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ACUTE ONSET JAUNDICE DURING THIRD TRIMESTER OF PREGNANCY: DIAGNOSTIC DILEMMA- SEPSIS /HELLP SYNDROME

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ABSTRACT Management of pregnant women with acute onset of Jaundice is an Obstetric Challenge because of its obscure etiology and high maternal and perinatal morbidity and mortality. The management of two pregnant women with acute onset of Jaundice during the third trimester is presented as difficulties were encountered in arriving at the etiology.

The first woman was a 32 year old primigravida at 31 weeks of gestation with fever and jaundice of 4 days duration with negative viral markers. Her serum bilirubin was 11.6 mg/dl and WBC count was 20,990 /mm3. She developed hypertension with hypertensive choroidopathy during the next 24 hrs and underwent Emergency LSCS for nonreactive NST and poor BPP. Her postoperative course was stormy requiring massive transfusion and ventilation for 8 days and prolonged ICU care. She ultimately developed Diabetes and there was evidence of chronic pancreatitis after 3 weeks of delivery.

The second woman was a 22 year old primigravida at 36 weeks of gestation with fever and Jaundice of 2 days duration with negative viral markers. Her bilirubin was 16 mg/dl and WBC count was 26,320/mm3.She had mild hypertension and grade 1 Hypertensive retinopathy and had normal vaginal delivery after labour induction. She developed fulminant hepatic failure with sepsis and AKI, deranged coagulation profile and suffered from large vaginal haematomas and severe anaemia within 72 hours of delivery and was managed effectively with massive transfusion, tranexamic acid and antibiotics.

KEYWORDS : Jaundice, Third trimester, DIC, Chronic Pancreatitis, Diabetes

INTRODUCTION:

Jaundice complicates about 3% of pregnancies. The incidence of jaundice during pregnancy in India varies from 0.4 to 0.9/1000 deliveries[1].The commonest cause of jaundice in pregnancy is viral hepatitis. Causes unique to pregnancy are hyperemesis gravidarum, acute fatty liver of pregnancy, intrahepatic cholestasis of pregnancy, pre eclampsia and HELLP syndrome out of which HELLP syndrome is the commonest[2]. *Sepsis induced cholestasis as a cause of Jaundice during pregnancy is not reported hence these case series is reported.*

Physiological changes in pregnancy can hinder the rapid diagnosis of jaundice in pregnancy and signs and symptoms are usually non specific. There is a physiological increase in alkaline phosphatase levels from placental production which can otherwise be used to diagnose cholestasis more accurately. Parameters that can be used in diagnosis include liver transaminase levels, GGT levels, Bilirubin levels, prothrombin time as these do not alter with pregnancy. The diagnosis of liver disease in pregnancy hence is challenging.

Jaundice in pregnancy is detrimental to both the life of the mother and the fetus. Hence rapid diagnosis and management is necessary. Causes of mortality in pregnant women with jaundice include hepatic encephalopathy, renal failure, DIC, and PPH and the MMR is reported to be 10%- 17% [1].

CASE NO.1:

A 32 year old primigravida, Mrs AJ, who had regular antenatal care elsewhere was referred at 31+3 weeks of gestation to our emergency care services in view of fever with jaundice of four days duration. Fever was of low grade intermittent type and associated with vomiting of two to three episodes per day. She had uneventful first and second trimester except that she was diagnosed with hypothyroidism and was on treatment with Eltroxin 100 µg daily. At admission she was conscious, deeply icteric, afebrile. Pulse rate was 96/min and BP was 120/70 mmHg. Her Respiratory rate was 28/min with normal vesicular breath sounds. CVS was normal. Abdominal examination revealed gross abdominal wall oedema and it was difficult to palpate the uterus. USG showed single live fetus with biometry corresponding to 32 weeks with normal liquor. On per vaginal examination, cervix was 2cms long and Os was closed. Fetal wellbeing was determined by Non-stress test (NST) which was normal. A provisional clinical diagnosis of Viral hepatitis was made and she was admitted to Obstetric ICU and monitored and further investigated.

She had proteinuria and hypertension during the next 24 hrs and received Tablet Labetalol 200mg thrice daily and prophylactic magnesium sulphate for imminent features of eclampsia. Her FDP was positive on post admission day 1and she was treated with injection tranexamic acid 500mg q8h iv and FFP at the rate of 25ml/kg body weight and empirical antibiotics (Inj.Ampicillin 2g q8h). Her fundus examination showed hypertensive choroidopathy. USG abdomen was repeated and there was hepatomegaly. Fetal evaluation after 24 hrs of admission showed a non reactive CTG with loss of beat to beat variability (Category 3) and BPP of 2/10, AFI-6 ; EFW-1.5kg. Hence Emergency LSCS was undertaken explaining fetal survival rate of 50% as per our neonatal survival data. There was 200 ml of ascites. An alive female baby was delivered with an APGAR of 5/10 which weighed 1500 gms and was resuscitated and shifted to nursery. Placenta was adherent to posterior wall and was removed manually. Uterine atonicity with a blood loss of 800ml was managed with uterotonics and bilateral uterine artery ligation and abdomen was closed with drain in situ. She received 1 PC 6 FFPs 4 Cryoprecipitate intra operatively. Her intra op Arterial blood gas analysis showed blood pH 7.2 and lactate was 4.5 mmol/L and revealed metabolic acidosis hence she was ventilated on SIMV mode and shifted to critica Patient was put on SIMV ventilation.

Her intraperitoneal drain output was 1100 ml fresh blood in 24 hrs. She received 10 FFPs 4 cryoprecipitate and one packed cell. And her INR was kept between 2.6 and 3.6 on the first postoperative day and her bilirubin rose to 13.3 mg/ dl and her GGT- 251. Investigations on first postoperative day showed Hb of 5.2gm/dl, platelets 1.25 lakhs and peripheral smear showed evidence of hemolysis. PT/INR 20.9/1.6. She received 4 PC and 4 FFP. Platelets dropped to 78,000 on day 2 and Hb was 7.8mg/dl and she received one more packed cell transfusion. She received FFP at the rate of 25 ml/kg bodyweight for the next 7days till PT /INR was normalised.l care unit . She was continued on syrup Lactulose and Tab.UDCA which were started at admission. ***Blood culture sent at admission grew E.coli sensitive to Meropenem***. She was given Inj.Meropenem 1 gram i.v thrice daily for seven days.

Peripheral line blood culture grew Candida sensitive to Voriconazole. Central line blood culture grew Acinetobacter baumannii sensitive to Colistin. She received Colistin 3 million I.U twice daily for 5 days and Voriconazole 200 mg twice daily for 14 days for Candidemia, Hepatitis viral markers were negative. She was extubated on postoperative day 6 and was put on CPAP. She was taken off from CPAP mode on postoperative day 8.

Her repeat investigations revealed high blood glucose levels 2 weeks post delivery. Endocrinology opinion taken and CECT revealed bulky pancreas (Fig) Serum lipase was 2108 IU/ml and a diagnosis of Chronic Pancreatitis was made. She was started on Inj. NPH Insulin 4-0-0-4 U S/C and titrated up to 20-0-0-10 U at discharge. Her bilirubin normalized 3 weeks later and she was discharged with baby after 40 days of NICU stay. Investigative profile and recovery is summarized in Table 1.The clinical features, management and course is summarized in Table 3

TABLE 1: Haematological and Biochemical Profile –Mrs. AJ

Investigations	At admission	1 week	2 weeks	3 week
Hemoglobin	13.4	7.1	9.5	9.9
Total WBC	20990	13200	7380	6820
Differential Count	N70L24	N80L27	N68L27	N68L26
Platelets	1.68 Lakh	47000	3.14Lakh	2.65Lakh
Peripheral smear	NCNC			NCNC
Glucose	67	171	163	294
Urea/Creat	45/1.63	49/0.97	21/0.89	20/0.75
AST/ALT	73	56/29	81/45	44/44
Bil T/D	11.66/2.54	10.71/2.37	9.88/2.14	1.24
ALP/GGT	500/307	131/66	201/129	231
PT/INR	41.5/3.62	14.1/1.04	13.9/1.03	12/1.0

Fig : CT Abdomen

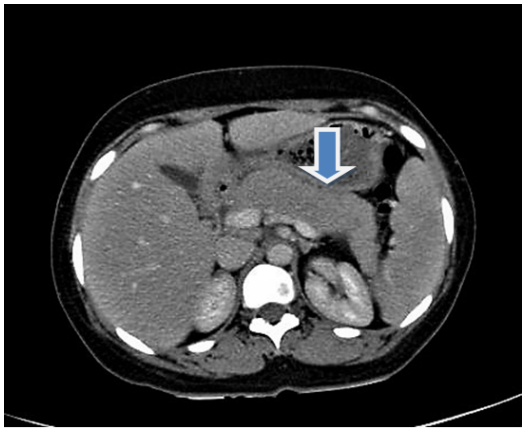

Figure shows enlarged and edematous Pancreas

CASE NO 2:

A 22-year-old primigravida, Mrs J, was admitted to our hospital at 36+1 weeks gestation with complaints of fever with jaundice for two days duration and pain abdomen of one day with one high BP recording of 128/96 mm Hg. She had regular antenatal care elsewhere and her pregnancy had been uneventful till 2 days ago. On examination, she was conscious, icteric Blood pressure was 120/80mmHg, Respiratory and Cardiovascular systems were normal. The epigastrium was tender, and the uterine size was corresponding to her dates and mildly acting and fetal heart sounds were good. Per vaginal examination revealed soft cervix which was 50% effaced with 1.5 cm dilatation. Ultrasound revealed an alive fetus with an EFW of 2.5 kg with AFI- 8.6 . She was initially admitted to septic labour room and later she was shifted to Eclampsia room as she was diagnosed to be pre-eclamptic with urine PCR 0.34 and BP 130/90. Five hours later she developed leaking per vaginum. She was given single dose of PGE1 25 microgram and she delivered vaginally 2 hours later resulting in precipitate labour. An alive male, was born with APGAR of 8/10 weighed 2.37 kg.

Postnatally she had tachycardia and excessive bleeding and diagnosed to have PPH after 12 hours . She had hypotension (80/50 mmHg) and her INR was 2.36 and she was resuscitated . Central line was secured and she was transfused with 4 units of FFPs and 2 units PC, 2 units of cryoprecipitate along with fluid resuscitation .She was started on empirical antibiotics inj.Ceftriaxone 2g i.v o.d, inj.Amikacin 750mg q 36 hrly, inj Metronidazole 500mg 8 hrly. Postnatally her Hb dropped upto 3.2 gms% and the total leukocyte count was 26,320/mm3 and differential count was neutrophils- 77%, lymphocyte 17%. Her platelet count was 40,000. Peripheral smear showed normocytic normochromic picture. FDP was negative. Her urine culture, blood culture and cervical culture were reported to be sterile. Bedside USG showed bilateral medical renal disease with mild ascites. Physician opinion was fulminant hepatic failure with sepsis and AKI and hence started with antihepatic encephalopathic measures.

She had persistant soaking of sterile vaginal pads. Episiotomy wound explored and hemostatic sutures taken and vagina was packed with acriflavin gauze. On Post natal day 2 she continued to bleed excessively and there was increased bulge of perineum, emergency ultrasound revealed right sided infra levator hematoma 3x4 cm which was evacuated under local anesthesia and the dead space was obliterated with 1-0 chromic catgut with figure of 8 sutures. On postnatal day 3 patient developed irrelevant talk, dyselectrolemia was diagnosed and sodium, potassium correction was carried out. Echo was normal. Fundus showed bilateral grade 1 hypertensive retinopathy. On postnatal day 4, USG revealed normal liver, spleen span with no esophageal varices and there was gross ascites. Paracentesis of 1 litre of ascitic fluid was done and sent for cytology and AFB smear. Hepatitis viral markers , CMV, leptospira were negative. Ascitic fluid reported glucose 106 mg/dl, protein 0.2 mg/dl, LDH 94 IU/L. It revealed scattererd neutrophilsand AFB staining was negative. She was started on albumin infusion, antihepatic encephalopathy measures syrup lactulose, inj.vit k, inj.thiamine 100 mg i.v o.d, inj.tranexamic acid 1g i.v 8th hourly and 25% dextrose 100ml every 6 hrly.

As the ascites was increasing, Tab. Rifaximin 550 mg b.d started and in view of Hypertension tab.Atenolol 25mg o.d started. She was transfused with one packed cell, four units of platelets as her Hb was less than 6 gms%. She had episodes of hypoglycemia in between which was treated with 25% dextrose. She received Amikacin and Meropenem for 10 days for persistent fever. Total leucocyte counts reduced gradually after starting antibiotics and came back to normal on postnatal day 4. PT/INR normalized after FFP transfusions. Her liver enzymes gradually reduced to normal and Bilirubin became normal 12 days after delivery Her investigative profile and recoveryare represented in Table 2.

TABLE 2: Investigative Profile over time-Mrs. J

Investigation	At admission	1 week	2 weeks	3 week
Hemoglobin	12.6	7.6	10	9.1
Total WBC	11770	17590	25980	9890
Differential Count	N78L14	N80L12	N66L17	N71L23
Platelets	1.5Lakh	80000	70000	1.4Lakh
Peripheral smear	NCNC	NCNC		NCNC
Glucose	61	60	63	71
Urea/Creat	26/1.51	37/1.12	35/0.98	22/0.86
AST/ALT	290/511	40/64	66/47	132/72
Bil T/D	11.83/2.98	8.66/2.31	2.91/0.93	1.25
ALP/GGT	1783/1410	567/24	508/65	369/103
PT/INR	47.7/4.23	24.9/2		

She developed lactational failure hence worked up for Sheehan's syndrome and her cortisol was 24.43 , TSH 5.06, Prolactin 48.20 which were all normal. She was discharged home 20 days after admission along with the baby. One month later she felt well and hemoglobin was 11.5 g/dl and renal and hepatic function tests were normal.

TABLE 3 - CLINICAL FEATURES AND PROGRESS

Clinical features	Case 1: Mrs.A Primigravida	Case 2: Mrs.B Primigravida
Age in years	32 yrs	22 yrs
Gestational age	31+4 weeks	36+1 weeks
Reason for referral	jaundice	Jaundice
Antenatal care	Optimum , Hypothyroidism	Optimum
Presenting symptoms		
Fever low grade	4 days	2 days
Jaundice	4 days	2 days
General condition		
Pulse	96/min	106/min
BP	120/70 mm Hg	120/80mm Hg
Icterus	++	++
Respiratoryrate	28/min	22/min
Rs auscultation	clear	Clear
CVS auscultation	No murmurs	No murmurs

Abdominal examination		
Hepatomegaly	++	+
Splenomegaly	+ 13.2 cms	-
Obstetric examination	Uterine size not made out.FHS- good. USG- 32 weeks	36 weeks, cephalic, FHS- good
Per vaginal examination	Cervix 2cm long- os closed	Cervix 50% effaced 1.5cm dilated
Fetal well being	Nst- Reactive	Nst- reactive
Provisional diagnosis	? Viral hepatitis	? Viral hepatitis
investigations		
Serum bilirubin	11.66/2.54	11.83/2.98
ALT/AST	73/83	511/290
LDH	806	1410
Hemogram		
Hemoglobin	13.4	12.6
Total WBC	20990/mm3	11770/mm3
Differential count	N70 L 24 E 0.6	N78 L14.4 E 0.6
Peripheral smear	NCNC (Hemolysis on Day2)	NCNC
Platelets	1.68 Lakh	1.5 Lakh
Blood sugar	67mg/dl	61mg/dl
Urea/ creatinine	45/1.63	26/1.51
PT/INR	41.6/3.62	47.7/4.23
Serum lactate	4.9	-
Fundus examination	Acute hypertensive choroidopathy	Grade1 hyperetensive retinopathy
Viral markers	Negative	Negative
Cultures		
Blood culture	E.coli	Sterile
Cervical swab culture	Sterile	Sterile
Urine culture	Sterile	Sterile
Maternal monitoring	Initially had mild hypertension later went into hypotension and shock	Initially had hypertension later went into hypotension and shock
Anti hepatic encephalopathic measures	Over 2 weeks	Over 2 weeks
Fetal monitoring	NST on day2 and BPP 2/10	Normal CTG throughout
Mode of delivery	Emergency caesarean	Induced labour – SVD
Post partum course	PPH, DIC	PPH, DIC, Vaginal hematomas
Ventilation	6 days, blood culture and tracheal aspirate- Acinetobacter baumanii	Nil
MANAGEMENT		
Tranexamic acid	yes	Yes
Packed cell	2	6
FFP/Cryoppt	12/4	10/6
Antibiotics		
Intial- empirical	Ampicillin	Ceftriaxone/amikacin/ meropenem
Later- specific	Meropenem/colistin/voriconazole	
Fulfills criteria fro sepsis	YES	YES
Sequelae	Chronic panreatitis Diabetes	-

DISCUSSION:

In both the cases we faced a dilemma in making a diagnosis whether to attribute jaundice to sepsis or to HELLP syndrome complicating pregnancy since both patients had hypertension with fever and jaundice at admission and both had fundus changes of hypertension. As both patients had high fever inspite of empirical antibiotic cover and had high leukocytosis contributing more towards a septic foci as a source for jaundice. Mrs AJ blood culture grew E. Coli as it was sent prior to start of empirical antibiotics and Mrs J received empirical antibiotics and the blood culture was sent while on antibiotics which was reported as sterile.

Sepsis induced jaundice is rare and some bacterial infections are reported to be associated with jaundice. Both gram-negative and gram-positive bacterial infections have been reported to cause jaundice[3]. In most instances of sepsis-induced jaundice, the infection is intra-abdominal and may include biliary infection, urinary tract infections or intra-abdominal abscesses[4]. However, jaundice has also been reported to be associated with pneumonia, meningitis and bacterial endocarditis . E. Coli is reported to cause cholestatic jaundice through bacteraemia due to UTI, cervicovaginal infection, pyelonephritis, diverticulitis, pneumonia, meningitis. Pneumococi is known to cause hepatocellular injury, necrosis, bile stasis and jaundice. Clostridium perfringens causes haemolytic jaundice, shock and even death due to massive hemolysis, hemoglobinuria , renal failure and death. Prognosis is very poor. Leptospirosis causes a severe presentation called Weils disease which is associated with high spiking fever, jaundice, renal failure and cardiovascular compromise. Salmonella Typhi causes endotoxinemia which leads on to biliary stasis, cholangitis and jaundice. Sepsis and bacterial infection accounts for around 20% cases of jaundice[5].

Mechanism of sepsis causing jaundice is through hemolysis, hepatocellular injury and dysfunction and cholestasis[6]. Kuppfer cells forming the reticuloendothelial system act as scavengers in removing the offending bacteria and toxins. Hypotension and hypoxia due to sepsis can cause kuppfer cell dysfunction and hepatocellular damage. TNF –α is released in turn and is implicated in endotoxin induced cholestasis.

HELLP syndrome causing jaundice accounts for 40%[7]. Mechanism of jaundice in HELLP syndrome is by vascular remodelling, uteroplacental insufficiency, thrombotic microangiopathy which leads on to microangiopathic haemolytic anemia and jaundice. In 5% , jaundice occurs as the first symptom of HELLP syndrome[5].

Severe coagulopathy, jaundice, hepatic encephalopathy, ascites, hypoglycemia, and a mild to moderate elevation of transaminase levels are the key features of AFLP[9] . In both the cases mentioned there had been overlapping features such as fever , jaundice, hepatomegaly, raised ALP/GGT, increased total leucocyte count , blood culture positivity, hypoglycaemia, hypotension, MODS and coagulopathy all pointing towards sepsis as the contributing factor of jaundice.

A new observation of sepsis causing pancreatitis leading to diabetes which had not been reported earlier in literature is diagnosed in the first case.

CONCLUSION:

Sepsis induced jaundice may be diagnosed when pregnant women present with fever, acute onset jaundice, leukocytosis, hepatomegaly, cholestasis, thrombocytopenia, coagulopathy and MODS. ICU care involving multidisciplinary approach is essential to manage the consequences.

Sepsis is to be considered as one of the differential diagnosis for acute onset jaundice in pregnancy and prompt evaluation for sepsis and treatment with higher antibiotics can reduce the morbidity and mortality. **Sepsis can induce Diabetes by causing chronic pancreatitis.**

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