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Liver Disease in the Pregnant Patient

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Disclosures

- In relation to this presentation, I declare no real or perceived conflicts of interest

UCSF Transplant

Case

ID: 33 yo woman G1P0, week 22 (second trimester), referred to hepatology clinic for abnormal liver tests on outpatient labs

PMH: Hypothyroidism

Meds: Levothyroxine, pre-natal vitamin

Labs:

- AST 50, ALT 70, AP 120, Tbili 0.5, Albumin 3.5
- WBC count 4.5, HCT 36, Plts 250

What's Normal in Pregnancy?

TEST	CHANGE	COMMENT
Alkaline Phosphatase	Increase	Made by placenta*
Albumin	Decrease	Hemodilution*
Hemoglobin	Decrease	
Platelets	Slight decrease (but normal range)	
Bilirubin	None	Warrant evaluation
AST and ALT		

** Changes often in second trimester*

Liver Disease in Pregnancy

Chronic Liver Diseases

- HCV & HBV
- PBC, PSC, AIH
- Budd Chiari Syndrome (BCS)
- MASLD/ALD
- Metabolic/Genetic: Wilson Disease, Hemochromatosis, A1AT deficiency

Unique to Pregnancy

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

Acute Co-Incident to Pregnancy

- Medications
- Viral: HAV, HEV, HSV, HBV, HCV
- Other: BCS, AIH

Other Liver Conditions

- Cirrhosis
- Liver Transplant

Liver Disease in Pregnancy

** Discussing today*

Chronic Liver Diseases

- HCV & HBV
- PBC, PSC, AIH
- Budd Chiari Syndrome
- MASLD/ALD
- Metabolic/Genetic: Wilson Disease, Hemochromatosis, A1AT deficiency

Unique to Pregnancy

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

Acute Co-Incident to Pregnancy

- Medications
- Other viruses (HAV, HEV, HSV, HBV, HCV)

Other Liver Conditions

- Cirrhosis
- **Liver Transplant**

HEPATOLOGY

PRACTICE GUIDANCES | HEPATOLOGY, VOL. 73, NO. 1, 2021

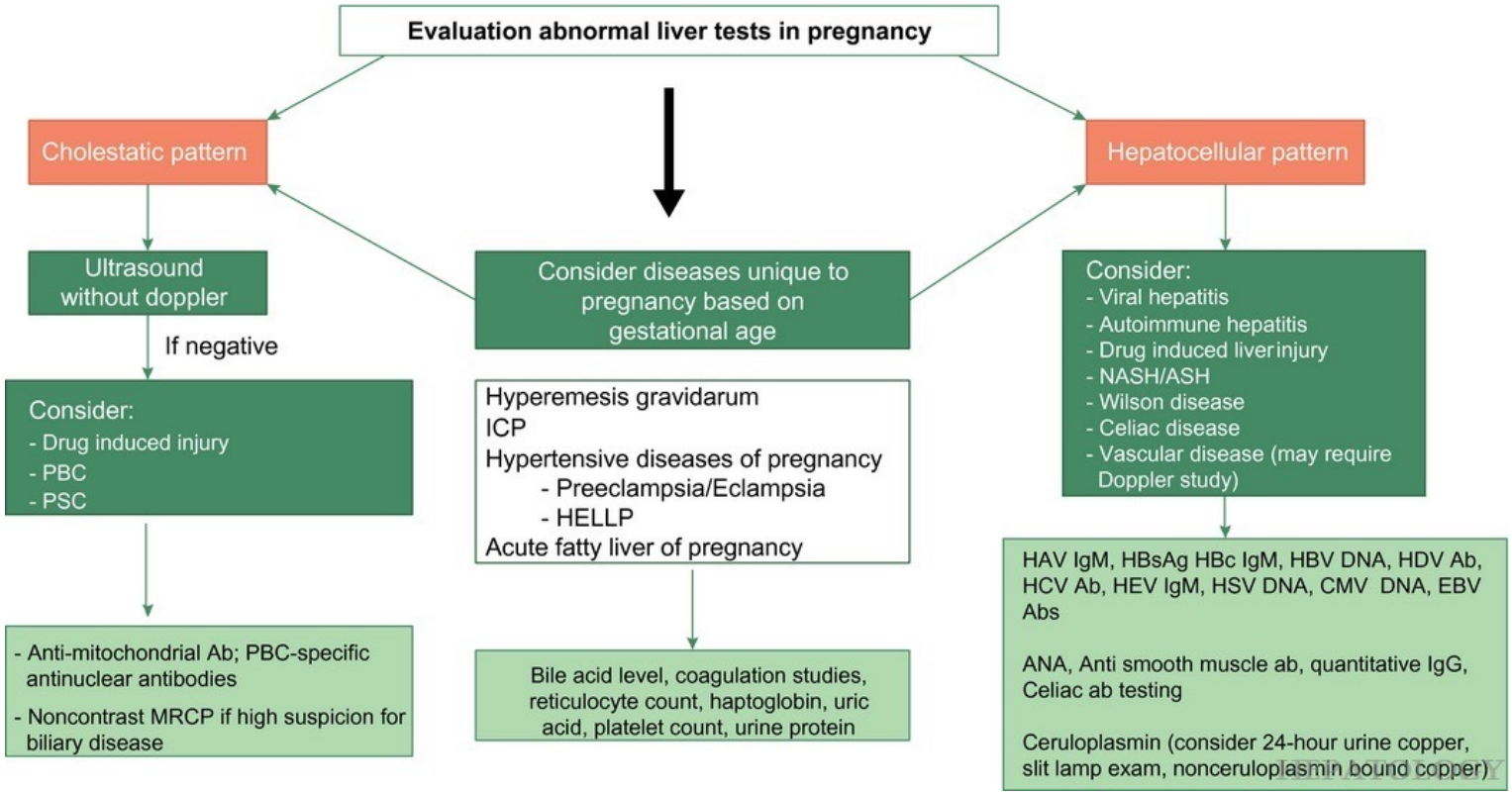
Reproductive Health and Liver Disease: Practice Guidance by the American Association for the Study of Liver Diseases

Monika Sarkar,[1] Carla W. Brady,[2] Jaquelyn Fleckenstein,[3] Kimberly A. Forde,[4] Vandana Khungar,[4] Jean P. Molleston,[5] Yalda Afshar,[6] and Norah A. Terrault[7]

Practice Guideline > J Hepatol. 2023 Sep;79(3):768-828. doi: 10.1016/j.jhep.2023.03.006. Epub 2023 Jun 30.

EASL Clinical Practice Guidelines on the management of liver diseases in pregnancy

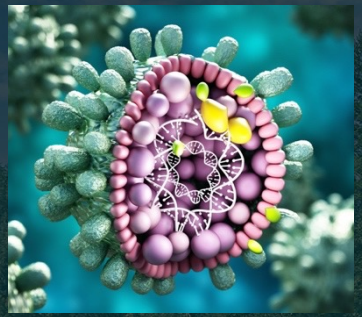
European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu; European Association for the Study of the Liver


Evaluation abnormal liver tests in pregnancy
Cholestatic pattern
Hepatocellular pattern
Ultrasound without doppler
If negative
Consider diseases unique to pregnancy based on gestational age
Consider:
- Viral hepatitis
- Autoimmune hepatitis
- Drug induced liver injury
- NASH/ASH
- Wilson disease
- Celiac disease
- Vascular disease (may require Doppler study)
Consider:
- Drug induced injury
- PBC
- PSC
Hyperemesis gravidarum
ICP
Hypertensive diseases of pregnancy
- Preeclampsia/Eclampsia
- HELLP
Acute fatty liver of pregnancy
HAV IgM, HBsAg HBc IgM, HBV DNA, HDV Ab, HCV Ab, HEV IgM, HSV DNA, CMV DNA, EBV Abs
ANA, Anti smooth muscle ab, quantitative IgG, Celiac ab testing
Ceruloplasmin (consider 24-hour urine copper, slit lamp exam, nonceruloplasmin bound copper)
- Anti-mitochondrial Ab; PBC-specific antinuclear antibodies
- Noncontrast MRCP if high suspicion for biliary disease
Bile acid level, coagulation studies, reticulocyte count, haptoglobin, uric acid, platelet count, urine protein

Imaging in Pregnancy / Breastfeeding

Test	Safe in Pregnancy?	Safe for Breastfeeding?
Ultrasound (+/- dopplers)	Yes	Yes
MRI/MRCP without contrast	Yes	Yes
MRI/MRCP with contrast	No	Yes
CT scan without contrast	Yes (if non-contrast MRI insufficient)	Yes
CT scan with contrast	Yes (if contrast necessary)	Yes

Hepatitis B Infection in Pregnancy



Hepatitis B Infection

- 26 year old W with perinatally acquired hepatitis B. Currently 16 weeks pregnant.
- HBeAg pos, ALT 18, HBV DNA 10,000,000 IU/ml. Not on antiviral treatment.

How should you manage her HBV during pregnancy?

Who to Treat in Pregnancy?

FOR MOM:

Standard indications…

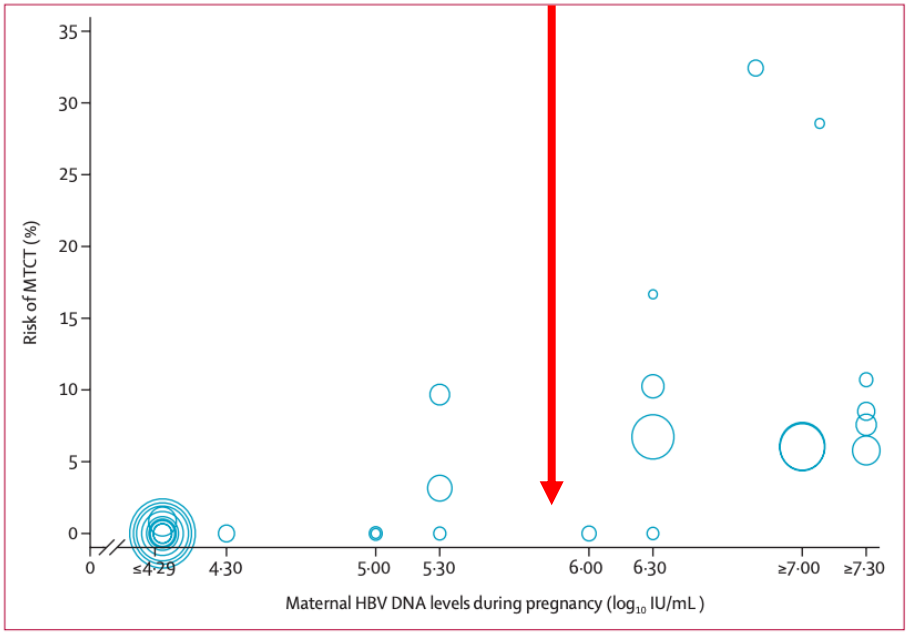
- Active HBV (elevated HBV DNA + ALT)
- 1st degree relative with HCC
- Advanced fibrosis

FOR BABY:

Risk of MTCT…

- Guided by HBV DNA level (even with normal ALT)

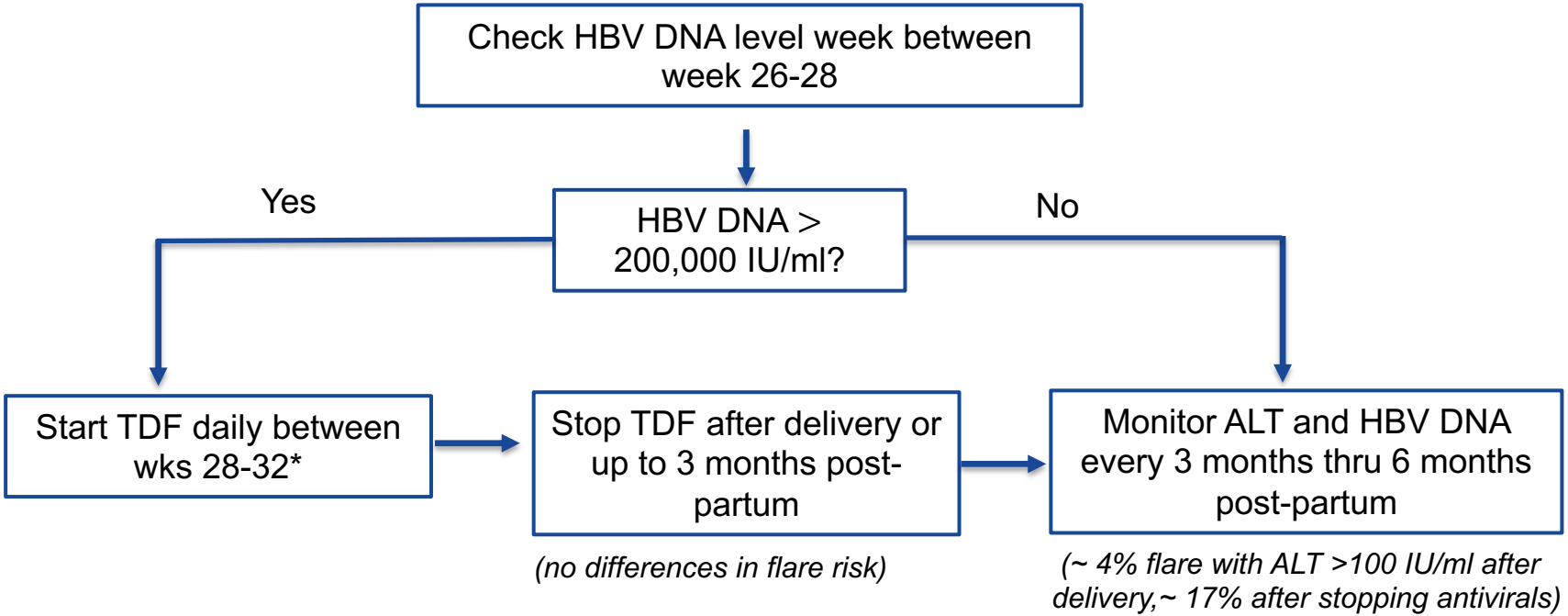
Maternal to Child Transmission (MTCT) Driven By Maternal HBV DNA Level at Delivery



Negligible risk with HBV DNA <200,000 IU/mL (<5.30 log IU/mL)

Boucheron P. *Lancet Infect Dis*. 2020.

Preventing MTCT



*Favor on earlier side to allow time for VL to decline

Hepatitis B Antivirals in Pregnancy

Antiviral	Pregnancy Safety
Tenofovir disoproxil fumarate (TDF)	Safe in pregnancy AND highest barrier of
Tenofovir	
Lamivudir	arrier of
Telbivudine	resistance
Entecavir	Harmful in animal studies, insufficient safety data in humans

INITIATE OR TRANSITION TO TDF or TAF IF TREATMENT NEEDED DURING PREGNANCY

**Expert recs since publication of 2021 AASLD Guidance, now supported by EASL Guidance*

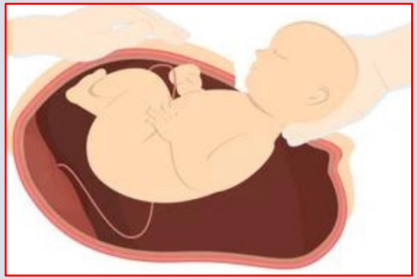
Most MTCT Occurs During Delivery

Intrapartum (uncommon)

- Maternal placental dysfunction
- Intra-amniotic bleeding related to chorionic villus sampling, amniocentesis

Peri-partum (most MTCT)

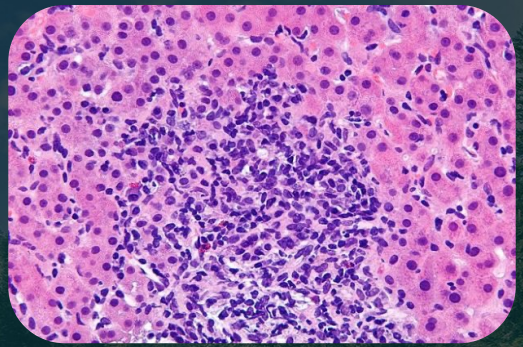
- Exposure to blood during delivery
- No difference in vaginal vs cesarean delivery



Post-partum (rare)

- No increased risks with breastfeeding
- Breastfeeding OK on TDF/TAF

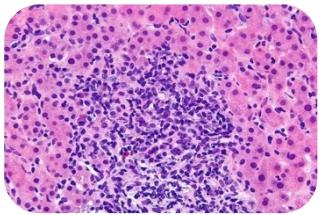
Autoimmune Hepatitis in Pregnancy



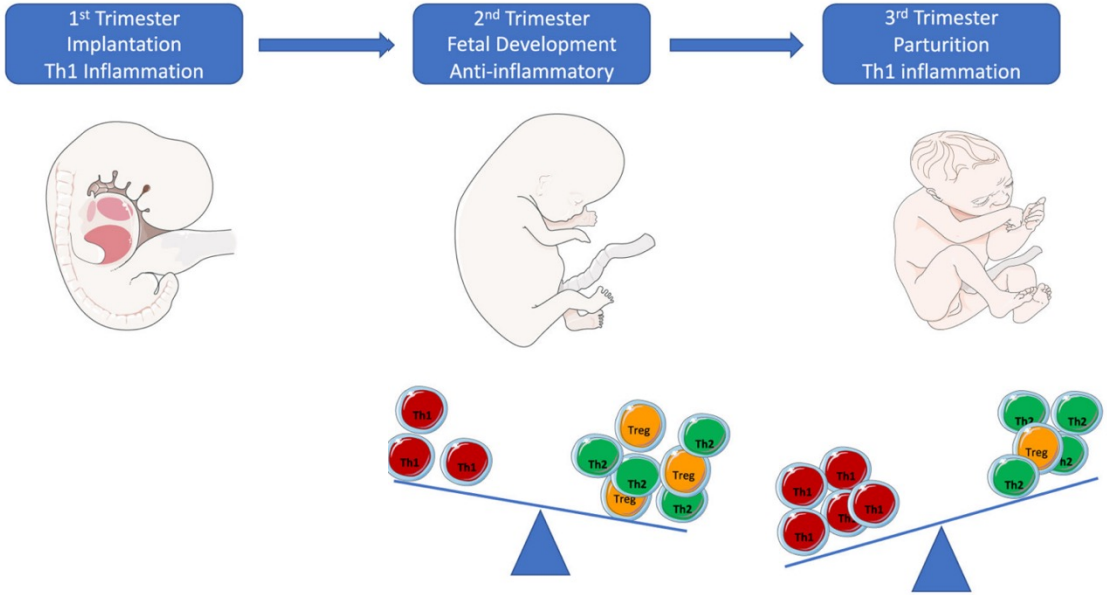
Autoimmune Hepatitis

- 29 yo W with non-cirrhotic AIH on azathioprine 50mg daily and budesonide 6mg daily for 2 years.
- Flared with brief attempt to lower budesonide dose last year.
- Now interested in pregnancy but wants to avoid drug exposure to the baby.

How do you counsel her about AIH management, obstetric, and liver-related risks?



Immune Tolerance in Pregnancy: Shift From Th2 to Th1



- **Estrogen + progesterone promote shift in immune response**
- **Th2:** Release of **anti-** inflammatory cytokines
- **Th1:** Release of **pro-** inflammatory cytokines

Graham et al. *J Autoimmun*. 2021; Bozward et al. *Frontiers of Immunology*. 2020.

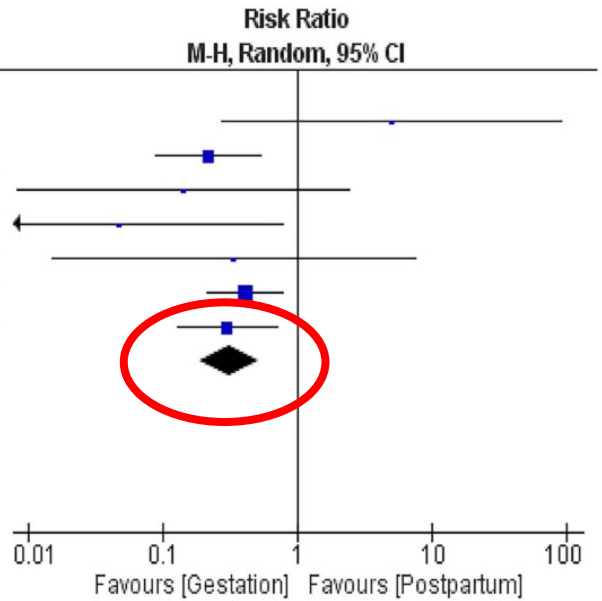
AIH Flares Less Common in Pregnancy

(B)

Study or Subgroup	Gestation Events	Gestation Total	Postpartum Events	Postpartum Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Flare up						
Braga 2016	2	9	0	9	2.9%	5.00 [0.27, 91.52]
Debora 2009	5	51	23	51	24.6%	0.22 [0.09, 0.53]
Izumi 2003	0	10	3	10	3.0%	0.14 [0.01, 2.45]
Llovet 2019	0	46	10	46	3.1%	0.05 [0.00, 0.79]
Roseli 2012	0	12	1	12	2.6%	0.33 [0.01, 7.45]
Schramm 2006	9	42	22	42	38.1%	0.41 [0.21, 0.78]
Westbrook 2012	6	81	20	81	25.7%	0.30 [0.13, 0.71]
Subtotal (95% CI)		**251**		**251**	**100.0%**	**0.31 [0.19, 0.52]**
Total events	22		79			

Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 6.94$, df = 6 (P = 0.33); $I^2 = 14\%$

Test for overall effect: Z = 4.52 (P < 0.00001)



Flares occur during pregnancy too
(5-20% vs 40-50% postpartum)

Si T et al. *APT.* 2022; Fischer et al. *Liver International.* 2023; Llovet et al. *CGH*. 2019; Westbrook et al. *J Autoimmunity.* 2012; Schram et al. *AJG.* 2012.

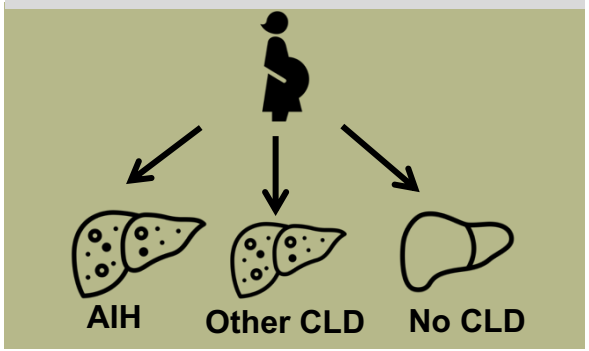
Pre-Conception Remission Is Key

Outcomes	Condition	Risk ratio	95% CI	*p* value
Flare during pregnancy	Portal hypertension	3.15	1.27–8.26	0.02
	Remission before conception	0.86	0.30–2.23	>0.99
	Previous pregnant history	0.21	0.04–0.96	0.07
Flare post-partum	Portal hypertension	1.78	0.58–5.21	0.39
	Remission before conception	0.14	0.02–0.65	0.01
	Previous pregnant history	1.24	0.47–2.74	0.71
Pre-term delivery	Portal hypertension	2.6	1.17–6.54	0.036
	Remission before conception	0.13	0.02–0.58	0.003
	Previous pregnant history	1.23	0.50–2.40	0.7

Si T et al. *APT*. 2022.

Maternal and Perinatal Outcomes With AIH in Pregnancy

- National Inpatient Sample pregnancy discharge data (2012-2016)
- Maternal and perinatal outcomes compared: AIH vs Other CLD; AIH vs No CLD in pregnancy



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JOURNAL OF THE AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

AIH in pregnancy increases risk of some maternal and perinatal events

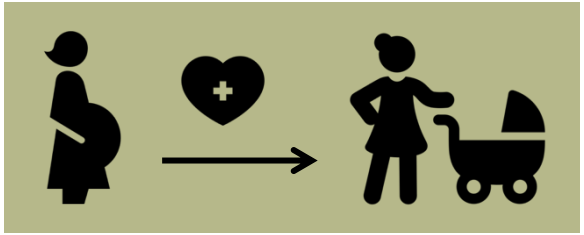
Pre-eclampsia, eclampsia, HELLP syndrome

Gestational DM

Preterm birth

**Adjusted for age, race, multiple gestation, cirrhosis, pre-existing metabolic dz (DM, HTN, hyperlipidemia)*

No increased risk for postpartum hemorrhage, maternal or perinatal death



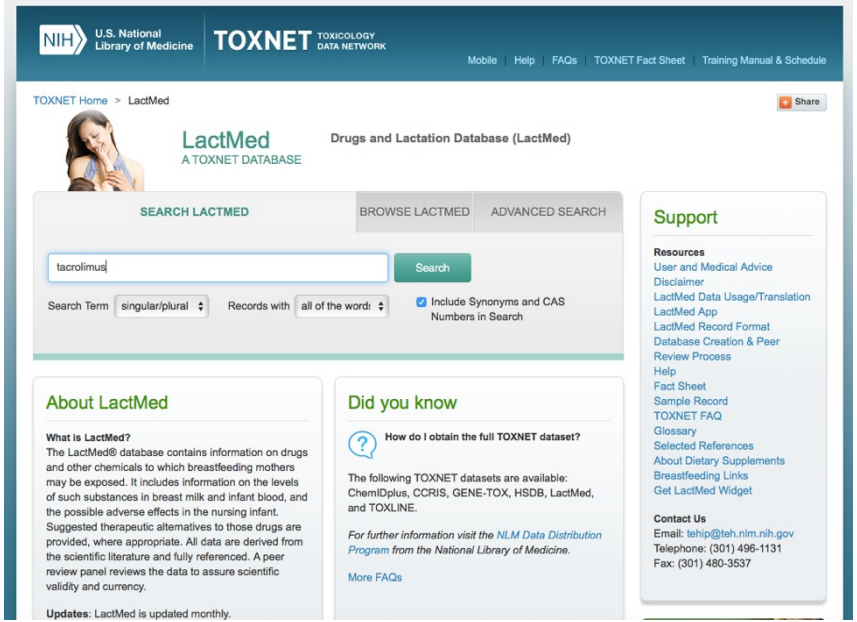
Wang,..Sarkar. *Hepatology*. 2022.

Immunosuppression in Pregnancy

IMS	Pregnancy Safety
Steroids ✓	Controversial risk of cleft palate with prednisone, larger studies failed to 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. Neonatal leukopenia, low plts, low immunoglobulins resolve by 1 year
Mycophenolic acid products (myfortic/cellcept) ✗	**Teratogenic in pregnancy/Miscarriage risk (25%)** -- fetal malformations affecting ears, limbs, heart, esophagus, and kidney

Immunosuppression in Lactation

IMS		Lactation Safety
Steroids	✓	Safe per LACTMED
Tacrolimus / Cyclosporine	✓	Probably safe per LACTMED- minimal exposure to infant
Azathioprine/6-MP	✓	Probably safe per LACTMED- minimal exposure to infant
Mycophenolic acid products (myfortic/cellcept)	✗	No human data for nursing. **Avoid**



HEPATOLOGY
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PRACTICE GUIDANCES | HEPATOLOGY, VOL. 73, NO. 1, 2021

Reproductive Health and Liver Disease: Practice Guidance by the American Association for the Study of Liver Diseases

GUIDANCE STATEMENTS

- Delaying conception until liver disease is well controlled on stable IMS doses for at least 1 year is suggested.
- Liver test monitoring during each trimester is suggested.
- More frequent monitoring (every 2-4 weeks) advised for first 6 months postpartum.

Cirrhosis in Pregnancy

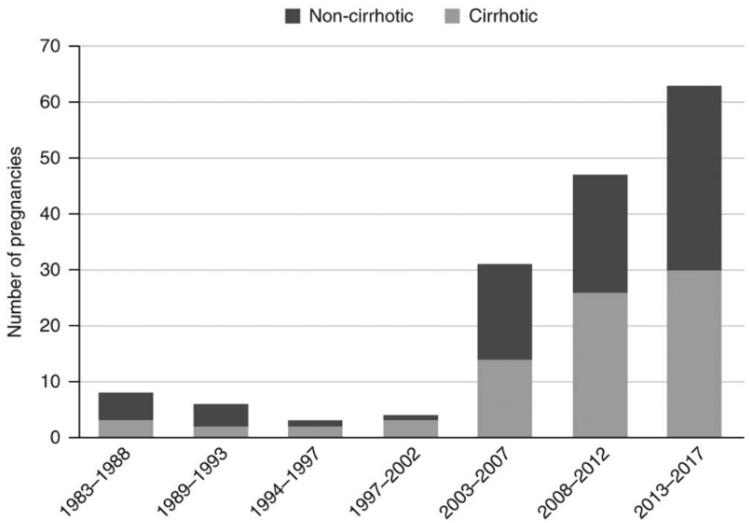
Cirrhosis in Pregnancy

- 36 yo W with compensated NASH cirrhosis and portal HTN (splenomegaly and platelets 120K)
- No prior EGD. MELD 8
- Now wants to become pregnant.

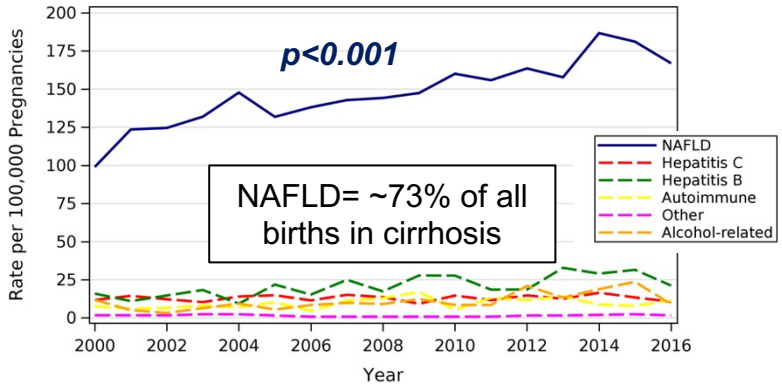
Does she warrant additional evaluation before conceiving?

Rising Pregnancies in Women With Cirrhosis

King's College Hospital 1983 to 2017
Pregnancies with CLD



Ontario, Canada (2000-2017)



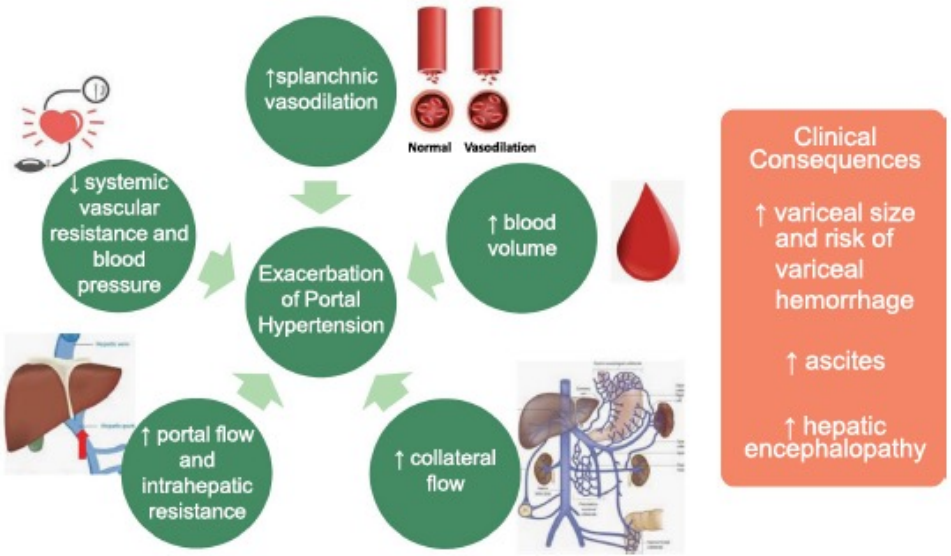
Gonsalkorala et al. *Am J Gastroenterol*. 2019; Flemming J et al. *Gastroenterology*. 2020; Sarkar et al. *CGH.* 2021.

Pregnancy With Cirrhosis

- Maternal mortality <2% in current era
- Variceal hemorrhage most frequent complication
- Complications more frequent if history of decompensation: (1.2% vs 13%)
- Pre-pregnancy MELD predicts maternal risks:
  - MELD ≤6 no complications
  - MELD ≥10 higher complications

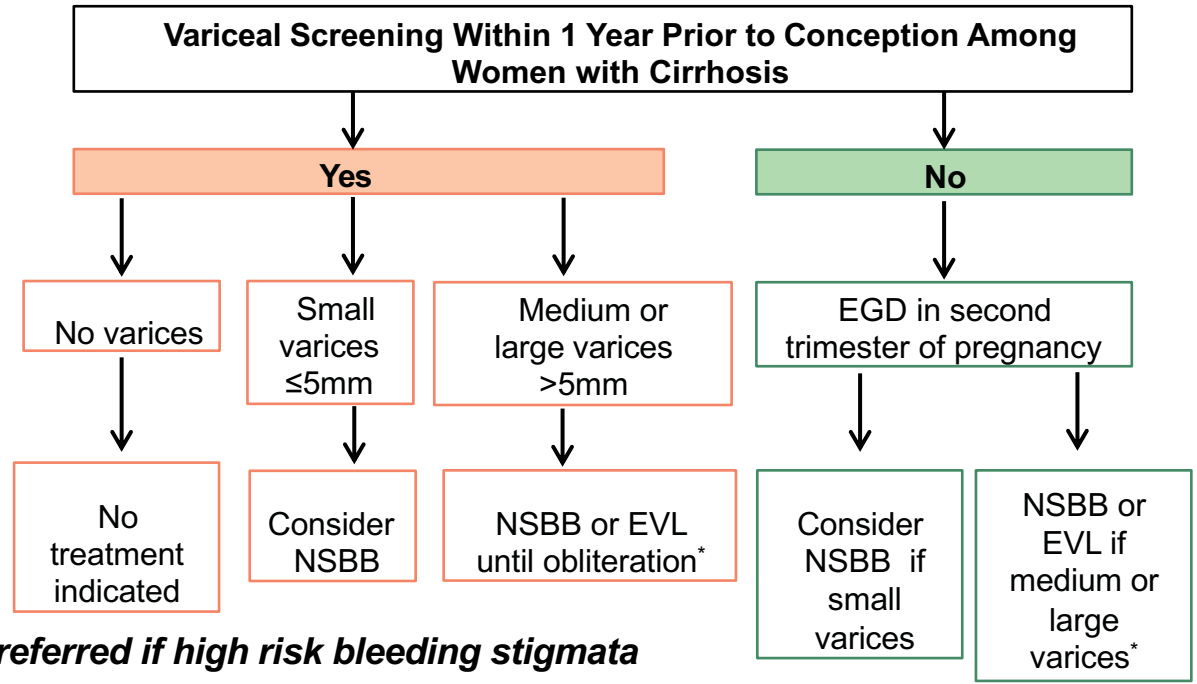
Westbrook et al. *CGH*. 2011; Flemming J et al. *Gastroenterology.* 2020; Huang et al. *AJG.* 2022.

Varices in Pregnancy



- Up to 20% maternal mortality
- Highest risks:
  - **Second trimester:** Intravascular volume expansion and enlarging uterus compressing IVC
  - **Delivery:** Enlarged uterus compressing IVC and repeated Valsalva maneuvers
- Mode of delivery- Guided by obstetric indications not presence of cirrhosis

AASLD Reproductive Health and Liver Disease Guidance. 2021.



EVL is preferred if high risk bleeding stigmata

AASLD Reproductive Health and Liver Disease Guidance. 2021.

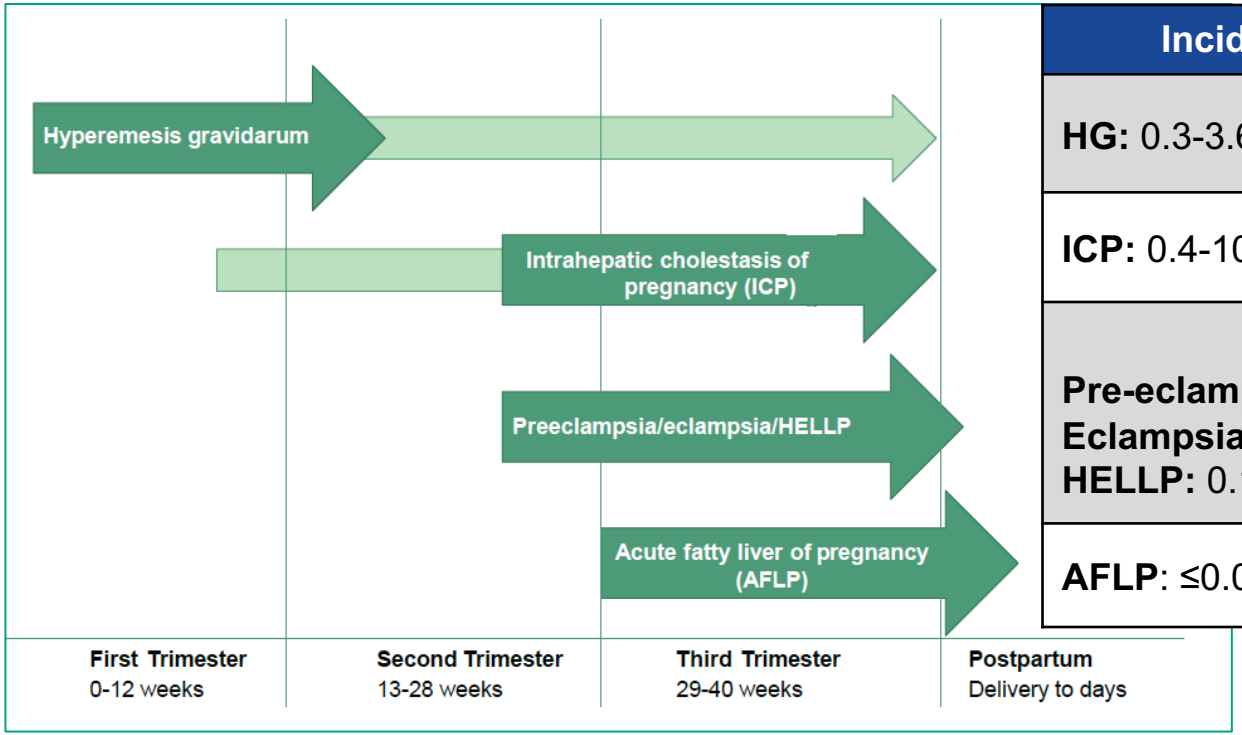
Variceal Bleeding and Pregnancy

Non-selective beta blockers	Pregnancy	Lactation	
Nadolol, Propranolol	**COMPATIBLE.** Rare reports of intrauterine growth restriction, neonatal respiratory depression, Infant hypoglycemia	**COMPATIBILE** Nadolol: Greater excretion into breast milk Propranolol: Highly protein bound, small amount excreted in breast milk	**Propranolol favored**
Carvedilol	No data	No data	

AASLD Reproductive Health and Liver Disease. *Hepatology*. 2021.

Pregnancy-Specific Liver Diseases

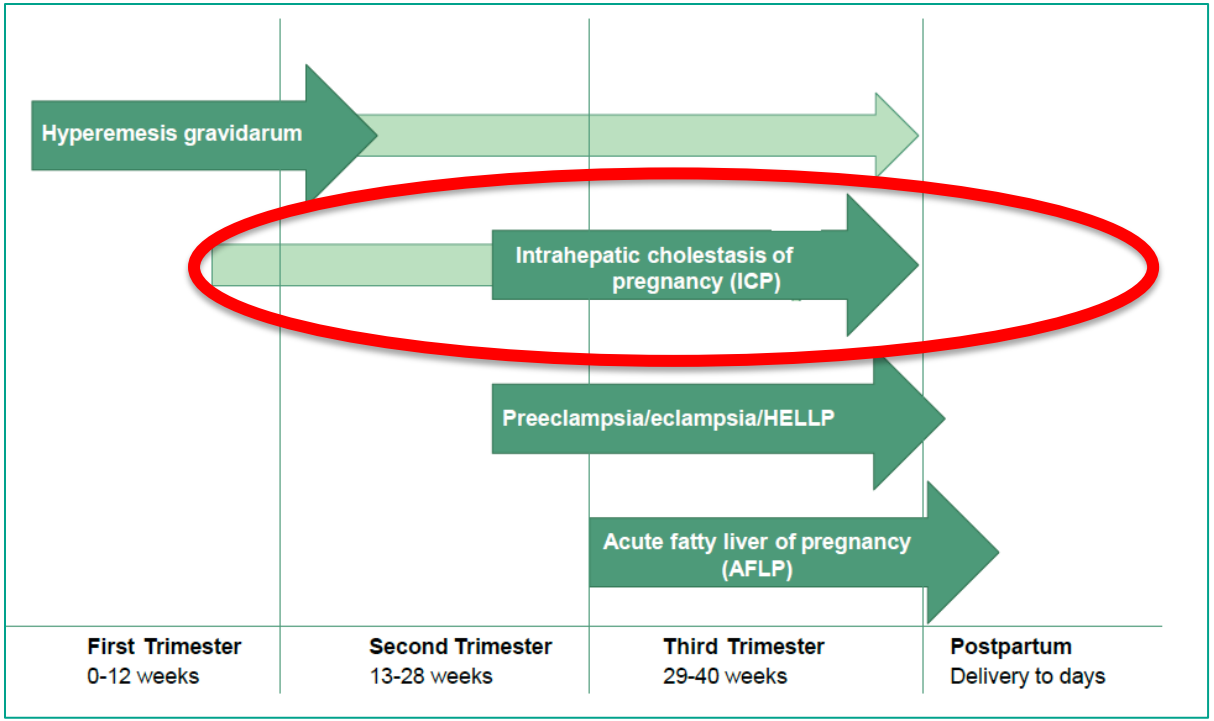
Pregnancy-Specific Liver Diseases



Incidence
HG: 0.3-3.6%
ICP: 0.4-10%
Pre-eclampsia: 8% **Eclampsia:** <0.01% **HELLP:** 0.1-1%
AFLP: ≤0.01%

AASLD Reproductive Health and Liver Disease. *Hepatology*. 2021.

Liver Diseases Unique to Pregnancy



AASLD Reproductive Health and Liver Disease. *Hepatology*. 2021.

Intrahepatic Cholestasis of Pregnancy (ICP)

Incidence: 0.4-10%

Risk factors:

- Advanced maternal age, multiple gestations, metabolic syndrome
- HCV infection
- Personal or family history of ICP, or cholestatic mutations (ABCB11, ABCB4, ATP8B1)

Clinical presentation:

- Itching (palms and soles), *without* rash

Labs:

- Total bile acids >10 µmol/L → in right clinic setting = diagnostic
- Liver enzymes 2-30 X ULN (not required to make the diagnosis)

Intrahepatic Cholestasis of Pregnancy (ICP)

Maternal risks:

- Minimal- genetic variants increase risk for BRIC/PFIC
- Pruritus and abnormal liver tests usually resolve post-partum (send cholestatic genetic work-up if not)

Fetal risks:

- Preterm birth, neonatal respiratory depression and asphyxia, and intrauterine fetal demise
- Highest risk with bile acids >100µmol/L
- Management = Ursodeoxycholic acid (UDCA)
  - Lowers bile acid levels
  - Improved fetal outcomes

Meta-analysis of ICP (n=6974 women): UDCA reduced spontaneous preterm birth (especially singleton pregnancies + BAs ≥40µmol/L

AASLD Reproductive Health and Liver Disease. *Hepatology*. 2021; Ovadia et al. *Lancet Gastro & Hep.* 2021.

Initial Case

ID: 33 yo woman G1P0, week 22 (second trimester), referred to hepatology clinic for abnormal liver tests on outpatient ***labs and itching of palms and soles.***

PMH: Hypothyroidism

Meds: Levothyroxine, pre-natal vitamin

Labs:

- AST 50, ALT 70, AP 120, Tbili 0.5, Albumin 3.5
- WBC count 4.5, HCT 36, Plts 250

Clinical Course

Work-up:

- ANA positive (1:40), BAs elevated 60 µmol/L
- Normal/negative: US, ASMA, IgG, HBsAg, HCV Ab, ceruloplasmin, iron studies, A1AT level
- Repeat AST 90 / ALT 170 / AP 120 / Tbili 0.5

Treatment: Ursodiol 13 mg/kg/day + delivered at 37 weeks

Outcome:

- At delivery BAs 20µmol/L, ALT nadir of 45
- 1 month postpartum: Liver tests + BAs normal, itching resolved, mom and baby well

Thank You!

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