are one of the HELLP syndrome components, a disorder associated with a worse prognosis. However, outside the spectrum of HELLP syndrome, upraised AST and/or ALT or their magnitude do not correlate with adverse maternal or fetal outcomes.

## Authors' contribution

Oliveira JC: data collection, research execution, text writing. Codes L: study design planning, text writing, statistical analysis and review. Lucca MMFB: data collection, research execution. Soares MAP: text writing, review and suggestions. Lyrio L: text writing, review and suggestions. Bittencourt PL: study design planning, text writing and review. All the authors made substantial contributions to the conception and design of the study.

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Oliveira JC, Codes L, Lucca MMFB, Soares MAP, Lyrio L, Bittencourt PL. Frequência e gravidade do envolvimento hepático em transtornos hipertensivos da gravidez. Arq Gastroenterol. 2022;59(3):340-4.

**RESUMO – Contexto –** Pré-eclâmpsia (PE) e eclâmpsia (E) estão entre as principais causas de morbimortalidade materna e fetal. Ambas estão associadas a comprometimento hepático com diferentes formas de evolução. **Objetivo** – O objetivo deste estudo foi avaliar a frequência e a gravidade do envolvimento hepático em gestantes internadas em uma unidade de terapia intensiva (UTI) com PE/E e avaliar sua influência em desfechos maternos e fetais adversos. **Métodos –** Pacientes hospitalizados entre janeiro 2012 e março 2019 com PE/E foram avaliados retrospectivamente quanto às anormalidades clínicas e bioquímicas relacionadas ao fígado e suas frequências foram posteriormente correlacionadas com os resultados materno-fetais. **Resultados –** Um total de 210 mulheres (idade média 31±6,4 anos, idade gestacional média 33,8±4,1 semanas) com PE/E foram incluídas no estudo. A maioria delas apresentava hipertensão grave (n=184), sintomas de dor abdominal (48%) e cefaleia (40%). Anormalidades das enzimas hepáticas foram observadas em 49% dos indivíduos, geralmente menos de cinco vezes o limite superior do normal. Hemorragia subcapsular e ruptura hepática espontânea foram identificadas em uma mulher que faleceu. Nenhuma paciente teve diagnóstico definitivo de esteatose hepática aguda da gravidez, nem insuficiência hepática aguda grave. Um total de 62% dos partos ocorreu antes de 37 semanas. A mortalidade fetal foi observada em 6 (3%) casos. Não houve correlação entre os níveis médios de enzimas hepáticas e os resultados maternos e fetais. **Conclusão** – Anormalidades bioquímicas hepáticas são frequentemente vistas em mulheres com PE/E, mas fora do contexto da síndrome HELLP, não estão associadas a resultados maternos e fetais adversos. As complicações relacionadas ao fígado são raras, mas podem ser fatais.

**Palavras-chave –** Gravidez; fígado; distúrbios hipertensivos; pré-eclâmpsia; eclampsia.

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