Pregnancy and Liver Disease

Gastro Foundation Fellow Weekend 2020

Bilal Bobat
Liver Unit WDGMC

Wits University Donald Gordon Medical Centre
Patient-centred. Independent. Academic.

MEDICLINIC

WITS TRANSPLANT
Progressive medicine, exceptional care.

Pregnancy and Liver Disease

- Normal Changes
- Changes that Mimic Liver Disease

Any Change in Bilirubin or the Transaminases need to be investigated
INR Measured as Normal

Test	Change in pregnancy
AST/ALT	⟷
Bilirubin	⟷
Prothrombin/INR	⟷
Albumin	↓
Alkaline phosphatase	↑
Hemoglobin	↓
Alpha fetoprotein	↑
5' nucleotidase	⟷
Gamma glutamyl transpeptidase	⟷

ALT, alanine transaminase; AST, aspartate transaminase; INR, international normalized ratio.

AMERICAN JOURNAL OF GASTROENTEROLOGY

ACG Clinical Guideline: Liver Disease and Pregnancy Tran, Tram T; Ahn, Joseph; Reau, Nancy S American Journal of Gastroenterology111(2):176-194, February 2016.

Table 2. Typical reference ranges for liver enzymes, by trimester.

Liver enzyme	Non-pregnant	Pregnant	1st trimester	2nd trimester	3rd trimester
ALT (IU/L)	0-40	-	6-32	6-32	6-32
AST (IU/L)	7-40	-	10-28	11-29	11-30
Bilirubin (μmol/L)	0-17	-	4-16	3-13	3-14
γGT (IU/L)	11-50	-	5-37	5-43	3-41
ALP (IU/L)	30-130	-	32-100	43-135	133-418
Albumin (g/L)	35-46	28-37	-	-	-
Bile acids (μmol/L)	0-14	0-14	-	-	-
Haemoglobin (g/L)		-	110-135	103-130	100-130
Platelets (10^3/ml)		212-135	-	-	-

Modified (with permission) from Walker I, Chappell LC, Williamson C "Abnormal Liver function tests in pregnancy" *BMJ 2013 Oct 25:34.*

Pregnancy and liver Disease, Westbrook R Dusheiko G J Hepatol. 2016 Apr;64(4):933-45.

Liver Disease in Pregnancy

Pregnancy Related

- Hyperemesis Gravidarum
- Intrahepatic Cholestasis
- Hypertensive Related Liver Disease
- AFLP

Non-Pregnancy Related

Coincidental

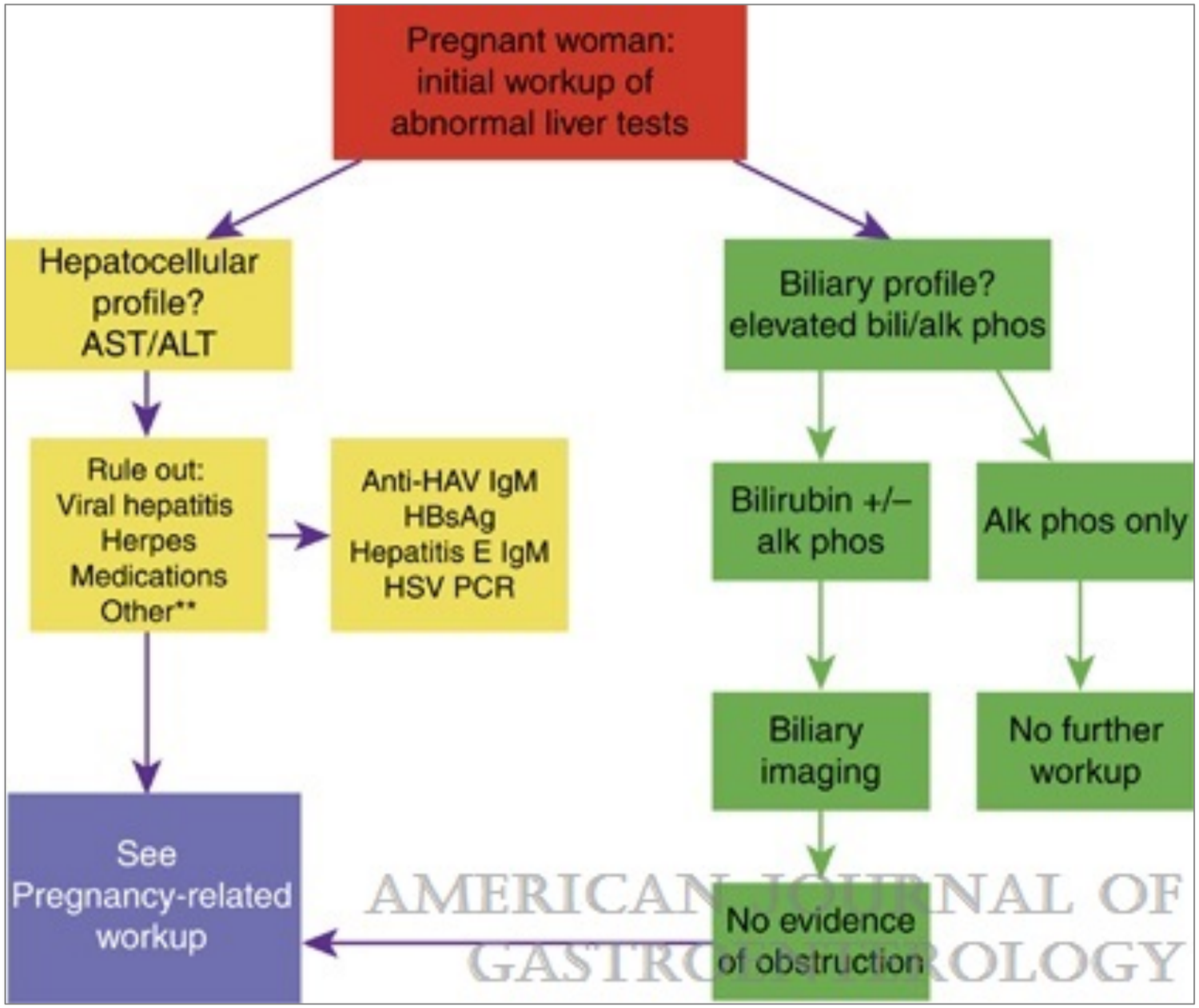
- AIH
- Viral
- DILI

Pre-existing Liver Conditions

- Cirrhosis
- Portal Hypertension
- Post Liver Transplant

Work Up

- History & Examination
- Ultrasound Modality of choice
- Teratogenicity >100Rad
- CT Abd 3.5Rad
- Gadolinium not recommended
- Endoscopy Safe



ACG Clinical Guideline: Liver Disease and Pregnancy Tran, Tram T; Ahn, Joseph; Reau, Nancy S American Journal of Gastroenterology111(2):176-194, February 2016.

Hyperemesis Gravidarum

- Severe Form of Nausea and Vomiting
- Intractable vomiting with Dehydration, Ketosis, LOW >5%
- HCG
- Vit B6/Doxylamine

Intrahepatic Cholestasis of Pregnancy

- Reversible Cholestasis
- Multiple Pregnancies
- UDCA 10-15mg/kg
- tsBA >40=↑Foetal Risk
- Abn Bile Transport Receptors
- Deliver at 37 weeks
- Later Sequelae

Ursodeoxycholic acid versus placebo in women with intrahepatic cholestasis of pregnancy (PITCHES): a randomised controlled trial

Lucy C Chappell, Jennifer L Bell, Anne Smith, Louise Linsell, Edmund Juszczak, Peter H Dixon, Jenny Chambers, Rachael Hunter, Jon Dorling, Catherine Williamson, Jim G Thornton*, for the PITCHES study group†*

Summary

Background Intrahepatic cholestasis of pregnancy, characterised by maternal pruritus and increased serum bile acid concentrations, is associated with increased rates of stillbirth, preterm birth, and neonatal unit admission. Ursodeoxycholic acid is widely used as a treatment without an adequate evidence base. We aimed to evaluate whether ursodeoxycholic acid reduces adverse perinatal outcomes in women with intrahepatic cholestasis of pregnancy.

Methods We did a double-blind, multicentre, randomised placebo-controlled trial at 33 hospital maternity units in England and Wales. We recruited women with intrahepatic cholestasis of pregnancy, who were aged 18 years or older and with a gestational age between 20 weeks and 40 weeks and 6 days, with a singleton or twin pregnancy and no known lethal fetal anomaly. Participants were randomly assigned 1:1 to ursodeoxycholic acid or placebo, given as two oral tablets a day at an equivalent dose of 500 mg twice a day. The dose could be increased or decreased at the clinician's discretion, to a maximum of four tablets and a minimum of one tablet a day. We recommended that treatment should be continued from enrolment until the infant's birth. The primary outcome was a composite of perinatal death (in-utero fetal death after randomisation or known neonatal death up to 7 days after birth), preterm

Lancet 2019; 394: 849–60
Published Online
August 1, 2019
http://dx.doi.org/10.1016/S0140-6736(19)31270-X

See **Comment** page 810

*Joint senior authors
†A full list of collaborators is provided in the appendix
Department of Women and Children's Health, School of Life Course Sciences, King's College London, London, UK
(Prof L C Chappell PhD,

Hypertensive Liver Disease

- Pre-Eclampsia
  - De Novo Hypertension after 20 weeks with Proteinuria
  - Severe when other maternal organ involvement or foetal distress

- HELLP

- Hepatic Rupture/Infarction/Haematoma
  - 50% Mortality

Acute Fatty Liver of Pregnancy

- Abnormality Mitochondrial Beta Fatty Acid Oxidation
- Supportive Management
- Prompt Delivery

Table 4. Swansea criteria for diagnosis of acute fatty liver of pregnancy

Six or more criteria required in the absence of another cause	
Vomiting	
Abdominal pain	
Polydipsia/polyuria	
Encephalopathy	
Elevated bilirubin	>14 µmol/l
Hypoglycaemia	<4 mmol/l
Elevated urea	>340 µmol/l
Leucocytosis	>11×10^6 cells/l
Ascites or bright liver on ultrasound scan	
Elevated transaminases (AST or ALT)	>42 IU/l
Elevated ammonia	>47 µmol/l
Renal impairment; creatinine	>150 µmol/l
Coagulopathy; prothrombin time	>14 s or APPT>34 s
Microvesicular steatosis on liver biopsy	

ALT, alanine transaminase; APPT, activated partial thromboplastin time; AST, aspartate transaminase.

ACG Clinical Guideline: Liver Disease and Pregnancy Tran, Tram T; Ahn, Joseph; Reau, Nancy S American Journal of Gastroenterology111(2):176-194, February 2016.

Pregnancy Related Liver Disease

Pattern of LFT changes	Likely diagnosis	Estimated proportion of pregnant women with abnormal LFTs that have each 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)	17%	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	49%	↑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)	22%	↑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)	4%	↑BP in most Proteinuria in most ↑Creatinine ↓Platelets ↑WBC ↓Plasma glucose
↑ALT (2-5 fold) tBA usually normal tBil usually normal	Hyperemesis gravidarum	8%	↑Thyroxine, ↓↓TSH† Hyponatraemia Hypokalaemia

Reproduced (with permission) from Walker I, Chappell LC, Williamson C "Abnormal Liver function tests in pregnancy" *BMJ 2013 Oct 25:34.*

Pregnancy Related Liver Disease

Table 3. Liver diseases unique to pregnancy

Disorder	Trimester	Management
HG	First through 20 weeks	Supportive management
IHCP	Second/third	Ursodeoxycholic acid 10–15 mg/kg Early delivery at 37 weeks
AFLP	Third	Women with AFLP should be delivered promptly Infant should be monitored for manifestations of deficiency of long-chain 3-hydroxyacyl-coenzyme A dehydrogenase including hypoketotic hypoglycemia and fatty liver
Eclampsia, preeclampsia	After 20 weeks	After 36 weeks, women with severe preeclampsia should be delivered promptly
HELLP	After 22 weeks	Delivery after 34 weeks Platelet transfusion to 40,000–50,000 cells/μl should be considered before delivery, especially if cesarean section is likely

ACG Clinical Guideline: Liver Disease and Pregnancy Tran, Tram T; Ahn, Joseph; Reau, Nancy S American Journal of Gastroenterology111(2):176-194, February 2016.

Pre-existing Liver Disease and Pregnancy

- Uncommon
- Maternal Mortality 10%
- Variceal Bleeding is the main driver

Pre-existing Liver Disease and Pregnancy

- Management still poorly defined
- Identify the at risk patient preconception
- Primary Prophylaxis
- Short 2nd stage of labour

Cholelithiasis

- Stone formation is accelerated by cholesterol supersaturation and GB hypo motility
- Cholecystitis 2nd most common surgical condition in pregnancy
- Complicated stone disease can lead to poor Maternal and foetal outcomes
- ERCP followed by Cholecystectomy
  - Maternal Complication rate of 4.3% and Foetal of 5.8%

Kuy S, Roman SA, Desai R *et al*. Outcomes following cholecystectomy in pregnant and nonpregnant women. Surgery 2009;146:358–66

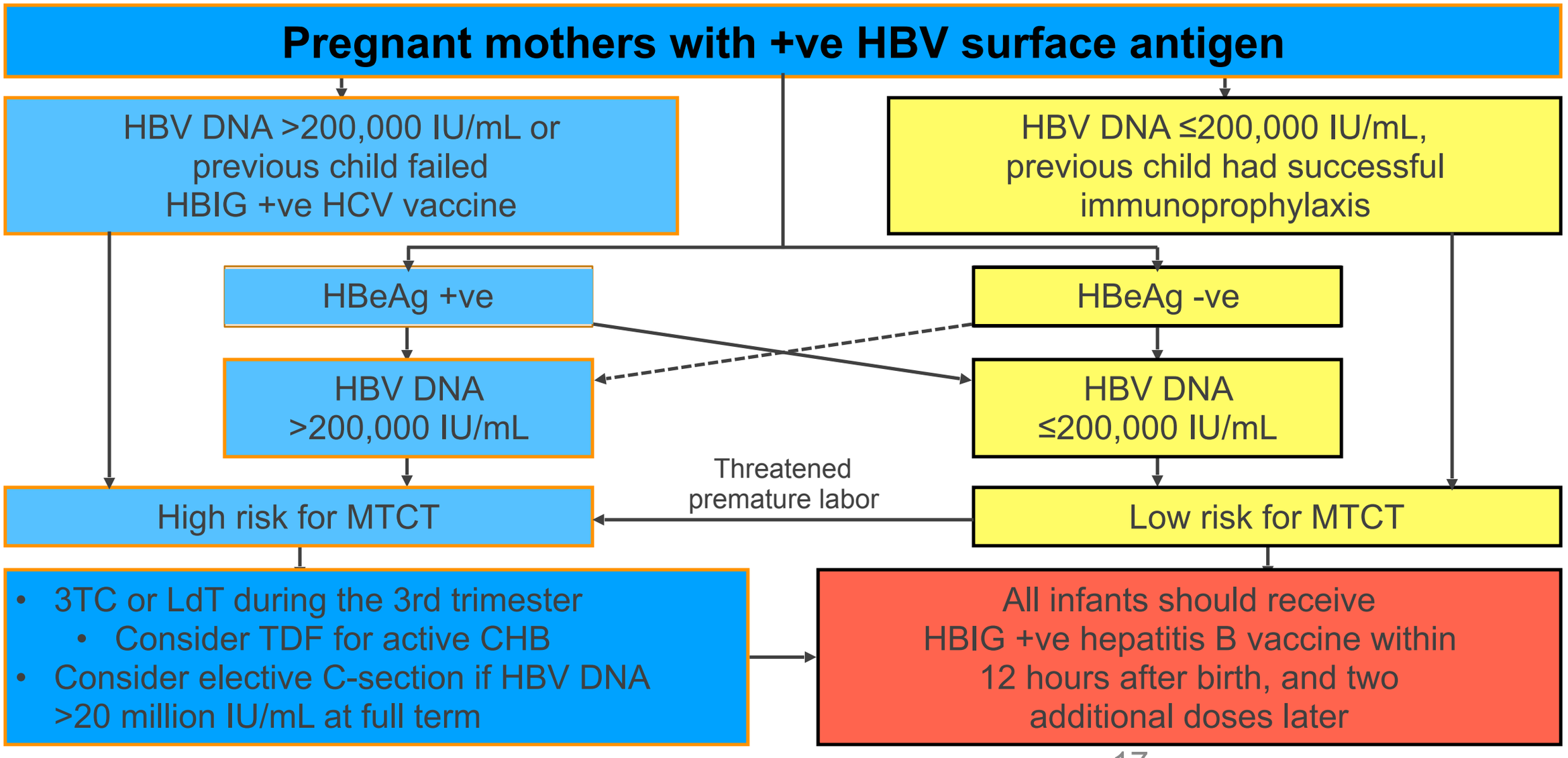
Liver Masses

- FNH/Heamangiomas
- Hepatic Adenoma

Coincidental Liver Disease

- HAV, HEV, HSV - Increased Severity
- AIH - Flares
- PBC

Proposed algorithm for the risk assessment and reduction of HBV MTCT by expert consensus



Expert Consensus of First Int Symp Hep B Infection in Special Populations , April 17-18, 2009, Beijing, China.
Pan CQ, et al. *Clin Gastroenterol Hepatol*. 2012;10(5):452-459.

Hepatitis C

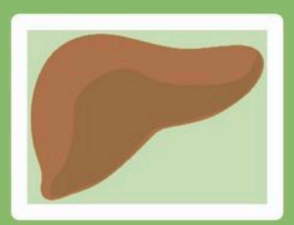
- 3-10% Risk of Vertical Transmission
- Screen at risk Woman
- Avoid Invasive procedures
- Breastfeeding encouraged

Thank you

LIVER DISEASE IN PREGNANCY: WHAT'S NEW

INCIDENCE

3% – 5%



Liver enzyme abnormalities in pregnancy

TRENDS

HELLP	**Most costly liver disease in pregnancy**
ICP	**Most common liver disease unique to pregnancy**
ACUTE HCV	**Rising incidence in childbearing women**
NAFLD	**Most common liver disease in childbearing women**

BY THE NUMBERS

100 µmol/L *Bile acid level threshold for stillbirth in ICP*	**20%** *Autoimmune hepatitis flares during pregnancy*
200,000 IU/mL *Threshold HBV DNA level for antiviral therapy to reduce mother to child transmission*	**5%** *Rates of variceal hemorrhage in pregnant women*

Brady. *Hepatol Commun*, 2020.

HEPATOLOGY COMMUNICATIONS
Open Access