Original Article

Frequency and Etiology of Altered Liver Function in Pregnancy

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ABSTRACT

OBJECTIVE: To determine the frequency of etiology of altered liver function in pregnancy in patients admitted to a tertiary care hospital.

METHODOLOGY: This was a Descriptive Cross-sectional study conducted at the Department of Obstetrics and Gynecology Liaquat University of Medical and Health Sciences Hyderabad from June 2017 to May 2018 after approval from the Ethical Review Committee and College Of Physicians And Surgeons Pakistan. A total of 370 patients with altered Liver Function Tests (LFT), 16 to 40 years of age, primi and multiparous in all trimesters of pregnancies, were included in this study. Patients with pre-existing liver disorders, hypertension, and diabetes mellitus and who have taken hepatotoxic medications in the past six months were excluded from the study. A Non-probability consecutive sampling method was used. Data was collected by preformed structure Performa and analyzed on (SPSS) version 22.

RESULTS: The mean age of the patients was 28.62±4.96 years. Pre-eclampsia was the most typical reason for liver dysfunction during pregnancy, accounting for 48.1% of the cases, followed by HELLP syndrome in 19.2%, acute fatty liver of pregnancy in 7.8%, Obstetric cholestasis accounted for 7% of the cases, and hyperemesis gravidarum 7.8% were found. Altered liver functions that are not directly related to pregnancy were Cholelithiasis (5.4%) and Viral Hepatitis (7%).

CONCLUSION: The prime reasons for abnormal liver function tests are pregnancy-related liver disorders. Prior and prompt care by the obstetric and gastroenterologist team can benefit this disheartening situation in underdeveloped countries.

KEYWORDS: Liver dysfunction, Altered liver function test (LFT), hyperemesis gravidarum, Cholelithiasis, Pre-eclampsia, Acute fatty liver, Obstetric cholestasis.

INTRODUCTION

Liver disorders during pregnancy are more prevalent than anticipated and possibly need specialized interventions[1]. It affects about 3% of all pregnancies[2]. Several physiological changes occur during pregnancy for the growth and structural development of a baby[3]. Liver physiology may change during pregnancy, which later on may progress to liver disease. The severity of the disease is related to morbidity and mortality[4]. Some liver diseases are specific to pregnancy, like acute fatty liver of pregnancy (AFLP) and Intrahepatic cholestasis of pregnancy (IHCP); some are multi-systemic diseases with hepatic manifestations, for example, preeclampsia[5], which is a widespread cause of maternal and perinatal mortality[6].

Elevated liver enzymes can sometimes be encountered in asymptomatic pregnant women[7]. Therefore, an early diagnosis is important[8] for further assessment and accurate management[9]. The history and clinical examination provide valuable devices for distinguishing between un-pregnancy and pregnancy-related causes such as non-alcoholic fatty liver disease, acute viral infection, autoimmune liver disease, and Budd-Chiari syndrome. The natural path of liver functions may be affected by a pregnancy, for example, by an increased risk of hemorrhage due to acute viral hepatitis E infection and hepatocellular adenoma[10].

Symptoms of liver dysfunction may differ according to the seriousness of liver injury, from Nausea, vomiting, fever, and abdominal pain to the signs of acute liver failure. Palmar erythema and spider angioma are usual physical examination findings in pregnancy; their presence may not specify underlying chronic liver disease[11]. Comprehension of pathogenesis and explanation of liver disease in pregnancy is nowadays advanced. Many classic diagnostic tests are available, and many more are under research, even though assessment for liver disease should begin with noninvasive testing[12], which includes laboratory and radiographic studies. Laboratory investigations such as liver enzyme abnormalities and radiographic tests include conventional liver ultrasound.

Further radiographic evaluation is needed; magnetic resonance imaging without contrast is bearable during pregnancy. Computed tomography in pregnancy must be carefully used due to the risks of ionizing radiation on the fetus. Invasive testing, such as liver biopsy and endoscopy, may be planned for proper management[3]. The definition of abnormal liver function test pertained

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to value higher than normal range as defined by local laboratory (bilirubin > 24micro mol/l, alkaline phosphatase (ALP) >103 U/L, gamma-glutamyl transpeptidase (GGT) >26 U/L, (ALT) Alanine Aminotransferase or Serum glutamic – pyruvic transaminase (SGPT) > 51 U/L, Aspartate aminotransferase (AST) > 33 U/L[17].

Prior diagnosis and timely decision for termination of pregnancy is the keystone of management. The life of the mother is the prime concern; hindrances in diagnosis and delivery may have adverse maternal and fetal outcomes.

This study will help us to know the burden of disease and will help us to understand the etiologies that affect our population better. In the long run, it may help us make protocols for early screening of common etiologies, leading to time management and a decrease in mortality.

METHODOLOGY

This Descriptive Cross-sectional study was conducted in the Department of Gynecology and Obstetrics, Liaquat University of Medical and Health Sciences, Jamshoro, Hyderabad, from June 2017 to May 2018 after the Ethical approval from the College Of Physicians And Surgeons Pakistan. A total of 370 pregnant women with altered liver function were included in this study. The sampling technique was nonprobability, which is consecutive sampling. All pregnant ladies 16 to 40 years of age, primipara, multipara, and grand multipara in all three trimesters with altered liver function tests admitted to Obstetrics and gynecology unit at Liaquat University Hospital were included in this study. All Patients with known pre-existing liver disorders, hypertension, or diabetes mellitus and patients who have taken hepatotoxic medications during the past six months were excluded.

The aim of the study was explained to the patients, and written informed consent was signed. Relevant investigations were sent, including Liver function test (LFT), blood sugar fasting, serum uric acid, Complete blood count (CBC), serum ammonia, serum creatinine, Prothrombin time (PT), International normalized ratio (INR) and serum lactate dehydrogenase (LDH) level. Ultrasound of the abdomen and pelvis was done, and HBsAg, anti-HCV antibody, and IgM for hepatitis A and E were analyzed. The data was collected on preformed structure Performa and analyzed on (SPSS) version 22. For qualitative data, booking status and outcome [Acute fatty liver, Hemolysis elevated liver enzymes and low platelet syndrome (HELLP), obstetric cholestasis, pre-eclampsia, hyperemesis, gravidarm, Cholelithiasis, viral hepatitis] were expressed as frequency and percentage. Mean and standard deviation were calculated for quantitative data (age, parity, gravida, and gestational age).

The outcome variables were stratified based on age groups, parity, gravida, gestational week of pregnancy, parity, and booking status. The post-stratification Chi-square test was applied to see the effect on outcome. A P-value of 0.05 was taken as statistically significant.

RESULTS

In this research, a total of 370 pregnant women with altered liver function tests were included. Some physiologic characteristics are shown in **Table I**. The average age of the patients was 28.62±4.96 years. Likewise, the average gestational age was 38.42 weeks, gravida 2.83, and parity 1.83 are revealed **(Table I)**. The frequency of etiology of altered liver function in pregnancy is presented in **Table II**. Pre-eclampsia was the most typical reason for liver dysfunction during pregnancy, accounting for 48.1% of the cases, followed by HELLP syndrome in 19.2%, acute fatty liver of pregnancy 7.8%, Obstetric cholestasis accounted to 7% of the cases, hyperemesis gravidarum 7.8%. Altered liver functions not directly related to pregnancy were Cholelithiasis at 5.4% and Viral Hepatitis at 7%.

Stratification analysis concerning gestational age and parity was performed and presented in **Table III**. Liver dysfunction due to pre-eclampsia, HELP syndrome, and obstetric cholestasis were more common in primigravida than in multigravida women. Only Cholelithiasis was found to be significantly varied in 3 groups of parity. We did not find any significant difference for any of the etiological factors between 36 -37 and more than 38 weeks, except pre-eclampsia and acute fatty liver of pregnancy. (**Table III**)

TABLE I: PHYSIOLOGIC CHARACTERISTICS IN A PREGNANT WOMAN

Variables	Mean ±SD	95 % Confidence Interval
Age (Years)	28.62±4.96	28.11-29.13
Gestational Age (Weeks)	38.42±1.12	38.30-38.53
Gravida	2.83±1.13	2.72-2.95
Parity	1.83±1.13	1.72-1.95

TABLE II: FREQUENCY FOR ETIOLOGY OF ALTERED LIVER FUNCTION IN PREGNANCY

Etiology of Altered Liver Function	Frequency	Percentage %
Acute Fatty Liver of Pregnancy	29	7.8
HELLP	71	19.2
Obstetric Cholestasis	26	7
Pre-eclampsia	178	48.1
Hyperemesis gravidarum	28	7.6
Cholelithiasis	20	5.4
Viral Hepatitis	26	7

TABLE III: FREQUENCY FOR ETIOLOGY OF ALTERED LIVER FUNCTION IN PREGNANCY BY GESTATIONAL AGE & PARITY

Etiology Of Altered Liver Function	Gestational age (Weeks)		P-Value	Parity			P-Value <0.05
	36-37 n=228	≥38 n=142		Primi n=203	Multi n=148	Grand multi n=19	
Acute Fatty Liver of Pregnancy	20(8.8%)	9(6.3%)	0.397	15(7.4%)	12(8.1%)	2(10.5%)	0.877
HELLP	41(18%)	30(21.1%)	0.455	41(20.2%)	28(18.9%)	2(10.5%)	0.589
Obstetric Cholestasis	15(6.6%)	11(7.7%)	0.669	19(9.4%)	7(4.7%)	0(0%)	0.115
Pre-eclampsia	111(48.7%)	67(47.2%)	0.779	105(51.7%)	64(43.2%)	9(47.4%)	0.291
Hyperemesis gravidarum	14(6.1%)	14(9.9%)	0.188	20(9.9%)	8(5.4%)	0(0%)	0.131
Cholelithiasis	14(6.1%)	6(4.2%)	0.428	1(0.5%)	15(10.1%)	4(21.1%)	0.0005
Viral Hepatitis	18(7.9%)	8(5.6%)	0.408	9(4.4%)	16(10.8%)	1(5.3%)	0.066

DISCUSSION

Pregnancy is characterized by numerous physiological changes that may lead to diverse gastrointestinal symptoms, raising the challenge for gastroenterologists and obstetricians[13]. Genuine interpretation of abnormal liver function tests is required to avoid misdiagnosis[14]. The younger age group has a higher prevalence of liver dysfunction. Our research shows that most women are 26-30 (**Table I**). The average age of the patients was 28.62±4.96 years. Most of the women were un-booked in our study for antenatal care and generally got admitted through the emergency department or referred from rural areas and secondary care hospitals. Similar facts are observed in the study conducted by Ling Yi C 2011[15] and Nagaria T 2005[16].

Most studies describe the source of abnormal LFT as pregnancy-related and range from 67 to 89 %[17,18]. Hypertensive disorders of pregnancy that involve the liver include pre-eclampsia/eclampsia and HELLP syndrome. Pre-eclampsia is seen in about 3% to 5% of pregnancies; hepatic dysfunction with pre-eclampsia is acknowledged for a long time[19]. Three to 10 percent of patients with pre-eclampsia may progress towards HELLP syndrome and account for 0.1 percent of all pregnancies[20,21]. In this research, Pre-eclampsia was the most common cause of altered liver function in pregnancy, calculating 48.1% of cases, followed by HELLP syndrome in 19.2% of cases (**Table II**). It often develops in the second half of pregnancy in genetically prone individuals[22]. The incidence of intrahepatic cholestasis during pregnancy varies from 0.1 to 1.5 % in pregnancies23; 7% of women had intrahepatic cholestasis during pregnancy in our study. In contrast, one Pakistani study conducted in Rawalpindi had a very low incidence of 0.4%[24]. In another study conducted by Ambros-Rudolph, the incidence was 2%, but the main concerns were the cutaneous lesions done by determatologists[22].

Acute fatty liver during pregnancy is an infrequent, certainly lethal disease characterized by microvesicular fatty infiltration of the liver leading to multiorgan failure. Because of the potential for rapid progression to coma and death, AFLP is considered to be an obstetrics emergency[25]. It affects 1 in 7000 to 16,000 pregnancies[26]. One study conducted by Knight et al. in the UK showed that the incidence of AFLP was 5 cases per 100,000 maternities[27]. On the other hand, our study is dissimilar from the above results and has shown that altered liver function in pregnancy is widespread. We found the frequency of AFLP was 7.8% as an etiology of altered liver function in pregnancy. Hyperemesis Gravidarum is a brutal form of Nausea and vomiting during pregnancy. In one series, hyperemesis gravidarum accounted for 32% of liver function test abnormalities among pregnant women of all gestational ages; 7.8% of patients in our study showed hyperemesis gravidarum as an etiology of altered liver function in pregnancy. Viral hepatitis is prevalent in developing countries; on the other hand, hepatitis E is associated with fulminant hepatic failure in pregnancy[28].

The evaluation and treatment of viral hepatitis during pregnancy need exceptional consideration. All five liver-specific viruses (hepatitis A, B, C, D, E) each have individual epidemiology and likelihood to progress towards chronic liver disease or other complications.[29] We did not find any significant difference for any of the etiological factors between 36 -37 and more than 38 weeks, except pre-eclampsia and acute fatty liver of pregnancy. (**Table III**) Cholelithiasis is found in about 6 percent of pregnant ladies. Pregnancy, multiparty, and obesity are the risk factors of cholelithiasis[30]. In our study, 5.4% of women had Cholelithiasis as a cause of altered liver function not directly related to pregnancy. Cholelithiasis was found to be significantly varied in 3 groups of parity.

CONCLUSION

The prime source of altered liver function tests is pregnancy-related disorders. Women with pre-eclampsia or HELLP syndrome are at higher risk for peri and postpartum complications, with consecutive comorbidities. Despite research and advancement in medical care, maternal and fetal outcomes are not gratifying. A structured approach, prior and prompt multidisciplinary care can bring bright results in the developing world.

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AUTHOR CONTRIBUTION

Najam H: Primary investigator, Data collection
Memon FP: Manuscript writing, Introduction
Naeem S: Data analysis, Results
Memon A: Data analysis, Discussion

REFERENCES

1. Zhuang X, Cui AM, Wang Q, Cheng XY, Shen Y, Cai WH et al. Liver dysfunction during pregnancy and its association with preterm birth in China: A prospective cohort study. EBioMedicine. 2017; 26: 152-156. doi: 10.1016/j.ebiom.2017.11.014.
2. Garcia-Romero CS, Guzman C, Cervantes A, Cerbon M. Liver disease in pregnancy: Medical aspects and their implications for mother and child. Ann Hepatol. 2019; 18(4): 553-562. doi: 10.1016/j.aohep.2019.04.009.
3. Brady CW. Liver disease in pregnancy: What's New. Hapatol Commun. 2020; 4(2): 145-156. doi: 10.1002/hep4.1470.
4. Westbrook RH, Dusheiko G, Williamson C. Pregnancy and liver disease. J Hepatol. 2016; 64 (4): 933-945.
5. Alese MO, Moodley J, Naicker T. Pre-eclampsia and HELLP syndrome, the role of the liver. J Matern Fetal Neonatal Med. 2021; 34(1): 117-123. doi: 10.1080/14767058.2019. 1572737.
6. Lao TT. Implications of abnormal liver function in pregnancy and non-alcoholic fatty liver disease. Best Pract Res Clin Obstet Gynaecol. 2020; 68: 2-11. doi: 10.1016/j. bpobgyn.2020.02.011.
7. Zhong Y, Zhu F, Ding Y. Early diagnostic test for acute fatty liver of pregnancy: a retrospective case -control study. BMC Pregnancy Childbirth. 2020; 20(1): 162. doi: 10.1186/s12884-020-2787-4.
8. Guarino M, Cossiga V, Morisco F. The interpretation of liver function test in pregnancy. Best Pract Res Clin Gastroenterol. 2020; 44-45: 101667. doi: 10.1016/j.bpg.2020.101667.
9. Frise C, Williamson C. Liver disease in pregnancy. Medicine (Baltimore). 2016; 43(11): 636–8. doi: doi: 10.1016/j.mpmed.2015.08.010.
10. Alghamdi S, Fleckenstein J. Liver disease in pregnancy and transplant. Curr Gastroenterol Rep. 2019; 21(9): 43. doi: 10.1007/s11894-019-0711-8.
11. Tran TT, Ahn J, Reau NS. ACG clinical guidelines: Liver disease and pregnancy. Am J Gastroenterol. 2016; 111(2): 176-194. doi: 10.1038/ajg.2015.430.
12. Gomes CF, Sousa M, Lourenco I, Martins D, Torres J. Gastrointestinal diseases during pregnancy: What does gastroenterologist need to know? Ann Gastroenterol. 2018; 31(4): 385-394.
13. Joshi D, James A, Quaglia A, Westbrook RH, Heneghan MA. Liver disease in pregnancy. Lancet. 2010; 375(9714): 594-605. doi: 10.1016/S 0140-6736(09)61495-1.
14. Ling Yi C, Barge N, Dalal AR. Study of jaundice in pregnancy in a tertiary care Institute in India. Bombay Hosp J. 2011; 53(2): 181-3.
15. Nagaria T, Agarwal S. Fetomaternal outcome in jaundice during pregnancy. J Obstet Gynecol India. 2005; 55(5): 424-27.
16. Wong HY, Tan JYL, Lim CC. Abnormal liver function tests in the symptomatic pregnant patient: the local experience in Singapore. Ann Acad Med Singapore. 2004; 33(2): 204-8.
17. Harish K, Nitha R, Harikumar R, Kumar KS, Varghese T, Sreedevi NS, et al. Prospective evaluation of abnormal liver function tests in pregnancy. Trop Gastroenterol. 2005; 26(4): 188-93.
18. Barron WM. The syndrome of pre-eclampsia. Gastroenterol Clin North Am. 1992; 21 (4): 851–72.
19. Roberts WE, Perry Jr KG, Woods JB, Files JC, Blake PG, Martin Jr JN. The intrapartum platelet count in patients with HELLP (Hemolysis, elevated liver enzymes, and low platelets) syndrome: is it predictive of later hemorrhagic complications? Am J Obstet Gynecol. 1994; 171 (3): 799-804. doi: 10.1016/0002-9378(94)90101-5.
20. Sibai BM, Ramadan MK, Chari RS, Friedman SA. Pregnancies complicated by HELLP syndrome (Hemolysis, elevated liver enzymes, and low platelets): subsequent pregnancy outcome and long-term prognosis. Am J Obstet Gynecol. 1995; 172(1 Pt. 1): 125-9. doi: 10.1016/0002-9378(95) 90099-3.
21. Ambros-Rudolph CM. Dermatoses of pregnancy -

clues to diagnosis, fetal risk, and therapy. Ann Dermatol. 2011; 23(3): 265-75.
22. Dang A, Agarwal N, Bathla S, Sharma N, Balani S. Prevalence of liver disease in pregnancy and its outcome with emphasis on obstetric cholestasis: a Indian scenario. J Obstet Gynecol India. 2010; 60(5): 413–8.
23. Rasheed S, Afghan S, Mazhar SB. What's fetomaternal outcome in patients with obstetric cholestasis? Ann Pak Inst Med Sci. 2009;5:211-5.
24. Liu J, Ghaziani TT, Wolf JL. Acute Fatty Liver Disease of Pregnancy: Updates in Pathogenesis, Diagnosis, and Management. Am J Gastroenterol. 2017; 112(6): 838-846.
25. Castro MA, Fassett MJ, Reynolds TB, Shaw KJ, Goodwin TM. Reversible peripartum liver failure: a new perspective on the diagnosis, treatment, and cause of acute fatty liver of pregnancy, based on 28 consecutive cases. Am J Obstet Gynecol 1999; 181(2): 389-95. doi: 10.1016/s0002-9378(99)70567-3.
26. Knight M, Nelson-Piercy C, Kurinczuk JJ, Spark P, Brocklehurst P, UK Obstetric Surveillance System. A prospective national study of acute fatty liver of pregnancy in the UK. Gut. 2008; 57(7): 951-956. doi: 10.1136/gut.2008.148676.
27. Beniwal M, Kumar A, Kar P, Jilani N, Sharma JB. Prevalence and severity of acute viral hepatitis and fulminant hepatitis during pregnancy: a prospective study from north India. Indian J Med Microbiol. 2003; 21: 184-5.
28. Terrault NA, Levy MT, Cheung KW, Jourdain G. Viral hepatitis, and pregnancy. Nat Rev Gastroenterol Hepatol. 2021; 18(2): 117-130. doi: 10.1038/s41575-020-00361-w.
29. Littlefield A, Lenahan C. Cholelithiasis: Presentation and Management. J Midwife Women's Health. 2019; 64(3): 289-297.