
2022 SCSG
LIVER
SYMPOSIUM
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THE RITZ CARLTON, LAGUNA NIGUEL

Liver Disease in Pregnancy

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Art from Clin Liver Dis (Hoboken). 2021 Feb 28;17(2):85

Disclosures

- Intercept, Speakers’ Bureau

Outline

- How to recognize liver disease in pregnancy
- Common liver diseases unique to pregnancy
- Management of pre-existing liver diseases during pregnancy
  - Hepatitis C
  - Hepatitis B
  - Autoimmune liver disease
  - Cirrhosis

Liver Disease in Pregnancy

Chronic liver disease

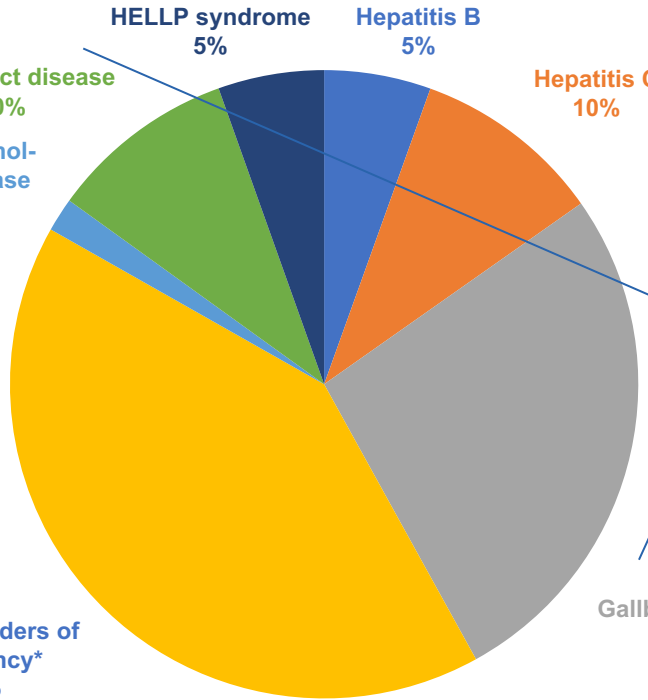
- Viral hepatitis (B,C)
- AIH, PBC
- Budd-chiari syndrome
- NAFLD/Alcohol liver disease
- Wilson, hemochromatosis, A1AT deficiency

Liver disease unique to pregnancy

- Hyperemesis gravidarum
- Preeclampsia/eclampsia/ HELLP
- Intrahepatic cholestasis of pregnancy
- Acute fatty liver of pregnancy

Nationwide Inpatient Sample
41,479,358 pregnancy hospitalizations in the US

HEPATIC DISEASES IN THE HOSPITALIZED US PREGNANT POPULATION 2002-2010



Rate 4.65/1000 pregnancy hospitalizations

*Includes AFLP, IHCP, icterus gravis pregnancy, necrosis of liver of pregnancy, and hepatorenal syndrome following delivery.

Rate 7.18/1000 pregnancy hospitalizations

Ellington, S. R. et al. *Am. J. Obstet. Gynecol.* 2015 Apr;212(4):524.e1-7.
Slide courtesy Nancy Reau, MD

Normal Physiologic Changes in Pregnancy

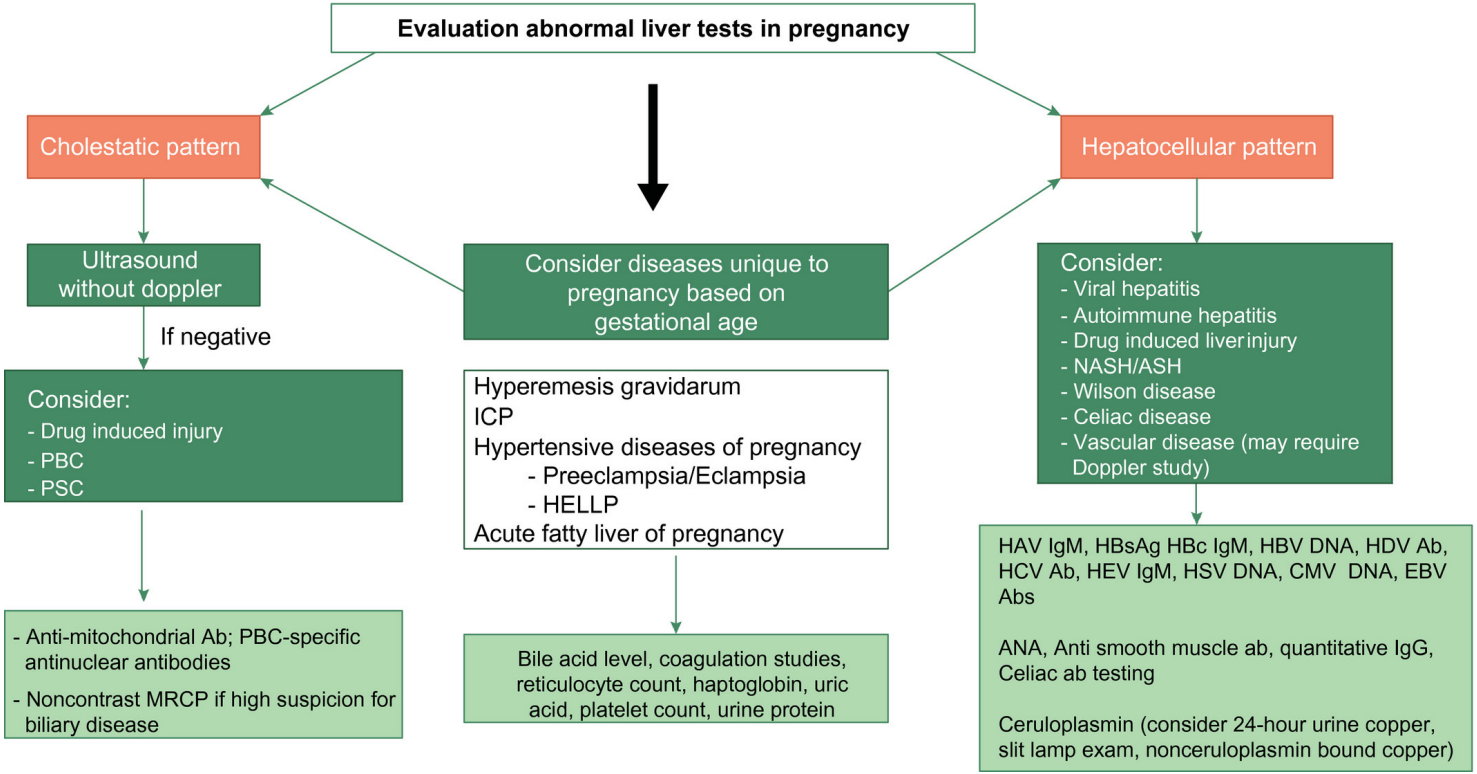
Blood test	Change	
Albumin		Dilutional
Hemoglobin		Dilutional
Alkaline phosphatase		Placenta
AFP		Placenta

Not Normal Physiologic Changes in Pregnancy

Any abnormalities in AST, ALT, or bilirubin

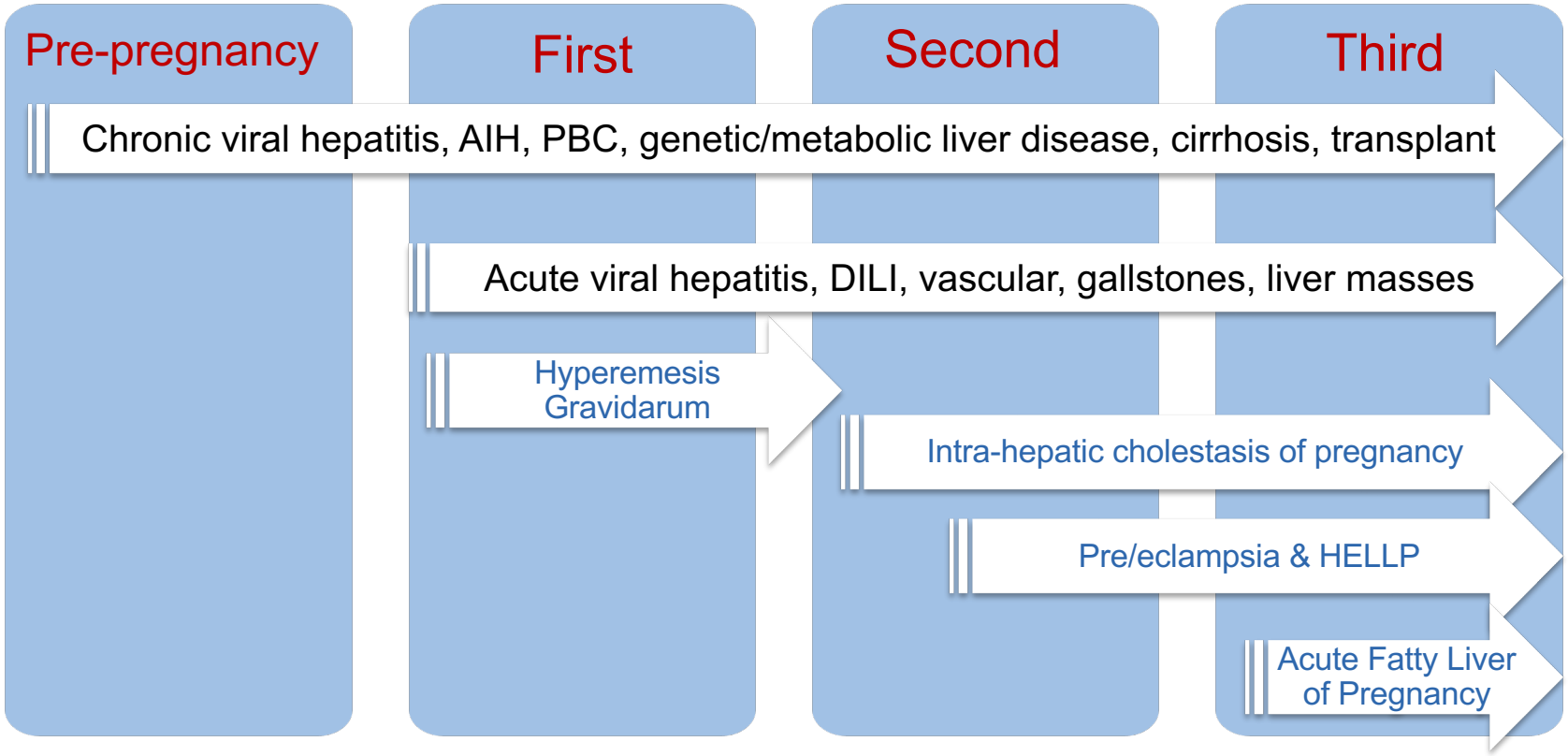
Further evaluation

Approach to Abnormal Liver Tests in Pregnancy



Sarkar M et al. *Hepatology*. 2021 Jan;73(1):318-365

Trimester Based Approach



Reau N et al. *Am J Gastroenterol*. 2022;117:S44

Liver Imaging in Pregnancy: What Is Safe?

Imaging Modality	Safe in pregnancy?
Ultrasound (without Doppler)	Yes
MRI/MRCP without contrast	Yes
MRI/MRCP with contrast	No (do not use gadolinium)
CT without contrast	Yes (but MRI wo con better)
CT with (ionidated) contrast	Yes, but only if essential

Sarkar M et al. *Hepatology*. 2021 Jan;73(1):318-365

Cholelithiasis

- Hormonal changes lead to decreased gallbladder motility and lithogenic bile
- Risk factors: high pre-pregnancy BMI
- Occurs in up to 10% of pregnancies, incidence of gallstone related complications 0.5% to 0.8%
- Ultrasound is imaging of choice
- Symptomatic cholecystitis: laparoscopic cholesystectomy and ERCP are safest in 2nd trimester
  - Pancreatitis → fetal demise

Sarkar M et al. *Hepatology*. 2021 Jan;73(1):318-365

Intrahepatic Cholestasis of Pregnancy

- Presentation: pruritus (before jaundice)
- Risk: multiple pregnancy, fertility treatment, genetics
- Labs:
  - AST/ALT can reach low 1000s IU/mL → no association with outcome
  - Typically normal total bilirubin and GGT
  - Bile Acids → pregnancy outcomes
    - BA >10umol/L
    - Poor outcome if >40 umol/L
    - Cholic acid levels ↑ and Chenodeoxycholic acid ↓

Westbrook R. H. et al. *J. Hepatol.* 2016; Joshi D. et al. *Lancet.* 2010

Intrahepatic Cholestasis of Pregnancy

Defined phenotypes are rare (<20%), however with early or recurrent IHCP may consider testing

Canalicular transporter	Biochemical/histological characteristics	Functional defect	Clinical spectrum
ATP8B1 (FIC1)	High serum bile salts; low GGT/ bland cholestasis with coarse and granular bile	Abnormal excretion of aminophospholipids; down-regulation of FXR	ICP, PFIC1, BRIC1, Byler disease
ABCB11 (BSEP) (1%)	High serum bile salts; low GGT/ portal tract fibrosis; bile duct proliferation	Abnormal bile acid secretion	ICP, Byler syndrome, PFIC2, BRIC2, drug-induced cholestasis, transient neonatal cholestasis
ABCB4 (MDR3) (16%)	High serum bile salts; elevated GGT/ fibrosis, vanishing bile duct syndrome; low phospholipids in bile	Defect in phosphatidylcholine floppase	ICP, PFIC3, LPAC, neonatal cholestasis, drug-induced cholestasis
ABCC2 (MRP2)	High serum conjugated bilirubin/ black liver pigmentation	Alteration in canalicular transport of conjugated metabolites	ICP, Dubin-Johnson syndrome

Westbrook RH et al. *J Hepatol*. 2016 Apr;64(4):933-45; Morisco F et al. *Dig Liver Dis*. 2016 Feb;48(2):120-37

Intrahepatic Cholestasis of Pregnancy: Management

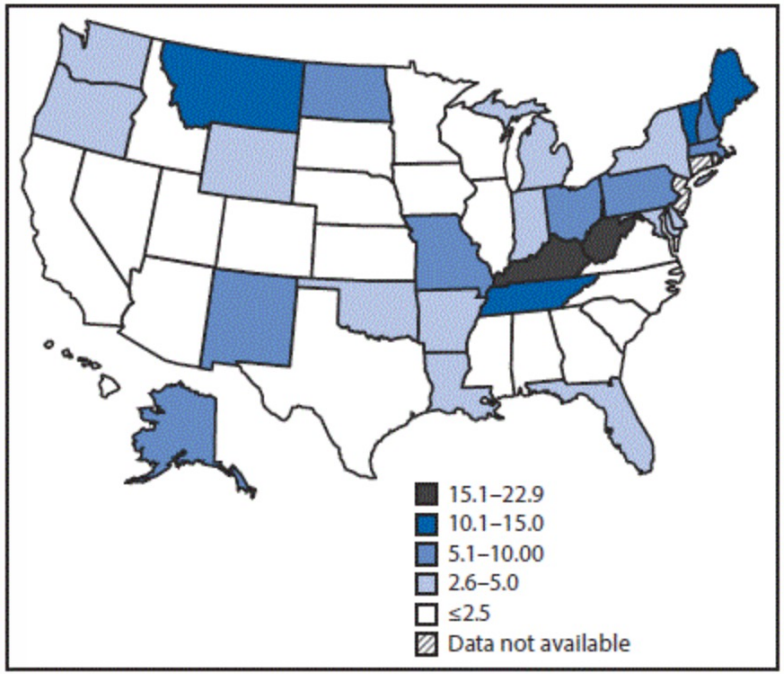
- Weekly bile acids
- Ursodeoxycholic acid 10-15mg/kg/day
  - 75% respond
- Deliver at 37 weeks
- Verify resolution and advise progesterone based contraception

Westbrook RH et al. *J Hepatol*. 2016 Apr;64(4):933-45; Kamimura K et al. *World J Gastroenterol*. 2015 May 7;21(17):5183-90

Viral Hepatitis B(HBV) and C(HCV) in Pregnancy

Rate of HCV Among Pregnant Women per 1,000 Live Births, by State in 2014

The national rate, from 2014, was 1 in 308.

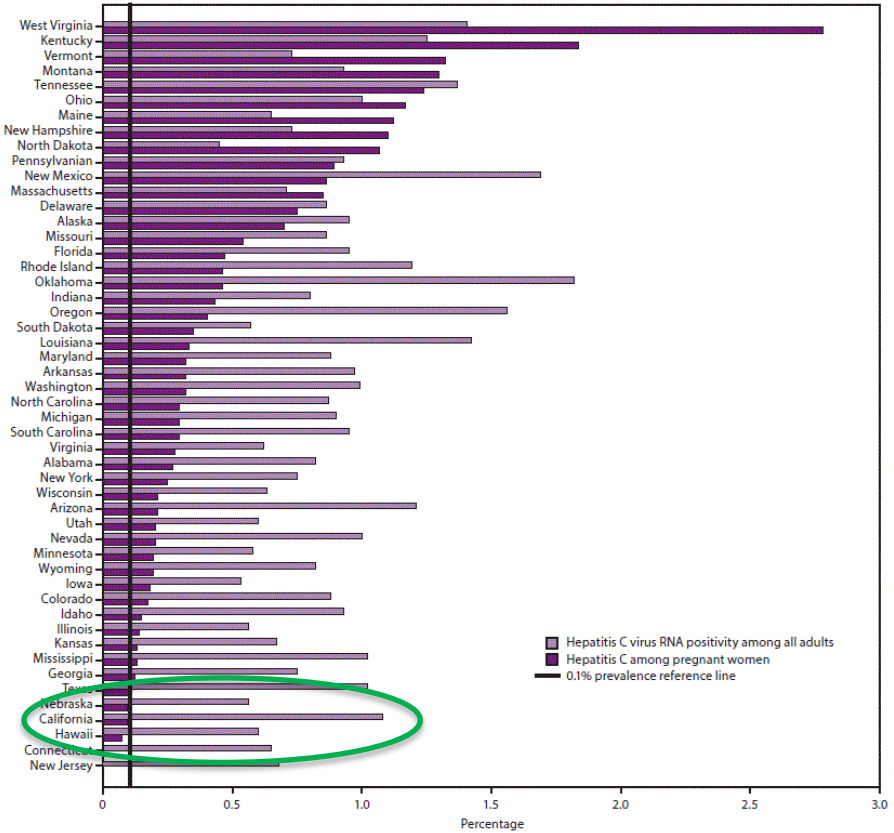


- 2009–2014 HCV at delivery increased 89%
- Substantial state-to-state variation
- 2014, the highest rate (22.6 per 1,000 live births) was in West Virginia, and the lowest (0.7) was in Hawaii

MMR *Weekly* / May 12, 2017 / 66(18);470–473

HCV Increasing in Women of Childbearing Age

Estimated prevalence of hepatitis C virus RNA positivity among all adults and hepatitis C among pregnant women, by state



Schillie S et al. *MMWR Recomm Rep*. 2020;69(No. RR-2):1–17

Consequences of Maternal Viremic HCV Infection

STUDY DESIGN

Population-based retrospective study using ICES data (2000-2018)

1,780 HCV RNA+ pregnancies

VS.

390 HCV Ab+/RNA- pregnancies

OUTCOMES

HCV screening performed in infants

1) HCV antibody test at 18 months of age or later OR

2) HCV RNA test within 2 to 24 months after delivery

Mother-to-child transmission (MTCT)

in infants who were appropriately screened: HCV Ab+ or RNA+

Adverse pregnancy outcomes

- Gestational diabetes
- Intrahepatic cholestasis of pregnancy

FINDINGS

- **Appropriate HCV screening**
  - 29% (n = 511/1,780)
- **MTCT (n = 18/511):**
  - 3.5% (95% CI: 1.9-5.2)
- **No MTCT if:**
  - RNA <3.5 $\log_{10}$ IU/ml
- **If HCV RNA ≥6 $\log_{10}$ IU/ml**
  - MTCT eOR 3.38, $p = 0.04$

Pregnancy outcomes HCV RNA+ *vs.* HCV Ab+/RNA-

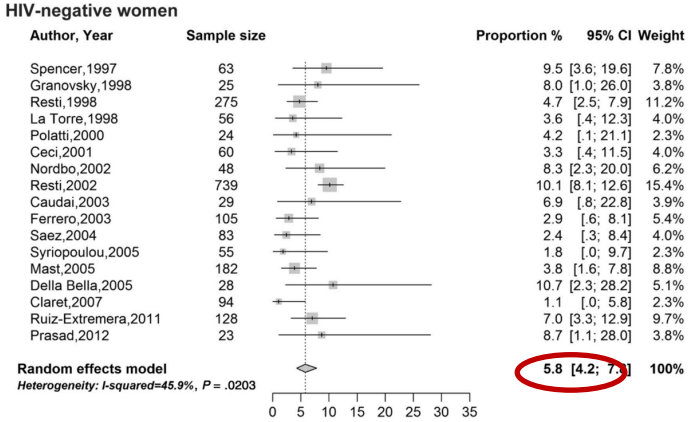
↑ **Intrahepatic cholestasis of pregnancy: OR 4.55**

Kushner T et al. *J Hepatol*. 2022 Nov;77(5):1256-1264

Hepatitis C: Risk of Vertical Transmission

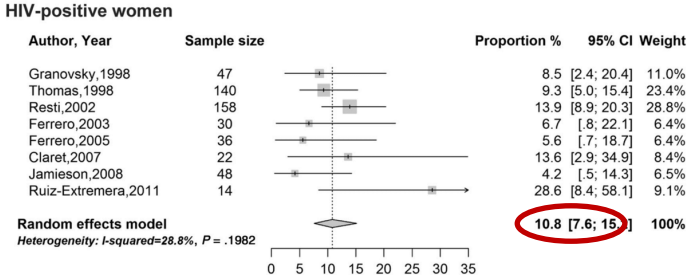
Systematic review and meta-analysis of 109 studies with HCV Ab+, RNA + mothers

HIV-Negative



5.8%

HIV-Positive



10.8%

Benova L et al. *Clin Infect Dis*. 2014 Sep 15;59(6):765-73

AASLD/IDSA Recommendations

Recommendations for Monitoring HCV-Infected Women During Pregnancy	
RECOMMENDED	**RATING**
HCV RNA and routine liver function tests are recommended at initiation of prenatal care for HCV-antibody–positive pregnant women to assess the risk of mother-to-child transmission (MTCT) and severity of liver disease.	I, B
All pregnant women with HCV infection should receive prenatal and intrapartum care that is appropriate for their individual obstetric risk(s) as there is no currently known intervention to reduce MTCT.	I, B
In HCV-infected pregnant women with pruritus or jaundice, there should be a high index of suspicion for intrahepatic cholestasis of pregnancy (ICP) with subsequent assessment of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and serum bile acids.	I, B
HCV-infected women with cirrhosis should be counseled about the increased risk of adverse maternal and perinatal outcomes. Antenatal and perinatal care should be coordinated with a maternal-fetal medicine (ie, high-risk pregnancy) obstetrician.	I, B

Hepatitis C: Vertical Transmission From Mother to Child

- No known intervention to reduce risk of vertical transmission
  - Cesarean delivery not recommended
  - Avoid internal fetal monitoring, prolonged rupture of membranes, and episiotomy during labor
- Do not discourage breast-feeding based on HCV infection

AASLD/IDSA. HCV guidance. September 2017; Mast EE et al. *J Infect Dis*. 2005;192:1880-1889; Ceci O et al. *J Pediatr Gastroenterol Nutr*. 2001;33:570-575; Shebl FM et al. *J Med Virol*. 2009;81:1024-1031; Jhaveri R et al. *Open Forum Infect Dis*. 2015;2:ofv089; SMFM et al. *Am J Obstet Gynecol*. 2017;217:B2-B12; Benova L et al. *Clin Infect Dis*. 2014;59:765-773; Delotte J et al. *J Matern Fetal Neonatal Med.* 2014;27:664-770.

AASLD/IDSA Recommendations for HCV Management During Pregnancy

- Treat HCV in women of reproductive age **before** pregnancy is considered

- HCV treatment during pregnancy **not recommended** due to lack of safety/efficacy data

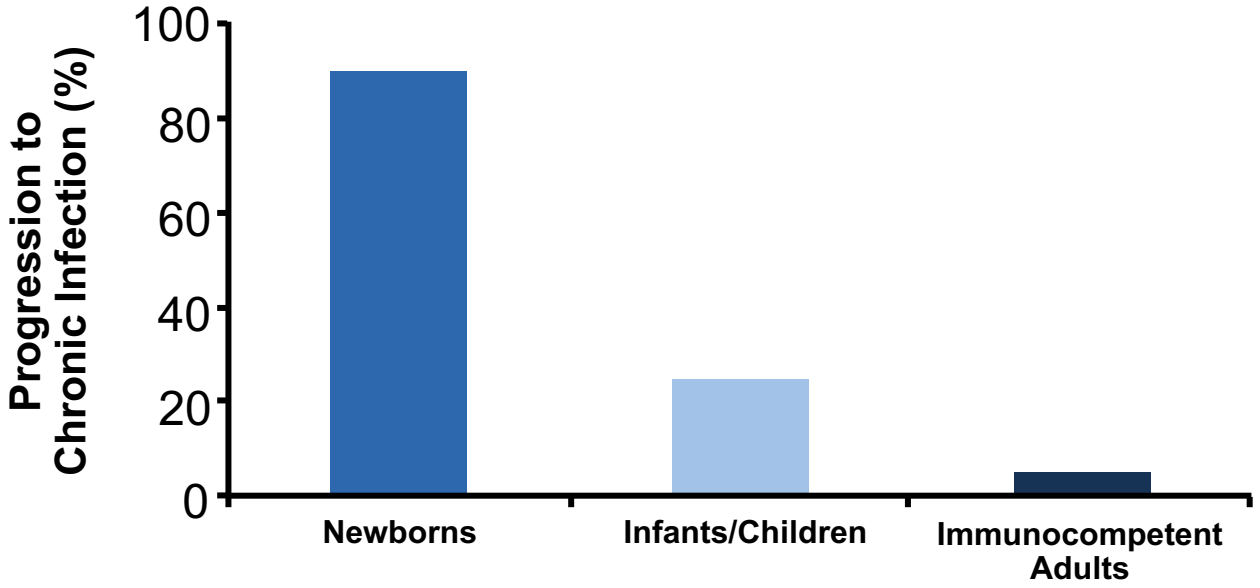
AASLD/IDSA. HCV guidance. September 2017.

HCV versus HBV in pregnancy: how is it different?

- Defined guideline recommendations versus risk based screening
- Defined guideline recommendations for prevention of transmission include drug based therapy for hepatitis B
- HBIG/vaccination for child at birth
- **HBV treatment as prevention in hepatitis B**

Preventing Perinatal Hepatitis B Transmission: Why Is It so Important?

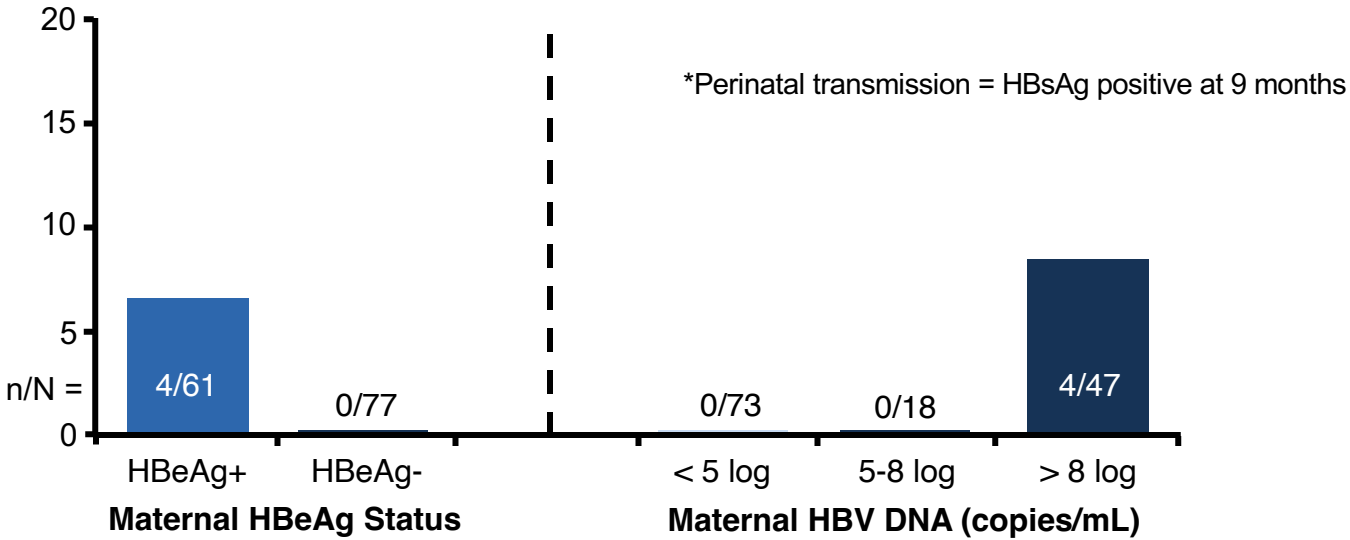
Risk of progression to chronic hepatitis B (HBV) infection is inversely related to age at infection



Lok AS et al. *Hepatology*. 2009 Sep;50(3):661-2.

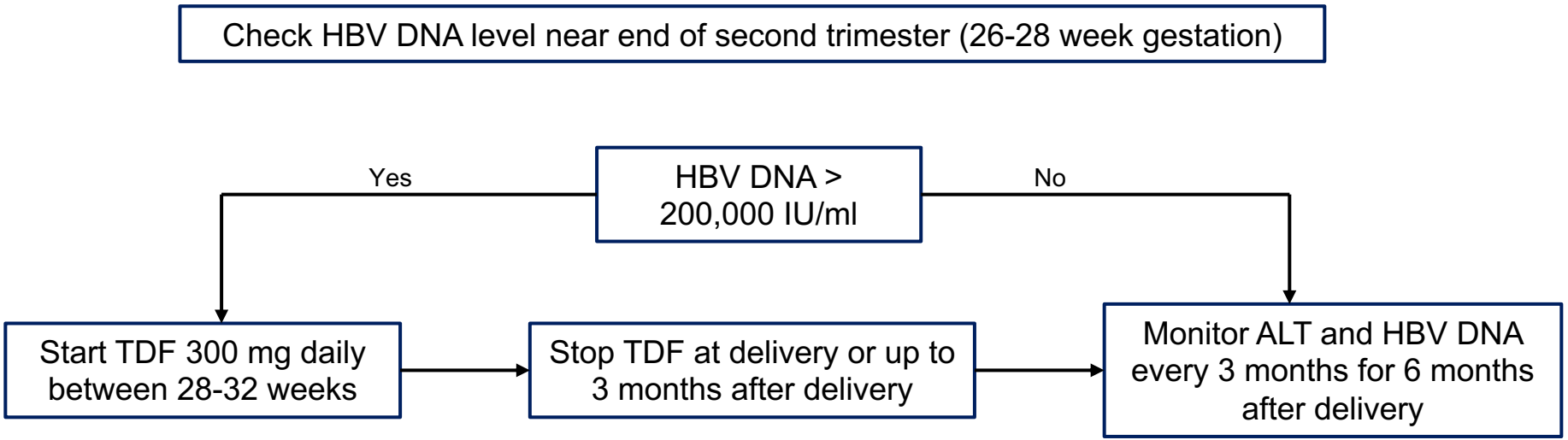
Perinatal HBV Transmission Is Related to Maternal HBV DNA Level

All infants received HBIG + first dose HBV vaccine within 12 hrs of birth and additional doses of HBV vaccine at 2, 4, and 6 mos



Wiseman E et al. *Med J Aust*. 2009 May 4;190(9):489-92.

Hepatitis B: How Do You Prevent Maternal to Child Transmission?



**1st trimester: check HBV DNA/replication and liver disease

Sarkar M et al. *Hepatology*. 2021 Jan;73(1):318-365.

TAF for Pregnant Women With Chronic HBV

A multicenter, prospective, real-world analysis of the safety and effectiveness of TAF and TDF in 207 pregnant Chinese women

Baseline Characteristics in Women Treated With TAF

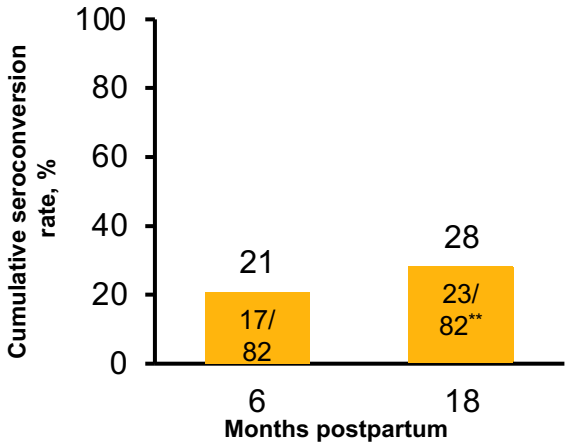
Baseline Characteristics	TAF n=103
Age, mean, years	29.3
Gestational age, mean, weeks	1.3
HBeAg positivity, n (%)	82 (80)
Viral load, mean, log_{10} IU/mL	5.1
ALT level, mean, U/L	122.2
Infants born, n	102*
Treatment duration, mean, weeks	101

MTCT and Infant Safety

MTCT 0%

Normal infant development† according to Chinese and WHO standards

HBeAg Seroconversion Rate in Women Treated With TAF



Authors' conclusions: TAF was found to be well tolerated and effective in pregnant women with CHB and their infants when administered from early pregnancy; safety and effectiveness were comparable with TDF

*One TAF-treated woman exposed to agricultural chemicals during early pregnancy underwent induced abortion at gestational age 23 weeks and 4 days due to diagnosis of cleft lip and palate
†Weight, height and head circumference.
**Month 18 follow-up was completed by 40 pairs of mothers and infants.

Zeng QL et al. EASL 2022. Poster #SAT349 (slide courtesy of C Holt).

TAF FDA label: Pregnancy

Pregnancy Exposure Registry:
There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to VEMLIDY during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263.

Risk Summary
Available data from the APR show no statistically significant difference in the overall risk of birth defects for tenofovir alafenamide (TAF) compared with the background rate for major birth defects of 2.7% in the U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP) (see Data). The rate of miscarriage is not reported in the APR. The estimated background rate of miscarriage in clinically recognized pregnancies in the U.S. general population is 15% to 20%.

In animal studies, no adverse developmental effects were observed when tenofovir alafenamide was administered during the period of organogenesis at exposure equal to or 51 times (rats and rabbits, respectively) the tenofovir alafenamide exposure at the recommended daily dose of VEMLIDY (see Data). No adverse effects were observed in the offspring when TDF was administered through lactation at tenofovir exposures of approximately 12 times the exposure at the recommended daily dosage of VEMLIDY.

Human Data:
Based on prospective reports to the APR of exposures to TAF-containing regimens during pregnancy resulting in live births (including over 200 exposed in the first trimester and over 80 exposed in the second/third trimester), the prevalence of birth defects in live births was 5.2% (95% CI: 2.7% to 8.8%) and 1.2% (95% CI: 0% to 6.5%) following first and second/third trimester exposure, respectively, to TAF containing regimens. Methodologic limitations of the APR include the use of MACDP as the external comparator group. The MACDP population is not disease-specific, evaluates women and infants from a limited geographic area, and does not include outcomes for births that occurred at less than 20 weeks gestation.

Autoimmune hepatitis and immunosuppression

Autoimmune Hepatitis (AIH) in Pregnancy

- AIH flares can occur anytime in pregnancy: pregnant women should be continued on their treatment with corticosteroids and/or AZA
- Highest risk period if within 3 months after delivery (~ 25% of women)
- Risk factors
  - No AIH treatment in pregnancy
  - Shorter remission before pregnancy (less than one year)

Sarkar M et al. *Hepatology*. 2021 Jan;73(1):318-365.

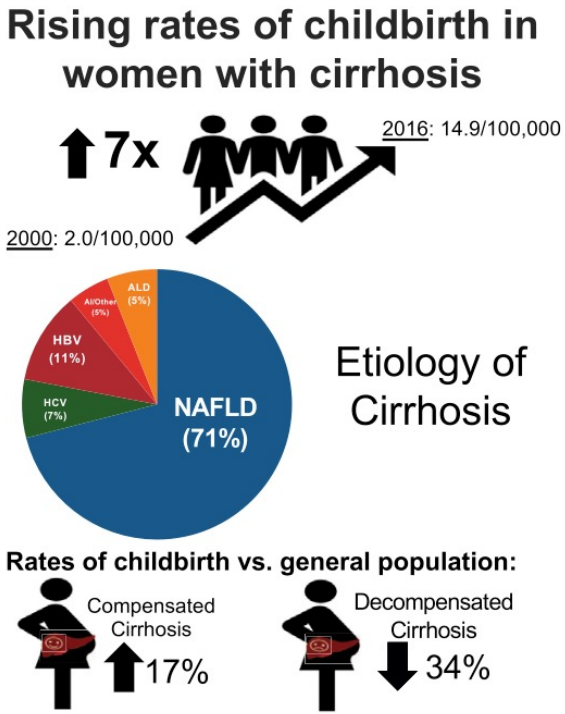
Immunosuppression in Pregnancy: AIH and Post Liver Transplant

Medication	Pregnancy Safety
Steroids	Controversial risk of cleft palate with prednisone, larger studies did not show consistent increased risk
Tacrolimus/Cyclosporine	May be associated with pre-term birth and low birth weight, transient fetal renal insufficiency/hyperkalemia
Azathioprine/6-MP	Associated with prematurity and low birth weight
Mycophenolic acid products (Myfortic/Cellept)	Teratogenic in pregnancy/miscarriage risk (25%) Fetal malformations affect ears, limbs, heart, esophagus, and kidney

Sarkar M et al. *Hepatology*. 2021 Jan;73(1):318-365.

Cirrhosis and Pregnancy

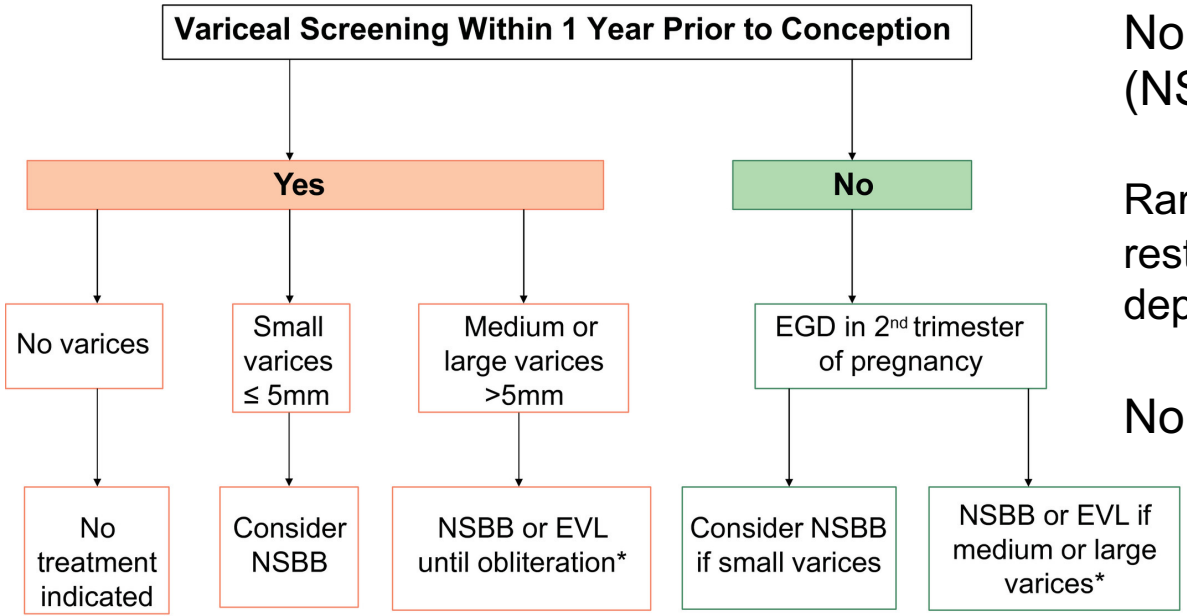
Rising Pregnancies in Women With Cirrhosis



- Maternal mortality less than 2%
- Variceal hemorrhage is the most frequent complication
  - Up to 20% maternal mortality

Flemming JA et al. *Gastroenterology*. 2020 Nov;159(5):1752-1762.e10.

Cirrhosis and pregnancy: screen for varices



*EVL is preferred if high risk bleeding stigmata (red wale signs, cherry red spots)

Non-selective beta blockers (NSBB): nadolol, propranolol

Rare reports of IU growth restriction, neonatal respiratory depression, infant hypoglycemia

No data for carvedilol

Sarkar M et al. *Hepatology*. 2021 Jan;73(1):318-365.

Conclusions

- Elevations in ALT, AST and bilirubin must be investigated during pregnancy
- Pregnancy induced liver disease is uncommon but prompt recognition is critical for appropriate management
- Viral hepatitis should be screened for to prevent transmission and to allow follow up in the child
- Pre-existing liver disease typically has minimal impact on pregnancy with the exceptions of portal hypertension and immunosuppression

Breastfeeding and Pregnancy Guidance

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Drugs and Lactation Database (LactMed)

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Bethesda (MD): National Institute of Child Health and Human Development; 2006-.

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The LactMed® database contains information on drugs and other chemicals to which breastfeeding mothers may be exposed. It includes information on the levels of such substances in breast milk and infant blood, and the possible adverse effects in the nursing infant. Suggested therapeutic alternatives to those drugs are provided, where appropriate. All data are derived from the scientific literature and fully referenced. A peer review panel reviews the data to assure scientific validity and currency.

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Fact Sheet. Drugs and Lactation Database (LactMed)

Drugs and Lactation Database (LactMed) - Glossary

Additional Resources

- AASLD Practice Guidance Reproductive Health and Liver Disease https://aasldpubs.onlinelibrary.wiley.com/doi/10.1002/hep.31559

- Upcoming patient guidelines are adaptations and patient-friendly summaries of published AASLD Guidances

- Clinical Liver Disease (CLD) Autoimmune Hepatitis Patient Page 2021 https://pubmed.ncbi.nlm.nih.gov/33680442/