

Maternal Aspects of Preeclampsia**Preeklampsinin Maternal Sonuçları****¹Barış Büke, ²Hasan Onur Topçu, ³Nilgün Kultürsay, ¹Mert Kazandı**¹Ege University, Department of Obstetrics and Gynecology, İzmir, Turkey²Dr.Zekai Tahir Burak Women Health Education and Research Hospital, Ankara, Turkey³Ege University, Department of Pediatrics, İzmir, Turkey**ABSTRACT**

Preeclampsia is almost exclusively a disorder of human pregnancy, the pathogenesis of which remains unknown. Preeclampsia affects 3 to 8% of all pregnancies and still remains a leading cause of maternal morbidity and mortality. Because of the defective uteroplacental unit associated with preeclampsia; adverse fetal, neonatal events usually observed in these cases. The adverse effects of preeclampsia on the maternal hematologic, cardiovascular and pulmonary, neurologic, renal, and gastrointestinal system are also important. The aim of this review is to underline the maternal adverse effects of preeclampsia.

Keywords: Preeclampsia; HELLP syndrome; hypertension; pregnancy complications.

ÖZET

Preeklampsia yalnızca insan gebeliğinde görülen bir hastalıktır, patogenezi bilinmemektedir. Tüm gebeliklerin % 3 ile 8 ini etkilemektedir ve hala maternalsmorbidite ve mortalitenin en sık nedenidir. Preeklampside bozulmuş uteroplacental üniteye bağlı olarak, bu olgularda fetal ve neonatal kötü sonuçlar görülebilmektedir. Fetal ve neonatal kötü sonuçların yanında, annede de hematolojik, kardiyovasküler, pulmoner, nörolojik, renal ve gastrointestinal sistemde anlamlı ölçüde kötü sonuçlar görülebilmektedir. Bu derlemede preeklampsiye bağlı oluşan kötü maternal sonuçların değerlendirilmesi amaçlanmıştır.

Anahtar Kelimeler: Preeklampsi, HELLP sendromu, hipertansiyon, gebelik komplikasyonları.

Introduction

Preeclampsia is a multisystem disorder that is unique to pregnancy, affecting 3 to 8% of all pregnancies (1). The combination of new-onset hypertension and proteinuria is essential for the diagnosis. Preeclampsia still remains a leading cause of maternal morbidity and mortality comprising 17% of maternal deaths in advanced gestations and accounts for 60,000 maternal deaths per year worldwide (1). Preeclampsia has adverse effects on the maternal hematologic, cardiovascular and pulmonary, neurologic, renal, and gastrointestinal system. This article reviews the pathological changes in these body systems during pregnancy complicated with preeclampsia.

Cardiopulmonary Complications

The cardiovascular physiology during preeclampsia is completely different from normal pregnant state. The main alterations are related to

decline of cardiac preload, affected by hemoconcentration due to pathologically diminished hypervolemia of pregnancy, increased cardiac after load caused by hypertension and endothelial dysfunction leading extravasation into the extracellular space, which creates the risk of pulmonary edema (2).

Approximately, total blood volume of an average size woman will increase from 3500 mL to 5000 mL during the pregnancy (3). Plasma volume reduction and hemoconcentration remain a hallmark of preeclampsia and seem to be directly proportional to the severity of the disease (4).

Several studies in which right heart catheterization performed, most patients with severe pre-eclampsia or eclampsia had high-normal or elevated systemic vascular resistance indexes, hyperdynamic left ventricular function, normal or increased pulmonary capillary wedge pressure in severe preeclampsia (5). In the state of superimposed preeclampsia with chronic hypertension; Cotton et al. showed (5) that systemic vascular resistance and left heart filling pressures increased and that caused to a

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decrease in cardiac output and an increase in pulmonary vascular hydrostatic pressure, which resulted as pulmonary edema. Cardiovascular complications of preeclampsia can include peripartum cardiomyopathy, ischemic and coronary artery heart disease, and pulmonary edema, acute lung injury, and acute respiratory distress syndrome.

Pulmonary Edema

Pulmonary edema which is described as accumulation of fluid in the pulmonary interstitial and alveolar spaces, considered as the most common cardiovascular complication of preeclampsia (6). The physiological changes in the cardiovascular system during pregnancy, including increased plasma blood volume, cardiac output, heart rate, and capillary permeability and decreased plasma colloid osmotic pressure are exaggerated in preeclampsia and those predispose women to develop pulmonary edema according to Starling equation. An increase in capillary leak and capillary fluid extravasation secondary to vascular endothelial damage may also develop pulmonary edema in preeclamptic women (6). In retrospective case series; it's reported that the incidence of pulmonary edema is increased in older and multi gravid women and especially in women with preexisting chronic hypertension (7, 8).

Diagnosis of pulmonary edema is made by clinical assesment with the signs like dyspnea and orthopnea along with signs of respiratory compromise tachypnea, auditory findings like crackles and rales, and hypoxemi. Arterial blood gas and chest X-ray will be helpful in the diagnosis and management. Kerley B lines, which are horizontal lines located laterally in the lower zones of the lung reaching the lung edge, are the initial findings of pulmonary edema. In the further stages, butterfly like pattern can be seen which is described as centrally localized shadows with a clear zone at periphery lung lobes. And also cardiac enlargement can be seen in further stages. Echocardiography is recommended to evaluate all pregnant women with pulmonary edema to exclude the other causes of cardiopulmonary compromise and also to find out the type of cardiac dysfunction (9).

An optimal treatment strategy should be established to expedite treatment results. Maternal fluid balance and electrolytes should be strictly monitored. Furosemide can be administered intravenously as a single dose of 10-40 mg over 2 minutes to promote diuresis. If adequate response is not obtained within 30-60 minutes, the dose should be increased to 40-60 mg to a maximum of 120 mg in 1 hour. Morphine sulfate can be administered intravenously as needed both for pain and to reduce the adrenergic vasoconstrictor stimuli to the pulmonary arteriolar and venous beds. As with the management of all parturients with preeclampsia, sodium and water should be modestly restricted and oxygen saturation can be monitored using a pulse oximeter and oxygen supplementation can be used to treat maternal hypoxemia. The patient's blood pressure should also be monitored and electrocardiogram and fetal heart rate tracing should be obtained. And also in patients with chronic hypertension and superimposed pre-eclampsia vasodilators will be helpful to reduce after load (10).

Acute Respiratory Distress Syndrome (ARDS)

ARDS is defined as respiratory failure with acute hypoxemia and increased alveolar-capillary permeability arising from diffuse and ongoing pulmonary inflammation (11). Common symptoms are tachypnea, dyspnea, cyanosis and tachycardia. Basilar crackles or wheezing can be present on auscultation of the chest. Pregnancy-related ARDS includes the diagnosis of the condition during pregnancy and within 6 weeks postpartum

(12). HELLP syndrome, pulmonary edema, and / or cardiopulmonary disease are the high risk conditions for developing pregnancy-related ARDS (13). ARDS during pregnancy is related with poor perinatal outcomes like perinatal asphyxia and perinatal death. There is not an established management strategy for ARDS during pregnancy. Multidisciplinary approach is recommended. Respiratory support is the first and most important stage of the management. For adequate fetal oxygenation PaO₂ should be over 70 mm Hg, which corresponds to a maternal SaO₂ of about 95%. Increased work of breathing, mental status deterioration, hemodynamic instability and inability to protect the airway or manage secretions are the indications for intubation (14). There is no consensus on the mode of delivery.

Peripartum Cardiomyopathy

Peripartum cardiomyopathy is an infrequent complication of preeclampsia (15). The definition of peripartum cardiomyopathy requires the following criteria; (16)

1-Development of cardiac failure in the last month of pregnancy or within five months of delivery;

2-Absence of an identifiable cause for the cardiac failure;

3-Absence of recognizable heart disease before the last month of pregnancy;

4-Left ventricular systolic dysfunction, ejection fraction (EF) below 45%.

There are multiple possible reasons for developing peripartum cardiomyopathy however the certain reason is unknown. Transient left ventricular remodeling and hyper trophy due to increased blood volume and cardiac output may be exaggerated function in women who develop peripartum cardiomyopathy. The hemodynamic stress of gestational hypertension and acute preeclampsia is more common in women with peripartum cardiomyopathy and may contribute to the development of heart failure (17). 50-60% of patients show complete or near-complete recovery usually within the first 6 months postpartum. Recent studies have presented a 95% 5-year survival rate (18). EF in women with peripartum cardiomyopathy at initial presentation was shown to be related with long-term outcome (19).

Ischemic Heart Disease—Myocardial Infarction

It's hard to diagnose myocardial infarction during pregnancy because of physiological changes and low level of suspicion. Up to date approximately 150 cases of myocardial infarction during pregnancy have been reported in the literature worldwide (20). Women with a recorded diagnosis of preeclampsia had nearly 3 times the risk of myocardial infarction than non-preeclamptic women (21) and interestingly infarction related to preeclampsia, is usually seen after administration of ergot alkaloids, bromocriptine, oxytocin, and prostaglandin. In a population-based study of 7543 cases, mortality due to ischemic heart disease was significantly higher among eclamptic women and those with preeclampsia than those with hypertension alone. Mortality due to ischemic heart disease had a 2-fold higher risk in multiparous women than primigravid women (22). In another prospective randomized controlled study; it was shown that Troponin I levels were significantly higher in the gestational hypertensive groups compared with controls, suggesting that coronary ischemia may be missed in patients with hypertensive disorders in pregnancy (23).

Long-Term Effects of Preeclampsia On Cardiovascular Health

Increased inflammatory markers; dyslipidemia, insulin resistance, endothelial dysfunction and oxidative stress which are associated with preeclampsia increase the risk of cardiovascular disease in later life (24). In several studies (24, 25), history of preeclampsia has been reported to be an independent risk factor for subsequent coronary artery disease. Also patients with coronary artery disease had preeclampsia more often in the first or any subsequent pregnancy than the control groups. After a review of 403,550 women in the Swedish Medical Birth Register over a 9-year period it's shown that development of ischemic heart disease is related with the severity of the hypertensive disease of pregnancy (25). Preeclamptic women have an increased risk of vascular disease, as hypertension over 14.1 years, ischemic heart disease over 11.7 years, stroke over 10.4 years, and venous thrombo embolism over 4.7 years. Overall mortality after preeclampsia was increased after 14.5 years (26). A recent review has demonstrated that women with severe, very early onset pre-eclampsia (before 24 weeks) have an increased risk of preeclampsia in subsequent pregnancies (27). And also it's demonstrated that women with a history of early onset severe preeclampsia had significantly more chronic hypertension and microalbuminuria than controls. Early onset, recurrent, or severe preeclampsia seems to be at highest risk of cardiovascular disease.

Neurologic Complications

Acute cerebral complications of preeclampsia, such as eclampsia, intracranial hemorrhage, and cerebral edema, account for approximately 75% of mortality due to preeclampsia (28). These conditions seem to be a continuum of the similar pathophysiology. Presence of tonic-clonic seizures during pregnancy and early postpartum period of preeclamptic patients is called as eclampsia (28). Intracerebral hemorrhage which is a well-known cerebro vascular complication of eclampsia may lead to maternal death or permanent disability according to the severity of the condition. Uncommon neurological presentations like blindness, altered state of consciousness, and coma can also be present as a part of this continuum. The average annual incidence rate of eclampsia vary between 0.3 and 0.6/1000 worldwide (29, 30). Experimental studies evaluating cerebrovascular adaptation to pregnancy and preeclampsia are far and few because of the ethical issues and technical challenges.

Hence, the pathogenesis of eclampsia remains unknown; current theories of eclampsia; endothelial cell dysfunction, which characterizes preeclampsia seems to play a central role in the theories trying to explain the cerebral abnormalities associated with eclampsia. The former theory suggests that, as a response to acute severe hypertension, cerebral overregulation leads to vasospasm. Diminished cerebral blood flow due to generalized vasospasm is thought to result as cytotoxic edema, ischemia, and tissue infarction (31). The recent theory suggests that sudden elevations in systemic blood pressure may exceed the cerebrovascular auto regulatory capacity and especially in the arterial boundary zones, regions of vasoconstriction and forced vasodilation develop (32). Eventually, increased hydrostatic pressure, hyperperfusion, and extravasation lead to vasogenic edema. This phenomenon is called as posterior reversible leucoencephalopathy syndrome (PRES) (33). In the face of alterations in cerebral perfusion pressure cerebral blood flow remains constant through cerebral autoregulation. Impaired cerebral autoregulation is considered to be the main reason of eclamptic encephalopathy

because the cerebral autoregulation depends on an intact vascular endothelium as the blood– brain barrier (34). Because of less sympathetic innervation and less ability for neurogenic response to blood pressure alterations; the seizures are commonly occipital in the beginning. In most of the patients, PRES is an acute cerebral illness with headache, nausea, altered mental function, visual disturbances, and seizures. However; patients with PRES may present without the traditional prodromal cerebral manifestations of hypertensive encephalopathy. Additionally, with only mild hypertension and concomitant endothelial damage, PRES syndrome may also develop (35).

Cerebral Hemodynamics and Neuroimaging in Preeclampsia

As the main branch of circle of Willis the middle cerebral artery carries nearly 80% of the flow to the hemispheres of the brain (36). Advances in neuroradiological imaging techniques helped physicians understanding the correlation between neurological symptoms and cerebrovascular hemodynamic changes characteristic for preeclampsia (37). Transcranial Doppler ultrasound studies demonstrated increased cerebral blood flow velocity in pre-eclampsia (36). Velocity-encoded phase contrast MRI is also used to study absolute cerebral blood flow in preeclampsia (37). This increased cerebral blood flow contributes to cerebro vascular auto regulatory breakthrough in PRES and eclampsia. Localized hypodense lesions in Computed Tomography imaging, at the gray-white matter junction in the parietooccipital lobes are typical for cases of eclampsia. Usually, these hypodense lesions are completely reversible (38). These lesions are not usually seen in patients with severe preeclampsia and chronic hypertension. In patients with different neurologic symptoms, such as lethargy, confusion, and blindness widespread diffuse cerebral edema can be seen, which carries the risk of life-threatening transtentorial herniation (39). MRI demonstrates hyperintense T2 lesions in the (sub) cortical regions of the parieto-occipital and temporal lobes which typically resolve without long-term sequel. But approximately one-fourth of eclamptic women may demonstrate persistent lesions several weeks postpartum and these lesions seem to represent brain ischemia (40). Studies using Diffusion- Weighted Imaging sequences, and Apparent Diffusion Coefficient mapping (ADC), showed that the origin of brain edema in eclampsia is primarily vasogenic however it may be associated with ischemic / cytotoxic changes in 20-25% of eclamptic women(41).

Hemorrhagic Complications of Eclampsia

The typical scenario for intracerebral hemorrhage is sudden death after eclamptic seizure. Cerebral hemorrhage is more common in older women with underlying chronic hypertension. Thalamus, cerebellum, and brain stem are the most frequently affected sites in these older hypertensive subjects (42). Occasionally, in young nulliparous patients who present with HELLP syndrome and eclampsia, cerebral infarction may transform into a hemorrhagic infarction. Only rarely, a ruptured aneurysm or arteriovenous malformation can lead to intra cerebral hemorrhage in women with preeclampsia (43). Subarachnoid hemorrhage cases are also reported in preeclampsia which are located over the convexity of the frontal / parietal lobes extending into the sylvian fissure. Permanent neurologic deficits were reported none of these patients (44).

Visual Disturbances Due To Eclampsia

Approximately, in 40% of preeclamptic women visual symptoms like scotomata, amaurosis, blurred vision, diplopia, chromatopsia and homonymous hemianopia, can be present (45). These visual disturbances may be due to focal cortical edema as well as retinal abnormalities (46). Visual disturbance due to focal cortical edema is called as cortical blindness. Cortical blindness is characterized by intact pupillary light reflexes, intact ocular movements, and normal ophthalmologic findings excluding a peripheral cause of blindness. Lesions in cortical blindness patients are seen particularly in the parieto-occipital area and are reversible on follow-up imaging (47). Most of these patients recover in a period varying from 2 hours to 21 days.

PRES Syndrome and Preeclampsia

Cerebral autoregulation in preeclampsia is abnormal, and it's hard to estimate the degree of dysfunction. However, the management guidelines assume that, the more severe the symptoms, the more likely a woman will develop an eclamptic seizure, upper limit of mean arterial pressure at which auto regulation operates is unknown. And also it should be kept in mind that as well as endothelial dysfunction, preeclampsia can regionally be affecting vascular smooth muscle function, so that, alterations in the cerebral circulation in preeclamptic women may occur minimal elevation in blood pressure and a mild clinical picture (48). Although the risk of convulsions ascends with the severity of preeclampsia, it's hard to rely on the level of blood pressure. In two recent studies; it's shown that almost one-fifth of eclamptic women have maximum systolic blood pressures of 140 mm Hg before the convulsions (50, 54). Those eclamptic women with borderline hypertension are often young primigravidas whose blood pressures have risen markedly from low levels. These findings made researchers to think that the critical threshold could be related to the patient's blood pressure prior the development of hypertension (49). Prompt diagnosis and treatment is of great importance. Lowering blood pressure below a threshold of 160/105 is an important stage of treatment, however blood pressure reduction alone does not always seem to prevent the development of either PRES or hemorrhagic stroke (50). Parenteral magnesium sulfate for the prevention and treatment of eclamptic seizures is also one of the cornerstones of the treatment strategies (51). Most of the seizures occur during the intrapartum and postpartum periods. Symptoms like persistent occipital or frontal headaches; blurred vision, photophobia, epigastric or right upper quadrant pain, and altered mental status are suggestive for eclamptic seizure, approximately seen 60-75% of the cases (52). The most reliable syndrome of a seizure seems to be severe headache; however, none of the clinical signs and symptoms are absolutely reliable. Since most of the peripartum seizures are related with epilepsy and eclampsia, focal neurological signs, prolonged coma, atypical or recurrent convulsions, and a prolonged return to complete recovery following delivery are the conditions requiring further examination and imaging modalities (53).

Long-Term Effects of Eclampsia

Recent studies showed that the paradigm that eclampsia is a condition of which the woman can expect full clinical recovery may need to be revised. In a study implemented 7 years postpartum, formerly eclamptic women had significantly more white matter lesions on MRI than normotensive group (54). Impaired cognitive functioning is reported, using a cognitive failures questionnaire after several years following an ec-

lamptic pregnancy (55). In a case control study, objective neurocognitive testing showed that maternal memory seems impaired several months after pregnancies complicated by severe preeclampsia (56). After the consideration of similar etiological link between migraine and preeclampsia a possible association is demonstrated (57). In patients who developed temporal lobe epilepsy months to years after PRES, hippocampal sclerosis has been reported (58). And also, a 3 to 5 fold increased risk for death from stroke in previously preeclamptic women are demonstrated. (59). As a result of all these findings it seems quite difficult to say that eclampsia is a condition which resolves completely.

Renal Complications of Preeclampsia

Mechanical and hormonal changes during pregnancy have a significant impact on renal anatomy and physiology. Renal length and volume increases by approximately 1 cm and 30% during pregnancy due to the increase in renal vascular and interstitial volume rather than the number of nephrons (60). Additionally, mild hydronephrosis and hydroureter are considered physiologic during pregnancy. Mechanical factors such as external compression of the ureter as well as myorelaxant effect of progesterone contribute to dilation of the renal pelvises. Because of dextrorotation of the uterus by the sigmoid colon, dilation of the renal pelvis is seen on the right with a 9:1 ratio. Renal blood flow increases by 80% above non-pregnant values as a function of the increased cardiac output. This contributes to an increase in GFR during pregnancy beginning at the 6th week of pregnancy with a peak at the end of the first trimester. As a result of the rise in GFR serum creatinine, blood urea nitrogen, and uric acid levels fall by approximately 50%. So that a normal value in non-pregnant state can represent renal impairment during pregnancy (62). Aminoaciduria up to 300 mg per day may be present during pregnancy. Selective aminoaciduria is pronounced, while excretion of some of the amino acids increases excretion of the others decreases. In preeclamptic pregnancies, renal blood flow and GFR decreases by 30%-40% and overt proteinuria occurs. Interestingly, in spite of a marked fall in GFR serum creatinine and blood urea nitrogen often remain in the normal range (63). At the microscopic level the pathognomonic lesion for preeclampsia is glomerular endotheliosis which is characterized by enlarged endothelial cells narrowing the capillary lumen. As a result of glomerular endotheliosis, the ultrafiltration reduces and this contributes a decrease in GFR, so that, the process of endotheliosis seems to be the major contributor factor to the clinical manifestations of preeclampsia (64,65). All of these microscopic findings distinguishing preeclampsia disappear in 8 weeks postpartum. The increased protein excretion, a hallmark of preeclampsia, is attributed to the loss of size and charge selectivity of the glomerular barrier. The amount of protein excreted in the urine varies widely, ranging from 300 mg to 10 g per day. As the pathological findings disappear, proteinuria disappears within 3-8 weeks after delivery but may persist for months rarely (66).

Renal failure due to Preeclampsia

In rare cases of severe preeclampsia, renal cortical necrosis and acute tubular necrosis can occur secondary to prolonged renal hypo perfusion. In two studies conducted in patient groups with preeclampsia and acute renal failure; the authors concluded that proper management of acute renal failure in patients with pure pre-eclampsia / eclampsia does not result in residual impairment on renal function (67, 68). In the setting of acute renal failure complicating HELLP syndrome maternal death rate was a little bit higher than those with pre-eclampsia / eclampsia (69).

Oliguria is the most frequent manifestation of severe renal impairment in pre-eclampsia, which is defined as less than 25-30 mL/hover 2 consecutive hours. Strict monitoring of fluid input and output, serum electrolyte levels, and vital signs is of paramount importance during the management of renal failure with preeclampsia. The underlying cause of oliguria is considered prerenal because of their stricted renal flow. So that, a fluid challenge with is generally recommended. If the oliguria or anuria persists, despite the replacement of fluid invasive monitoring may be warranted (70). During the seizure prophylaxis with magnesium sulfate, levels of the drug should be closely monitored because of its renal excretion. Several studies (70-72) focussed on the long term renal implications of pre-eclampsia have contradiction in their results. While some of them are suggesting that a history of preeclampsia contributes to chronic renal disease, especially focal segmental glomerulosclerosis, the others deny such an association.

Chronic Renal Disease and Preeclampsia

It's clearly known that patients with chronic renal disease have an increased risk of pre-eclampsia. It is believed that the degree of renal insufficiency, rather than the underlying renal disease, is the primary determinant of outcome in these patients (73). In a study conducted in women with moderate or severe renal insufficiency who become pregnant with a serum creatinine greater than 2.5 mg/dL, it is demonstrated that 70% of women will deliver before term and over 40% will develop preeclampsia (73).

Pregnant patients with SLE need particular concern during pregnancy. There is an increased risk of preeclampsia among SLE patients, as it occurs in approximately 13% of those patients. If the disease has renal involvement the rate of preeclampsia can reach to 66% (74). The presence of anti phospholipid antibodies, preexisting thrombocytopenia, diabetes mellitus, and a diagnosis of pre-eclampsia in a prior pregnancy are some of the risk factors increasing the rate of preeclampsia for a pregnant SLE patient (75). It can be hard to distinguish preeclampsia from lupus nephritis, because the most common renal manifestation in patients SLE is proteinuria. In such condition urine microscopy will be useful (76).

Similar to pregnant patients with SLE, in renal transplant recipients the diagnosis of preeclampsia can be difficult, because many of these patients have hypertension and proteinuria in excess of 300 mg / 24 hours at baseline (77). Hence, the diagnosis of pre-eclampsia in renal transplant recipients requires a low threshold to evaluate patients for evidence of worsening hypertension, end-organ dysfunction, or worsening proteinuria, all of which may indicate preeclampsia.

Gastrointestinal Complications of Preeclampsia

The term HELLP syndrome (H for hemolysis, EL for elevated liver en-

zymes, and LP for low platelets) is used in 1982 first, by Weinstein. He described a group of severe preeclamptic patient, complicated by thrombocytopenia, abnormal peripheral smear, and abnormal liver function tests, which constitute a different clinical entity (78). Hemolysis, which is the hallmark of the triad of the syndrome, defined as the micro angiopathic hemolytic anemia characterized with low haptoglobin, elevated direct bilirubin, LDH levels and abnormal peripheral smear (schistocytes, burr cells, echinocytes) (79). To diagnose elevated liver enzymes, there is no constant value in the literature and also no consensus on which test to use. Similarly there is no consensus among various published reports regarding the diagnosis of thrombocytopenia. Hence, Martin and colleagues (80) from University of Mississippi constituted a classification for HELLP syndrome called Mississippi Criteria after a retrospective review of 302 patients with HELLP syndrome. According to that classification, class 1 HELLP syndrome is defined as a platelet count below 50,000 / mm³, whereas platelet count between 51,000 and 100,000/mm³ is defined as class 2 and a platelet count between 101,000 and 150,000 / mm³ is defined as class 3. The clinical findings of HELLP syndrome can interfere with a long list of diseases. In a recent review by Sibai, (81) it's concluded that HELLP syndrome requires the presence of all the following: platelet count less than 100,000/mm³, an AST level >70 IU/L, abnormal peripheral smear, an LDH serum level >600 IU/L, and/or bilirubin level >1.2 mg/dL. Those who do not have all these parameters are considered to have partial HELLP syndrome (81). The laboratory criteria for HELLP syndrome were shown in Table 1.

In several studies it's reported that the mean age among patients with HELLP syndrome are higher than other preeclamptic patients, and HELLP syndrome is more frequent in multiparous patients and patients who don't have another medical complications like diabetes and SLE. Also, conservative management is demonstrated to be a risk factor for HELLP syndrome (82).

Although, no symptoms or signs are diagnostic for HELLP syndrome, patients usually present remote from term, complaining of epigastric or right upper quadrant pain. It's considered that, this pain results from obstruction to blood flow in the hepatic sinusoids, which are blocked by intravascular fibrin deposition (79). Also, symptoms like nausea, vomiting, malaise are present in most of the patients. Severe hypertension (systolic blood pressure >160mmHg, diastolic blood pressure >110mmHg) is also not a constant finding in HELLP syndrome. In several studies; it's demonstrated that no more than half of the patients had an admission blood pressure >160 / 110mmHg (81-83)

Pathology Findings of HELLP Syndrome

In a study conducted by Barton and colleagues (84), liver biopsies were obtained under direct visualization during cesarean delivery and histopathology findings were correlated with clinical and laboratory findings. Statistical analysis demonstrated that periportal hemorrhage and fibrin deposition differ according to the severity of the disease. However, no

Table 1: Laboratory Criteria for HELLP Syndrome

	AST	LDH	Platelet Count
Sibai et al. ⁸²	≥70 U/L	≥600 U/L	< 100 000 /mm ³
van Pampus et al. ⁸⁶	≥50 U/L	≥600 U/L	< 100 000 /mm ³
Martin et al. ⁸⁰	≥40 U/L	≥600U/L	< 150 000 /mm ³

significant relation was demonstrated between laboratory findings and histopathology. Although steatosis occurred in only one-third of the patients, it was correlated significantly with abnormalities in platelet count, aspartate amino transferase, and total bilirubin (84). As a result of that study and case reports it is concluded that the classic hepatic lesion associated with the HELLP syndrome is periportal or focal parenchymal necrosis.

Management

As in the management of severe preeclampsia, in the management of HELLP syndrome; patients should be hospitalized immediately and observed in a delivery unit. All of the patients should receive intravenous (IV) magnesium sulfate as prophylaxis against convulsions antihypertensive medications like hydralazine, labetalol and nifedipine to keep systolic blood pressure less than 155mmHg or diastolic blood pressure less than 100 mm Hg. And then fetal well-being should be evaluated by non stress test and biophysical profile, and ultrasonographic biometry should be obtained for possible fetal growth restriction. Finally, it must be decided whether immediate delivery is indicated based on the maternal and fetal status (81).

Several studies were conducted on the expectant management of HELLP syndrome, aiming to improve neonatal morbidity and mortality (85-87). As a conclusion of all these studies; it's demonstrated that laboratory abnormalities can reverse in a subgroup of patients, but no high-quality evidence is demonstrated to improve overall perinatal outcome in patients with HELLP syndrome. So that it seems expectant management of HELLP syndrome, remains an investigational approach and is contraindicated in women with disseminated intravascular coagulation (DIC) (85-87). It's suggested that the use of corticosteroids may shorten the duration of recovery in both laboratory and clinical findings (88). But there is no consensus on this suggestion according to several studies on this issue. In a trial by Fonseca et al, which is implemented in 132 pregnant patients with HELLP syndrome, patients used a regimen of 10 mg IV dexamethasone or placebo every 12 hours until delivery and 3 additional doses after delivery. As a result of that study it is noted that although the time of recovery of laboratory tests were not shortened by treatment, in the subgroup analysis; patients with severe HELLP syndrome (platelet count <50,000 / mm³) given dexamethasone had faster platelet count recovery and shorter hospitalization than controls (88). But in another trial implemented in only postpartum patients no benefit could be demonstrated (89).

The definitive therapy for HELLP syndrome is delivery whenever fetal lung maturation is achieved. HELLP syndrome is not an indication for immediate delivery by cesarean section. Patients presenting with well-established labor should be allowed to deliver vaginally in the absence of obstetrical contraindications. In patients with an unripe cervix and gestational age under 30 weeks, prostaglandin induction or elective cesarean sections are options for delivery management. Meperidine can be the drug of choice for obstetric analgesia. Epidural anesthesia should be used with caution and it's not suggested with a platelet count of less than 75,000 / mm³. Platelet transfusion is recommended in all patients with a platelet count of less than 20,000 / mm³. Correction of thrombocytopenia is of particular importance before cesarean section. It's advised to increase platelet count at least up to 40,000 / mm³ before delivery. To minimize the risk of hematoma formation, the bladder flap should be left open and a subfacial drain should be used for 24-48 hours (81).

Hepatic Complications

Subcapsular hematoma, rupture of subcapsular hematoma and hepatic infarction are the possible complications of HELLP syndrome. When marked elevations in serum amino transferases are established, these complications should be considered. Most cases are seen in the late second or third trimester of pregnancy, and occasionally in the immediate postpartum period. Serum amino transferase levels usually over 1000-2000 IU/L or higher and concomitant fever are typical findings for hepatic infarction. It's demonstrated that these patients may have an underlying procoagulant state, such as the antiphospholipid syndrome (90, 91).

Hepatic hematoma typically presents with abdominal pain, shoulder pain, nausea, and vomiting and most of the patients have severe thrombocytopenia and amino transferase levels over 1000-2000 IU/L or higher. If hepatic rupture occurs, swelling of the abdomen because of hemoperitoneum and shock rapidly follows (92). Volume replacement and blood transfusion as needed are recommended for a contained hematoma. The patient should be closely monitored for hemodynamics and coagulation status and serial assessment of the sub capsular hematoma should be done with ultrasound or CT. And also it is important to avoid exogenous sources of trauma to the liver for preventing rupture of the hematoma (93).

Rupture of a sub capsular hematoma of the liver is a life threatening complication of HELLP syndrome, which is a surgical emergency requiring acute multi disciplinary treatment. The surgical options include packing and drainage, ligation of the hemorrhaging hepatic segments, embolization of the hepatic artery, loosely suturing omentum or surgical mesh to the liver and use of an argon beam coagulator. In a retrospective study; among 35 cases analyzed since 1976, there was an 82% overall survival for the 27 cases managed by packing and drainage, whereas only 25% of 8 patients undergoing hepatic lobectomy survived (94). In a review of 53 cases with HELLP syndrome-associated liver rupture, by Reck et al. (95), it is reported that HELLP syndrome-associated liver rupture carried a mortality of 39% in spite of surgical interventions. They recommended an interdisciplinary approach including the use of temporary packing of the liver to control bleeding and noted a liver transplant as a last choice must be considered.

There is limited data for liver transplant for intractable hemorrhage due to HELLP syndrome-associated sup capsular hematoma. As a result of a few number of studies on this issue, the authors suggest that potential candidates are only those in whom all other measures fail to control hemorrhage, or when the liver has become devascularized such that there is no other alternative (96).

Survival of patients with subcapsular hematoma or rupture is associated with prompt diagnosis and immediate medical or surgical stabilization. These patients should be managed

in an intensive care unit with close monitoring of hemodynamic parameters and fluid status to avoid the potential for pulmonary edema or respiratory compromise. The data on subsequent pregnancy outcome after a subcapsular hematoma of the liver in pregnancy are limited. According to these limited data; such patients can have subsequent normal maternal and fetal outcomes (97).

Recurrence of HELLP syndrome in Subsequent Pregnancies

In a study, the rate of recurrence was reported in women with a history of HELLP syndrome, as 6% (98). Sibai et al. reviewed 212 pregnancies following pregnancy with HELLP syndrome and demonstrated that the incidence of preeclampsia varied from 19% in normotensive women to 75% in those with underlying hypertension (99).

Pancreatic Involvement of Preeclampsia

The incidence of pancreatic involvement of preeclampsia is 1 / 3428 and 1 / 1333, respectively in two different studies. These patients present with similar symptoms and signs with non-pregnant patients (100, 101).

As preeclampsia has been associated with vascular endothelial injury it is concluded that ischemia with preeclampsia can damage pancreas and gall bladder as well as liver (102). And it is recommended that delivery will be appropriate if pancreatic involvement occurs with HELLP syndrome (102).

Pancreatic Involvement of Preeclampsia

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