Dr Ashok Kumar

- Director-Professor, Department of Obstetrics & Gynaecology

Maulana Azad Medical College & Lok Nayak Hospital, New Delhi

- Member, Governing Council, ICOG

•MD (All India Institute of Medical Sciences, New Delhi)
•Ph D (Tokyo Women's Medical University, Tokyo)

Participated in Second Advanced Managerial Talent Training workshop on Focused Ultrasound Surgery Technology. Chongqing. 2018

- Research Papers > 110 Indexed & > 80 Non indexed

•Thyroid hormonal changes during pregnancy,
•Calcium supplementation during pregnancy for preventing hypertensive disorders (included in a Cochrane review in 2010),
•Hepatitis E (reviewed in Obstetrics & Gynecology Survey 2005),
•latent Celiac disease in reproductive performance,
•Recurrent pregnancy loss - dydrogesterone (included in the European Progestin Club Guidelines 2015, ESHRE Guidelines 2018),
•Periodontal Disease and GDM, Preeclampsia
•Yuva FOGSI Oration 2004
•Golden Jubilee Commemoration Award Lecture of National Academy of Medical Sciences (India) 2013
• FOGSI - Corion award 2008 for best scientific work

• Editorial Member: IJMR and Archives of Obst & Gynae
• Reviewer for many national & international journals.

Fulminant Hepatic Failure in Pregnancy

Diagnostic Approach

Dr. Ashok Kumar

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Fulminant Hepatic Failure in Pregnancy

Diagnostic Approach

Fulminant Hepatic Failure in Pregnancy

- **development of coagulation abnormality,**

  usually an international normalized ratio of >1.5

  and

- **any degree of mental alteration (encephalopathy) in a patient without preexisting liver disease.**
- **Interval from onset of jaundice to encephalopathy :**

  < 26 weeks duration.

American Association for the study of liver diseases (AASLD), 2011

Hepatic Failure

Acute Liver Failure

Fulminant Hepatic Failure

Acute Hepatic Necrosis

.

Trey C, Davidson CS. The management of fulminant hepatic failure. Prog Liver Dis. 1970;3:282-98.

Gimson AE, O'Grady J, Ede RJ, et al. Late onset hepatic failure: clinical, serological and histological features. Hepatology. 1986 Mar-Apr;6(2):288-94

Lee WM, Squires RH Jr, Nyberg SL, et al. Acute liver failure: summary of a workshop. Hepatology. 2008 Apr;47(4):1401-15.

Classification of Liver Failure

Interval from onset of jaundice to development of hepatic encephalopathy,

- **Hyperacute if occurring within 7 days**
- **Acute if occurring between 8 and 28 days**
- **Subacute if occurring between 29 days and 12 weeks.**

O'Grady JG, Schalm SW, Williams R.
Acute liver failure: redefining the syndromes.
Lancet. 1993 Jul 31;342(8866):273-5

- **Fulminant if occurring within 2 weeks**
- **Subfulminant if occurring between 2 and 12 weeks.**

Bernuau J, Rueff B, Benhamou JP.
Fulminant and subfulminant liver failure: definitions and causes.
Semin Liver Dis. 1986 May;6(2):97-106.

Classification of Liver Failure

Interval from onset of hepatic illness to development of hepatic encephalopathy:

- **Fulminant if occurring within 8 weeks**

Trey C, Davidson CS.
The management of fulminant hepatic failure.
Prog Liver Dis. 1970;3:282-98

- **Late onset if occurring between 8 and 26 weeks.**

Gimson AE, O'Grady J, Ede RJ, et al.
Late onset hepatic failure: clinical, serological and histological features.
Hepatology. 1986 Mar-Apr;6(2):288-94.

Fulminant Hepatic Failure in Pregnancy : Causes

1. **Pregnancy associated acute liver disease**

- **Pre-eclampsia/eclampsia with liver infarction**
- **Syndrome of haemolysis, elevated liver enzymes and low platelets (HELLP Syndrome).**
- **Acute hepatic rupture**
- **Acute fatty liver of pregnancy**

Fulminant Hepatic Failure in Pregnancy : Causes

2. **Exacerbated by pregnant state**

- **Viral hepatitis**
- **Budd-Chiari syndrome with portal vein thrombosis**
- **Gallstone disease**

Fulminant Hepatic Failure in Pregnancy : Causes

3. Unrelated to pregnant state

- **Drug-induced liver disease- acetaaminophen, alcohol**
- **Toxins/ mushroom poisoning**
- **Shock**
- **Trauma**
- **Decompensation of pre-existent liver disease.**

Fulminant Hepatic Failure in Pregnancy : Causes

- **Most common cause**

Acute Viral Hepatitis

- **Etiological agent**

Hepatitis E Virus.

Hepatitis E in Pregnancy
Fulminant and Fatal

The risk of ALF is increased in the setting of acute viral hepatitis and pregnancy, particularly hepatitis E infection.

Khuroo MS, Kamili S. Aetiology, clinical course and outcome of sporadic acute viral hepatitis in pregnancy. J Viral Hepat. 2003 Jan;10(1):61-9.

ALF & Hepatitis E in Pregnancy

ALF in pregnant women with acute hepatitis E infection : 69%

- **Khuroo MS, Kamili S. Aetiology, clinical course and outcome of sporadic acute viral hepatitis in pregnancy. J Viral Hepat. 2003 Jan;10(1):61-9.**

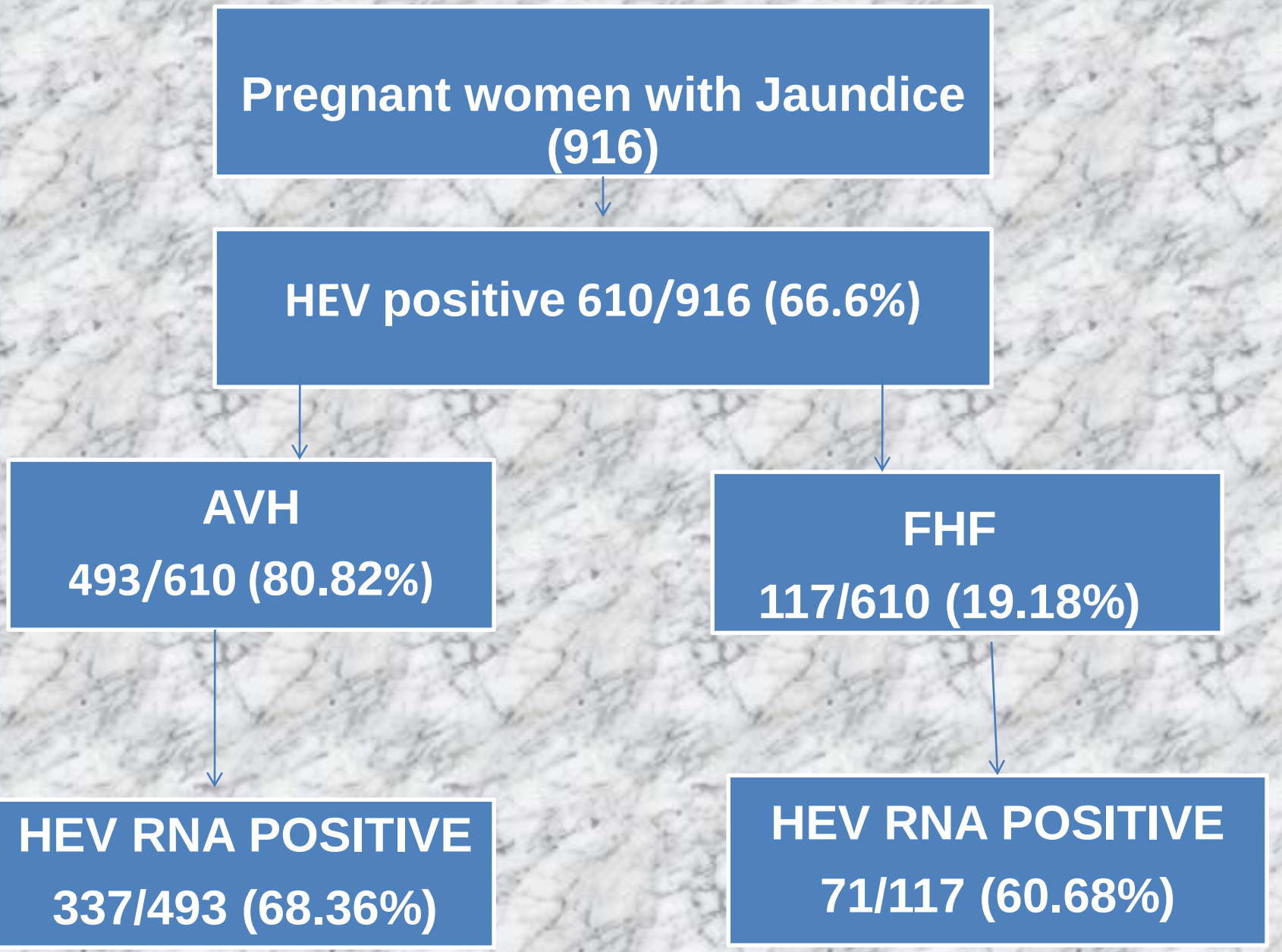
Study of Hepatitis E infection during Pregnancy

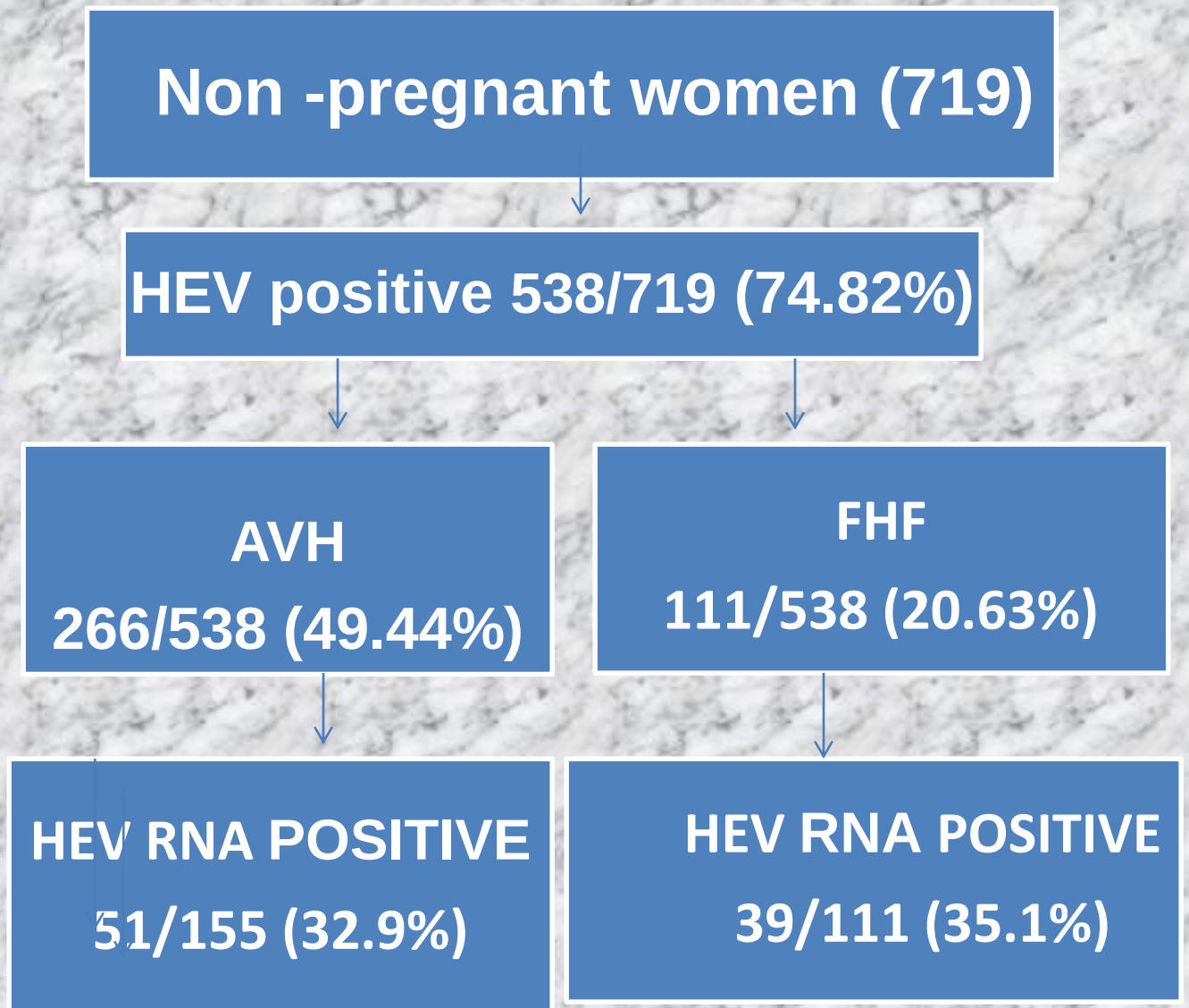
Pregnant women with jaundice (Cases)

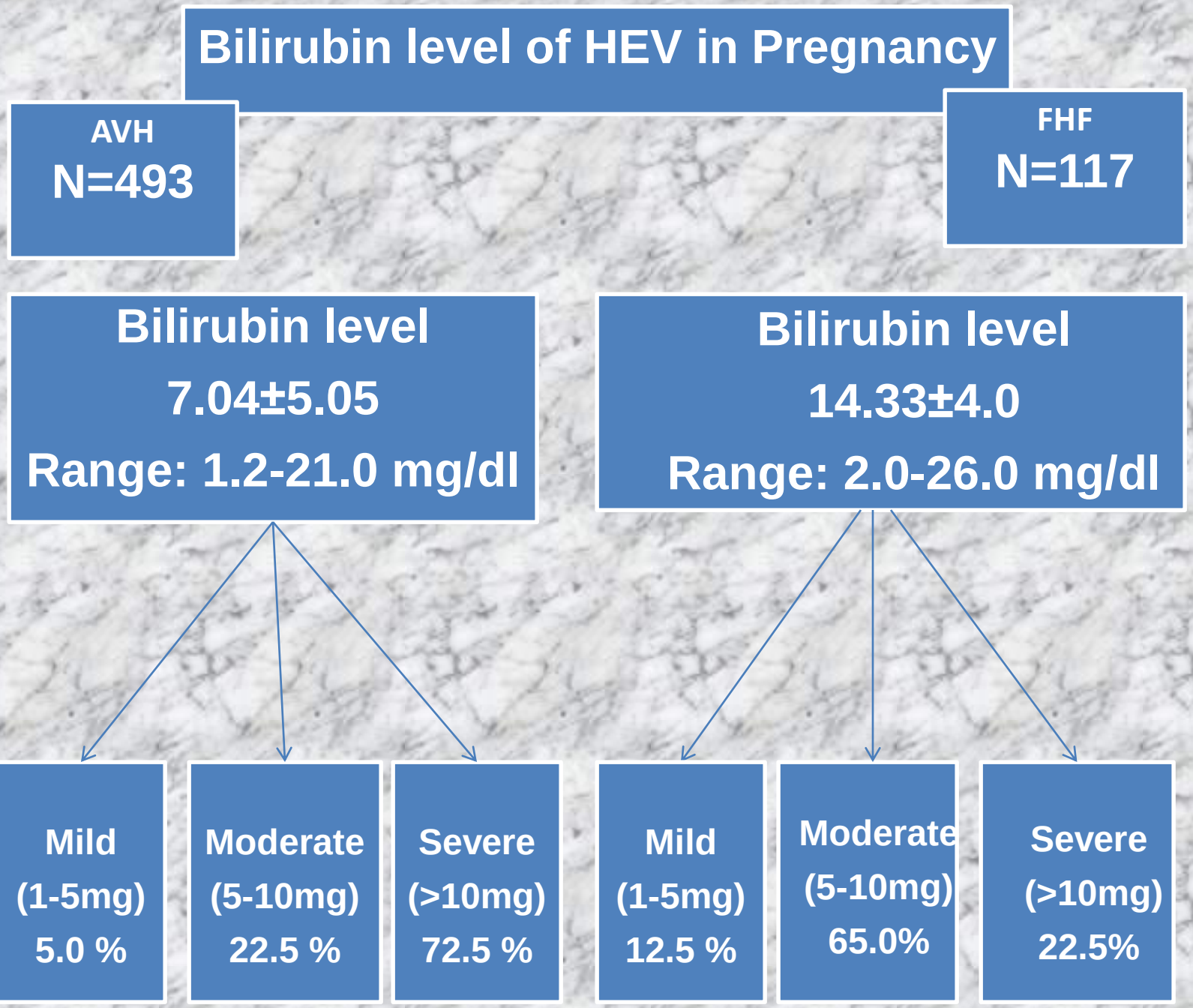
- Number of pregnant women with jaundice studied-916

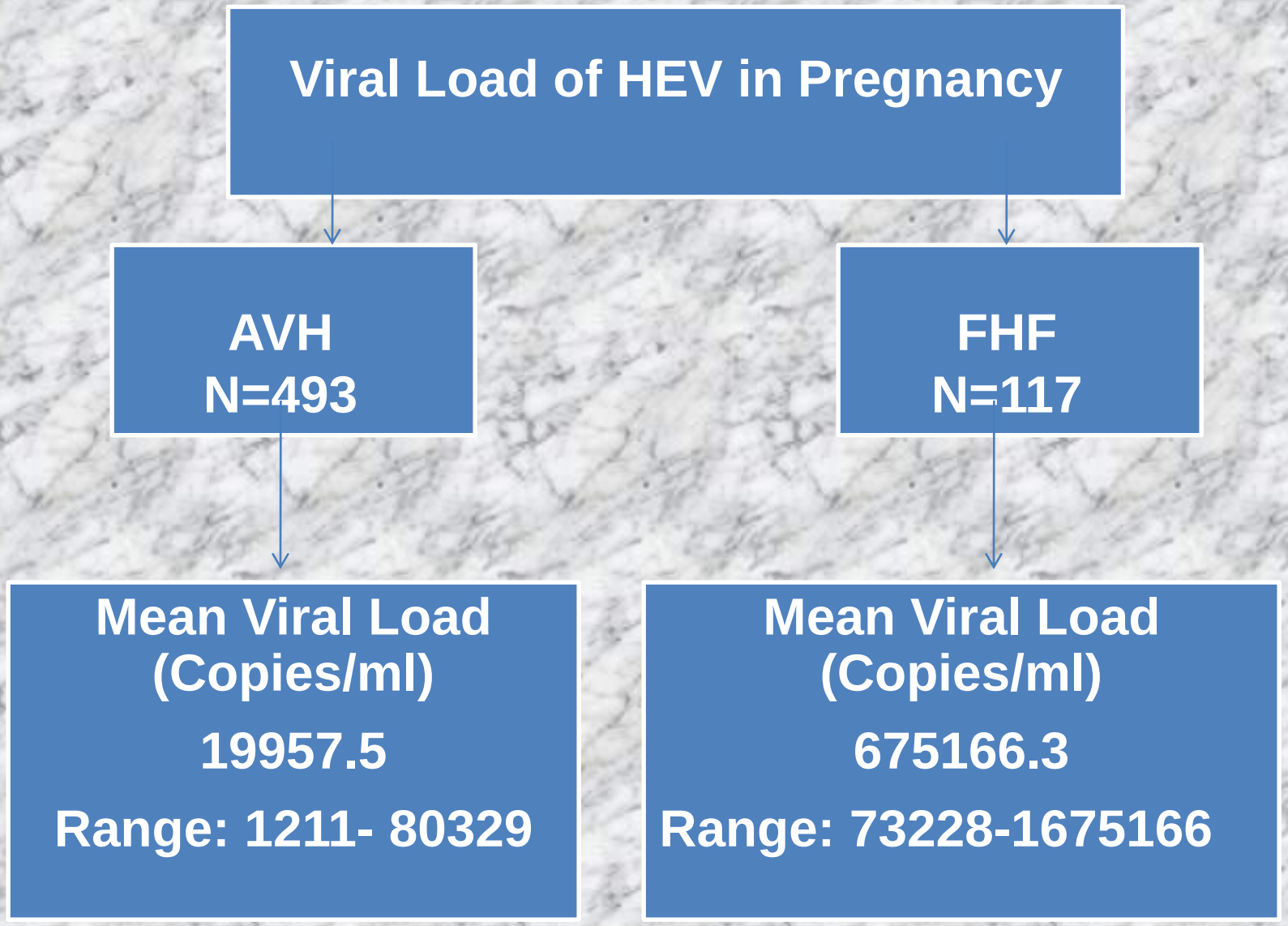
- Mean age was 24.67±3.63 yrs
- Mean gestational age was = 35+3 wks

- Number of HEV positivity-610/916 (66.67%)


Pregnant women with Jaundice (916)
HEV positive 610/916 (66.6%)
AVH
493/610 (80.82%)
FHF
117/610 (19.18%)
HEV RNA POSITIVE
337/493 (68.36%)
HEV RNA POSITIVE
71/117 (60.68%)


Non -pregnant women (719)
HEV positive 538/719 (74.82%)
AVH
266/538 (49.44%)
FHF
111/538 (20.63%)
HEV RNA POSITIVE
51/155 (32.9%)
HEV RNA POSITIVE
39/111 (35.1%)


Bilirubin level of HEV in Pregnancy
AVH
N=493
FHF
N=117
Bilirubin level
7.04±5.05
Range: 1.2-21.0 mg/dl
Bilirubin level
14.33±4.0
Range: 2.0-26.0 mg/dl
Mild
(1-5mg)
5.0 %
Moderate
(5-10mg)
22.5 %
Severe
(>10mg)
72.5 %
Mild
(1-5mg)
12.5 %
Moderate
(5-10mg)
65.0%
Severe
(>10mg)
22.5%


Viral Load of HEV in Pregnancy
AVH
N=493
FHF
N=117
Mean Viral Load (Copies/ml)
19957.5
Range: 1211- 80329
Mean Viral Load (Copies/ml)
675166.3
Range: 73228-1675166

Hepatitis E Pregnancy

Incidence of hepatitis E infection is increased among pregnant women and is associated with a higher hepatitis E viral load, increased risk of ALF, and increased mortality.

Khuroo MS, Kamili S. Aetiology, clinical course and outcome of sporadic acute viral hepatitis inpregnancy.

J Viral Hepat. 2003 Jan;10(1):61-9.

Kar P, Jilani N, Husain SA, et al. Does hepatitis E viral load & genotypes influence the final outcome of ALF during pregnancy?

Am J Gastroenterol. 2008 Oct;103(10):2495-501

JMV-12-3009.R2(23508)

Journal of Medical Virology 9999:1–7 (2012)

IF'16 – 2.37

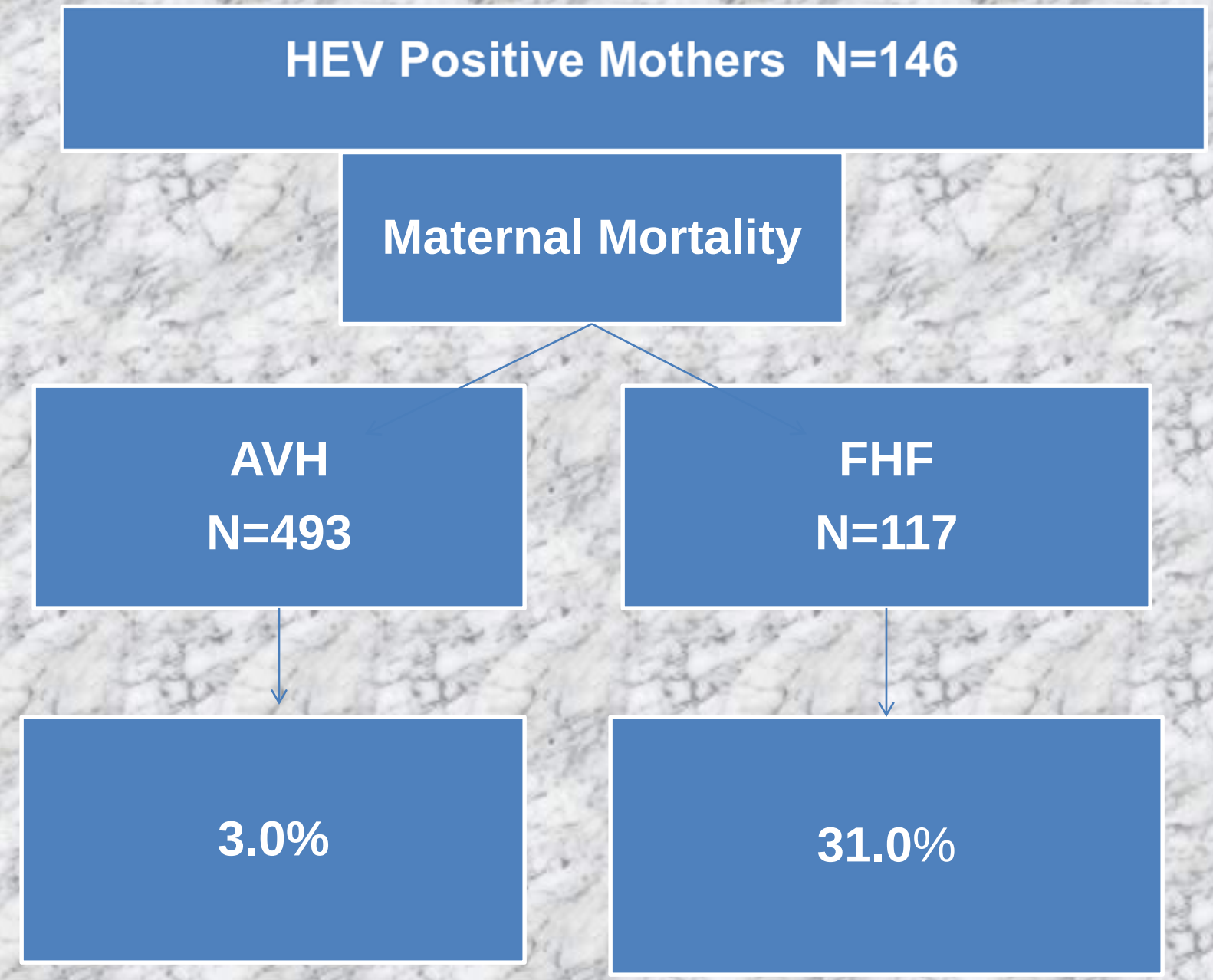
Does High Viral Load of Hepatitis E Virus Influence the Severity and Prognosis of Acute Liver Failure During Pregnancy?

Jayanta Borkakoti,[1] Rajib Kishore Hazam,[1] Asim Mohammad,[1] Ashok Kumar,[2] and Premashis Kar[1]*

HEV related 163 ALF which included 105 pregnant.

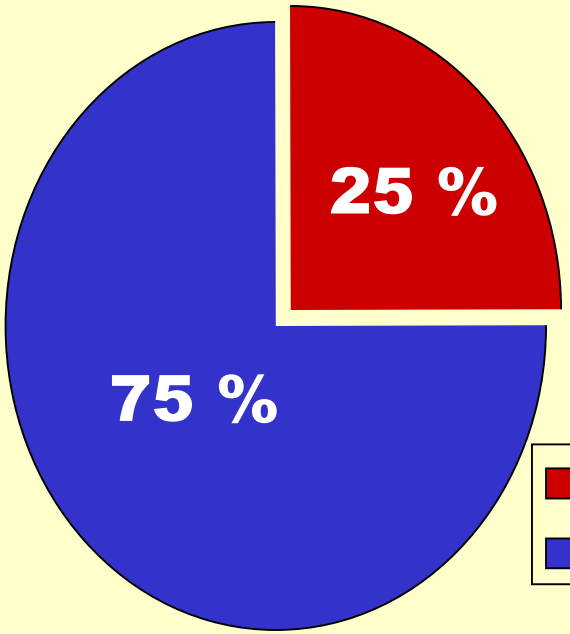
Viral load of HEV was also significantly higher in the pregnant ALF patients as compared with that of pregnant women with AVH ($P < 0.0001$).

High viral load of HEV during pregnancy could be one of the factors responsible for the severity of the infection during pregnancy.

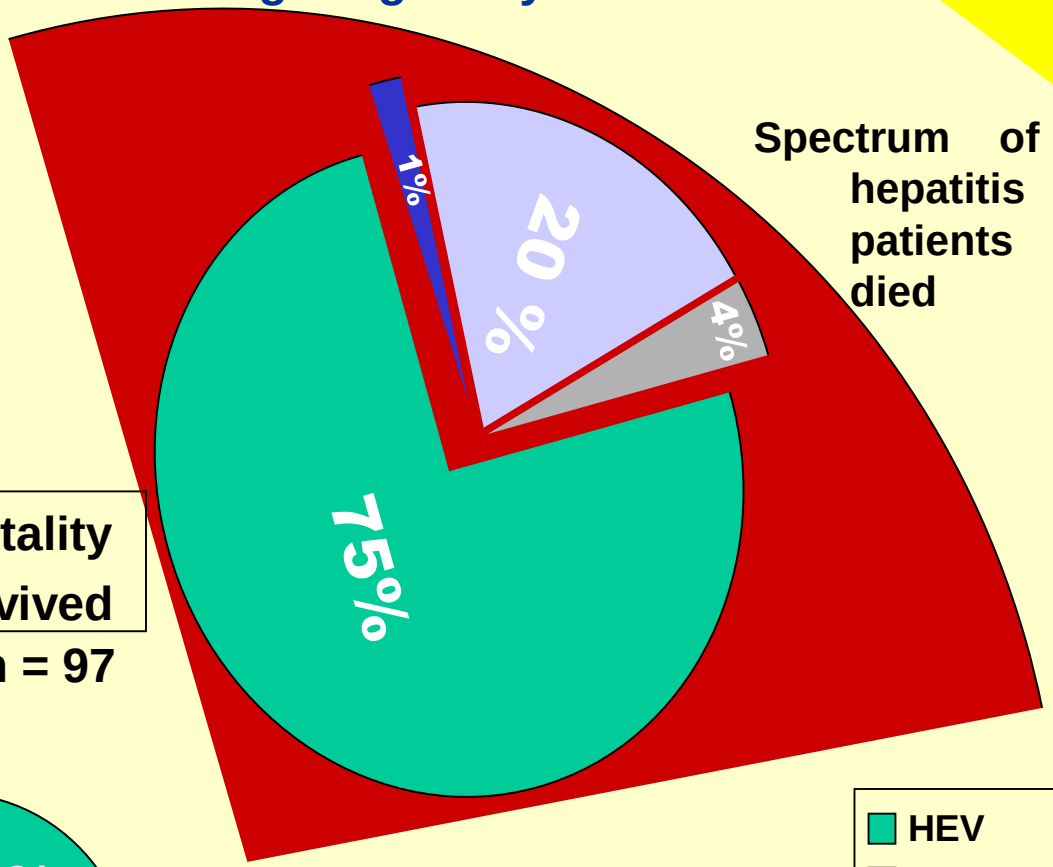

HEV Positive Mothers N=146
Maternal Mortality
AVH
N=493
FHF
N=117
3.0%
31.0%

Mortality

Viral Hepatitis during Pregnancy

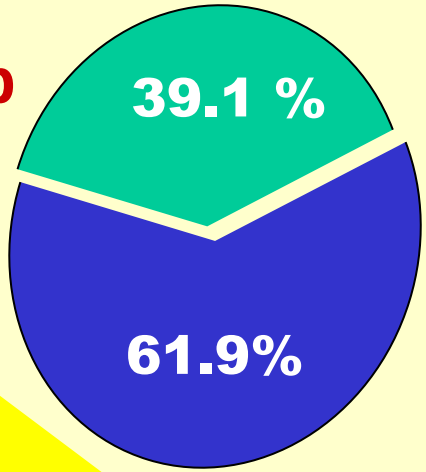


Mortality
Survived
n = 97



Spectrum of viral hepatitis in patients who died

HEV
Group

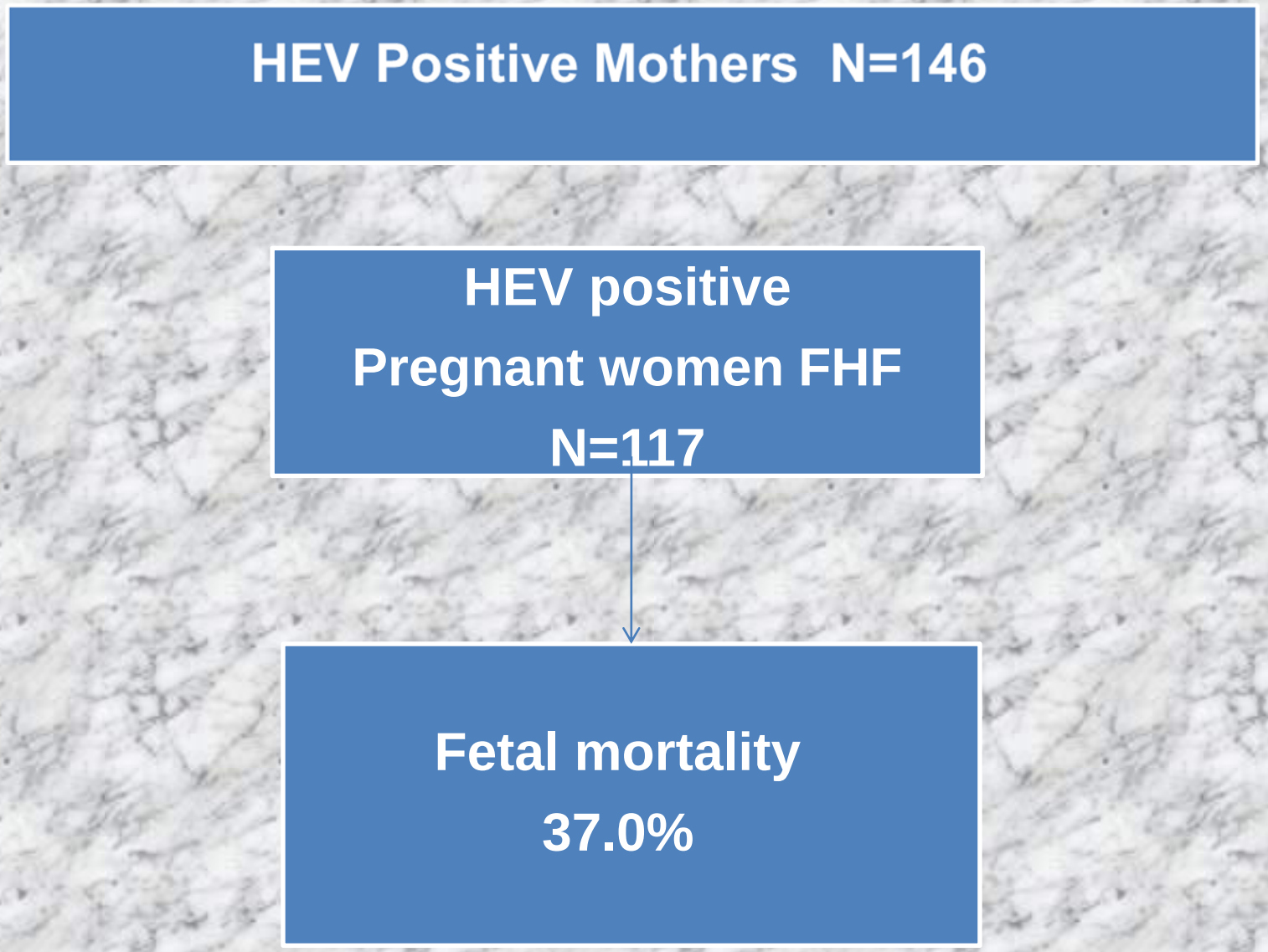


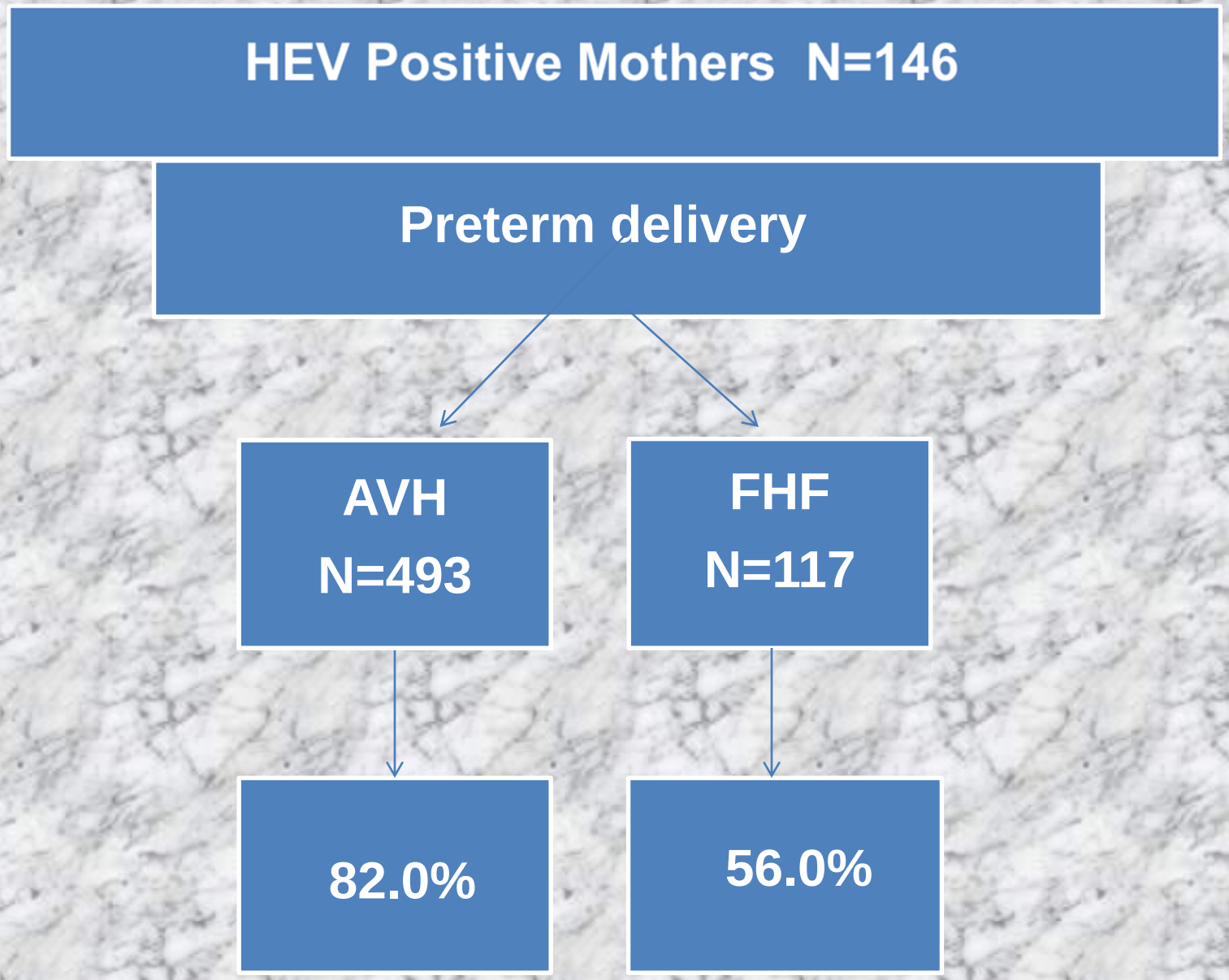
Mortality in HEV cases

Mortality
Survived
n = 46

HEV
HAV + HEV
HBV + HEV (2/24)
NON A-E (5/24)
HAV (1/24)

n = 24


HEV Positive Mothers N=146
HEV positive
Pregnant women FHF
N=117
Fetal mortality
37.0%


HEV Positive Mothers N=146
Preterm delivery
AVH
N=493
FHF
N=117
82.0%
56.0%

International Journal of Gynecology and Obstetrics 85 (2004) 240–244

International Journal of GYNECOLOGY & OBSTETRICS

www.elsevier.com/locate/ijgo

IF'16 – 2.17

Article

Hepatitis E in pregnancy

A. Kumar[a,*], M. Beniwal[a], P. Kar[b], J.B. Sharma[a], N.S. Murthy[c]

[a]*Department of Obstetrics and Gynaecology, Maulana Azad Medical College, New Delhi, India*
[b]*Department of Medicine, Maulana Azad Medical College, New Delhi, India*
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Received 22 July 2003; received in revised form 17 November 2003; accepted 19 November 2003

- **Eighty-one percent of FHF cases and 37.25% of acute viral hepatitis cases were caused by HEV.**

- **Preterm deliveries 66%**
- **Mortality rate 26.9%.**
- **Vertical transmission 33.3% of cases.**

Kumar A, Beniwal M, Kar P, Sharma JB, Murthy NS.
Hepatitis E in Pregnancy.
Obstet Gynecol Survey 2005, 60(1):7-8

Arch Gynecol Obstet
DOI 10.1007/s00404-017-4501-y

IF'16 – 2.09

CrossMark

MATERNAL-FETAL MEDICINE

Impact of maternal nutrition in hepatitis E infection in pregnancy

Ashok Kumar[1,7] · Sheetal Sharma[1] · Premashish Kar[2] · Sarita Agarwal[3] · Siddhartha Ramji[4] · Syed Akhtar Husain[5] · Sudha Prasad[1] · Shashi Sharma[6]

AVH

- Total protein & MUAC -predictors for Bilirubin,
- BMI - Viral load level,
- Protein, prealbumin, folate, TSFT - Prothrombin time.

ALF

- Prealbumin - Bilirubin levels
- MUAC - prothrombin time

Arch Gynecol Obstet
DOI 10.1007/s00404-017-4501-y

IF'16 – 2.09

CrossMark

MATERNAL-FETAL MEDICINE

Impact of maternal nutrition in hepatitis E infection in pregnancy

Ashok Kumar[1,7] · Sheetal Sharma[1] · Premashish Kar[2] · Sarita Agarwal[3] · Siddhartha Ramji[4] · Syed Akhtar Husain[5] · Sudha Prasad[1] · Shashi Sharma[6]

CONCLUSION

Malnutrition might confer a higher predisposition for HEV infection during pregnancy.

Lower levels of nutritional parameters are associated with
-increased severity in terms of occurrence of ALF
-predispose towards it during HEV infection.

It is possible that low nutritional status involves in mechanism that altered immune response during pregnancy which may be responsible for the severe liver injury seen in HEV infection during pregnancy.

ALF : Complications

- Cerebral edema
- Coagulopathy
- Gastrointestinal bleeding
- Pulmonary complication
- Sepsis
- Renal failure,
- Hypoglycemia,
- Acidosis
- Shock.

Step-by-step diagnostic approach

Diagnosis of ALF

- **History, including: chronology of events prior to presentation;**
- **Physical exam;**
- **Laboratory studies**

Step-by-step diagnostic approach

Exclusion of alternative causes,

-including acute presentations of chronic liver diseases.

Clues for presence of an underlying chronic liver disease:-

- **Splenomegaly,**
- **Spider angiomata,**
- **Palmar erythema,**
- **Ascites.**

Symptoms and Signs of ALF

Nonspecific symptoms:-

- **Jaundice : defining feature of ALF.**
- **Nausea and vomiting**
- **Malaise**
- **Abdominal Pain**
- **Ecchymoses**
- **Hepatic encephalopathy, coagulation disturbances in severe cases.**

Symptoms and Signs of ALF

- **Hepatic Encephalopathy (common)**

Interval : Onset of encephalopathy in relation to jaundice is important in

- **Patient's level of consciousness.**

Assessment of prognosis and further characterization of ALF.

Obstetric Examination

- Gestational Age
- Uterine contraction (Labor/Preterm labor)
- Placental Localisation
- Fetal well Being
- Fetal Growth, Birth weight.

Encephalopathy

- **Grade at the time of presentation : Important factor linked to prognosis.**
- **Subsequent changes in severity of hepatic encephalopathy play a role in management decisions during hospitalization**
- **Advanced grades : Associated with severe complications- cerebral edema and intracranial hypertension**

Symptoms and Signs of ALF

Cerebral edema

- **Common complication of ALF**

-Advanced grades of hepatic encephalopathy --- Hyperacute presentations.

- **Intracranial Hypertension**

-Abnormal pupillary reflexes,

-Muscular rigidity,

-Decerebrate posturing in advanced stages.

Neurologic examination

- to characterize the degree of hepatic encephalopathy
- to assess for evidence of intracranial hypertension

Laboratory Studies

- **Provide valuable prognostic information**
- **Identify early development of complications.**

Laboratory Studies

Diagnosis & Etiology

- Coagulation tests,
- Viral serologies,
- Autoimmune markers,
- Toxicology screening

Overall clinical status

- Hematology,
- Acid-base balance,
- Renal dysfunction
- Hepatic dysfunction.

Tests

Viral hepatitis PCR studies

- **HBV DNA,**
- **Herpes simplex virus DNA,**
- **HCV RNA.**

May assist in establishing the diagnosis, particularly in the acute setting, when serologies may be negative.

Additional viral serologies or PCR studies for EBV, CMV, *Varicella zoster* , and adenovirus may also be considered as these can be associated with ALF.

1st test to order

Liver function tests

- Hyperbilirubinemia
- Elevations in liver enzymes : variable
- Prothrombin time/INR

Basic Metabolic Panel

- Elevated BUN and creatinine,
- Metabolic derangements Na, K
- CBC-

  Leukocytosis, Anemia, Thrombocytopenia

- Blood type and screen
- Arterial blood gas

Tests

Factor V level

- A low result in the presence of hepatic encephalopathy may be predictive of mortality, particularly in patients with ALF secondary to viral hepatitis.

low (<20% to 30% of normal)

Viral hepatitis serologies

- antihepatitis A IgM, antihepatitis B core IgM, hepatitis B surface antigen, antihepatitis C IgG, and antihepatitis E IgM.

Autoimmune hepatitis markers

- Serological markers including antinuclear antibody (ANA), antismooth-muscle antibody, and quantitative immunoglobulins (IgG)

Test

Chest x-ray

- To assess for findings such as aspiration pneumonia

Abdominal ultrasound with Doppler

- Evidence of hepatic vein thrombosis associated with Budd-Chiari syndrome.
- Abdominal sonography may reveal hepatic surface nodularity suspicious for preexisting cirrhosis;
- Hepatomegaly,
- Splenomegaly,

Investigations

- CXR: Initial imaging
- Abdominal Doppler imaging to assess hepatic vein thrombosis associated with Budd-Chiari syndrome.
- Head CT : Cerebral edema or other underlying pathology in advanced encephalopathy.
- Blood, urine, and sputum cultures

Chronic hepatitis B

- • Hepatitis B surface antigen carriers are up to 9 times more likely to develop ALF in the setting of acute hepatitis, regardless of etiology.

- • Individuals with chronic hepatitis B infection are also at risk of developing co-infection with hepatitis D virus, which is associated with a greater frequency of severe hepatitis and ALF compared with hepatitis B alone.

HIV and hepatitis C coinfection

- **Individuals with HIV infection have an overall greater risk of ALF when they are coinfected with hepatitis C.**
- **This risk may be increased as much as 4-fold in the setting of highly active antiretroviral therapy (HAART).**

Kramer JR, Giordano TP, Souchek J, et al.
Hepatitis C coinfection increases the risk of fulminant hepatic failure in patients with HIV in the HAART era.
J Hepatol. 2005 Mar;42(3):309-14

Differential Diagnosis

Differential Diagnosis

Intrahepatic cholestasis of pregnancy

Combination of pruritus and elevated serum bile acid, both reversible within 4–6 weeks after pregnancy and after exclusion of other potential aetiologies

Obstructive Jaundice : 2-4 wks post pruritis

Bil <5mg%
ALPx4
ALT AST 2-10 fold
BA 10-100 fold

Differential Diagnosis

1. **HEELP syndrome**

- Syndrome of haemolysis, elevated liver enzymes and low platelets with an incidence of 1 in 1000 pregnancies.
- Presents with right upper quadrant pain with nausea, vomiting with elevated blood pressure.
- Laboratory abnormalities include elevated bilirubin and LDH levels along with moderately elevated liver transaminases with platelet count < 1lakh/ml.

Preeclampsia-Elampsia

Hepatic Involvement

ALP

Transaminases 10-20 fold

Bil <5mg%

HELLP

Hemolysis –Indirect Bil

Transaminases 10-20 fold

Bil<5mg%

Thrombocytopenia

HELLP : Tennessee System

Complete Syndrome	Incomplete Syndrome
AST &/or ALT >40	Any 1 or 2
Platelet <100,000	
LDH>600	
AST>70	

D/D Acute fatty liver of pregnancy

- **Acute fatty liver of pregnancy is a rare and fatal disease that occurs in third trimester of pregnancy. Deficiency of long chain hydroxy acyl dehydrogenase enzyme has been implicated in the pathology of the disease.**
- **Clinical presentation include vague pain abdomen, nausea, slowly developing jaundice. As liver parencymal damage progresses, hepatic encephalopathy with hypoglycemia ensues.**

- **Laboratory abnormalities in acute fatty liver of pregnancy include**
- **Liver transaminases elevations of < 1000IU/L,**
- **Prolongation prothrombin time,**
- **Decreased fibrinogen,**
- **Elevated bilirubin,**
- **Severe hypoglycemia.**

Crit Care Med 2005

Table 5. Swansea diagnostic criteria for the diagnosis of acute fatty liver of pregnancy.

Six or more of features below in the absence of other aetiology
Vomiting
Abdominal pain
Polydipsia/polyuria
Encephalopathy
Bilirubin (>14 µmol/L)
Hypoglycaemia (<4 mmol/L)
Leucocytosis (>11 x 10^6/L)
Elevated uric acid (>340 µmol/L)
Elevated ammonia (>42 IU/L)
Ascites or bright liver on USS
Elevated transaminases (>42 IU/L)
Renal impairment (creatinine >150 µmol/L)
Coagulopathy (PT >14 s or APTT >34 s)
Microvesicular steatosis on biopsy

Differential diagnosis between haemolysis, elevated liver enzymes, and low platelets syndrome and acute fatty liver of pregnancy.

	HELLP	AFLP
Prevalence (%)	0.2–0.6	0.005–0.01
Onset	Third trimester or post-partum	Third trimester or post-partum
Family history	No	Occasionally
Onset of preeclampsia (%)	70–80	50
Clinical features	Haemolysis (anaemia) Thrombocytopenia (50,000 platelets)	Liver failure, coagulopathy, encephalopathy hypoglycemia, DIC
Aminotransferases	Mild increase (may be up to 10–20 fold)	300–500 UI/L typically
Bilirubin	<5 mg/dL unless massive necrosis	>5 mg/dL
Liver imaging	Hepatic infarcts, hematomas, rupture	Fatty infiltration
Histology	Patchy/extensive, necrosis, periportal haemorrhage, fibrin deposits	Microvescicular steatosis in zone 3
Maternal mortality (%)	1–25	7–18
Foetal/perinatal mortality (%)	11	9–23
Recurrence in subsequent pregnancy (%)	4–19	25 (fatty acid oxidation defects)

Table 3. Typical pattern of LFTs, and additional investigations, in v

Pattern of LFT changes	Likely diagnosis	Recommended additional investigations
↑ALT (1.5-8 fold) ↑tBA (1.5-15 fold) tBil usually normal	Intrahepatic cholestasis of pregnancy (also known as obstetric cholestasis)	Viral serology Anti-mitochondrial and anti-smooth muscle antibodies Abdominal USS
↑ALT (2-5 fold) tBA usually normal tBil usually normal	Pre-eclampsia with hepatic impairment	↑BP in most Urinalysis for protein U&E, creatinine ↓Platelets
↑ALT (2-30 fold) tBA usually normal ↑tBil (1.5-10 fold)	HELLP syndrome (haemolysis, elevated liver enzymes, and low platelets)	↑BP in most Proteinuria in most ↑Creatinine ↓Platelets in all ↑LDH
↑ALT (3-15 fold) tBA usually normal ↑tBil (4-15 fold)	Acute fatty liver of pregnancy (AFLP)	↑BP in most Proteinuria in most ↑Creatinine ↓Platelets ↑WBC ↓Plasma glucose
↑ALT (2-5 fold) tBA usually normal tBil usually normal	Hyperemesis gravidarum	↑Thyroxine, ↓↓TSH† Hyponatraemia Hypokalaemia

Differential Diagnosis

Fulminant viral hepatitis

- **Fulminant hepatitis in pregnancy is caused by hepatitis E virus. It is due to diminished cellular immunity and high levels of steroid hormones influencing viral replication.**
- **Presents with jaundice and liver function test abnormalities (transaminases are elevated 10 times normal).**

Indian J Anaesth 2015

5. **Budd- Chiari syndrome**

- The most common cause of the above condition include myeloproliferative disorders.
- Hypercoagulable state associated with pregnancy also poses the risk for the development of disease.
- Rapid development of ascites is a striking feature. Venography is useful to locate the site of occlusion.

Test Result

arterial ammonia

• Characteristically elevated if hepatic encephalopathy is present. This may be useful when differentiating between other causes of altered mental status; however, it is a nonspecific test. High ammonia levels to >200 micromol/L are more specific and may predict an increased risk of developing intracranial hypertension.[55]

elevated

HIV test

• Risk of ALF is increased in patients with HIV and hepatitis C coinfection.

may be positive

urinalysis and urine sodium

• Should be obtained if renal dysfunction is present. Etiologies of renal failure in ALF may include hypovolemia, acute tubular necrosis, and hepatorenal syndrome.

proteinuria, sediment, low urine sodium (<10 mEq/L)

surveillance cultures

• Blood, urine, and sputum cultures should be obtained at regular intervals once advanced grade of encephalopathy develops.

may be positive

Coombs test

• If hemolysis is present, a Coombs test may further differentiate between Wilson disease, which is associated with a Coombsnegative hemolysis, versus autoimmune hemolysis, which is typically Coombs-positive.

positive or negative

liver biopsy

• The transjugular approach is preferred given the potential bleeding

risk associated with coagulopathy during ALF. In addition to a general

histopathologic evaluation, attention should be given to assess for the

presence of viral inclusions that may suggest acute herpes simplex

hepatitis, hepatic copper levels if Wilson disease is suspected, and

for features suggestive of autoimmune hepatitis. Liver biopsies are

rarely performed in the setting of ALF because they are not required

to confirm a diagnosis and generally do not have an impact on clinical

management or prognosis.

hepatocellular necrosis,

microvesicular steatosis,

viral inclusions, elevated

hepatic copper

CT scan of head

• Should be considered once grade 3 to 4 hepatic encephalopathy

develops to assess for presence of cerebral edema or other

underlying pathology.

cerebral edema,

hemorrhage