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Pregnancy Complicated By Chronic Liver Disease

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Abstract

Introduction: Pregnancy is unusual in women with severe chronic liver disease due to hypothalamic pituitary dysfunction which may result in infertility. A favourable outcome for the pregnancy is possible but is dependent on the type well as severity of the un-derlying condition and any associated co-morbidities. Multidisclipinary patient centric approach , along with a compliant patient and family support will enable optimum outcome .

Patients And Methods: Ten pregnancies with chronic liver disease over a fifteen year period were followed up antenatally and postnatally in sevice tertiary care hospitals . Nine patients with autoimmune hepatitis were diagosed antenatally and were on medication prior to conception and were under mul-tidisciplinary care.One patient with portal hyperten-sion was diagnosed post partum .

Results : We present ten patients of pregnancy with chronic liver disease . Nine patients had auto-immune hepatitis. One patient had portal hyperten-sion . In this study, 6/9 patients(66.6%) were treated with azathioprine (AZA) and 8/9 patients (88.8%) with prednisolone. Antenatally patients remained and one patient had postabortal exacerbation .There were five live births(56%) and three preterm deliveries (33%).There were three first trimester miscarriages (44%). There were no neonatal or maternal deaths . The patient with portal hypertension had an antenatal intrauterine fetal death and had Acute Postpar-tum Decompensation with multiorgan failure and disseminated intravascular coagulation and was man-aged under multidisciplinary care successfully .

Conclusion: The spectrum of chronic liver disease in pregnancy may range from a mild to a severe pattern. Women with less severe disease,well con-trolled preconceptually, well compensated liver function , without features of portal hypertension and without any critical co-morbidity can become pregnant and have a generally favourable pregnancy out-comes. In patients who become pregnant , maternal problems in terms of exacerbation of underlying dis-eaease process bleeding from esophageal varices and preterm labour and hepatic decompensation can take place . In the fetus ,miscarriage , fetal growth retardation ,stillbirth or neonatal death can result. The need for disease control before, during pregnancy and in the postpar-tum period, careful materno fetal surveillance during pregnancy, and enhanced medical multidisciplinary involvement is emphasised.

Keywords: Chronic liver disease, Pregnancy

Introduction

Liver diseases in pregnancy although rare but they can seriously affect mother and fetus. All liver diseases with pregnancy can lead to increased maternal and fetal morbidity and mortality. The spectrum of liver disease in pregnancy, can vary from the mild form in which there occur increase in liver enzymes to the severe form, where

liver failure affecting the entire system and resultant increased maternal mortality and morbidity. Though at times chronic liver disease can be detected antenatally and treatment optimized, any type of liver disease can develop during pregnancy or pregnancy may occur in a patient already having chronic liver disease. It is difficult to identify features of liver disease in pregnant women because of physiological changes of normal pregnancy which can mimic the sign and symptoms of liver dis-eases . Therefore extreme care and vigilance in recog-nizing the clinical and laboratory abnormalities in pregnancy is a paramount for an early and accurate diagnosis. This could lead to a timely intervention and successful outcome. Autoimmune hepatitis (AIH) is an autoimmune liver disorder and usually affects young women at childbearing age **1**.As a result of improved medical care , more patients are becoming pregnant **2**.These pregnancies are managed as high risk preg-nancies under multidisciplinary care . Flare up of auto-immune process and or hepatic decompensation can take place either in the antenatal or postnatal period. Besides the probability of serious adverse outcome in the mother , pregnancy in these patients is associated with a higher than normal rate of miscarriage, still-birth, intrauterine growth retardation and preterm delivery either spontaneous or iatrogenic **3**. In the portal hypertension with oesophageal varices, the risk of bleeding is higher during pregnancy, particularly in the second half of gestation and needs to be treated either prophylactically or therapeutically *4.* In AIH the fetal outcomes are generally good and comparable to fetal outcomes in other autoimmune disorders *5.* The aim of this study was to review our experience with pregnancies with chronic liver disease and their out-come.

Patients And Methods

Ten pregnancies with chronic liver disease over a fifteen year period were followed up antenatally and postnatally in sevice tertiary care hospitals. Nine pa-tients had autoimmune liver disease, one patient diag-nosed with portal hypertension during the postpartum period .Patients were followed by a multidisciplinary team, of Gastroenterologist , Intensivist ,and Obstetri-cians . Enhanced medical contact was enforced with antenatal visits fortnightly upto to 28 weeks of preg-nancy, and thereafter weekly. Baseline investigations were done at the first antenatal visit ,liver function evaluated, ultrasonography of liver was performed and periodic hepatic evaluation was performed monthly. Cervical length assessment was performed at 16, 24 and 30 weeks of gestation . Periodic fetal evauation was carried out . The fetal growth was mon-itored with a monthly ultrasound .As a prophylactic measure steroid therapy for surfactant induction was done at 30 weeks of gestation. According to the clinical profile of the patient ante-partum fetal monitoring was instituted generally around 32 weeks of gestation . Monthly review was carried out by the multidisciplinary team to ensure continuity of care, symtoms if any were evaluated , clinical examination carried out , laboratory reports and radiological reports scrutinized as well as roadmap for further care was discussed .Periodic con-tact was maintained with the family members as well , keeping them involved and stressing the need of strict compliance with medication and regular followup . The timing ,and mode of delivery were dis-cussed with the materno-fetal specialist along with anaesthesiologist and neonatologist and the haema-tologist was also involved at this juncture and the haematologist was also involved at this juncture. Pos-sible critical scenarios were discussed with the family members as well as the rest of the multidisciplinary team ..The clinical profile of the patients with auto-immune hepatitis is as per Table 1.

Table 1 Antenatal clinical profile of the patients with Autoimmune Hepatitis.

PREGNANCY	Age	Obstetrical Histo-ry	CO-MORBIDITY	MEDICATION PRIOR TO PREGNANCY
1	28	G3 P0 A2	Hypothy-roididsm ,pregnancy induced HTN	Azathioprine 50mg 2 BD Prednisolone 5mg /day
2	31	G1 P0	Gestational DM	Azathioprine 50mg 2 BD Prednisolone 7.5mg/day
3	33	G1 P0	Antiphospholipid AB+	Azathioprine 50mg 2 BD, Prednisolone 5mg/day
4	30	G1 P0	Pregnancy induced HTN	Azathioprine 50mg 2 BD
5	31	G2 P1 L0	IHCP	Prednisolone 7.5mg/day , UDCA 300mg tds
6	27	G1 P0	HYPOTHROIDISM	Pednisolone 7.5mg/day, hydroxychloroquine 400mg/day
7	29	G1 P0	HYPOTHROIDISM	Azathioprine 50 mg 2 BD, prednisolone 5mg/ day
8	27	G1 P0	Gestational DM	Prednisolone 7.5mg/day
9	29	G3 P1 A1	HYPERTHROIDISM	Prednisolone 7.5mg Azathioprine 5omg 2 BD

Disease activity during pregnancy

Two patients (22,2%) had a first trimester miscar-riage and experienced a postabortal exacerbation . One patient showed elevation of hepatic enzymes during the first trimester before a miscarriage. This resolved spontaneously after the pregnancy loss. The disease remained stable in the other pregnancies. There was no alteration in liver function during this period . The various co- morbidities were well con-trolled under multidisciplinary care .There were no clinical exacerbations during puerperium.

Obstetrical outcome All patients started obstet-ric evaluation by the 10th week of pregnancy. As regards co-morbidities three patients had hypothy-roidism , two patient had gestational diabetes melli-tus and two patients had pregnancy induced hyper-tension . One patient tested positive for antiphos-pholipid anibodies and was medicated with acetyl-salicylic acid (ASA) 75mg/day and enoxaparin 40mg/d and one patient had hyperthyroidism There were three first trimester miscarriages (33.3% of pregnan-cies). Four patients (44.4 %) had a vaginal deliv-ery .Two patients (22.2%) had a ceasarean delivery . One was for abruptio placentae and the other was for fetal distress. There was no fetal growth re-striction, stillbirths, fetal malformations or neonatal deaths. Contraception was advised in accordance to the couples wishes .Long term followup was ad-vised .

The tenth case was of pregnancy with portal hyper-tension diagnosed postnatally .

32 year old primigravida, booked case, h/o subfertili-ty for 10 years, admitted to a service hospital on 23 Jul 2016 with h/o Amenorrhoea of 34 weeks (LMP – 24/11/16, EDD – 01/08/16), Intrauterine foetal death (IUFD) and Pregnancy induced hypertension (PIH), BP – 150/100 mmHg. Initial workup for subfertility, thy-roid, cardiac, liver, renal and collagen disorders was negative. Lady conceived after a course of Anti Tu-bercular Treatment (ATT) given for bilateral tubal block. On 22/06/16 due to intrauterine growth retar-dation (IUGR), pedal and abdominal wall oedema, lady was admitted to to a tertiary care service hospi-tal . She was normotensive, PIH profile and fundos-copy was normal. Estimated foetal weight 1.35 kg, colour Doppler and biophysical profile was normal.

Lady went against medical advice and thereafter ad-mitted on 23 Jul 2011. On admission, general condition – stable, pulse – 100/min, BP – 140/100 mmHg, mild pallor, no icterus. FH = 28-30 weeks, cephalic and ab-sent foetal heart sounds. Systemic examination, fun-doscopy and admission PIH profile normal. Bedside ultrasound confirmed IUFD. Labour induced and lady had a normal delivery on 24/7/16- macerated baby (female), 1.28kg. Immediately postpartum, patient decompensated and developed massive ascites. There-after her course was complicated by DIC, jaundice and multi-organ failure, for which she was aggressively managed. She gave no past history of jaundice, hema-temesis, melena, encephalopathy or coagulopathy.

Table 2 Postpartum clinical profile of the patients with Autoimmune Hepatitis.

Pregnancy	Medication During Pregnancy	Outcome Of Preg-Nancy	Neonate	Post-Partum Out-Come
1	Azathioprine 50mg 2 BD Prednisolone 5mg /day Acetylsalicylic acid 75mg/day	Spontaneous vaginal delivery at 35weeks	2800g Apgar Index 9/10 1st minute/5thminute	Uneventful
2	Azathioprine 50mg 2 BDPrednisolone 7.5mg/day	First Trimester Miscarriage	-	Post abortion exacerbation
3	Prednisolone 7,5mg/day (dose increment at the end of second tri-mester up to 60 mg/day) . Hydroxychloroquine 400mg/day . Enoxaparin 40mg/day .Azathioprine 50mg 2 BD Acetylsalicylic acid 75mg/day	Emergency Lscs At 33 Weeks For Abruptio Placentae	1750 Gms Apgar Index 8/9 At1st minute/5thminute	Post Partum Hyper-Tension Resolved By 14 Day
4	Azathioprine 50mg 2 BD	Vaginal Delivery At 37 Weeks Of Preg-Nancy	3150gm Apgar Index 8/9 1st minute/5th minute	Help Syndrome
5	Prednisolone 7,5mg/day Ursodeoxycholic acid 300mg tds	Ceasaran Delivery At 37 Weeks Of Preg-Nancy For Fetal Dis-Tress	2650gm Apgar Index 6/8 1st minute/5th minute	Uneventfull
6	Prednisolone 7,5mg/day Hydroxychloroquine 400mg/day	Vaginal Delivery At 38 Weeks Of Preg-Nancy	2750gm Apgar Index 5/7 1st minute/5th minute	Postpartum Hemorrhage Postpartum Depression
7	Azathioprine 50mg 2 BD Prednisolone 40mg/day	First Trimester Miscarriage		
8	Azathioprine 50mg 2 BD	Spontaneous Vagi-Nal Delivery		
9	Prednisolone 7.5mg/	First Trimester Miscarriage		

Disease activity during pregnancy

Two patients (22,2%) had a first trimester miscarriage and experienced a postabortal exacerbation . One patient showed elevation of hepatic enzymes during the first trimester before a miscarriage. This resolved spontaneously after the pregnancy loss. The disease remained stable in the other pregnancies. There was no alteration in liver function during this period . The various co- morbidities were well controlled under multidisciplinary care .There were no clinical exacer-bations during puerperium.

Obstetrical outcome All patients started obstet-ric evaluation by the 10th week of pregnancy. As re-gards co-morbidities three patients had hypothyroid-ism , two patient had gestational diabetes mellitus and two patients had pregnancy induced hyperten-sion . One patient tested positive for antiphospholipid anibodies and was medicated with acetylsalicylic acid (ASA) 75mg/day and enoxaparin 40mg/d and one patient had hyperthyroidism There were three first trimester miscarriages (33.3% of pregnancies). Four patients (44.4 %) had a vaginal delivery .Two patients (22.2%) had a ceasarean delivery . One was for abrup-tio placentae and the other was for fetal distress. There was no fetal growth restriction, stillbirths, fetal malformations or neonatal deaths. Contraception was advised in accordance to the couples wish-es .Long term folloThe tenth case was of pregnancy with portal hypertension diagnosed postnatally .

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Figure 1 Hemoglobin profile during hos-pitalization.

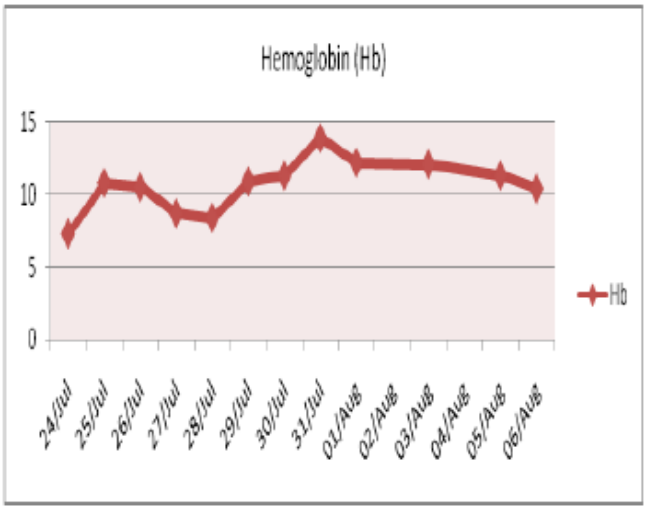


Figure 2 Total leucocyte profile during hos-pitalization

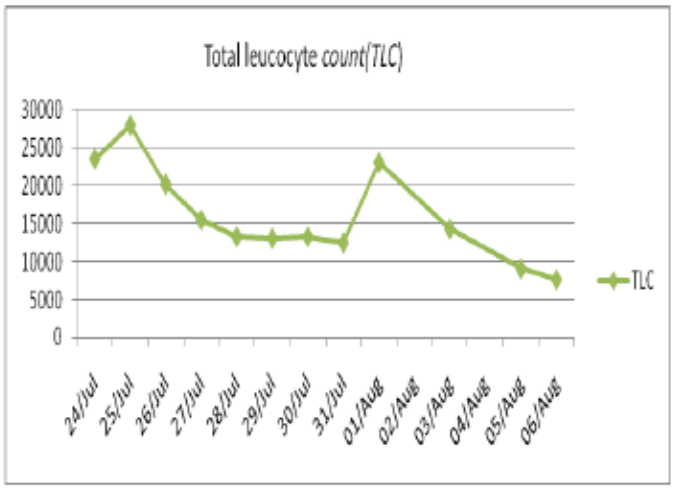


Figure 3 Platelet profile during hospitalization

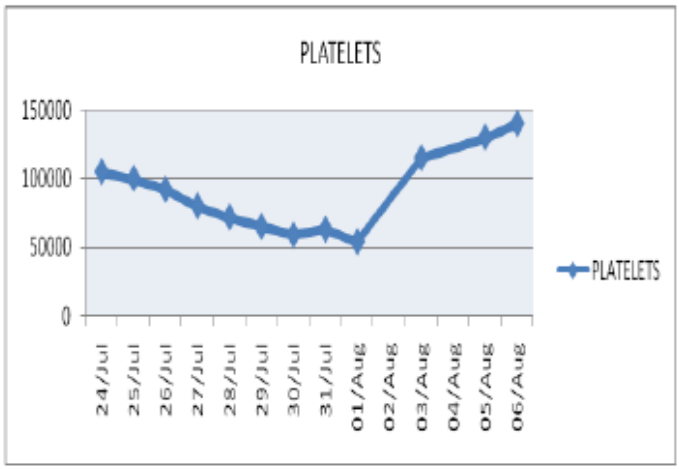


Figure 4 Prothrombin time and international normalized ratio during profile during hospitalization

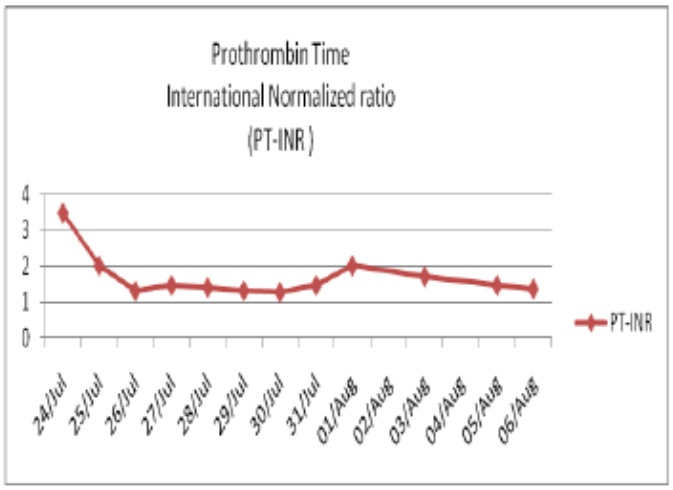


Figure 5 Serum bilirubin profile (S. Bil) and Direct bilirubin profile (D.Bil) profile during hospitalization.

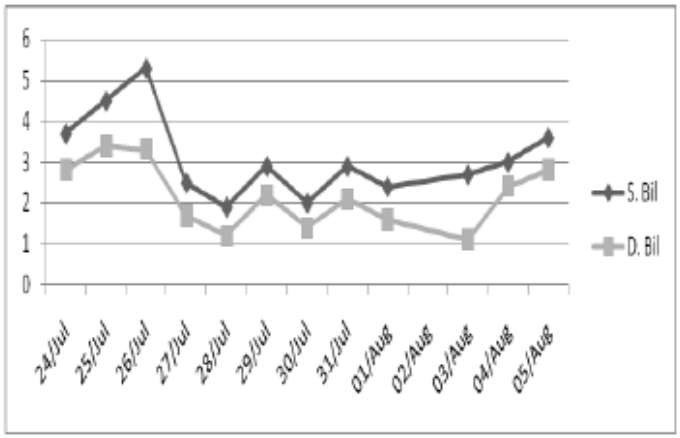


Figure 6 Liver enzymes Alanine transainase (ALT) and Aspartate transaminase (AST)) profile during hospitalization

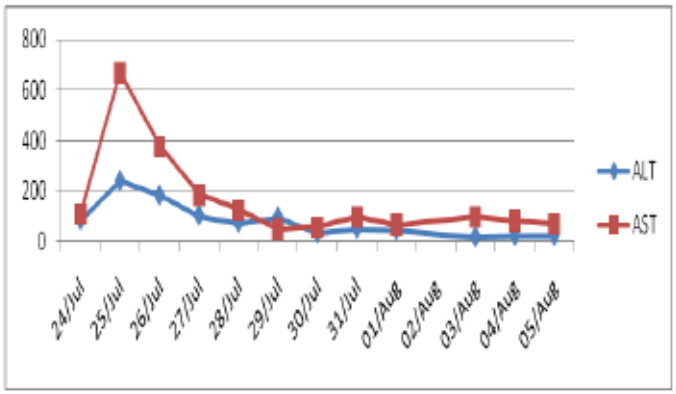


Figure 7A and 7B Renal function tests Se-rum urea (S.Urea) and Creatinine) profile dur-ing hospitalization

Figure 7 A

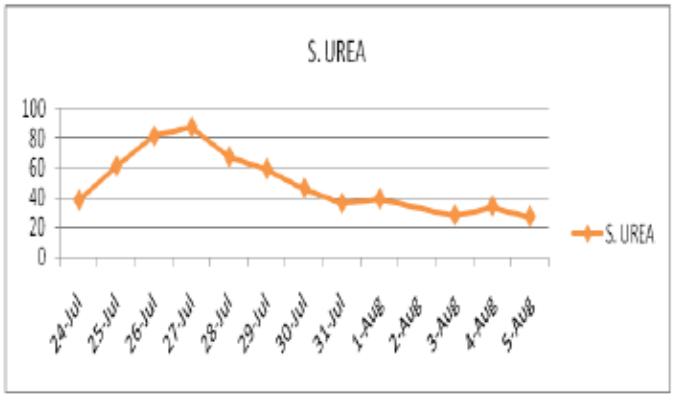


Figure 7 B

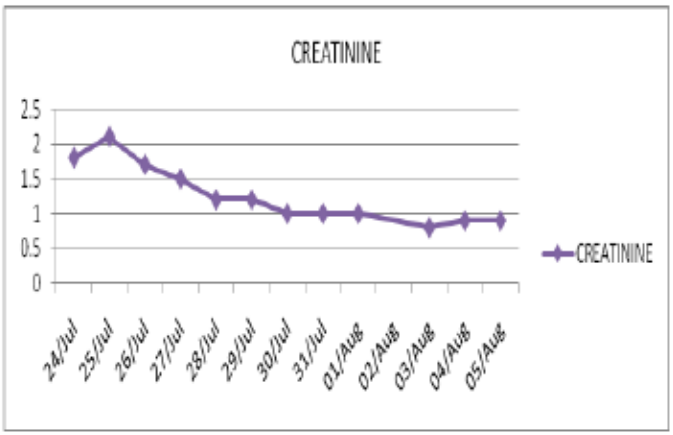
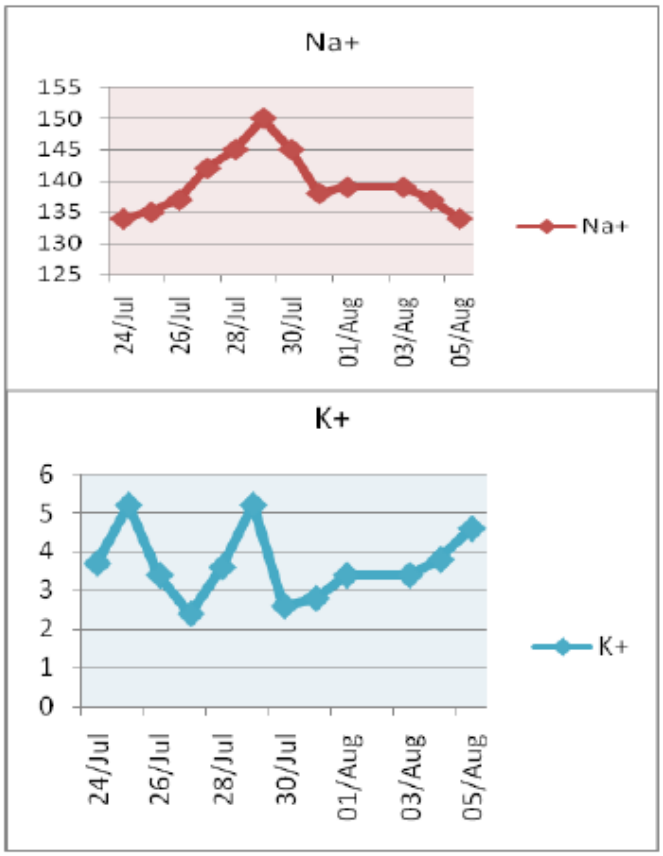


Figure 8 Serum electrolytes Sodium (Na+) and potassium (K+)) profile during hospitalization



Ascitic fluid analysis, Abdominal paracentesis was done, 1.5 litres of ascitic fluid removed, revealed: Se-rum Ascites Albumin Gradient SAAG 2.1 (high SAAG), RBC-9700/cubic mm, WBC- 450/cubic mm, ADA 10 (at a serum albumin of 3.1gm %) , Hepatitis B(HBsAg)negative, Anti Hepatitis C (HCV) Negative, Antinucle-ar antibody (ANA) negative, Serum Ceruloplasmin 24.80mg% (20-60), no Kayser-Fleische r(KF)Ring on Fundoscopy. An **Upper gastrointestinal endoscopy** showed Grade II Oesophageal Varices, **Ultrasound Liver** showed small course liver with large ascites. An **Magnetic resonance imaging (MRI) abdomen** re-vealed liver with altered signal intensity pattern and evidence of atrophy of left lobe, no focal lesion seen, no retroperitoneal lymphadenopathy.Lady was found to have chronic liver disease with portal hyperten-sion . The aetiology of chronic liver disease remained unclear with the available workup. Patient gradually recovered and was discharged . She was advised strongly against conception and referred to a Liver unit for further management. Discharged on Tab Lasilactone 1 BD, Tab Inderal 20mg BD, Haematinics and Calcium.

Discussion

Chronic liver disease in pregnancy can be due to chronic hepatitis B or C, Alcoholic Liver Dis-ease, Wilson's disease, Autoimmune Hepatitis and Primary Biliary Cirrhosis. Factors which influence preg-nancy outcomes depends upon the severity of liver disease and underlying aetiology, compensated versus decompensated liver function, presence of Portal Hy-pertension. During pregnancy there are increased chances of Cholestasis and pruritus , liver decompen-sation , ascites , torrential variceal bleeding and post-partum hemorrhage**1.**Chronic liver disease can result in reduced fertility potential,predispose to increased rate of miscarriage, preterm labours, intrauterine foe-tal growth retardation , intrauterine foetal death and high caesarean rate **2.** For suspicion of chronic liver disease during pregnancy tests include Hepatic Viral Screen, ANA and Ceruloplasmin Screen, Fundoscopy for Kayser-Fleischer Ring,Ultrasound and MRI Abdo-men **3.** All pregnant woman with abnormal amino transferases or jaundice should undergo an abdominal ultrasound **4.** In general in patients with mild degree of liver disease,who are well compensated,

display no features of portal hypertension and have no associat-ed co-morbidities, generally have a favourable out-come in pregnancy. Patients with chronic liver disease face certain risks during pregnancy. All pregnancy patients with cirrhosis be screened for varices starting in the second trimester and started on beta blockers if indicated. The 20-25% of pregnant women with cir-rhosis may have variceal bleeding, especially during the second trimester, when portal pressures peak, and during delivery because of straining to expel the fetus **5.** Endoscopic banding of esophageal varices seems justifiable during pregnancy **6.** There are no published systematic reviews or meta-analyses on the management of cirrhosis or portal hypertension dur-ing pregnancy, likely because of the paucity of cases of cirrhosis in reproductive age women and the in-creased prevalence of infertility in them. General prin-ciples of management inpatients of pregnancy with chronic liver disease include multidisciplinary care in specialized centres by a hepatologist , fertility special-ist , materno-fetal and obstetrician with high risk preg-nancy management skills, along with anaesthesiolo-gist and neonatologist **4 .** Recent data suggest that AIH may have an initial presentation during pregnan-cy, an intrapartum flare risk of upto 20% and postpar-tum flare risk of up to 30–50% **7,8.** Treatment for AIH is based on immunosuppression with corticosteroids and/or AZA,. Pregnancy does not contraindicate im-munosuppressive therapy. Treatment is prednisone and azathioprine (FDA category D at doses <100mg/day). Both are safe in pregnancy. If flares occur, ad-minister steroids or increase in steroid dose. For im-munosuppression, azathioprine remains the safest choice.Treatment options vary, but AZA appears to be generally safe and without adverse outcomes for mother or baby. Strict supervision is required and patients need to be monitored carefully during preg-nancy and for several months post partum **9 .** The presence of autoantibodies may be reflective for ad-verse pregnancy outcome in AIH patients. Close moni-toring of both mother and fetus is essential due to a high rate of maternal and fetal complications **10 .** In-vasive procedures are generally avoided in pregnancy and labour . Close foetal monitoring is done to moni-tor fetal growth . In case of severe fetal growth re-striction, foetal distress or hyperbilirubinemia in the mother early delivery is indicated .. Prolonged labour and complicated deliveries are to be avoided. Vaginal deliveries with assisted, short second stage are prefer-able, as abdominal surgery is avoided. But in patients with known large varices, caesarean section is recom-mended to avoid increases in portal pressure and risk of variceal bleeding. Universal precautions are advo-cated peripartum The favorable obstetric outcome is a realistic expectation in patients with autoimmune hepatitis.**11 .**

Conclusion

Liver disease in pregnancy can pre-sent with subtle changes in liver biochemical profile or with fulminant hepatic failure. In pregnancy these causes serious adverse effects on both mother and fetus. Due to continous progress in medical field better understanding of the pathogenesis of these disorders, new treatment option and high standard clinical care, the maternal and fetal mortality has de-creased but a realistic counselling is to be provided to the patient as well as the family members along with emphasis on close monitoring , enhanced medical contact ,total compliance with instructions and drugs and care at a multidisciplinary centre to ensure opti-mal outcome and thereafter prolonged and regular lifelong followup .

Conflict Of Interest

The authors declare no con-flict of interest .

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