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Viral Hepatitis in Pregnancy – *"Unravelling the Mystery"*

HEV in Pregnancy - Management of fulminant hepatic failure - Medical Management in ICU".

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Outline

- Burden and outcomes of HEV ALF in pregnancy
- Pathogenetic mechanism
- D/D from diseases specific to pregnancy
- Medical Management
    - Routine
    - Specific to pregnant state
    - Specific to HEV infection
- Timing and decision for Liver transplant

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Burden of Disease

- HEV has the highest rate of mortality caused by liver failure than other viral hepatitic agent
- Globally-2400 to 3000/year stillbirths

Country, year	No. of cases (N)	Number of females overall (%)	Pregnancy	Percentage of female patients with pregnancy associated liver failure	Etiology of ALF (HEV)	Overall mortality reported (pregnant females)
USA,[20] 2012	1696	1173 (69%)	16	1.5%	Nil	NR
UK,[21] 2009	422	257 (61%)	? NR	NR	Nil	NR
Germany,[22] 2012	109	69 (63%)	3	NR	Nil	33%
Australia,[23] 2004	80	64 (80%)	? NR	NR	Nil	NR
India,[24] 2008	1015	590 (58%)	249	38.5%	59.4%	54%
India,[25] 2003	180	111 (62%)	49/83	59%	96%	66%
France,[26] 2008	363	–	? NR	2%	Nil	NR
Japan,[27] 2011	856	423 (49%)	? NR	NR	Nil	NR

Shalimar Et. Al. J Clin Exp Hepatol 2013;3:213–224

Impact of HEV on Maternal and Fetal Outcomes

Maternal mortality in 15% to 25% of cases

- Coagulopathy, DIC, encephalopathy and cerebral edema of ALF -70% of HEV infected pregnant women
- Hepatic coma-poor prognosis mortality ~ 100%

Fetal mortality -third trimester.

- Preterm delivery- poor infant survival rates
- Miscarriage,stillbirth, or neonatal death in 56% of infants.
- Infant deaths within a week-15% to 50%

Kar. P. Exp Rev Gastro Hepatol. 2019 Mar;13(3):205-211

Maternal and Fetal Outcomes in Pregnant Women with Acute Hepatitis E Virus Infection

Sharda Patra, MS; Ashish Kumar, MD, DM; Shubha Sagar Trivedi, MS; Manju Puri, MS; and Shiv Kumar Sarin, MD, DM

Variable	HEV-Infected Women (n = 132), n/n (%)	Non–HEV-Infected Women (n = 88), n/n (%)	Relative Risk (95% CI)	P Value
Maternal mortality rate				
Overall	54/132 (41)	6/88 (7)	6.0 (2.7–13.3)	<0.001
Patients with fulminant hepatic failure	54/73 (74)	6/18 (33)	2.2 (1.1–4.3)	0.001
Second trimester	18/27 (66)	0/7 (0)	–	0.002
Third trimester	36/46 (78)	6/11 (54)	1.4 (0.8–2.5)	0.11
Patients without fulminant hepatic failure	0/59 (0)	0/70 (0)	–	1.00
Medical complications				
Coagulation defect†	104/132 (79)	32/88 (36)	2.2 (1.6–2.9)	<0.001
Nasal or gastrointestinal hemorrhage	25/132 (19)	4/88 (4)	4.2 (1.5–11.6)	0.002
Leukocyte count ≥11 × 10^9 cells/L	86/132 (65)	31/88 (35)	1.8 (1.4–2.5)	<0.001
Serum creatinine concentration ≥34 μmol/L (≥2 mg/dL)	39/132 (30)	4/88 (4)	6.5 (2.4–17.5)	<0.001
Ascites	33/132 (25)	5/88 (6)	4.4 (1.8–10.8)	<0.001
Clinical signs of increased intracranial tension	27/132 (20)	1/88 (1)	18.0 (2.5–130.1)	<0.001

Key findings :

- HEV infection-AVH in 60%
- Fulminant hepatic failure was more common (RR, 2.7 [95% CI, 1.7 to 4.2)
- Maternal mortality was greater (RR, 6.0 [CI, 2.7 to 13.3]
- More frequent obstetric complications,antepartum hemorrhage,IUD
- Poor fetal outcomes

Ann Intern Med. 2007;147:28-33

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Pathogenetic Mechanism

Immunological changes- accommodate fetus

- Decrease in cell-mediated immunity

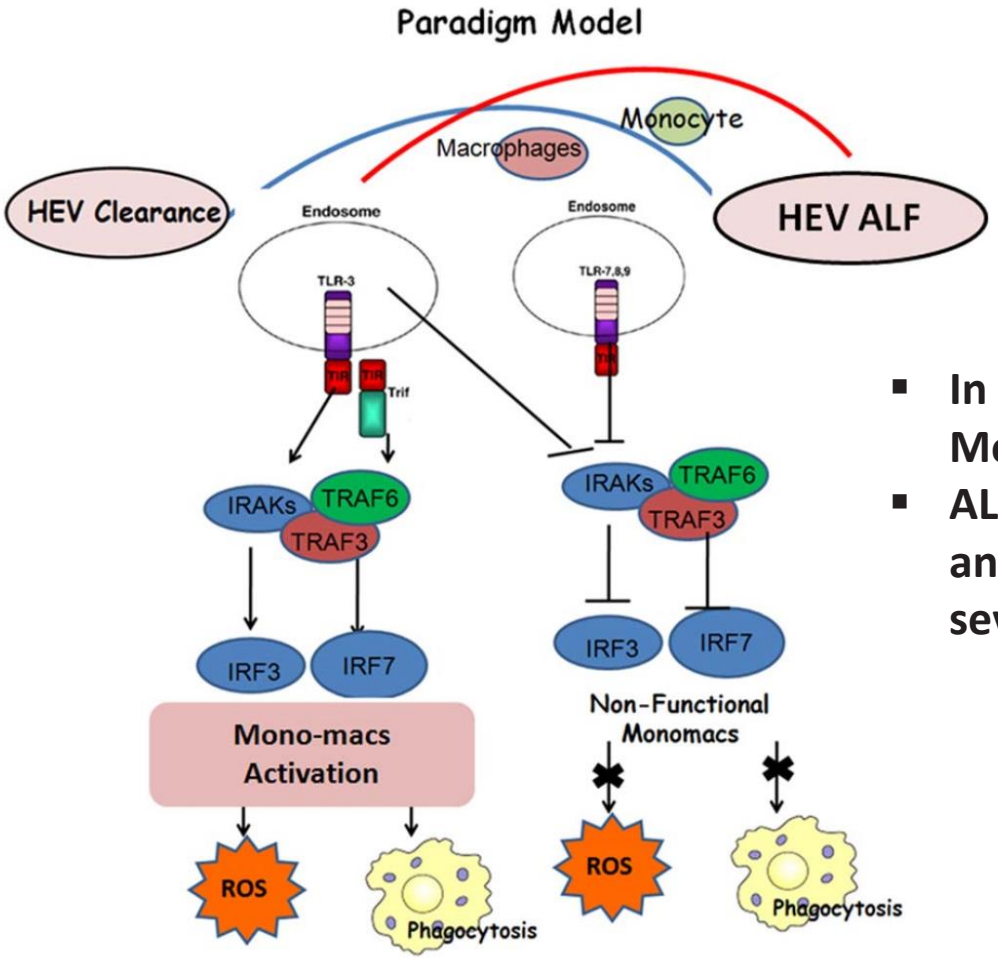
  Shift in Th1/ Th2 balance
  Decrease in the CD4/ CD8 Ratio

  Cytokines Inc. TGF-ß, IL-4 and IL-10

- Hormonal Changes : Increase in estrogen, progesterone and CMI
  Lymphocyte apoptosis-NF-ƘB pathway(Absent p65 component)
- Oxidative stress (reduced glutathione)
- Micronutrient and folate deficiency
- Coagulopathy- Inc. PPH

Navaneethan et.al.Liver Int. 2008 November ; 28(9): 1190–1199

Impaired Monocyte-Macrophage Functions and Defective Toll-Like Receptor Signaling in Hepatitis E Virus-Infected Pregnant Women With Acute Liver Failure



- In self-limiting HEV infection- Mono-macs are potent
- ALF-E defective TLR signaling and reduced phagocytosis lead to severe liver injury and mortality

Sehgal et.al.Hepatology2015;62:1683-1696)

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Diseases classification

- **Pregnancy related liver disease**
  - **First trimester**
  - **Hyperemesis gravidarum**
  - **Second and third trimesters**
  - **Intrahepatic cholestasis of pregnancy**
  - **Hypertension related liver diseases**
  - **Preeclampsia, eclampsia, and the HELLP syndrome**
  - **(hemolysis, elevated liver enzymes, low platelet counts)**
  - **Liver infarction/liver rupture**
  - **Acute fatty liver of pregnancy**
- **Non-pregnancy related - Pre existing liver disease**
  - **Portal hypertension, cirrhosis, primary biliary cirrhosis**
  - **Autoimmune hepatitis**
  - **Wilson disease**
  - **Chronic infection with hepatitis B or hepatitis C virus and other viruses**
  - **Alcoholic liver disease**
  - **Pregnancy post LT**
- **Coincidentally with pregnancy**
  - **Autoimmune**
  - **Viral -Acute viral hepatitis and other viral infections**
  - **Alcohol-related diseases**
  - **Gallstone disease**
  - **Budd-Chiari syndrome**

Differential Diagnosis of ALF in Pregnancy

	HELLP	AFLP	Viral Hepatitis
Risk factors	Prior pregnancy with HELLP Multiple gestation Extremes of age	Primigravida Multiple gestation Male fetus	Same as nonpregnant (blood, fecal/oral transmission depending on type)
Typical gestational age of onset	>20 wk	>24 wk	Any, evenly distributed through trimesters
Prior/family history?			
Typical clinical features	Hemolysis Thrombocytopenia Elevated liver function tests With/without hypertension With/without proteinuria DIC and liver failure (rare)	Liver failure Coagulopathy Encephalopathy Hyperammonemia Hypoglycemia DIC Jaundice	Liver failure Coagulopathy Encephalopathy DIC — — —
Diagnosis			
AST/ALT levels	Mild, up to 20× normal	300–500 IU/L but may vary	>1000 IU/L
Bilirubin	<5 mg/dL	<5 mg/dL but may be higher	Variable
Imaging	Normal in most, infarcts, hematomas, capsular rupture (rare)	Fatty infiltration	Normal
Outcomes			
Maternal mortality	1%	7%–18%	41%–54% (hepatitis E)
Fetal/perinatal mortality	11% (gestational age dependent)	9%–23% (gestational age dependent)	69% (hepatitis E) 39% (HSV)
Recurrence	25%, aspirin therapy starting at 16 wk may decrease risk	High if LCHAD deficiency, otherwise rare	None

Crit Care Clin 32 (2016) 61–72

Diagnostic Evaluation

Hematology
- Complete blood count
- Type and screen
- PT
- aPTT
- INR
- Lactate

Serum Chemistry
- Electrolytes
- Liver function tests (ALT, AST, GGT, bilirubin, albumin)
- Amylase
- Lipase

Arterial Blood Gas
- Lactate
- Ammonia

Toxicology Screen
- Acetaminophen
- Cocaine
- Alcohol

Autoimmune
- ANA
- Anti–smooth muscle antibody
- Microsomal antibodies

Hepatitis Serology
- Anti-HAV IgM
- HBsAg
- Anti-HBc IgM
- Antihepatitis E

Additional Viral Serology
- CMV
- EBV
- HSV
- HIV

Other
- Ceruloplasmin
- Serum copper

Crit Care Clin 32 (2016) 61–72

Pregnancy-associated acute liver disease and acute viral hepatitis: Differentiation, course and outcome☆

Harshad Devarbhavi[1,2,*], Walter K Kremers[3], Ross Dierkhising[3], Lakshmi Padmanabhan[4]

Variable	PAALD ($N = 46$)	VH ($N = 41$)	Odds ratio (95% CI)[b]	p-Value[b]
Features				
Age (years)	23.9 ± 4.6	24.5 ± 4.9	1.03 (0.94, 1.13)	0.57
Primigravida	22 (47.8%)	18 (43.9%)	0.85 (0.36, 1.99)	0.71
Gestation weeks	32.3 ± 6.5	31.2 ± 6.3	0.97 (0.91, 1.04)	0.42
Hypertension	30 (65.2%)	1 (2.4%)	0.01 (<0.001, 0.07)	<.0001
Encephalopathy	19 (42.2%)[a]	4 (9.8%)	0.15 (0.04, 0.45)	0.0004
Abdominal pain	13 (28.3%)	8 (19.5%)	0.62 (0.22, 1.66)	0.34
Oliguria	15 (34.1%)[a]	0 (0.0%)	<0.001 (0.0, 0.10)	<0.0001
Ascites	35 (76.1%)	3 (7.3%)	0.03 (0.01, 0.09)	<0.0001
Outcomes				
Death	19 (41.3%)	3 (7.5%)	0.12 (0.03, 0.38)*	0.0002*
Fetal death	24 (53.3%)	4 (9.8%)	0.10 (0.03, 0.28)*	<0.0001*

Multivariate logistic regression model for differentiating VH vs. PAALD

Variable	Odds ratio (95% CI)	p-Value
Hypertension	0.009 (<0.001, 0.069)	0.0001
Ascites	0.018 (0.003, 0.085)	<0.0001

H. Devarbhavi et al. / Journal of Hepatology 49 (2008) 930–935

Biochemical Factors

Variable	PAALD ($N = 46$)	VH ($N = 41$)	Odds ratio (95% CI)[a]	p-Value[a]
Hemoglobin (g/dl)	10.30 ± 3.5	10.29 ± 2.3	1.00 (0.86, 1.15)	0.99
WBC (10^9/L)	26 ± 35.2	15.7 ± 13.8	0.98 (0.93, 1.00)	0.05
LDH (U/L)	1084.7 ± 1168	415.4 ± 255.8	0.997 (0.994, 0.999)	0.0003
Serum creatinine (mg/dl)	2.43 ± 1.5	1.17 ± 1.25	0.39 (0.22, 0.63)	<0.0001
Blood urea nitrogen (mg/dl)	52 ± 30	25 ± 34	0.96 (0.94, 0.98)	0.0001
Uric acid (mg/dl)	8.39 ± 2.9	5.82 ± 3.5	0.76 (0.60, 0.92)	0.0037
Glucose mg/dl	70.8 ± 43.7	83.0 ± 57.9	1.005 (0.996, 1.016)	0.29
FDP	941.8 ± 232.6	806.7 ± 400.5	0.999 (0.996, 1.001)	0.16
Prothrombin time (s)	33.0 ± 22.5	21.0 ± 7.1	0.93 (0.88, 0.97)	0.0003
aPTT (s)	55.2 ± 25.9	45.2 ± 27.1	0.982 (0.955, 1.003)	0.11
Platelets (10^9/L)	79218 ± 58603	205189 ± 88621	1.024 (1.015, 1.036)*	<0.0001
Total proteins (mg.dl)	5.26 ± 0.98	6.07 ± 0.78	2.85 (1.67, 5.34)	<0.0001
Albumin (mg/dl)	2.34 ± 0.49	2.96 ± 0.56	14.81 (4.64, 63.29)	<0.0001
Total bilirubin (mg/dl)	9.88 ± 6.9	11.18 ± 5.5	1.03 (0.97, 1.11)	0.33
Direct bilirubin (mg/dl)	6.78 ± 4.9	6.62 ± 2.8	0.99 (0.89, 1.10)	0.85
AST (U/L)	268 ± 295	828 ± 1045	1.001 (1.001, 1.003)	0.0003
ALT (U/L)	186 ± 138	576 ± 729	1.003 (1.001, 1.006)	<0.0001

Multivariate logistic regression models for clinical and laboratory variables predicting mortality

Model variable types considered	Variable	Odds ratio (95% CI)	p-Value	C
Clinical variables only or clinical variables/easy labs	Abdominal pain	5.68 (1.52, 24.31)	0.0125	0.85
	Oliguria	7.47 (1.77, 36.72)	0.0086	
	Ascites	5.17 (1.36, 23.33)	0.0206	
Clinical and all laboratories	Total bilirubin	1.17 (1.06, 1.32)	0.0053	0.83
	Oliguria	14.09 (3.58, 67.60)	0.0003	

H. Devarbhavi et al. / Journal of Hepatology 49 (2008) 930–935

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Does Hepatitis E Viral Load and Genotypes Influence the Final Outcome of Acute Liver Failure During Pregnancy?

Group	Viral Load IU/mL	Genotype
AVH PREG (N = 7)	343.29 ± 216.44	1
AVH NON-PREG (N = 6)	$13.83 \pm 7.8^{*}$	1
FHF PREG (N = 14)	$5.87 \times 10^{4} \pm 1.5 \times 10^{5}$	1
FHF NON-PREG (N = 3)	$199.2 \pm 225.5^{*}$	1

Kar. P. et.al.Am J Gastroenterol 2008;103:2495–2501

Therapy specific to HEV infection

Ribavirin- Teratogenic

Safety in pregnancy not established

Sofosbuvir- Additive effect with ribavirin- replicon

Genotype 3 chronic infection

Category B drug pregnancy

Need of controlled trials

Kar. P. Exp Rev Gastro Hepatol. 2019 Mar;13(3):205-211

Management related to Pregnant State

- Management of abortions, preterm labor, and still birth are same as for a normal pregnancy.
- Increased risk of bleeding-Coagulopathy
- No role of termination of pregnancy
- Vaginal delivery is preferable
- Induction of delivery not recommended

  Coagulopathy, hemodynamic instability

  increase in the intracranial pressure
- Continuous fetal monitoring
- Successful reports of Liver transplantation with viable fetus

Shalimar Et. Al. J Clin Exp Hepatol 2013;3:213–224
Kar. P. Exp Rev Gastro Hepatol. 2019 Mar;13(3):205-211

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Principles of Medical Managment

- Multimodality team approach-critical care specialists, obstetrician, hepatologists gastroenterologists, neonatologists, and transplant surgeons.

- Few evidence-based recommendations for managing the pregnant woman with ALF.

- Management of ALF should be guided by the same principles followed for the nonpregnant patient

Crit Care Clin 32 (2016) 61–72

Management	
Early Identification of red flag signs/ symptoms	
Referral to a Tertiary Care Hospital –Ensure Minimum Risk of Transportation	
Admission to ICU- Grade 3 or 4 hepatic encephaloapthy	
Nutrition	
General care	
Fluid and Electrolyte management	
Managing Hepatic Encephalopathy and Ammonia and Seizure	
Management of Cerebral edema & raised intracranial pressure	
Correction of coagulopathy- delivery	
Prevention and Treatment of renal failure	
Prevention and Treatment of Infection	
Respiratory Failure and ventilator management	
Hemodynamics and Cardiovascular monitoring	
Liver Transplantation	

Management	
Early Identification of red flag signs/ symptoms	Any degree of altered sensorium in a patient of acute liver injury should not be ignored.
Referral to a Tertiary Care Hospital and Risk of Transportation	Managing a ALF patient in resource poor setting should be avoided. Early referral is needed. Patient with HE preferred to be transported to shorter distance, air ambulance and with mechanical ventilation.
Admission to ICU	All patients of ALF should be preferably be admitted to ICU Indications- Advanced Hepatic Encephalopathy Hemodynamic Instability Metabolic Acidosis
Early identification for LT	Prognostic model KCH } *None validated for pregnancy Dynamic Models Pregnancy related ALF-Expedited delivery

Auzinger G.and Wendon J.Current Opinion in Critical Care 2008, 14:179–188

Management of Hemodynamics

General care	1. Avoid light, crowded places,frequent position change, bowel enema for purging. 2. Prefer Minimal endotracheal suctioning, 3. Avoid hypothermia or fever, prolonged hypoxia or hypercarbia.
Fluid & Electrolyte management	▪ Invariably intravascular volume depletion, due to 'insensible' fluid losses, vomiting and poor oral intake. ▪ Early and adequate fluid resuscitation is therefore mandatory 1. Normal saline or balanced fluid i.e. plasmalyte to be preferred. Avoid Hartman solution or ringer lactate 2. Watch for hyperchloremic metabolic acidosis 3. Hyponatremia or hypernatremia to be avoided with a target of 145-155meq/l
Hemodynamics and Cardiovascular monitoring	1. Invasive monitoring with CVP line, PiCCO or real time monitor (FlowTrac with facility for extra vascular lung water is preferred 2. Pulmonary catheter to be avoided. 3. Hypotension to be avoided- Norepinephrine first line ,Terli (controversial)

Auzinger G.and Wendon J.Current Opinion in Critical Care 2008, 14:179–188

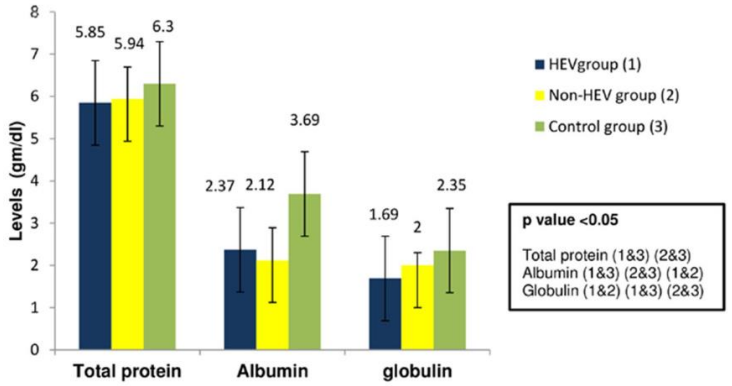
Nutritional Management

Nutrition	1. No restrictions of enteral feeding and should be started within 24 hours. 2. Calories- 25-30Kcal/kg/day 3. Consideration of parenteral nutrition in absence of enteral nutrition is of no major concern 4. No protein restriction needed 5. Immune nutrition with arginine or glutamine avoided due to fear of ammonia production. 6. Hypoglycemia to be prevented, RBS should be maintained around 90-120mg/dl. Avoid 5D & consider 20-25% dextrose infusion at low dose to avoid cerebral edema. 7. Monitor and correct hypophosphatemia

Auzinger G.and Wendon J.Current Opinion in Critical Care 2008, 14:179–188

Impact of maternal malnutrition

Characteristics	Pregnant women			*p* value		
	HEV group ($N = 103$)	Non-HEV group ($N = 110$)	Control group ($N = 144$)			
	(1)	(2)	(3)	1 vs. 2	1 vs. 3	2 vs. 3
BMI (kg/m^2)	16.35 ± 1.30	16.60 ± 1.83	19.77 ± 3.56	0.14	<0.00001	<0.00001
MUAC (m)	0.22 ± 0.02	0.23 ± 0.02	0.25 ± 0.01	0.34	<0.00001	<0.00001
TSFT (mm)	12.67 ± 9.95	11.84 ± 1.52	11.91 ± 0.54	0.84	0.006	0.001
ASN (m)	1.53 ± 0.02	1.53 ± 0.02	1.53 ± 0.01	0.38	0.44	0.085
Serum prealbumin (mg/dl) $n = 70$[a]	28.25 ± 1.35	28.41 ± 1.21	34.18 ± 1.55	<0.00001	<0.00001	<0.00001
Serum folate (ng/ml) $n = 70$[a]	6.14 ± 0.54	7.36 ± 0.71	4.95 ± 0.45	<0.00001	<0.00001	<0.00001



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

Management of Brain

Hepatic Encephalopathy and Ammonia and Seizure	1. Don't delay in mechanical ventilation with worsening sensorium or Grade III-IV HE. 2. Sedate –Decrease the CMR and metabolic deman 3. Routine prophylaxis for seizure is not needed. 4. Higher-level ammonia >122meq/l to be avoided . 5. Role of LOLA is not established
Cerebral edema & raised intracranial pressure	1. Invasive monitoring for ICP discouraged 2. Non-invasive monitoring-ONSD, TCD 3. Mannitol to be avoided with serum osmolarity >320 mOsm/L or onset of AKI 4. Hypertonic saline or mannitol to be used as bolus not maintenance infusion 5. Artificial Liver Support Therapies(CRRT, HVP, MARS)- More data is needed Case to case basis

Auzinger G.and Wendon J.Current Opinion in Critical Care 2008, 14:179–188

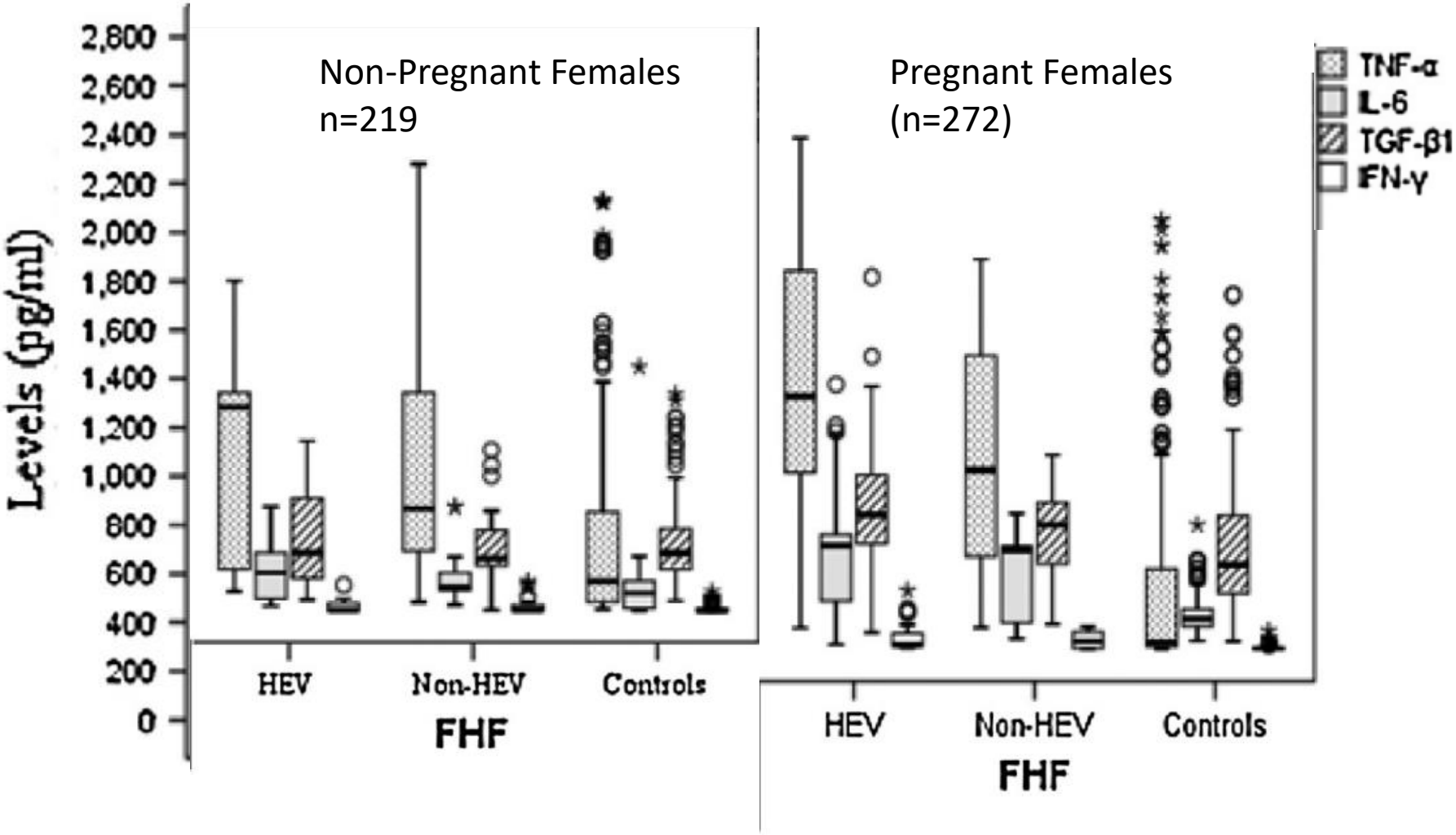
Management	
Correction of coagulopathy	Routine prophylactic correction of coagulopathy with FFP, Cryoprecipitate or platelet is discouraged in absence of any active bleeding or high-risk intervention.
Prevention and Treatment of renal failure	1. Avoid nephrotoxic drugs, dehydration. 2. Early RRT is preferred over late 3. Avoid SLED or HD in patents of ALF. Consider CCRT.
Prevention and Treatment of Infection	1. Prophylaxis with antibiotics and antifungals for high-risk cases with severe liver dysfunction, mechanical ventilation or multiorgan failure. 2. Universal precaution i.e. topical bacterial decontamination, with oral chlorhexidine and chlorhexidine bathing (soaked wipes) needed
Respiratory Failure and ventilator management	1. Early endotracheal intubation, rapid sequence induction, low tidal volume, low PEEP preferred 2. Sustained hyperventilation and permissive hypercapnia is contraindicated in ALF.

Auzinger G.and Wendon J.Current Opinion in Critical Care 2008, 14:179–188

Relevance of systemic inflmmatory response syndrome!

Association of cytokines in hepatitis E with pregnancy outcome

Ashok Kumar [a,*], Salam Gyaneshwori Devi [a], Premashis Kar [b], Sarita Agarwal [c], Syed Akhtar Husain [d], Ram Kumar Gupta [a], Shashi Sharma [e]



A Kumar et al. / Cytokine 65 (2014) 95–104

? Role of N-Acetylcysteine

NAC- Antioxidant and replenishes glutathione levels

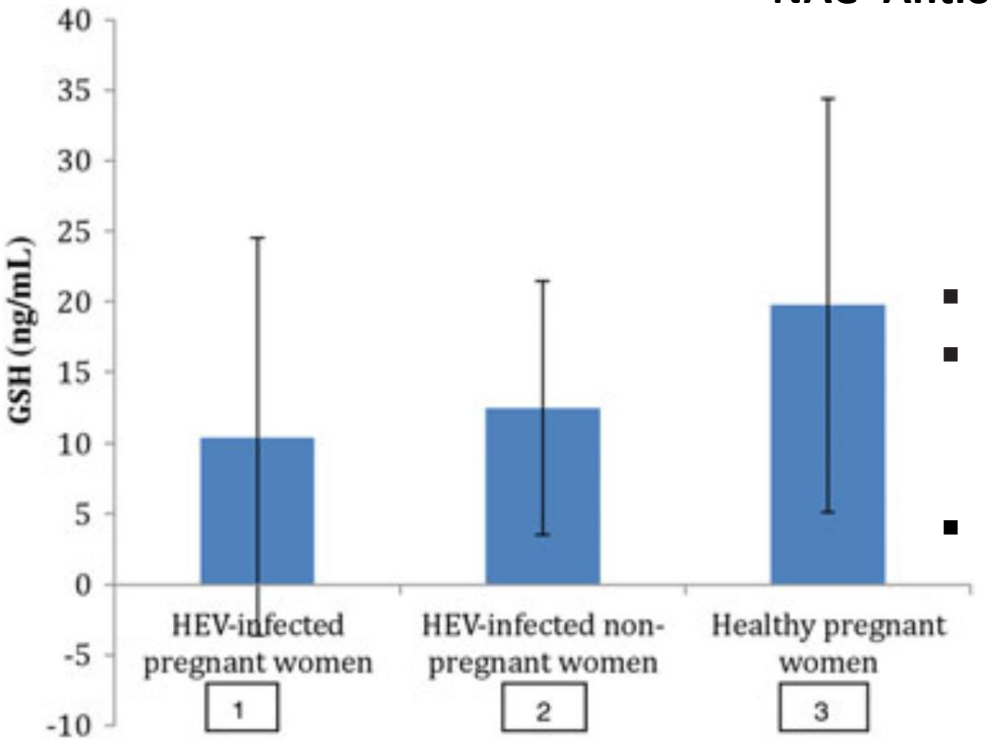


Figure 1 Serum reduced glutathione levels (GSH) in various study groups ($p < 0.05$) (1 vs 3 & 2 vs 3).

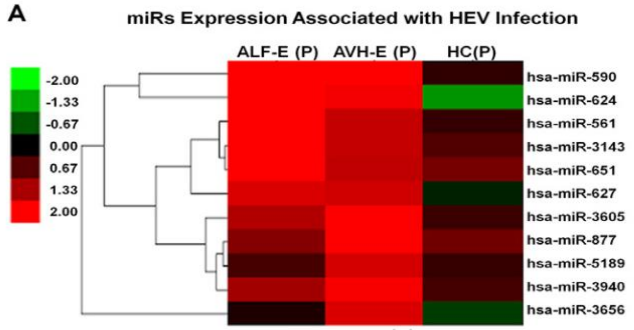
- Oxidative stress –Pregnant with HEV
- Serum GSH ≤10.88 ng/mL during pregnancy can be used for risk stratification for HEV infection.
- Adverse outcomes

**30 patients in each group*

Bhatnagar et.al.J. Obstet. Gynaecol. Res. 2016

Need of Biomarkers!

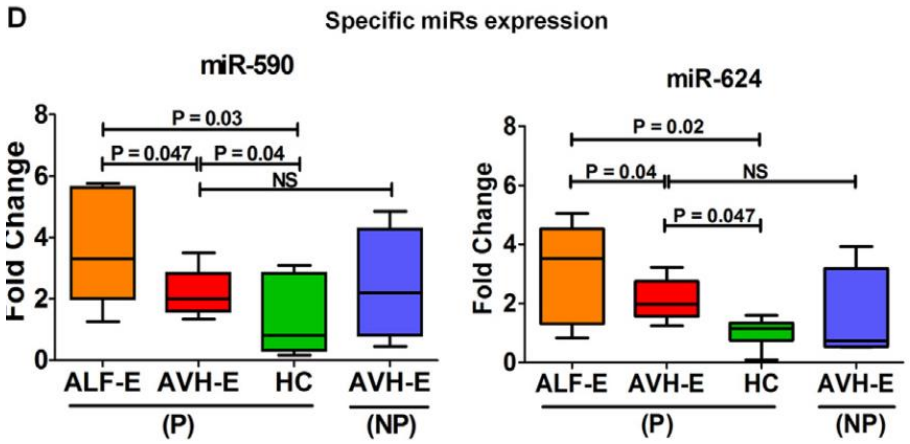
miRNA signatures can predict acute liver failure in hepatitis E infected pregnant females



B

Fold Change Expression

miRs	ALF-E(P) (Log² Ratio)	AVH-E(P) (Log² Ratio)	HC(P) (Log² Ratio)	AVH-E(NP) (Log² Ratio)
hsa-miR-590	2.92	1.55	0.64	3.11
hsa-miR-624	2.53	1.55	0.42	2.06
hsa-miR-561	3.56	2.11	0.36	1.22
hsa-miR-627	1.72	1.63	-0.26	2.56
hsa-miR-651	2.96	1.51	0.92	2.89
hsa-miR-877	1.04	2.39	0.88	2.66
hsa-miR-3143	2.04	1.92	-1.17	1.37
hsa-miR-3605	1.40	2.94	0.48	2.11
hsa-miR-3656	0.23	1.71	-0.47	1.22
hsa-miR-3940	1.28	1.95	0.53	2.16
hsa-miR-5189	0.55	1.67	0.42	2.03



Trehanpati et.al.Heliyon. 2017 Apr 6;3(4):e00287

Summary

- Hepatitis E infection in pregnancy is associated with poor maternal and fetal outcomes
- Fulminant hepatic failure and maternal mortality are more common in third trimester.
- Important to differentiate from Pregnancy asso. Liver disorders
- Treatment-Supportive with diligent monitoring and intensive care.
- Therapeutic termination of pregnancy is not recommended based on current evidence.
- Indications and timing of liver transplantation for ALF is controversial.

Thank you!