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Liver diseases in pregnancy and outcomes: A retrospective study from Saudi Arabia

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Abstract

Liver diseases unique to pregnancy are common causes of both maternal and fetal mortality and morbidity. We retrospectively studied liver diseases unique to pregnancy, including hyperemesis gravidarum (HG); intrahepatic cholestasis of pregnancy; eclampsia; preeclampsia; hemolysis, elevated liver enzymes, and a low platelets (HELLP) syndrome; and acute fatty liver of pregnancy. We collected data including maternal age, gestational weeks at presentation and at delivery, mode of delivery, number of parity, and laboratory markers at 0, 1 week, and within 24 hours after delivery; from 112 patients (mean age, 29.8 years) from April 2015 - March 2017. SPSS 22 was used for statistical analysis. We The commonest liver disease in pregnancy was pre-eclampsia followed by HG. HG patients were younger compared with those with eclampsia and preeclampsia (P=0.025). Gestational week at presentation and the week of delivery were significantly greater for preeclampsia/eclampsia and HELLP patients compared to HG. Primigravida represented 42.9% of our patients. Fetal complications were reported in 29 (26%) of cases. Of those, 17 had fetal or neonatal death. Fourteen mothers (12.5%) had ICU admission. Pregnancy related liver diseases are important causes for fetal mortality and morbidity. Maternal age and gestational weeks are important predictors of fetal and maternal outcomes. *(Afr J Reprod Health 2021; 25[3]: 121-129).*

Keywords: Epidemiology, liver diseases, pregnancy, fetal, maternal

Résumé

Les maladies du foie propres à la grossesse sont des causes courantes de mortalité et de morbidité maternelles et fœtales. Nous avons étudié rétrospectivement les maladies du foie propres à la grossesse, y compris l'hyperemesis gravidarum (HG); cholestase intrahépatique de la grossesse; éclampsie; prééclampsie; hémolyse, élévation des enzymes hépatiques et syndrome de bas taux de plaquettes (HELLP); et stéatose hépatique aiguë de la grossesse. Nous avons recueilli des données comprenant l'âge maternel, les semaines de gestation à la présentation et à l'accouchement, le mode d'accouchement, le nombre de parité et les marqueurs de laboratoire à 0, 1 semaine et dans les 24 heures suivant l'accouchement; de 112 patients (âge moyen, 29,8 ans) d'avril 2015 à mars 2017. SPSS 22 a été utilisé pour l'analyse statistique. Nous La maladie hépatique la plus courante pendant la grossesse était la pré-éclampsie suivie de l'HG. Les patients atteints de HG étaient plus jeunes que ceux atteints d'éclampsie et de prééclampsie (P = 0,025). La semaine gestationnelle lors de la présentation et la semaine de l'accouchement étaient significativement plus importantes pour les patients prééclampsie / éclampsie et HELLP par rapport à HG. Primigravida représentait 42,9% de nos patients. Des complications fœtales ont été rapportées dans 29 (26%) des cas. Parmi ceux-ci, 17 ont eu un décès fœtal ou néonatal. Quatorze mères (12,5%) ont été admises à l'USI. Les maladies hépatiques liées à la grossesse sont des causes importantes de mortalité et de morbidité fœtales. L'âge maternel et les semaines de gestation sont des prédicteurs importants des issues fœtales et maternelles. *(Afr J Reprod Health 2021; 25[3]: 121-129).*

Mots-clés: Epidémiologie, maladies du foie, grossesse, fœtus, maternel

Introduction

Liver disorders in pregnancy are a major cause of maternal and fetal morbidity and mortality[1,2]. They can be divided into non-pregnancy related diseases and liver diseases unique to pregnancy. Non-pregnancy related diseases are either pre-existent during pregnancy or coincidental with pregnancy, including: viral hepatitis, gallstones, autoimmune hepatitis, vascular diseases (Budd Chiari), or drug induced liver injury[1-3]. Etiologically, liver diseases unique to pregnancy are related to either gestation

or its complications, such as hyperemesis gravidarum, intrahepatic cholestasis of pregnancy, eclampsia, pre-eclampsia, HELLP syndrome, and acute fatty liver of pregnancy[1-4]. Management of liver diseases in pregnancy requires coordination between obstetricians and gastroenterologists/hepatologists, usually involving the delivery of the fetus and supportive care[1-4].

Hyperemesis gravidarum

Hyperemesis gravidarum (HG) refers to severe nausea and vomiting that occurs during early pregnancy. This usually resolves by the 20th week of gestation but in some cases may persist throughout the pregnancy and resolves after delivery. Symptoms may be severe, requiring hospitalization and fluid replacement. The incidence of HG is 0.3-2% in all pregnancies. Liver test abnormalities are seen in 50–60% of women with HG in the form of a mild elevation in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels. In rare cases, AST and ALT levels have been found to be more than 20 times the upper limit of normal. Management of liver disease in HG is mainly supportive. Antiemetics such as promethazine, metoclopramide, or ondansetron may be used. Intravenous fluid hydration and electrolyte replacement is the mainstay of treatment. Outcomes of liver disease due to HG are generally favorable[1-6].

Intrahepatic cholestasis of pregnancy

Intrahepatic cholestasis of pregnancy (IHCP) is the most common liver disease of pregnancy. The incidence of IHCP is 0.3-5.6%. It presents as persistent pruritus typically in the palms and soles and may involve the whole body most intensely at night. The onset usually occurs in the second and third trimesters and resolves with delivery. Jaundice following pruritus may occur in up to 10-25% of patients. Other symptoms include fatigue, anorexia, epigastric pain, and steatorrhea due to fat malabsorption leading to vitamin K deficiency, prolonged prothrombin time, and postpartum hemorrhage. Risk factors of IHCP include advanced maternal age, multiparity, prior episode of cholestasis secondary to oral contraceptive use, and a previous or family history of IHCP.

Elevated serum bile acid levels (>10 μmol/L) confirm the presence of cholestasis with increased cholic acid levels and decreased chenodeoxycholic acid levels. Most complications occur when bile acid levels exceed 40 μmol/L. AST levels are also elevated with values >1,000 U/L. Hyperbilirubinemia may also affect the myometrial contractility and can cause chorionic vein constriction leading to premature delivery, fetal distress, and intrauterine fetal death. Overall, maternal outcomes are favorable.

Management of IHCP aims to relieve pruritis, improve hyperbilirubinemia, and minimize fetal morbidity and mortality. The first line of treatment is ursodeoxycholic acid (UDCA) at 10-15 mg/kg maternal body weight. UDCA was found to be superior over cholestyramine, S-adenosyl-L-methionine, and dexamethasone. Antihistamines may be used for symptomatic relief of the pruritis. Early delivery at 37 weeks is encouraged, because of increased risk of intrauterine death during the last month of gestation[1-7].

Preeclampsia/ Eclampsia

Preeclampsia refers to the development of hypertension (≥140/90 mmHg), edema, and proteinuria (≥300 mg/24 h) after the 20th week of pregnancy, and it is associated with. renal, liver, neurological, or haematological dysfunction ***Eclampsia*** refers to the onset of seizures in a woman with pre-***eclampsia***. Although liver involvement is not frequent, it reflects severe pre-eclampsia with significant perinatal morbidity and mortality. The incidence of pre-eclampsia is 3-10% in all pregnancies. Patients may complain of epigastric or right upper quadrant pain due to underlying hepatomegaly. In preeclampsia, AST levels can be mildly or strikingly elevated, however the magnitude of the liver chemistry abnormalities correlates with the risk of adverse maternal outcomes but not with adverse fetal outcomes. There are risks to both the mother and the fetus when eclampsia occurs, including intrauterine growth restriction, low birth weight, placental abruption, fetal distress, maternal pulmonary edema, maternal renal failure, amaurosis fugax or retinal detachment, cerebral edema, and/or intracerebral hemorrhage. Maternal mortality from preeclampsia/eclampsia is rare but may approach

15-20% in developed countries. Fetal mortality rate is also rare, occurring in 1-2% of births. Magnesium sulfate is used to treat and prevent convulsions. The agents of choice for blood pressure control are hydralazine and/or labetalol. The only effective treatment is delivery of the fetus and the placenta[1-6].

Hemolysis, elevated liver tests, and low platelets syndrome

Hemolysis, elevated liver Enzymes and low platelets (HELLP) syndrome can either occur as a complication of preeclampsia/eclampsia or it can occur on its own in the third trimester or postpartum. Up to 12% of women with severe preeclampsia experience HELLP syndrome, occurring in 0.2-0.8% of all pregnancies. Patients may be asymptomatic or complain of upper abdominal pain, nausea and vomiting, headache, lower limb edema, or weight gain. Around 5% of patients may develop jaundice. A possibility of overlap of HELLP syndrome and acute fatty liver of pregnancy has been suggested due to an association with a defect in long-chain 3-hydroxyacyl-coenzyme A dehydrogenase (LCHAD). Risk factors include race (Caucasian), multiparity, family history of HELLP, and extremes of maternal age[1-3].

AST elevations range from mild to markedly elevated levels. Thrombocytopenia is usually observed with a platelet count under 100000/mL. Mildly elevated serum bilirubin levels (usually < 5 mg/dL), lactate dehydrogenase (LDH) levels > 600 IU/L, and fragmented red blood cells (schistocytes) and burr cells on peripheral blood smears are compatible with the underlying hemolysis. Prothrombin time is usually normal except in severe cases, which are complicated by disseminated intravascular coagulation.

Liver biopsy is not needed to diagnose HELLP syndrome. However, if indicated, the biopsy can show periportal hemorrhage and intrasinusoidal fibrin deposition, typical of pre-eclampsia. Hepatic steatosis is present but is usually modest and not as extensive as in patients with acute fatty liver of pregnancy[1-3,5].

The definitive treatment of HELLP syndrome is delivery. After delivery, neither the mother nor the infant has long term liver involvement. The outcome of the infant is appropriate for gestational age. If gestational age is beyond 34 weeks, immediate delivery is recommended. If the gestational age is between 24 and 34 weeks, corticosteroids should be given to expedite fetal lung maturity 48 hours prior to induction. In some patients with severe HELLP syndrome, platelet transfusion, hemodialysis, or plasmapheresis may be required. Close monitoring of the mother and fetus is recommended before and after delivery for up to 48 hours postpartum. Full recovery is noted in the majority of patients[1-6].

Acute fatty liver of pregnancy

Although rare, acute fatty liver of pregnancy (AFLP) is considered the most serious liver disease in pregnancy as it carries significant maternal and perinatal mortality. AFLP is a sudden and catastrophic event occurring in the third trimester of gestation with a median gestational age of 36 weeks. It is caused by microvascular fatty infiltration leading to encephalopathy and hepatic failure. Incidence of AFLP ranges from 1:10000 to 1:15000 pregnancies. Patients may be asymptomatic or can present with nausea, vomiting, headache, anorexia, abdominal pain mainly in the right upper quadrant, jaundice, edema, polydipsia, polyuria, and hepatic encephalopathy. Hepatic failure occurs in the form of coagulopathy, hepatic encephalopathy, and hypoglycemia. There is concomitant preeclampsia in nearly half of the patients. Autosomal inherited genetic mutations are most strongly associated with AFLP, especially the LCHAD mutation G1548C. Other risk factors for developing AFLP include low body mass index, nulliparity, twin pregnancies, and male sex fetus. Maternal mortality rate from AFLP is around 2%, and perinatal mortality rate is around 11%. LCHAD deficiency was found in about 20% of infants of mothers diagnosed with AFLP. These infants carry an elevated risk of developing non-ketotic hypoglycemic coma followed by death if they fast or are stressed. AST levels are usually mild to markedly elevated and bilirubin is < 5 mg/dL (may be high in severe forms). Definitive diagnosis is confirmed through liver biopsy, which appears as microvascular fatty infiltration mainly in zone 3 with relative sparing of the periportal areas, mild portal inflammation, and cholestasis. However, this

picture may sometimes be mixed with that caused by viral hepatitis or pre-eclampsia[1-3,6]. Diagnosis and management should be prompt. Regardless of gestational age, early termination of pregnancy is essential for maternal and fetal survival (C-section or vaginal delivery within less than 24 h of diagnosis). The encephalopathy and AST levels are expected to improve within 2-3 days postpartum but may take up to 4 weeks. Patients that are initially critically ill, develop complications of liver failure, deteriorate despite termination of pregnancy, or have delayed improvement in their liver function tests should be transferred to a specialized liver center and evaluated for liver transplantation, which will offer the best chance for survival. Carriers of the LCHAD mutation have a higher risk of recurrence of AFLP in 20-70% of subsequent pregnancies. These patients will require closer monitoring during their pregnancies[1-6].

The objective of this study is to estimate the frequency and characteristic of liver disease unique to pregnancy at King Abdulaziz University Hospital Tertiary Academic Center in Kingdom of Saudi Arabia (KSA), to determine the magnitude and trends of these diseases, and evaluate maternal and neonatal complications.

Methods

This retrospective study reviewed charts of patients who were admitted to the obstetric unit or the labor room between April 2015 and April 2017 and were referred to the Hepatology service. Inclusion criteria were diagnoses of liver diseases unique to pregnancy, including HG, IHCP, eclampsia, pre-eclampsia, HELLP syndrome, and AFLP.

We collected both maternal and fetal data from the hospital information system and patients' electronic files. The maternal data included age (maternal age at time of presentation with pregnancy associated liver disease). Age was further subcategorized into three groups: younger than 21 years, 21-35 years, and older than 35 years. We collected data on the gestational week and the trimester of presentation. We collected data on the number of parity and either primi- or multi- gravida. We categorized the patients according to admission diagnosis as follows: HG, HELLP syndrome, pre-eclampsia, eclampsia, IHCP, or AFLP. We looked for the presence of maternal mortality and factors that were ssociated with maternal death. We recorded systolic and diastolic blood pressures at admission and calculated the mean blood pressure [(systolic BP + diastolic BP)/2]. We obtained delivery data, including gestational week at delivery or termination of pregnancy; induction of labor; mode of delivery whether vaginal, cesarean section, or assisted vaginal delivery. Whenever available, we recorded laboratory data at admission, at one week after admission and within 24 hours after delivery on the following: Hemoglobin (Hg), Platelets count (Plat), AST, ALT, alkaline phosphatase (ALkp), Gama glutamyl transferase (GGT), international normalize ratio (INR), bilirubin, serum LDH, and serum creatinine. However, we did not obtain the after delivery result for Hg to avoid a possible bias of intrapartum or post-partum bleeding. We identified patients who had elevated serum LDH more than 600 IU/L and those who had proteinuria more than 3.5 gm in 24 hours. We identified patients who developed ascites, required ICU admission, had loss of consciousness, or required dialysis.

For the fetal data, we obtained neonatal complications if present, and the types of neonatal complication, including low birth weight, respiratory distress syndrome, premature labor, stillbirth, or birth asphyxia. We defined the final fetal outcome as either alive or deceased.

Statistical analysis

We used SPSS version 22 (Armonk, NY: IBM Corp.) for all statistical analyses. Descriptive data included frequencies, means, and SDs. We used Chi square analysis to compare categorical data and Student t-test and one-way analysis of variance (ANOVA) with post-hoc analysis to test differences between different groups. A P-value < .05 was considered significant.

Results

The total number of patients was 112. The mean age was 29.8 years, SD 6.87 (range, 15-45). Most patients (62.5%) were in the 21-35 year age group. Table 1 shows the distribution of ages across all patients.

Table 1: Age group distribution of all patients according to the type of liver disease in pregnancy

Age group in years	Type of liver disease in pregnancy					Number of patients	Percent of all patients
	HG	HELLP	Pre-eclampsia	Eclampsia	IHCP		
<21 year	5	0	9	1	0	15	13.4%
21-35	17	2	44	6	1	70	62.5%
>35	0	1	25	1	0	27	24.1%
Total	22 (19.6%)	3(2.7%)	78 (69.6%)	8 (7.1%)	1 (0.9%)	112	

P=.025

HG, hyperemesis gravidarum; HELLP, hemolysis, elevated liver tests, and low platelets syndrome; IHCP, intrahepatic cholestasis of pregnancy

Table 2: Distribution of patients according to the diagnosis and the trimester of presentation of liver disease in pregnancy

		Maternal complication group 1					Total
		HG	HELLP	Pre-eclampsia	Eclampsia	IHCP	
Trimester	1st	19	0	0	0	0	19
	2nd	3	0	6	0	0	9
	3rd	0	3	79	1	1	84
Total		22	3	85	1	1	112

HG, hyperemesis gravidarum; HELLP, hemolysis, elevated liver tests, and low platelets syndrome; IHCP, intrahepatic cholestasis of pregnancy

Table 3: Comparison between hyperemesis gravidarum, hemolysis, elevated liver tests, and low platelets syndrome and Pre-eclampsia/Eclampsia in terms of gestational weeks and maternal age

Dependent Variable	Diagnosis for comparison	P value	95% Confidence Interval	
			Lower Bound	Upper Bound
Gestational week at presentation	HG & HELLP	<.001	-29.74	-16.83
	HG & PE/E	<.001	-25.19	-20.10
	HELLP & PE/E	.967	16.83	29.74
			-5.50	6.78
Gestational week at delivery	HG & HELLP	.006	-21.69	-2.97
	HG & PE/E	.001	-19.16	-4.49
	HELLP & PE/E	.978	2.97	21.69
			-5.51	6.54
Maternal age	HG & HELLP	.171	-17.20	2.32
	HG & PE/E	.020	-8.14	-.57
	HELLP & PE/E		-2.32	17.20
		.712	-6.23	12.40

HG, hyperemesis gravidarum; HELLP, hemolysis, elevated liver tests, and low platelets syndrome; PE/E, pre-eclampsia/eclampsia

The most common liver disease in pregnancy was preeclampsia (~70%) followed by HG (~20%). Table 1 shows the distribution of the patients according to diagnosis. Patients with HG were younger compared with those with pre-eclampsia/eclampsia (P=.025, Table 1). Patients with pre-eclampsia/eclampsia were significantly older than those with HG, but there was no difference in the age of patients with pre-eclampsia/eclampsia compared to HELLP patients. Similarly, the gestational week at presentation and the week of delivery were significantly greater for pre-eclampsia/eclampsia and HELLP patients compared to HG.

For the distribution of trimester of pregnancy at diagnosis, the majority 84 (75%) were in the third trimester, 19 (17%) were in the first trimester, and 9 (8%) were in the second trimester. There was significant difference in the distribution of pregnancy related liver diseases according to the

trimester. HG was predominant in the first trimester and pre-eclampsia was predominant in the third trimester (p<.001, Table 2).

With regards to the number of pregnancies, 48 patients (42.9%) were primigravida and the remaining were multigravida. There was no difference in the rate of occurrence of different pregnancy related liver diseases between primigravid and multigravida mothers (p=0.64). The mean blood pressure (BP) at admission was 125 mmHg, SD 22.7 (79.5-179). There was a significance difference in the mean BP at admission between patients with HG and HELLP (mean 91.68 SD 1.74 vs. 145.83 SD 21 respectively p=.033). Similarly, the mean BP at admission was significantly higher in pre-eclampsia compared to HG (mean 132.54 and SD 15.55 versus 91.6 and SD 8.2, p<.001).

There was no significant difference in the mean BP at admission between eclampsia and HELLP patients, nor between the mean BP at admission between the eclampsia and the preeclampsia group (mean 136, SD 16.58 and 132 SD 15.55 respectively, p=0.59). We analyzed the differences between three groups for clinical features, laboratory features, and complications using ANOVA. Group 1 included patients with HG, Group 2 included patients with HELLP, and group 3 included patients with both eclampsia and pre-eclampsia. Only one patient had IHCP, thus she was excluded from the ANOVA analysis. There was a significant difference between the three groups in maternal age (p=.017), gestational week at presentation (p<.001), and gestational week at delivery (p=.001). Table 3 show the post-hoc analysis for the ANOVA test.

The liver enzymes on presentation and on follow-up varied from normal to > 10 times the upper limit of normal. On the other hand, the serum bilirubin did not show severe elevation on admission or during follow-up. Table 4 shows the lab results at presentation, at 1 week, and after delivery. When comparing AST, ALT, GGT, serum bilirubin, serum albumin, LDH, INR, creatinine, Plt count, and Hg at admission across the HG, HELLP and pre-eclampsia/eclampsia groups, only a few parameters showed significant differences. HG, Plt count, serum albumin, and serum bilirubin improved in group 1, while creatinine and LDH were higher in groups 2 and 3 (Table 5).

Delivery data

Labor was medically induced in 55 (49.1%) patients. Pregnancy was terminated in 71 (63.4%) patients via Cesarean section (CS). Two (1.7%) women underwent assisted/instrumental delivery. The remaining 39 (34.82%) underwent vaginal delivery. There was no difference in delivery mode between the groups (p=0.09).

Fetal complications were reported in 30 (26.7%) cases, and of those, 16 (14.3%) experienced stillbirth, one (.9%) patient experienced an early neonatal death 6 (5.4%) had low birth weight, 3 (2.7) had premature labor, and 1(.9%) had fetal respiratory distress syndrome. Additional 3 (2.7%) had fetal complications but the type was not recorded. There was no difference in the occurrence of all neonatal complications or subtypes of neonatal complication in relation to the maternal diagnosis (p= 0.158 and p=0.39, respectively). Fetal or neonatal death was reported in 13 preeclampsia patients, 2 HG patients, and in HELLP and eclampsia of fetal death was reported for each of them (p=0.02 between groups).

On multiple regression analysis, primigravid mothers, gestational weeks at presentation, and gestational weeks at the time of delivery showed significant association with fetal complications with a p value of .024,.023 and .027 respectively. ICU admission was reported in 14 (12.5%) (8 eclampsia, 5 pre-eclampsia and 1 HELLP, the difference between groups was significant p=0.006) Moreover, three patients (2.7%, 1 eclampsia and 2 pre-eclampsia) lost consciousness before delivery (p=0.053). Two pre-eclampsia patients (1.8%) had ascites, and one pre-eclampsia patient (.89%) required dialysis. In addition, nine (8%) (6 pre-eclampsia. 2 HELLP, and 1 eclampsia) patients had serum LDH > 600 IU/L during admission and 5 (4.5%) (pre-eclampsia., and 1 eclampsia) had proteinuria (lab value of >3.5/g/24hours). We did not report maternal mortality in relation to liver disease in pregnancy during the study period.

Table 4: Mean and SD for gestational week and Laboratory results at presentation and after 1 week and after delivery*

Parameter	Normal range	Minimum	Maximum	Mean	SD
gestational week at presentation		7	43	29.35	9.938
gestational week at delivery		17	43	33.63	4.612
Hg at presentation	12-15 g/dL	8	16	11.42	1.654
Hg at week 1		7	13	10.21	1.651
platelets at presentation	150-450 K/µL	62	525	227.97	85.264
platelets at week 1		81	694	262.16	124.476
platelets after delivery		10	545	202.28	88.083
AST at presentation	15-37 U/L	7	891	54.07	124.557
AST at week 1		7	113	38.98	25.873
AST After delivery		10	438	52.51	74.167
ALT at presentation	30-65 U/L	10	2417	57.25	238.015
ALT at Week 1		8	176	40.98	33.059
ALT after delivery		9	437	40.89	65.708
total bilirubin at presentation	0-17 µmol/L	1	43	6.15	5.652
total bilirubin at week 1		1	14	4.99	2.536
total bilirubin after delivery		1	26	5.99	4.887
Alkaline Phosphatase at presentation	50-136 U/L	3	1041	157.94	125.112
Alkaline phosphatase at week 1		64	691	168.05	106.847
Alkaline phosphatase after delivery		4	984	155.75	116.280
GGT at presentation	5-85 U/L	2	258	24.44	38.880
GGT at week1		3	562	49.65	89.867
GGT after delivery		3	239	21.59	36.364
Serum albumin at presentation	35-50 g/L	6	43	23.78	6.459
serum albumin at week 1		10	28	19.73	4.135
serum albumin after delivery		9	27	19.01	3.842
INR at presentation	1.1-1.4 s	1	4	.98	.332
INR at week 1		1	1	.89	.093
INR after delivery		1	1	.92	.085
LDH at admission	100-210 U/L	136	1723	312.24	236.184
LDH at week		218	750	408.50	137.083
LDH after delivery		150	1517	394.21	284.353
lactic acid	0.4-2	1	421	48.33	139.754
creatinine at presentation	53-115	28	550	70.99	53.932
creatinine at week 1	Umol/L	27	660	78.29	93.884
creatinine after delivery		30	400	83.15	62.002
uric acid at admission*	155-428	241	447	357.63	69.108
uric acid after delivery*	Umol/L	305	645	416.00	154.838

*The results after delivery were obtained within 24 hours after delivery

**The results were available for only 8 patients

HG, hyperemesis gravidarum; HELLP, hemolysis, elevated liver tests, and low platelets syndrome; IHCP, intrahepatic cholestasis of pregnancy; LDH, lactose dehydrogenase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, amma-glutamyl transferase; INR, international normalized ratio

Discussion

In this paper, we reported the patterns and the outcomes of pregnancy associated liver disease from Saudi Arabia. Our results showed that among our cohort and during the study period, pre-eclampsia associated liver abnormality was the most common pregnancy associated liver disease. This is inconsistent with the current literature, where IHCP is recognized as the most common pregnancy associated liver disease[2,4]. This might be related to the high rate of pre-eclampsia among our cohort. On the other hand, Pereira et al. showed that pre-eclampsia represents 70% of all cases of severe pregnancy associated liver disease[8]. The majority of our patients were younger than 35 years in age. Previous data on pregnancy associated liver disorders showed that HELLP syndrome and IHCP are likely to be associated with older maternal age[1,4]. In our cohort, 27/112 patients were older than 35 and the majority experienced pre-eclampsia. Patients with HG were more likely to be

Table 5: Element that showed significant difference in the laboratory result across different diagnosis

Variable of difference	Diagnosis for comparison	Mean Difference (I-J)	Sig.	95% Confidence Interval	
				Lower Bound	Upper Bound
Hg at presentation	HEG & Eclamp/Ecalamp	.956*	.036	.05	1.86
Platelets at presentation	Eclamp/Ecalamp& HEG	59.537*	.009	12.53	106.54
Alk phos at presentation	Eclamp/Ecalamp& HEG	12.66	<001	49.4	164
Total bilirubin at presentation	HEG& Eclamp/Ecalamp	3.683*	.026	.36	7.01
Serum albumin at presentation	HEG & HEELP	15.789*	<.001	9.22	22.36
Serum albumin at presentation	HEG & Eclamp/Ecalamp	12.075*	<.001	9.38	14.77
LDH at presentation	HEELP&HEG	636.333*	.001	218.70	1053.96
LDH at presentation	HEELP & Eclamp/Ecalamp	549.121*	<.001	248.12	850.13

HG hemoglobin, hyperemesis gravidarum; HELLP, hemolysis, elevated liver tests, and low platelets syndrome; IHCP, intrahepatic cholestasis of pregnancy; PE/E, pre-eclampsia/eclampsia; LDH, lactose dehydrogenase

younger than patients with pre-eclampsia and eclampsia. To our knowledge, no studies have compared the age of patients with pregnancy associated liver disease. There was no significant difference in age between the pre-eclampsia/eclampsia patients and HELLP patients. This may be because both HELLP and pre-eclampsia/eclampsia are associated with similar underlying pathology in the same group of patients, where HELLP is considered as the severe form of pre-eclampsia[1,2,4].

Most of our patients were in the third trimester of pregnancy. Accordingly, the majority of our patients had pre-eclampsia, eclampsia, and HELLP, as these diseases are usually third trimester disorders[1-6]. On the other hand, most of our patients with HG were in the first trimester of pregnancy, which is consistent with the clinical presentation of HG[1-4,9]. Furthermore, this was supported by the gestational age of presentation from our study. The mean BP was not different among pre-eclampsia/eclampsia and HELLP patients; however, HG patients had comparatively lower BP. This is consistent with the underlying common pathology for pre-eclampsia/eclampsia and the severe form, HELLP. On the other hand, patients with severe forms of HG are more likely to be dehydrated and volume depleted[1-4,10].

The significant differences in laboratory parameters between groups reflects the severity of the underlying pathology in patients with HELLP and eclampsia compared to HG. Moreover, serum LDH in patients with HELLP was significantly different when compared to both HG and eclampsia/pre-eclampsia, reflecting the associated hemolysis in HELLP pathogenesis[2,5,6,11]. Because stable patients were discharged early from the hospital, we were not able to obtain the results of liver function tests and other laboratory tests on longer follow-up. Many of the discharged patients did not attend follow-up appointments after discharge. However, we would expect most of the laboratory parameters to show an improvement within a few weeks after delivery[1,2,5].

Our results did not show significant differences in the delivery methods between different groups. This might be due to the importance of early delivery of the fetus with the appropriate method according to the maternal and fetal status to avoid maternal and fetal complications[1-3,12]. We reported more than one quarter fetal complications or mortality, representing 15% of all patients. This is higher than reported by Pereira et al, who reported an infant mortality rate of 9% amongst 46 women with severe pregnancy related liver disease[8]. However, general mortality due to pregnancy related liver disease varies between 10-30%, according to the disease severity[3,13]. The complication rate did not show any significant differences between the different groups. On the other hand, most of the fetal mortality was related to eclampsia/pre-eclampsia. These findings show that eclampsia is an important cause for fetal mortality, necessitating early recognition, close monitoring, and treatment[11,14]. In our cohort, maternal age and gestational age were found to be associated with fetal morbidity and mortality. This is similar to the

literature, showing a higher rate of fetal complications with the extremes of maternal age and premature delivery of the fetus in severe pregnancy related liver disease[1,2,5,15]. We observed maternal morbidity and ICU admission in about 13% patients, but none of our patients had maternal or perinatal mortality. Among different forms of pregnancy associated liver disease, maternal mortality varies from 1-60%, according to the nature and severity of disease[1,2,5,8,11,13].

Ethical approval

The ethical approval was obtained from the research ethics committee at the Faculty of Medical Sciences, King Abdulaziz University, Jeddah Saudi Arabia. No 544-17. The consent was waived due to this being a retrospective study.

Limitations

This work represents the situation in only one center from Saudi Arabia. More data from other centers is needed, particularly from those centers specializing in obstetric medicine with large volumes of pregnant women under their care. Another limitation was the retrospective design of this study, which did not allow for follow-up of the included patients after delivery. More data is required regarding the improvement of liver parameters on longer follow up

Conclusion

We have shown that liver diseases related to pregnancy represent important causes for maternal and fetal complications among patients from our cohort. Early recognition and management will help in reducing both fetal and maternal complications.

Conflict of interest

None to declare for all authors.

Author's contribution

All authors participated equally in this work from planning the research to editing the manuscript.

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