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# Impact of Elevated Liver Markers during Pregnancy

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**ABSTRACT**
The physiological changes in liver function in pregnancy are commonly transient, rarely permanent. Disorders arising in pregnancy, such as pre-eclampsia and eclampsia, acute fatty liver of pregnancy (AFLP), hemolysis, elevated liver enzyme and low platelets (HELLP) syndrome, cholestasis, hyperemesis gravidarum and isolated cases of raised liver enzymes canhave serious implications. Proper interpretation of liver function tests (LFTs) at an early stage can lead to timemanagement and may reduce complications in both mother and fetus. Normal LFTs do not always mean that the liver isnormal. A number of pitfalls can be encountered in the interpretation of basic blood LFTs. The commonly used LFTsprimarily assess liver injury rather than hepatic function. Abnormal LFTs may indicate that something is wrong with theliver, and they can provide clues to the nature of the problem but this is not always the case. The various biochemical tests,their pathophysiology, and an approach to the interpretation of abnormal LFTs are discussed in this review. Commonlyavailable tests includealanine transaminase, aspartate transaminase, alkaline phosphatase, bile acid, serum bilirubin, serumalbumin and prothrombin time.

**Keywords:**Liver function tests, pregnancy, delivery, obstetric

## I. INTRODUCTION

Changes in liver biochemical profile are normal during pregnancy. However, severe liver disease, although rare, can occur and must be recognized at an early stage to reduce morbidity and mortality for mother and infant. Here we provide an overview of the liver conditions that are primarily associated with pregnancy and the effect of pre existing liver disease in pregnancy.

Normal Liver FunctionInPregnancy:

Although the increase in the cardiac output peaks at32 weeks, the blood flow in the liver remains theSame or in some studies decreases.In a prospective analysis of aspartate transaminase (AST), alanine transaminase (ALT), bilirubin andGamma-glutamyl transferase (GGT) in 430 pregnantWomen it was found that these tests were about 20%Lower in pregnant women when compared withLaboratory reference ranges [4].Liver disease in pregnancy should be considered inThree categories:Pre-existing disease, disease specific to pregnancyAnd coincidental acute liver or biliary tree disease.

Serum albumin concentration falls in normal pregnancyAnd is thought to relate to the increase in total plasma volume. This may persist for several months after delivery.Serum alkaline phosphatase (ALP) increases and may reach2 to 4 times baseline level. This relates to placental production. In general, alanine aminotransferase (ALT), aspartateAminotransferase (AST), bilirubin, and gamma-glutamylTranspeptidase (GGT) concentrations remain normal, butElevations require further investigation. Table 1 summarizesThe biochemical changes seen during normal pregnancy.Ultrasound, if required, remains the preferred imagingModality. When further detailed images are needed, MRIWithout contrast is safe.

**Quantitative tests of Liver Functions :**

Limitations of the various biochemical tests have prompted the search for more sensitive and quantitative tests of liver function. Though these tests are currently limited to research centres they include [1]:Indocyanine green clearance, C-aminopyrine breathtest [2], antipyrine clearance, galactose eliminationcapacity, and C-caffeine breath test [3].

**Liver DisorderUniqueToPregnancy:**

Hyperemesis Gravidarum:

Hyperemesis Gravidarum Occurs in 0.3% to 2% of pregnancies, usually within the First trimester.1 Serum aminotransferases can be elevated by Up to 20 times the upper limit of

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normal. Jaundice is rare. Liver function tests normalize after the resolution of vomiting. Treatment is supportive with thiamine supplements, fluid replacement, and antiemetics.

Intrahepatic Cholestasis of pregnancy (ICP):

ICP isdefined as pruritus and raised serum bile acids occurring inthe second half of pregnancy that resolves after delivery.The incidence of ICP ranges from 0.1% to 1.5% of pregnancies.2,3 The cause of ICP remains unclear but is thought tobe related to abnormal biliary transport across the canalicular membrane. Mutations have been reported in the ABCB4And ATP8B1 genes, which encode phospholipid transporters, and in the ABCB11 gene, which encodes the principalBile salt transporter and the main bile acid receptor.4 ICPShould be suspected in women with pruritus without aRash. Aminotransferase activity can be increased by up to20 times normal. Risk factors include family history andPrevious cholestasis with the oral contraceptive. The keyDiagnostic test is fasting serum bile acid concentrationOf> 10 lmol/L. Maternal morbidity is low, but the risk ofFetal complications including preterm labor and intrauterineDeath is increased. Ursodeoxycholic acid is safe and widelyused.

Acute fatty Liver of pregnancy (AFLP):

AFLP is a rare, potentially life-threatening disease that affects 1 in 7000 to 16,000 pregnancies.An abnormality in mitochondrialBeta-oxidation is recognized as the cause of this condition;6The resultant reduced hepatic capacity to metabolize long-chain fatty acids leads to hepatotoxicity. AFLP usually presentsIn the third trimester. Presentation ranges from nausea andAbdominal pain to acute liver failure. Laboratory abnormalitiesInclude raised transaminases, international normalized ratio (INR), bilirubin, and serum uric acid levels. Patients withMore severe diseases may have disseminated intravascularCoagulation. Hypoglycemia is a poor prognostic sign. ImagingMay detect fatty infiltration. Microvesicular steatosis is a characteristic histopathological appearance.

Change InIndividualEnzymeSpecificToLiverDiseaseInPregnancy(SeeTable 1,2,3,):

Aspartate transaminase and alanine transaminase Markers of hepatocellular injury. The most commonly used markers of hepatocyte injury are AST (formerly serum glutamic-oxaloacetic transaminase) And ALT (formerly serum glutamate-pyruvate transaminase). AST is present in cytosolic and mitochondrial Isoenzymes and is found in the liver, cardiac muscle Skeletal muscle, kidneys, brain, pancreas, lungs, Leucocytes and red cells [5]. It is less sensitive and Specific for the liver. ALT, a cytosolic enzyme is found in its highest Concentrations in the liver and is more specific to the Liver [5]. Hepatocyte necrosis in acute hepatitis, toxic Injury or ischemic injury results in the leakage of Enzymes into the circulation. As markers of hepatocellular injury, AST and ALT also lack some Specificity because they are found in skeletal muscle. Levels of these aminotransferases can rise to several Times normal after severe muscular exertion or other Muscle injury, as in poliomyelitis [6], or in the Presence of hypothyroidism. In fact, AST and ALT Were once used in the diagnosis of myocardial Infarction. Slight AST or ALT elevations (within 1.5 times The upper limits of normal) do not necessarily Indicate liver disease. Part of this ambiguity has to Do with the fact that unlike the values in many other Biochemical tests, serum AST and ALT levels do not Follow a normal bell-shaped distribution in the Population [7]. Instead, AST and ALT values have A skewed distribution characterised by a long ‘tail’ at The high end of the scale [8]. The ALT distributions In males and nonwhites (i.e. blacks and Hispanics) Tend to have a larger tail at the high end, so that more Values fall above the upper limits of normal set for the Average population [9,10]. AST and ALT values are higher in obese patients, Probably because these persons commonly have fatty Livers [11]. ALT levels have been noted to decline With weight loss [12]. Depending on the physician’s Point of view, the upper limits of normal for AST and ALT levels could be set higher for more obese Persons.

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**Table 1. Common liver disorder in different trimestersof pregnancy**.

| Differential diagnosis | Trimester of pregnancy |
|---|---|
| Hyperemesis gravidarum | First |
| Gallstones | |
| Viral hepatitis | |
| Drug-induced hepatitis | |
| Intrahepatic cholestasis of pregnancy* | |
| Intrahepatic cholestasis of pregnancy | Second |
| Gallstones | |
| Viral hepatitis | |
| Drug-induced hepatitis | |
| Pre-eclampsia/eclampsia* | |
| HELLP syndrome* | |
| Intrahepatic cholestasis of pregnancy | Third |
| Pre-eclampsia/eclampsia | |
| HELLP syndrome | |
| Acute fatty liver of pregnancy | |
| Heptic rupture | |
| Gallstones | |
| Viral hepatitis | |
| Drug-induced hepatitis | |

**Table 2.Pregnancy associated liver disease -recurrence rate.**

| Pregnancy associated liver disease | Rate of recurrence (%) | Incidence (%) |
|---|---|---|
| Intra-hepatic cholestasis of pregnancy | 40–60 | 0.7 |
| HELLP | 4–27 | 0.2–0.6 |
| Acute fatty liver of pregnancy | Occasionally | 0.01 |
| Pre-eclampsia | 2–43 | 5–7 |

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**Table 3Liver disease specific to pregnancy and maternal fetaloutcome**

| Liver diseases specific to pregnancy | Maternal outcome | | Fetal outcome | | Neonatal outcome |
|---|---|---|---|---|---|
| | Maternal mortality | Morbidity | Perinatal mortality | Morbidity | |
| Obstretic cholestasis | Caeseran section rates: 10–36%<br>Postpartum haemorrhage: 2–22%<br>Recurrence rate: 60–70% | | 10.6/1000<br>Passage meconium:12% (T)<br>25% (PT) | Prematurity: 7–25% | |
| Pre-eclampsia | mortality: 1.8% | | | | |
| HELLP syndrome | Mortality: 2%<br>Abruptio placenta: 16%<br>Acute renal failure: 8%<br>Subcapsular liver Hematoma: 1%<br>Retinal detachment: 1%<br>DIC: 15%<br>Pulmonary edema: 8%<br>Recurrance: 2–6% | Hepatic failure:15% | 7–20%<br>14% | Prematurity: 70%<br>IUGR | |
| Acute fatty liver of pregnancy | 10–21%<br>Hypoglycemia<br>Renal failure:<br>pre-eclampsia: 20–40%<br>Deranged clotting: | Hepatic failure: | | 27–33% | Mortality: 7% |
| Hyperemesis gravidarum | Wernickes encephalopathy:<br>Korasakoffs psychosis:<br>Central pontine myelinolysis:<br>DVT: | | Low birth weights | | |
| Hepatic rupture and infarction | 16–60%<br>Coagulopathy<br>Hepatic abscess<br>Pleural effusion | Shock | 40–60%<br>Prematurity | | |

Alkaline Phosphate:

ALP originates mainly from two sources: liver and Bone [13]. The enzymes may be present in a variety Of other tissues namely intestine, kidney placenta and Leucocytes. The serum ALP level rises during the 3rd Trimester of pregnancy because of a form of the Enzyme produced in the placenta. When serum ALP Originates from bone, clues to bone disease are often Present, such as recent fracture, bone pain or Paget's Disease of the bone like the GGT value, the ALP Level can become mildly elevated in patients who are Taking phenytoin [14]. If the origin of an elevated serum ALP level is in Doubt, the isoenzymes of AP can be separated by Electrophoresis. However, this process is expensive and usually unnecessary because an elevated GGT Level, an elevated 50-nucleotidase level and otherLFT abnormalities, usually accompanies an elevatedLiver ALP value.Persistently, elevated ALP values in asymptomaticPatients, especially women, can be caused by primary biliary cirrhosis, which is a chronic inflammatory disorder of the small bile ducts.[15]

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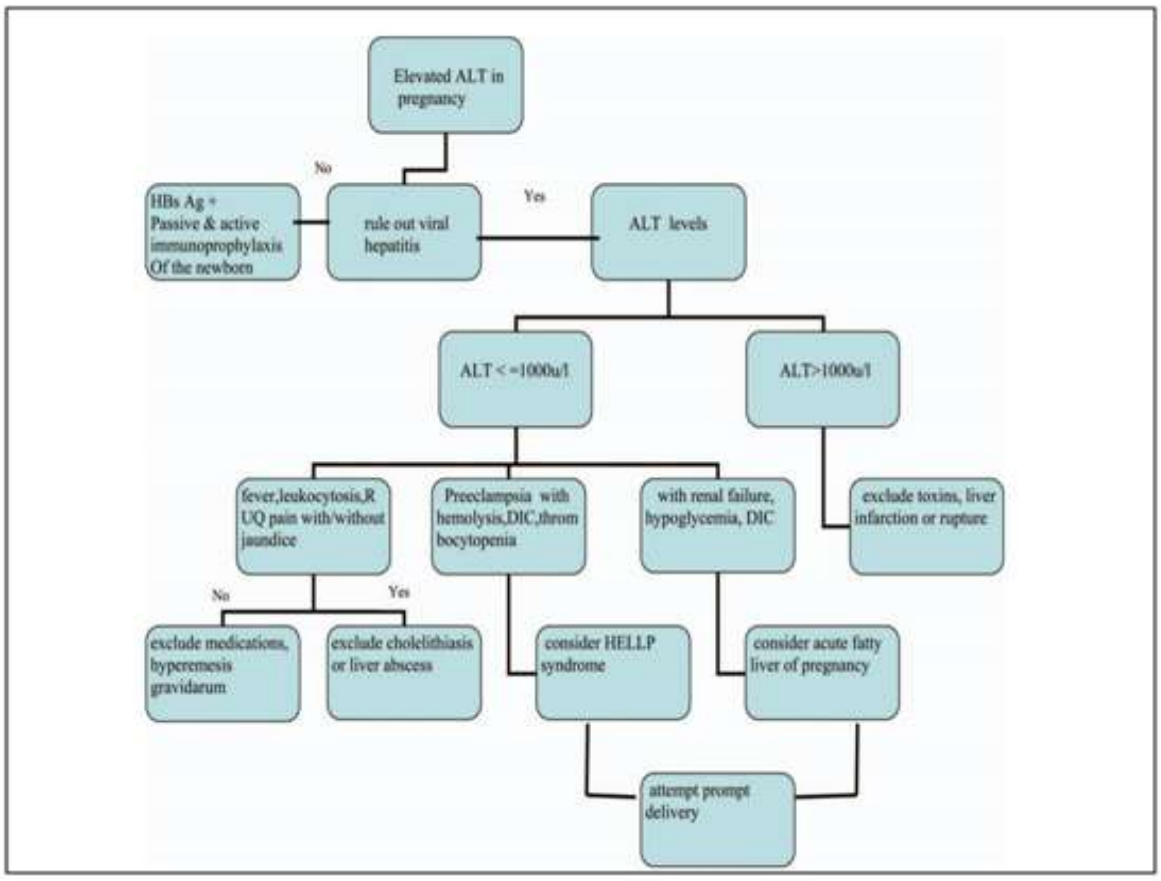


**Fig 1 Management of raise ALT in pregnancy.**

Common cause of raised ALP:Physiological Women in the third trimester of pregnancy adolescents Benign, familial (because of increased intestinal ALP). Pathological- bile duct obstruction, Primary biliary Cirrhosis, Primarysclerosincholangitis, Drug induced cholestasis – for example, anabolic steroids,Dult bile ductopenia, metastatic liver disease, bone disease.[16]

Bile Acid:

Bile acids are synthesised in the liver from cholesterol. The different bile acids are cholic, chenodoxycholic and deoxycholic acids. Serum bile acids areElevated in almost 92% of patients with obstetricsCholestasis. While raised transaminase and bilirubinis found in only 60% and 25%, respectively.[17-19] The rateof fetal complications increases when maternalSerum bile acid levels become elevated in womenwho develop intra-hepatic cholestasis of pregnancy (ICP). In a prospective cohort study conductedbetween February 1999 and January 2002 in SwedenICP (defined as pruritus in pregnancy plus 10 mmol/lOr more of serum bile acids) occurred in 1.5% of45,485 pregnancies recorded. The probability of theFetalcomplications of spontaneous preterm deliveries, asphyxial events, and meconium stainigof aminotic fluid, placenta and membranes rose by 1.5–2% for each additional mmole/l of maternal serum bile acids when the total level of bile acids exceeded 40 mmol/l.[20,21] No increase in fetal risks was detected in ICP patients with bile acid levels 540 mmol/l. Most of the woman with ICP (81%) had serum bile acids levels between 10 and 39 mmol/l (mild form), whereas the other 19% had serum bile acid levels more than 40 mmol/l (severe form) [22].

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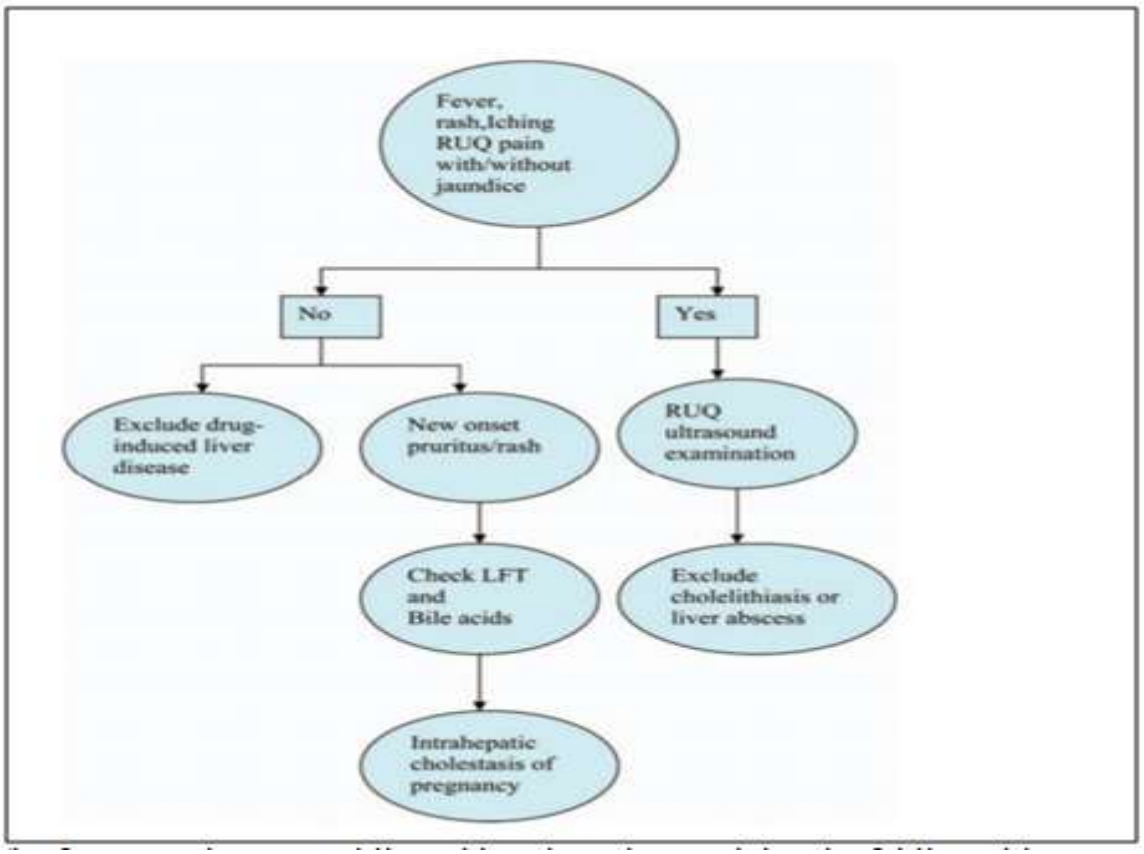


**Fig.2 Bile acid protocol in pregnancy**.

**KEY POINTS**

Abnormal liver tests may present in an asymptomatic patient.[23]

A good clinical history and physical examination Are often rewarding.

Liver tests often become abnormal in non-hepatic diseases.

If a systematic approach is adopted the cause is often apparent.[24]

An ultrasound should also be performed in Symptomatic patients with liver enzyme abnormalities or those with evidence of hepatic dysfunction (increased bilirubin or prothrombin time, or decreased albumin) and in those with biochemical Evidence of cholestasis.[25]

## II. CONCLUSION

Liver disease during pregnancy is a poorly studied topic and posses a challenge for both the gynecologist and hepatologists. Challenges involve diagnosis and determining the appropriate Treatment for the safety of both mother and baby. Liver disease in pregnancy is a complex issue that deserves a multidisciplinary approach. Nearly 3% of pregnancies are complicated by liver disease, and severe pregnancy-related liver disease Can have fatal consequences for the both mother and child. Diagnostic and therapeutic decisions must consider the implications for both, and rapid diagnosis is indispensable for severe Cases because the decision of immediate delivery is important for maternal and fetal outcomes. In pregnant women with suspected liver disease, it is essential to distinguish between the 2 main categories of liver disease: non-pregnancyrelated liver disease and the few diseases that are directly related to pregnancy. Pregnancy-related liver disease is the most frequent cause of liver dysfunction during pregnancy. We also need to keep in mind that pregnancy is associated with many normal physiological changes that should be considered in the diagnosis of liver disease. Pregnancy-related liver disorders exhibit trimester-specific characteristics in their occurrence, whereas non-pregnancy-related liver diseases can occur at any time.

## REFERENCE

[1]. Kallen B. Hyperemesis during pregnancy and delivery outcome: a registryStudy.

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Eur J Obst Gynecol Reprod Biol1987;26:291-302.
[2]. Reyes H. The enigma of intrahepatic cholestasis of pregnancy: lessons fromChile. Hepatology 1982;2:87-96.
[3]. Schneider G, Paus TC, Kullack-Ublick GA, Meier PJ, Wienker TF, Lang T,Et al. Linkage between a new splicing site mutation in the MDR3 alias ABCB4Gene and intrahepatic cholestasis of pregnancy. Hepatology 2007;45:150-158.
[4]. Williamson C, Mackillop L, Heneghan MA. Diseases of the liver, biliarySystem, and pancreas. Chapter 63. In: Creasy RK, Resnik R, Greene,MF, Iams JD, Lockwood CJ, Creasy and Resnik's Maternal-Fetal Medicine: Principles and Practice. 7th ed. Philadelphia, PA: Elsevier-Saunders;2014.
[5]. Reyes H, Sandoval L, Wainstein A, Ribalta J, Donoso S, Smok G, et al. AcuteFatty liver of pregnancy: a clinical study of 12 episodes in 11 patients. Gut1994;35:101-106.
[6]. Castro MA, Fassett MJ, Reynolds TB, Shaw KJ, Goodwin TM. Reversible peripartum liver failure: a new perspective on the diagnosis, treatment, and causeOf acute fatty liver of pregnancy, based on 28 consecutive cases. Am J ObstetGynecol1999;181:389-395.
[7]. Ch'ng CL, Morgan M, Hainsworth I, Kingham JG. Prospective study of liverDysfunction in pregnancy in Southwest Wales. Gut 2002;51:876-880.
[8]. Egerman RS, Sibai BM. HELLP syndrome. Clin ObstetGynecol1999;42:381-389.
[9]. Martin JN Jr, Rose CH, Briery CM. Understanding and managing HELLP syndrome: the integral role of aggressive glucocorticoids for mother and child.Am J ObstetGynecol 2006;195:914-34.
[10]. Joshi D, James A, Quaglia A, Westbrook RH, Heneghan MA. Liver disease inPregnancy. Lancet 2010;375:594-605.
[11]. Poupon R, Chretien Y, Chazouillieres O, Poupon RE. Pregnancy in womenWithursodeosxycholic acid-treated primary biliary cirrhosis. J Hepatol 2005;42:418-419.
[12]. Mushahwar IK. Hepatitis E virus: molecular virology, clinical features, diagnosis, transmission, epidemiology, and prevention. J Med Virol2008;80:646-58.
[13]. Mendez-Sanchez N, Chavez-Tapia NC, Uribe M. Pregnancy and gallbladderDisease. Ann Hepatol 2006;5:227-230.
[14]. Yasuda K, Okuda K, Endo N, Ishiwatari Y, Ikeda R, HayashiH, Yokozeki K, Kobayashi K, Iris Y. Hypoaminotransferasemia in patients undergoing long-term hemodialysis: clinicalAnd biochemical appraisal. Gastroenterology 1995;109:1295–1300.
[15]. Gitlin N, Serio KM. Ischemic hepatitis: widening horizons.Am J Gastroenterol 1992;87:831–836.
[16]. Cohen JA, Kaplan MM. The SGOT/SGPT ratio – anIndicator of alcoholic liver disease. Dig Dis Sci 1979;24:*-835–838.
[17]. Diehl AM, Potter J, Boitnott J, Van Duyn MA, HerlongHF,Mezey E. Relationship between pyridoxal 50-phosphateDeficiency and aminotransferase levels in alcoholic hepatitis.Gastroenterology 1984;86:632–636.
[18]. Barron WM. The syndrome of pre-eclampsia. GastroenterolClin North Am 1992;21:851–872.
[19]. Roberts WE, Perry KG Jr, Woods JB, Files JC, Blake PG,Martin JN Jr. The intra-partum platelet count in patients withHELLP (hemolysis, elevated liver enzymes, and low platelets)Syndrome: is it predictive of later hemorrhagic complications?Am J ObstetGynecol1994;171:799–804.
[20]. Sibai BM, Ramadan MK, Chari RS, Friedman SA. Pregnancies complicated by HELLP syndrome (hemolysis, elevatedLiver enzymes, and low platelets): subsequent pregnancyOutcome and long-term prognosis. Am J ObstetGynecol1995; 172(1 Part 1):125–129.
[21]. Barton JR, Riely CA, Adamec TA, Shanklin DR, Khoury AD,Sibai BM. Hepatic histopathologic condition does notCorrelate with laboratory abnormalities in HELLP syndrome(hemolysis, elevated liver enzymes, and low platelet count).Am J ObstetGynecol 1992;167:1538–1543.
[22]. Cameron IT, van Papendorp CL, Palmer RM, Smith SK,Moncada S. Relationship between nitric oxide synthesis andIncrease in systolic blood pressure in women with

hypertension in pregnancy. Hypertens Pregnancy 1993;12:85–92.

[23]. Hepburn IS, Schade RR: Pregnancy-associated liver disorders. Dig Dis Sci, 2008; 53: 2334–58

[24]. Arrese M, Macias RIR, Briz O et al: Molecular pathogenesis of intrahepatic Cholestasis of pregnancy. Expert Rev Mol Med, 2008; 10: e9

[25]. Beuers U, Pusl T: Intrahepatic cholestasis of pregnancy-a heterogeneous Group of pregnancy-related disorders? Hepatology, 2006; 43: 647–49