Advances in the Management of Viral Hepatitis during Pregnancy.

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No disclosures

Outline of my talk

- Overview of hepatitis and pregnancy.
- Case of hepatitis B
- Case of hepatitis C.
- Case of Hepatitis E
- Review of literature with the cases.
- CLD and pregnancy
- Safety of endoscopy in pregnancy
- Take home points/conclusion.

Challenges of liver disease in pregnancy

- Liver disease is a dreadful complication in pregnant patients and can be life threatening to both mother and fetus.
- Majority of the these are self limiting but in some case it can lead to fulminant hepatic failure.
- General physicians and specialist's, all confronted with these patients during their practice..
- Safety of medicine??
- Referral chain ???
- 2 lives at stake- Time of delivery?? . A critical decision.
- Extreme vigilance and prompt management is crucial.

Liver Disease in Pregnancy and fulminant hepatic failure in Pakistan

Etiology

- Etiology of the disease was Hepatitis E in 28 (53.8%)
- Hepatitis B in 9 (17.3%)
- Hepatitis C in 7 (13.5%)
- HELLP syndrome in 7 (13.5%)
- Acute fatty liver of pregnancy in 1 (3.57%) case.

Prognosis

- Maternal mortality was 15 (28.8%)
- Fetal mortality was 40 (77%).
- Only 12 (23.1%) newborns remained alive.

ZP Brohi et al Etiology, clinical features and outcome of fulminant hepatic failure in pregnancy J Pak Med Assoc. 2013 Sep;63(9):1168-71

Physiologic changes in the liver during

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.

- Cardiac output is increased by 40–45%- increases in the renal, uterine, and skin blood flow but little change in the liver blood

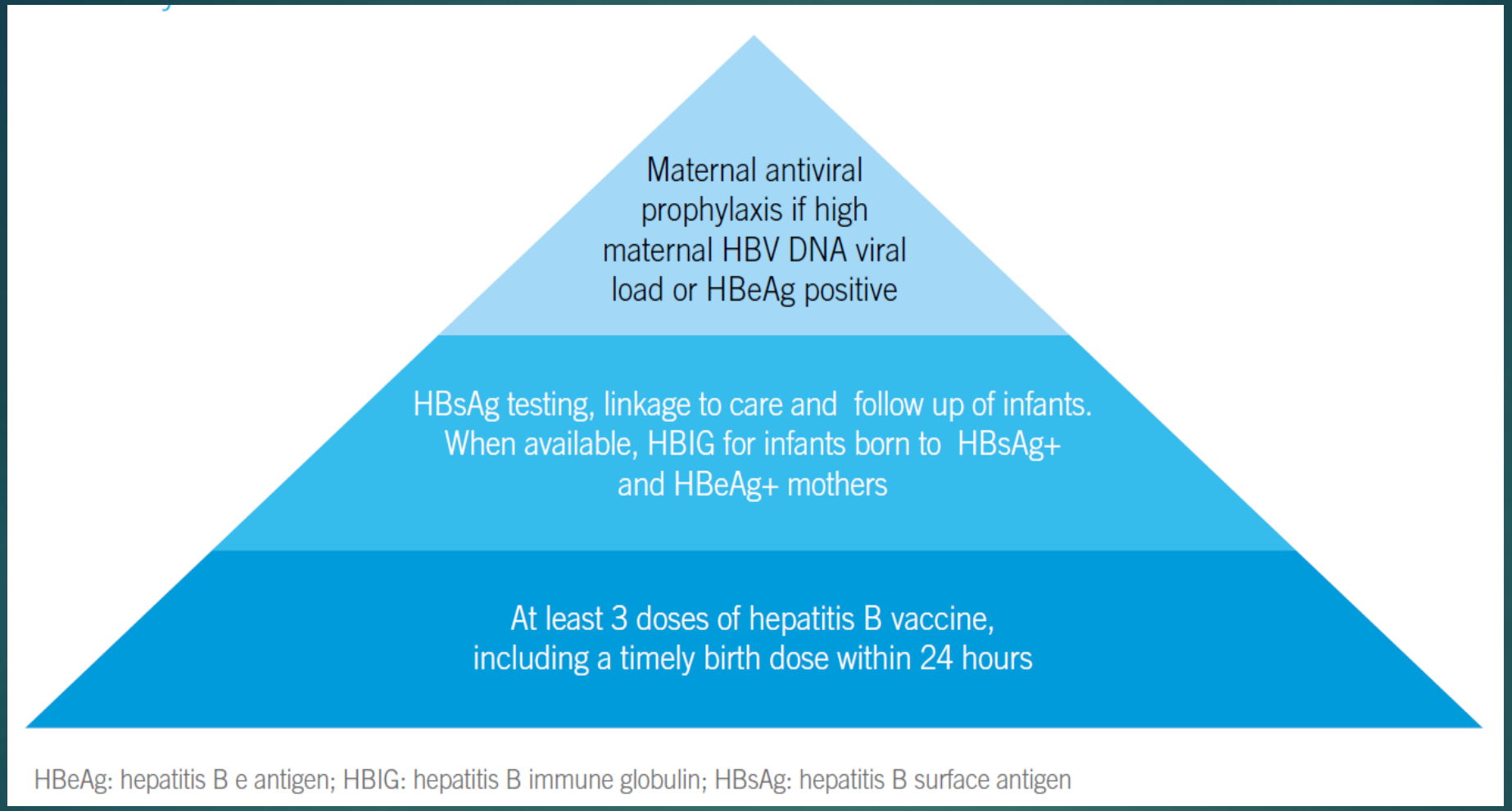
- Any abnormality seen in transaminases and bilirubin needs further evaluation

Robson SC et al. Br J Obstet Gynaecol 1990 ; 97 : 720 – 3 .

Hepatitis B in pregnancy

Key points of WHO guidelines 2020

- Prevention of MTCT is a part of WHO's core strategy to achieve elimination of HBV worldwide.
- Universal screening of HBV is a must during pregnancy.
- For elimination a reduction of HepBsAg prevalence to 0.1% in children of 5 years of age
- Antiviral prophylaxis is needed together with vaccination (Birth dose)and IG for effective MTCT.
- Timing of stopping antiviral prophylaxis after delivery in inactive HBV + mothers is debatable. Close monitoring is required for flares.



Prevention of MTCT of HBV: Guidelines on antiviral prophylaxis in pregnancy. WHO 2020

Case.
Hepatitis B.

- 2o years old girl k/c of Hepatitis B since birth, currently not on treatment is getting married and has come to you for counselling and advice?
- She has several questions in her mind, which are
- 1) Can her husband gets hep B from her?
- 2) What if she gets pregenant? Are drugs safe in pregnancy?
- 3) How can you prevent vertical transmission to newborn.?
- 4) Is it must to go for C- section or normal vaginal delivery is an option?
- 5) Can she continue breast feeding?

- What test will you order?
- CBC, PT, Albumin, LFT, Delta Ab, Hep C Ab, QHBV PCR, HBV eAg, HBV eAb,
- Ultrasound Abdomen, fibroscan.
- Family screening.

Facts….
Hepatitis B

- Transmission occurs via parental or mucosal exposure to infected body fluids.
- In countries endemic for HBV perinatal exposure accounts for most transmission.
- The risk of developing chronic hepatitis B is inversely related to age at infection(90% of infants, 30% of children< 5yrs, 2-6% infected as adults progress to chronic disease).
- WHO, CDC and ACOG recommend screening of all pregnant for HBV with HBsAg.

World Health Organization. Media Centre. Hepatitis B. Fact sheet. Updated July 2013. Available at: http://www.who.int/mediacentre/factsheets/fs204/en/. Accessed April 4, 2014

Clinical outcomes (HBV)

- The course of HBV in pregnancy is similar to that in general population.
- Risk of FHF after acute infection is <1%.
- No association was found with HBV and intrauterine growth restriction or preeclamsia.

Reddick KLB, Jhaveri R, Gandhi M, et al. Pregnancy outcomes associated with viral hepatitis. J Viral Hepat 2011;18:394–8

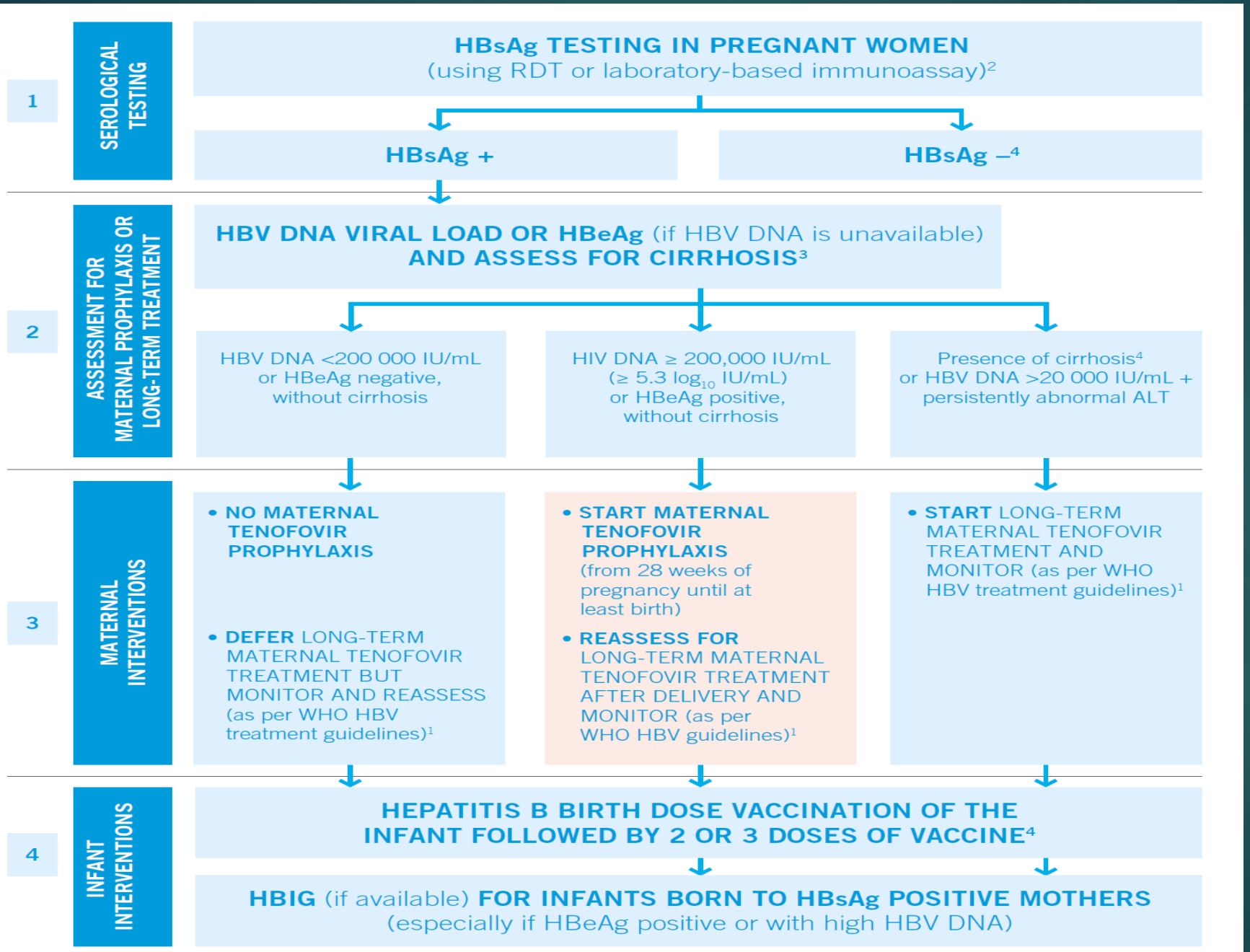

1
SEROLOGICAL TESTING
HBsAg TESTING IN PREGNANT WOMEN
(using RDT or laboratory-based immunoassay)[2]
HBsAg +
HBsAg –[4]
2
ASSESSMENT FOR MATERNAL PROPHYLAXIS OR LONG-TERM TREATMENT
HBV DNA VIRAL LOAD OR HBeAg (if HBV DNA is unavailable)
AND ASSESS FOR CIRRHOSIS[3]
HBV DNA <200 000 IU/mL or HBeAg negative, without cirrhosis
HIV DNA ≥ 200,000 IU/mL (≥ 5.3 log10 IU/mL) or HBeAg positive, without cirrhosis
Presence of cirrhosis[4] or HBV DNA >20 000 IU/mL + persistently abnormal ALT
3
MATERNAL INTERVENTIONS
• NO MATERNAL TENOFOVIR PROPHYLAXIS
• DEFER LONG-TERM MATERNAL TENOFOVIR TREATMENT BUT MONITOR AND REASSESS (as per WHO HBV treatment guidelines)[1]
• START MATERNAL TENOFOVIR PROPHYLAXIS (from 28 weeks of pregnancy until at least birth)
• REASSESS FOR LONG-TERM MATERNAL TENOFOVIR TREATMENT AFTER DELIVERY AND MONITOR (as per WHO HBV guidelines)[1]
• START LONG-TERM MATERNAL TENOFOVIR TREATMENT AND MONITOR (as per WHO HBV treatment guidelines)[1]
4
INFANT INTERVENTIONS
HEPATITIS B BIRTH DOSE VACCINATION OF THE INFANT FOLLOWED BY 2 OR 3 DOSES OF VACCINE[4]
HBIG (if available) FOR INFANTS BORN TO HBsAg POSITIVE MOTHERS
(especially if HBeAg positive or with high HBV DNA)

TABLE 1
Pregnancy classification of antiviral therapy

Antiviral drug	Pregnancy category
Adefovir	C
Entecavir	C
Interferon alfa-2b	C
Lamivudine	C
Pegylated interferon alfa-2a	C
Telbivudine	B
Tenofovir	B

Why Tenofovir disoproxil fumarate?(TDF)

TDF is preferred because of

- Minimal the risk of resistance during treatment
- High efficacy in preventing MTCT
- What about Temofovir Alfenamide?

Tenofovir Alafenamide for Pregnant Chinese Women With Active Chronic Hepatitis B: A Multicenter Prospective Study

Qing-Lei Zeng,[*,a] Hong-Xu Zhang,[‡,a] Ji-Yuan Zhang,[§,a] Shuo Huang,[*,a] Wei-Zhe Li,[*,a] Guang-Ming Li,[‖,a] Ya-Jie Pan,[*,a] Ying-Hua Feng,[¶] Zhi-Qin Li,[*] Guo-Fan Zhang,[#] Jiang-Hai Xu,[**] Wan-Bao Lin,[‡‡] Guang-Hua Xu,[§§] Na Liu,[§§] Guo-Qiang Zhang,[‖‖] Guo-Tao Li,[‖‖] Wei Li,[¶¶] Yan-Li Zeng,[¶¶] Ning Song,[##] Meng Wang,[***] Da-Wei Zhang,[§] Zhi-Min Chen,[‡‡‡] Guang-Lin Cui,[§§§] Juan Li,[*] Jun Lv,[*] Yan-Min Liu,[*] Hong-Xia Liang,[*] Chang-Yu Sun,[*] Yi-Hua Zhou,[‖‖‖] Zu-Jiang Yu,[*] and Fu-Sheng Wang[§]

Clinical Gastroenterology and Hepatology 2021

RESULTS: One hundred three and 104 pregnant women were enrolled and 102 and 104 infants were born in the TAF and TDF groups, respectively. In the TAF group, the mean age, gestational age, alanine aminotransferase level, and viral loads at treatment initiation were 29.3 years, 1.3 weeks, 122.2 U/L, and 5.1 $\log_{10}$ IU/mL, respectively. TAF was well-tolerated, and the most common adverse event was nausea (29.1%) during a mean of 2 years of treatment. Notably, 1 (1.0%) TAF-treated pregnant woman underwent induced abortion due to noncausal fetal cleft lip and palate. No infants in either group had birth defects. In the TAF group, the hepatitis B e antigen seroconversion rate was 20.7% at postpartum month 6, infants had normal growth parameters, and no infants were positive for HBsAg at 7 months. The TDF group had comparable safety and effectiveness profiles.

CONCLUSIONS: TAF administered throughout or beginning in early pregnancy is generally safe and effective for pregnant women with active CHB and their infants.

Antivirals and Breastfeeding

- Breastfeeding not contraindicated.
- Antivirals are minimally excreted in breast milk .
- Unlikely to cause significant toxicity.
- The unknown risk of low-level exposure to the infant should be discussed with mothers.

Recommendations of HBV females who desire pregnancy.

- Women with mild liver disease, low viremia
  - Pregnancy before treatment
- Women with moderate liver disease, no cirrhosis
  - Treatment before pregnancy; if response, stop treatment before pregnancy
- Women with advanced liver disease
  - Treatment before and during pregnancy; continue treatment after delivery
- Women with mild liver disease, very high viremia
  - Treatment in last trimester with "B" category drug

- Wedemeyer H, et al. Dtsch Med Wochenschr. 2007;132:1775-1782.
- EASL Clinical Practice Guidelines. J Hepatol.

Management of Hepatitis B in Pregnancy: A Challenge

Hepatitis B virus (HBV) is a highly infectious DNA virus and it is estimated that 350 – 400 million people are chronically infected worldwide.[1] Women of child bearing age with chronic HBV infection remain an important source of vertical transmission. According to recent data from United States centers of disease control and prevention, prenatal screening for Hepatitis BsAg (HBsAg) is universal; 97% of women undergo screening during pregnancy.[2] Accurate figures from developing countries are missing but estimates are quite low. All infants born to HBsAg positive mothers should get active and passive Hepatitis B immunization.[1]

During pregnancy, decision regarding initiation, continuation or stopping of treatment depends upon multiple factors. In a series of mothers with high viral load, the risk of vertical transmission was as high as 28%.[3] Women with high viral load and HBeAg positivity have higher chance of vertical transmission. Assessment of mother's liver status is the key to decide about management. Women with mild liver disease and low viremia can wait till the pregnancy is over. Whereas, in those patients with mild liver disease but high viral loads (HBV DNA > 10^8 copies/ml), antiviral treatment should start at 32 weeks and continue at least 4 weeks postpartum as it is observed that if mothers' viral load can be decreased, the risk of perinatal transmission is also reduced. If previous child was HBV positive, then the risk of perinatal transmission may be higher, so the threshold for treatment may be lower (HBV DNA > 10^6 copies/ml). Women with advanced liver disease should continue with antiviral treatment (category B drugs) (Table I).[4]

Interferon is not recommended in pregnancy. All oral antivirals are either inhibitor of nucleoside or nucleotide polymerases. Tenofovir is an ideal treatment in pregnancy because of its safety profile. Lamivudine and Telbivudine are two alternate agents, but no longer considered as first line agents because of its antiviral resistance.

Most women of child bearing age are likely to have mild disease and treatment can be delayed. Those women who are already on antiviral before delivery, the decision to continue it during pregnancy depends upon the risk of decompensation during or after pregnancy. Majority of safety data on HBV antiviral come from antiretroviral pregnancy registry (APR).[5] Tenofovir was given to 606 pregnant women in their first trimester and 336 women in their second trimester, the rate of birth defects associated with Tenofovir ranged from 2.3% and 1.5% respectively, which is similar to background rate.[5]

Table I: Pregnancy classification of antiviral therapy.

Antiviral drug	Pregnancy category
Adefovir	C
Entecavir	C
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Lamivudine	C
Pegylated Interferon alpha-2a	C
Telbivudine	B
Tenofovir	B

Pregnancy Category B: Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well controlled studies in pregnant women or animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester.

Pregnancy Category C: Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Management of HBV in pregnancy is complicated and challenging. Before initiating treatment, risks and benefits must be weighed carefully. Major determinants of perinatal transmission are previous transmission of HBV to fetus, viral count and mothers' liver condition. Larger multicentre, randomized long-term follow-up studies are required on this topic. These patients should ideally be managed in tertiary care centre, under close follow up with hepatologist.

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1. World Health Organization. Hepatitis B: fact sheet 2004 [Internet].2004. Available from: http://www.who.int/mediacentre/factsheets/fs204/en/
2. Schrag SJ, Arnold KE, Mohle-Boetani JC, Lynfield R, Zell ER, Stefonek K, *et al*. Prenatal screening for infectious disease and opportunities for prevention. *Obstet Gynecol* 2003; **102**:753-60.
3. Van Zonneveld M, Van Nunen AB, Niesters HG, De Man RA, Schalm SW, Janssen HL. Lamivudine treatment during pregnancy to prevent perinatal transmission of Hepatitis B virus infection. *J Viral Hepat* 2003; **10**:294-7.
4. Lok AS, MacMahon BJ. Chronic Hepatitis B: update 2009. *Hepatology* 2009; **50**:1-36.
5. Interim report. The antiretroviral pregnancy registry [Internet]. 2013. Available from: http://www.apregistry.com/forms/interim_report.pdf

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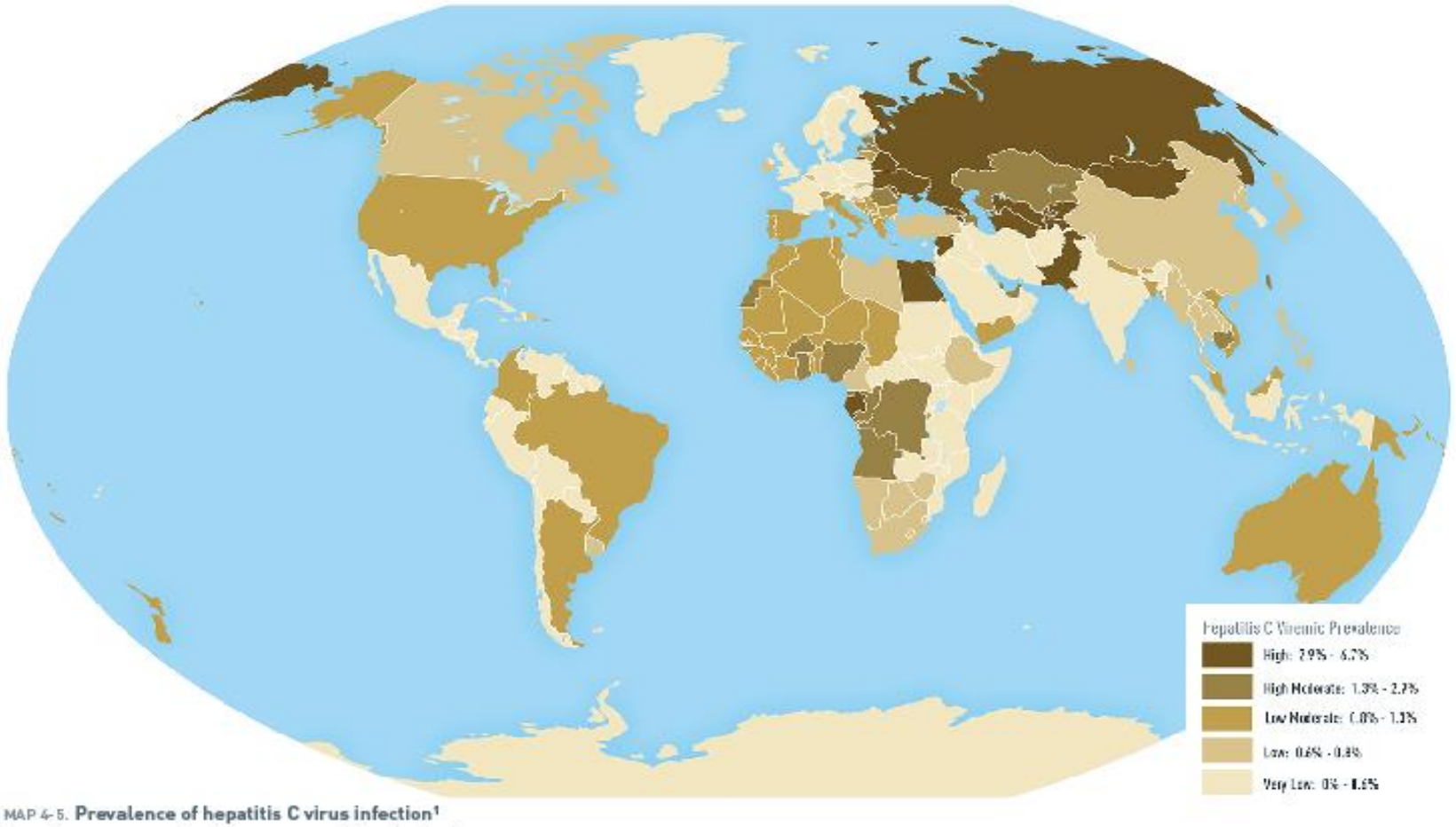
Hepatitis C in Pregnancy



MAP 4-5. **Prevalence of hepatitis C virus infection**[1]

Boundary representation is not necessarily authoritative.

[1] Disease data source: Gower et al. Global epidemiology and genotype distribution of the hepatitis C virus infection. J Hepatol. 2014 Nov;61(1 Suppl):S45-57. doi: 10.1016/j.jhep.2014.07.027. Epub 2014 Jul 30.

Hepatitis B and hepatitis C in southeast and southern Asia: challenges for governments

Suzanne Wait, Emily Kell, Saeed Hamid, David H Muljono, Jose Sollano, Rosmawati Mohamed, Samir Shah, Mamun-Al-Mahtab, Zaigham Abbas, Jennifer Johnston, Tawesak Tanwandee, Jack Wallace

Lancet Gastroenterol Hepatol 2016; 1: 248–55

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In 2015, the Coalition to Eradicate Viral Hepatitis in Asia Pacific gathered leading hepatitis experts from Bangladesh, India, Indonesia, Malaysia, Pakistan, the Philippines, and Thailand to discuss common challenges to the burden posed by hepatitis B virus (HBV) and hepatitis C virus (HCV), to learn from each other's experience, and identify sustainable approaches. In this report, we summarise these discussions. Countries differ in their policy responses to HBV and HCV; however, substantial systemic, cultural, and financial barriers to achievement of elimination of these infections persist in all countries. Common challenges to elimination include limited availability of reliable epidemiological data; insufficient public awareness of risk factors and modes of transmission, leading to underdiagnosis; high rates of transmission through infected blood products, including in medical settings; limited access to care for people who inject drugs; prevailing stigma and discrimination against people infected with viral hepatitis; and financial barriers to treatment and care. Despite these challenges, promising examples of effective programmes, public–private initiatives, and other innovative approaches are evident in all countries we studied in Asia Pacific. The draft WHO Global Health Sector Strategy on Viral Hepatitis 2016–21 provides a solid framework upon which governments can build their local strategies towards viral hepatitis. However, greater recognition by national governments and the international community of the urgency to comprehensively tackle both HBV and HCV are still needed. In all countries, strategic plans and policy goals need to be translated into resources and concrete actions, with national governments at the helm, to enable a sustainable response to the rising burden of hepatitis B and C in all countries.Introduction

Short Communication

Hepatitis-C Infection: Are we really committed to eliminate? Could it become the second Polio for Pakistan?

Lubna Kamani[1], Baseer Sultan Ahmad[2], Hamid Ali Kalwar[3]

ABSTRACT

Pakistan's hepatitis C virus (HCV) burden is one of the highest in the world. Around eight million people live with HCV in Pakistan according to a National Hepatitis Survey. Most HCV-infected people are unaware of their infection status culminating in delayed diagnosis and treatment, progressing to end stage liver disease, cirrhosis, and hepatocellular carcinoma (HCC), thereby raising the disease load for a developing country with limited resources. Blood transfusions and injections with reused syringes lead to increased HCV rates in Pakistan. According to a survey viral infections like hepatitis C, hepatitis B and HIV were not screened in more than half of the blood transfusions done in Pakistan. Hepatitis C elimination requires financial support from the local government and private organizations, commitment from civil societies across the world and a dedicated political will. Without defining effective planning and strategy it is our fear that it could become the second Polio for Pakistan.

Case
Hepatitis C

- 32 years old lady banker by profession came to your clinic for counselling and further management of hep C as she is getting married soon
- She was treated with Pegylated interferon and Ribavirin in 2013.
- Family history is positive for CHC without HCC.
- Her current Labs and ultrasound showed that she has compensated CTP Class A cirrhosis and her hepatitis PCR is positive.
- She had several questions regarding her disease?

Questions.

- What is the risk of MTCT of hepatitis C?
- How risky will be the pregnancy in her case.
- Doe she required treatment before, during or after preganacy?
- Safety of medicine during pregnancy.
- What harmful effect does this virus has on unborn child and afterwards.
- Does she requires endoscopy preconception and its risk during pregnancy.
- Out come of pregnancy in her case.
- Normal vaginal delivery or C-section?

Universal screening: AASLD and CDC

- It will allow appropriate assessment of liver disease and linkage to care after delivery
- It allows screening and care of exposed child

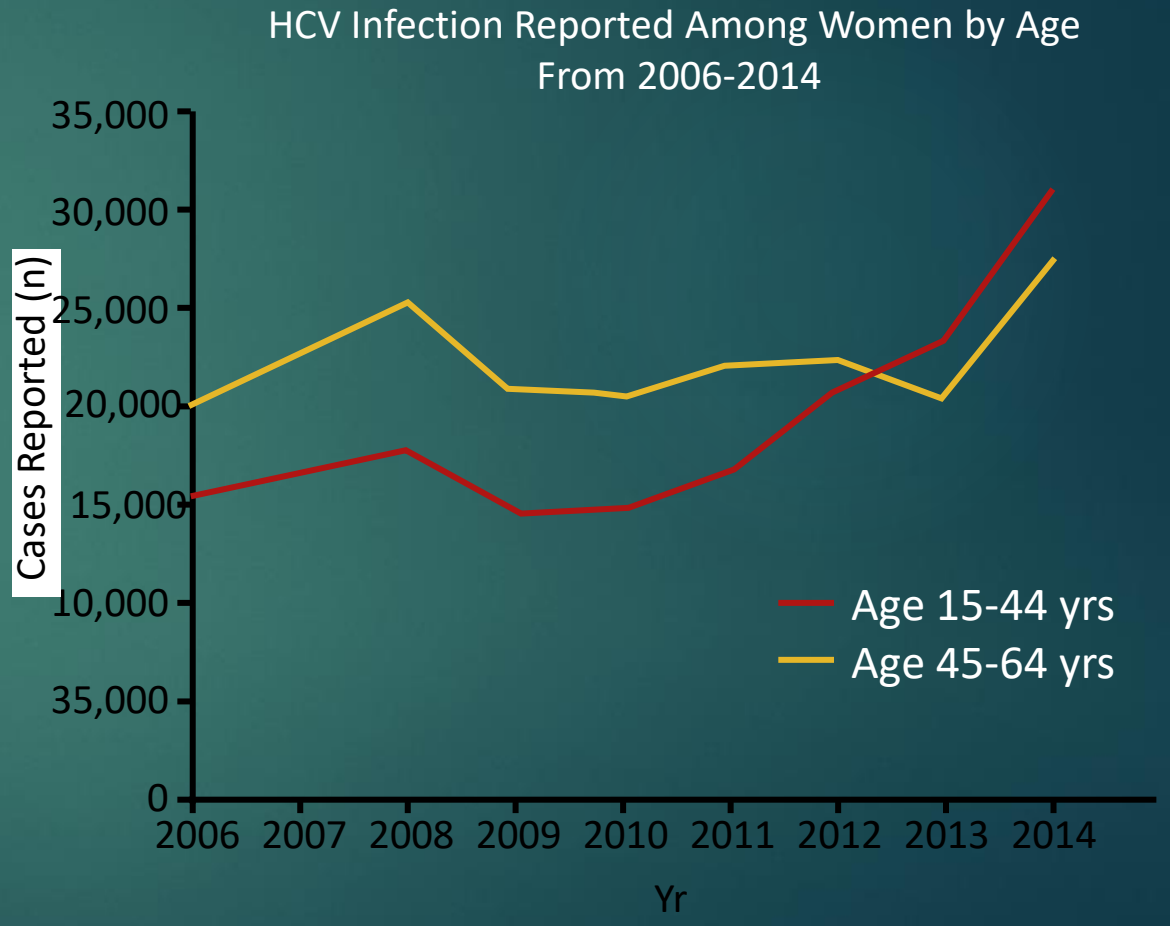
Munoz-Gamez J.A. Med Clin 2016

- It also enables application of special recommendations for HCV pregnant patient
  - Preference of amniocentesis over chorionic villus sampling if needed
  - Avoid internal fetal monitoring during labor
  - Avoid prolonged rupture of membrane.

Hughes BL. Am. J. Obstet. Gynecol 2017

HCV in Women of Childbearing Age

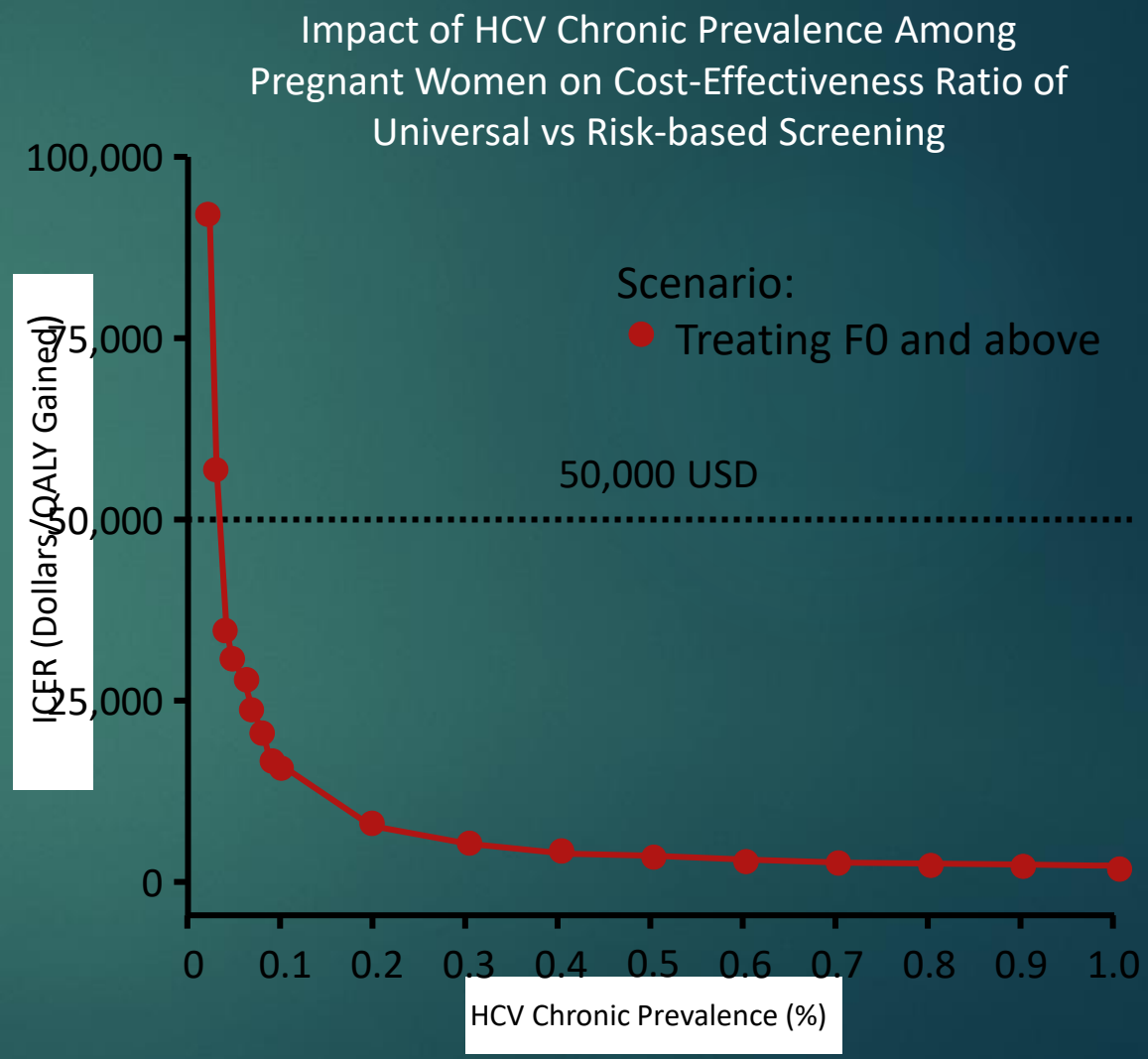
- In pooled data from the National Notifiable Diseases Surveillance System and the Quest laboratory database
  - Among women of childbearing age:
    - Number of **acute** cases of HCV **increased 3.4-fold**
    - Number of **past or present cases doubled**
    - Case number **higher** in **younger** vs older **women** since 2013



Ly. Ann Intern Med. 2017;166:775.

Is Universal HCV Screening During Pregnancy Cost-Effective?

- Incremental cost-effectiveness ratio analysis comparing universal and risk-based screening
- Universal screening of ~ 5 million pregnant women in 2018 could **result in detection and treatment of an additional 33,000 women and 300 children born with HCV**
- HCV screening cost-effective even in low prevalence areas and across all fibrosis stages



Chaillon. Clin Infect Dis. 2019;69:1888.

What Is the Effect of HCV Infection on Pregnancy?

- HCV may have negative effects but difficult to tease apart from effects of associated factors (eg, injection drug use)

Meta-analysis of > 4,000,000 women with > 5000 HCV infection cases[1,2*]

Birth Outcome	OR With vs Without HCV (95% CI)
Preterm birth[1]	1.62 (1.48-1.76)
Intrauterine fetal growth restriction[2]	1.53 (1.40-1.68)
Low birth weight[2]	1.97 (1.43-2.71)

Swedish Birth Registry: > 1 million women, > 2000 births to HCV+ women, 2001-2011[3]

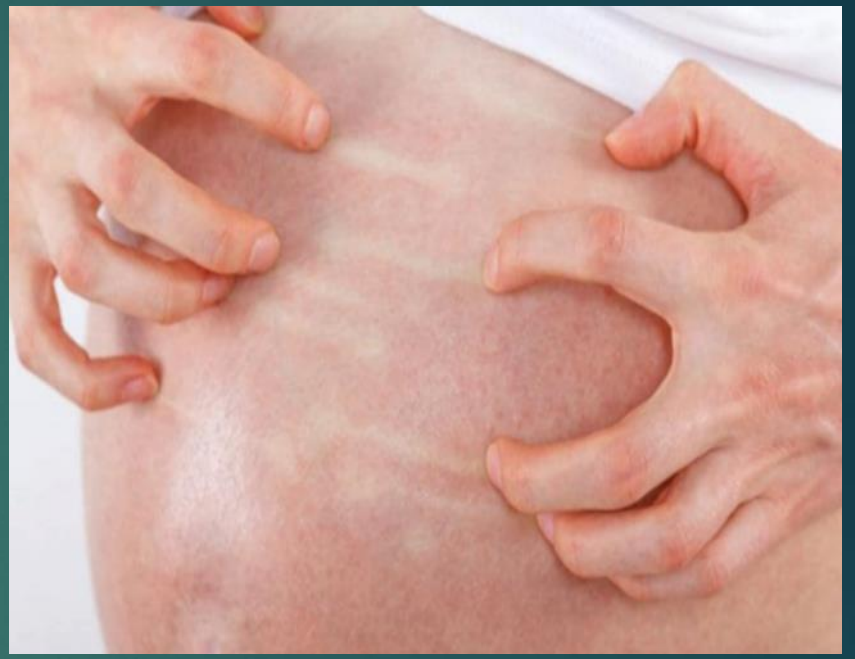
Birth Outcome	aRR With (n = 1,091,913) vs Without (n = 2056) HCV (95% CI)
Preterm birth	1.32 (1.08-1.60)
Late neonatal death	3.79 (1.07-13.79)

*1. 4,186,698 participants with 5218 HCV infection cases; 2. 4,185,414 participants with 5094 HCV infection cases.

1. Huang. J Viral Hepat, 2015;22:1033. 2. Huang. Medicine (Baltimore). 2016;95:e4777.
3. Stokkeland. Eur J Epidemiol. 2017;32:617.

HCV and ICP

- Population-based cohort study in Sweden included 11,000 women with ICP and 11,000 healthy women[1]
  - ICP HR with vs without HCV: 4.16 (95% CI: 3.14-5.15)
- Meta-analysis of 3 studies of ICP in pregnancy (N = 95429) in women with (n = 308) vs without HCV[2]
  - ICP pooled OR with vs without HCV: 20.40 (95% CI: 9.39-44.33)



Counsel women with HCV on the increased risk of ICP!

1. Marschall. Hepatology. 2013;58:1385. 2. Wijarnpreecha. Clin Res Hepatol Gastroenterol. 2017;41:39.

Facts….

- Despite recent advances in the pathogenesis and treatment, HCV in pregnancy has been a neglected condition and improved public health response to these populations is needed.

- Hepatitis C generally does not reduce the likelihood of a women becoming pregnant, unless there is advanced cirrhosis.

Hepatitis C Virus in Pregnancy.

Am J Perinatol. 2013 February

Facts….

- Much remains unknown about the dynamics of chronic HCV infection during and after pregnancy, as well as in the neonatal period.
- No clinical intervention has been clearly studied and proved to reduce the vertical transmission risk.
- Vertical transmission is the leading cause of childhood HCV infection in developing world.

Arshad M, El-Kamary SS, Jhaveri R. Hepatitis C virus infection during pregnancy and the newborn period - are they opportunities for treatment? Journal of viral hepatitis. 2011

Vertical transmission….

- Worldwide, the seroprevalance of HCV in pregnant women is thought to be anywhere from 0.15% to 2.4% but much higher in countries like Egypt where it is estimated to be as high as 8.6% but vertical transmission was low

  AbdulQawi K et al.Prospective study of prevalence and risk factors for hepatitis C in pregnant Egyptian women and its transmission to their infants. *CroatMed J* 2010

- In spite of the high hepatitis C positivity in pregnant population, the rate of vertical transmission to the neonate remains low (2-8%)

  Aziz S et al. Vertical transmission of hepatitis C virus in low to middle socio-economic pregnant population of Karachi. Hepatol Int 2011

Transmission.

- HCV-monoinfected pregnant women have a 2–8% risk of viral transmission to their infant.
- Risk of transmission increases to 2-4 fold with HIV co-infection.
- Mother-to-infant transmission of HCV may be intrauterine, intrapartum, or postnatal.

Cottrell EB et al. Reducing risk for mother-to-infant transmission of hepatitis C virus: a systematic review for the U.S. Preventive Services Task Force. Annals of internal medicine. 2012

Risk of MTCT of HCV by Maternal HIV Serostatus

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

HIV-negative women

Author, Yr	Sample Size	Proportion, %	95% CI	Weight, %
Spencer, 1997	63	9.5	(3.6-19.6)	7.8
Granovsky, 1998	25	8.0	(1.0-26.0)	3.8
Resti, 1998	275	4.7	(2.5-7.9)	11.2
La Torre, 1998	56	3.6	(0.4-12.3)	4.0
Polatti, 2000	24	4.2	(0.1-21.1)	2.3
Ceci, 2001	60	3.3	(0.4-11.5)	4.0
Nordbo, 2002	48	8.3	(2.3-20.0)	6.2
Resiti, 2002	739	10.	(8.1-12.6)	15.4
Caudai, 2003	29	6.9	(0.8-22.8)	3.9
Ferrero, 2003	105	2.9	(0.6-8.1)	5.4
Saez, 2004	83	2.4	(0.3-8.4)	4.0
Syriopoulou, 2005	55	1.8	(0-9.7)	2.3
Mast, 2005	182	3.8	(1.6-7.8)	8.8
Della Bella, 2005	28	10.7	(2.3-28.2)	5.1
Claret, 2007	94	1.1	(0-5.8)	2.3
Ruiz-Extremera, 2011	128	7.0	(3.3-12.9)	9.7
Prasad, 2012	23	8.7	(1.1-28.0)	3.8
Random effects model		5.8	(4.2-7.8)	100

Heterogeneity: I-squared = 45.9%, *P* = .0203

5.8%

HIV-positive women

Author, Yr	Sample Size	Proportion, %	95% CI	Weight, %
Granovsky, 1998	47	8.5	(2.4-20.4)	11.0
Thomas, 1998	140	9.3	(5.0-15.4)	23.4
Resti, 2002	158	13.9	(8.9-20.3)	28.8
Ferrero, 2003	30	6.7	(0.8-22.1)	6.4
Ferrero, 2005	36	5.6	(0.7-18.7)	6.4
Claret, 2007	22	13.6	(2.9-34.9)	8.4
Jamieson, 2008	48	4.2	(0.5-14.3)	6.5
Ruiz-Extremera, 2011	14	28.6	(8.4-58.1)	9.1
Random effects model		10.8	(7.6-15.2)	100

Heterogeneity: I-squared = 28.8%, *P* = .1982

10.8%

Benova. Clin Infect Dis. 2014;59:765.

Risk Factors…

- Viral Load.
- High viral load holds increased risk of vertical transmission.
- Vertical transmission increases if the maternal serum HCV viral load is above 10^6 copies/mL.
- Maternal serum HCV-RNA viral load may fluctuate during pregnancy, it is recommended to repeat the HCV-RNA load in the third trimester.
- Genotype.
- No effect of genotype on vertical transmission.

Mast EE et al. Risk factors for perinatal transmission of HCV and the natural history of HCV infection acquired in infancy. *J Infect Dis* 2005

Risk Factors…

- Mode of Delivery.
- More controversial is the effect of mode of delivery on vertical transmission.
- Few studies in the past recommend the use of elective CS to prevent the possible obstetric risks in order to lower the incidence of HCV vertical transmission.
- Large-scale multicenter research project conducted in Europe, have failed to show significant evidence to prove its protective effect.

Ceci O et al. Vertical transmission of hepatitis C virus in a cohort of 2,447 HIV-seronegative pregnant women: a 24-month prospective study. *J Pediatr Gastroenterol Nutr* 2001

Van Ham MA. A retrospective study of intraoperative and postoperative maternal complications of caesarean section during a 10-year period. *Eur J Obstet Gynecol Reprod Biol* 1997

Can MTCT Be Prevented During and After Pregnancy?

Variable	Studies (N)	Precision of Evidence	Summary of Findings
Elective C/S vs vaginal delivery	4 cohort studies (N = 2080)	Low	**Inconsistent results** with trends in opposite directions in highest quality studies
All C/S vs vaginal delivery	11 cohort studies (N = 2308)	Low	**No association** between mode of delivery and risk of HCV transmission
Invasive fetal monitoring vs none	3 cohort studies (N = 928)	Low	**Inconsistent results**: 1 good quality study (N = 181) showed increased risk of HCV transmission (aOR: 6.7, 95% CI: 1.1-36); another (N = 724) showed no association (RR: 1.2, CI: 0.7-2.2)
Prolonged rupture of membranes vs no	2 cohort studies (N = 245)	Low	Membrane rupture > 6 hrs before delivery **increased risk of transmission** (OR: 9.3, 95% CI: 1.5-18)
Breastfeeding	14 cohort studies (N = 2971)	High	**No association** between breastfeeding women with HCV and transmission to infants

Cottrell. Ann Intern Med. 2013;158:109.

DIAGNOSIS OF PERINATAL TRANSMISSION.

- Consider children born to anti-HCV positive mothers infected with HCV when:

(1) HCV RNA is detected in at least two serum samples and at least three months apart during the first year of life; and

(2) HCV antibody is positive after 18 months of age.

Testing of HCV antibody is of limited value before 18 months of age due to passive transfer of maternal antibodies.

Davison SM. Perinatalhepatitis C virus infection: diagnosis and management. *Arch Dis Child* 2006

MTCT: Most Common Cause of HCV in Children

- 25% to 40% of infants clear HCV by 2-3 yrs of age[1]
- Impact of HCV infection in children on quality of life[1,2]
  - Reduced physical functioning[1,2]
  - Executive function impairment in 20% of children with HCV[1]
  - Worse cognitive functioning vs children without HCV[1]
    - Parental emotional impact and decrement in parental quality of life[1]
- Higher rates of cirrhosis in children who acquire HCV through MTCT[1]
- Hepatocellular carcinoma is second most common hepatic malignancy in children[1,3]

1. Murray. Diseases of the Liver in Children. Springer. 2014. 2.Nydegger. J Gastroenterol Hepatol. 2008;23:226. 3. Modin. J Hepatol. 2019;70:371.

AASLD: Treatment of Women of Childbearing Age

Recommendation Regarding HCV Treatment and Pregnancy	Rating
For women of reproductive age with known HCV infection, antiviral therapy is recommended before considering pregnancy, whenever practical and feasible, to reduce the risk of HCV transmission to future offspring	I, B

- Counsel about benefit of antiviral treatment before pregnancy
- If a woman becomes pregnant while receiving HCV DAA therapy, providers should discuss the risks vs benefits of continuing treatment
- Ribavirin is contraindicated in pregnancy due to teratogenicity (wait at least 6 mos after completion of ribavirin therapy to get pregnant)

AASLD. HCV in Pregnancy. https://www.hcvguidelines.org/unique-populations/pregnancy.

Safety of DAAs in Pregnancy

DAA	Pregnancy	Lactation	Fertility	Historical FDA Classification
Glecaprevir/ pibrentasvir	No birth defects reported in animal data	Detected in rat milk; no human data	No effect on fertility in rats; no human data	None assigned
Ledipasvir/ sofosbuvir	No birth defects reported in animal data	Detected in rat milk; no human data	No effect on fertility in rats; no human data	B*
Sofosbuvir/ velpatasvir	Increase in visceral malformations with velpatasvir alone in rabbits	Detected in rat milk; no human data	No effect on fertility in rats; no human data	None assigned

*Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.

AASLD. Hepatology. 2020;[Epub]

Ledipasvir plus sofosbuvir in pregnant women with hepatitis C virus infection: a phase 1 pharmacokinetic study

Catherine A Chappell, Kimberly K Scarsi, Brian J Kirby, Vithika Suri, Anuj Gaggar, Debra L Bogen, Ingrid S Macio, Leslie A Meyn, Katherine E Bunge, Elizabeth E Krans, Sharon L Hillier

Findings From Oct 1, 2016, to Sept 30, 2018, 29 pregnant women were screened and nine (31%) were enrolled. Eight (89%) women were included in the primary analysis. Ledipasvir and sofosbuvir exposures were similar in the pregnant women versus the non-pregnant reference group (geometric mean ratio of AUC_{tau} ledipasvir 89·3% [90% CI 68·7–116·1]; sofosbuvir 91·1% [78·0–106·3]).

Interpretation Ledipasvir–sofosbuvir was safe and effective without clinically meaningful differences in drug exposure among pregnant versus non-pregnant women.

www.thelancet.com/microbe **Vol 1 September 2020**

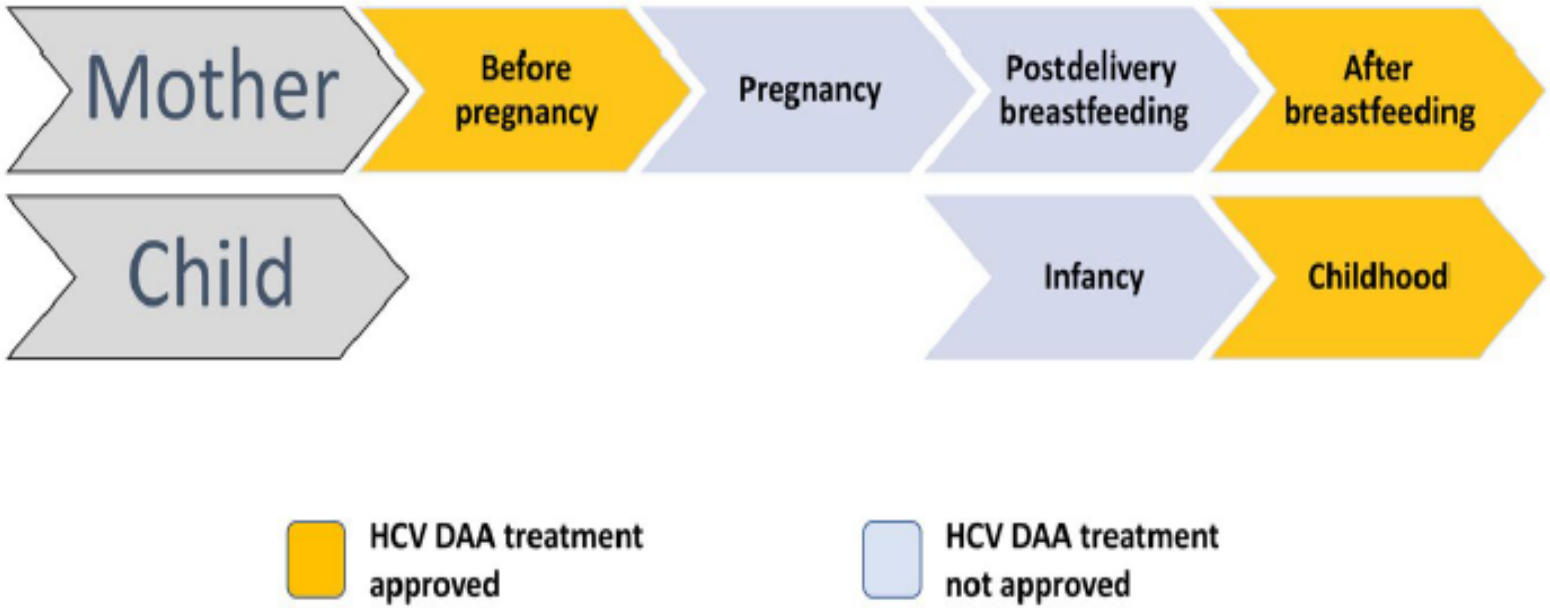
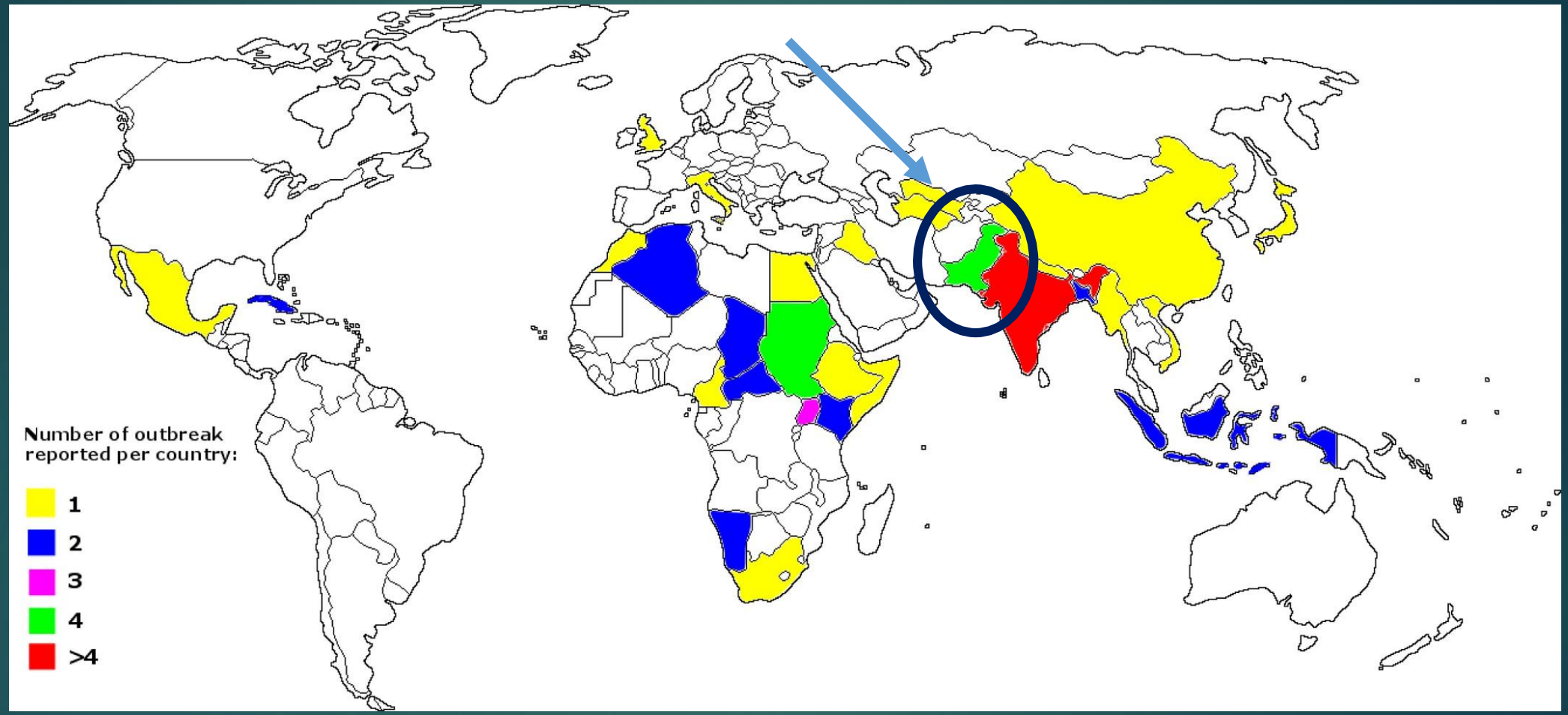


FIG. 1. Potential times during the pregnancy care cascade for DAA therapy.

Hepatitis E in Pregnancy

The global burden of hepatitis E outbreaks: a systematic review



The global burden of hepatitis E outbreaks: a systematic review, Volume: 37, Issue: 1, Pages: 19-31, First published: 20 August 2016, DOI: (10.1111/liv.13237)

Case

- 25-year-old lady- gestational amenorrhea of 29 weeks presented with 2 day history of
  - Irritability and confusion
  - Jaundice
- Yellow discoloration of skin/ sclera and dark colored urine
- No clay colored stools or itching.
- No history of abdominal pain or fever.
- History of decreased appetite present

Case

- **Examination.**

  + Icterus

  - B.P: 100/60 mm of Hg- Pulse: 115/min
  - R/R: 16/ min- SpO2: 90%
  - Flapping tremors present

- **Abdomen:**

  - Generalized tenderness present. B/S +ve.
  - Fundal height palpable at 28 weeks.
  - No evidence of free fluid in peritoneal cavity.

Case

- WBC: 26.9 x 10^3/µL- Hb: 11.7g/dl PLT: 528 x 103/µL
- Creatinine: 0.6mg/dl- Urea: 10mg/dl
- T.Bili: 15.5 g/dl
  - Conjugated: 8.1
  - Unconjugated: 7.4
- ALT: 804 U/L AST: 356 U/L ALP: 514 U/L
- Serum albumin: 2.1 g/dl
- PT: 28.6 (13) APTT: 108 (32) INR: 2.4

Case

- USG abdomen and obstetrical ultrasound
  - Normal echotexture liver, 16cm in size, smooth margins, normal spleen and PV. Mild ascites present.
  - Intrauterine fetal demise at 29 weeks.

Case

Viral Serology:

- HBs Ag, anti HBc IgM: Negative.
- Anti-HCV antibodies: Negative.
- Anti-HAV IgM: Negative.
- Anti-HEV IgM antibodies: Positive

Case

- Final Diagnosis.
  - Fulminant liver failure due to acute hepatitis E with intrauterine demise.

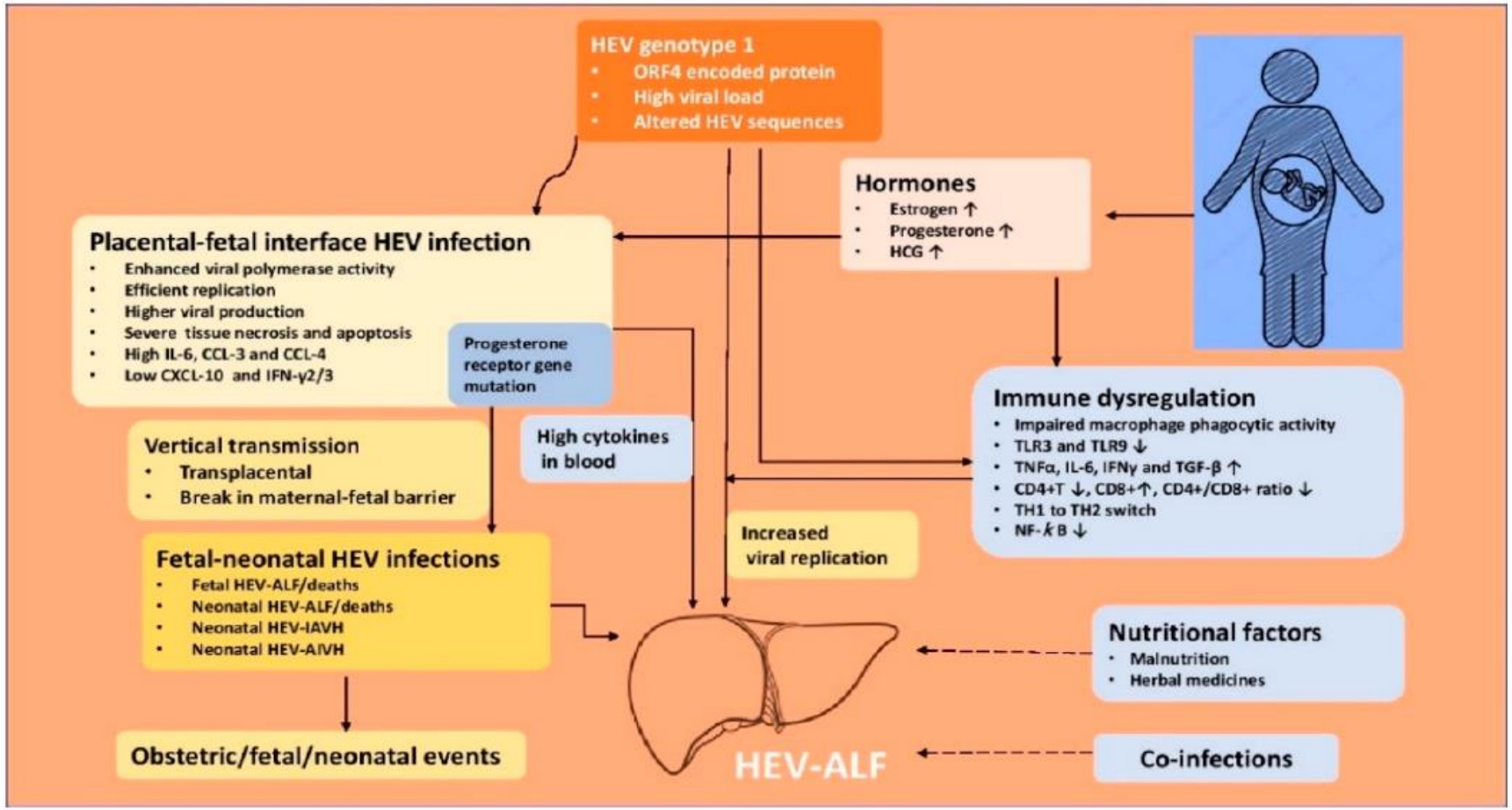


Figure 3. Pathogenesis of hepatitis E virus-related acute liver failure in pregnancy. IAVH = icteric acute viral hepatitis, AIAVH = Anicteric acute viral hepatitis, HEV-ALF = Hepatitis E virus related acute liver failure.

Khuroo MS. Hepatitis E and Pregnancy: An Unholy Alliance Unmasked from Kashmir, India. Viruses. 2021 Jul 9

Mirror Syndrome

- Maternal DIC and hepatic encephalopathy due to toxic metabolites produced by fetus with ALF.
- Better survival, rapid recovery from ALF in mothers who delivered early on expectant basis
- Long gestational period after onset of coma dangerous for mother.
- DIC limited to mothers who delivered babies with ALF, not normal or non-fulminant HEV

J Viral Hepat. 2016 Feb. Hepatitis E: an emerging global disease - from discovery towards control and cure.
Khuroo MS, Khuroo MS.
Indian journal of gastroenterology, Banaitsh, Saunder, Parik et al, Departments of Gastroenterology, *Medicine and #Obstetrics and Gynecology N Medical College and BYL Nair Ch. Hospital, Mumbai 2007

Treatment

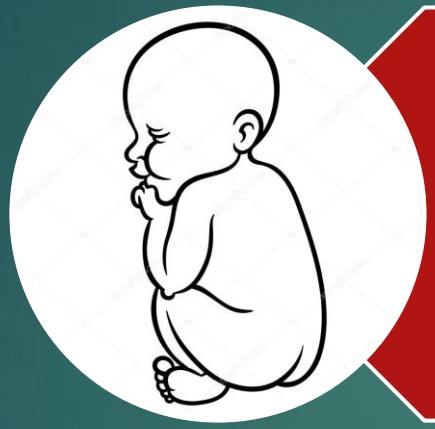
Acute hepatitis E

- Supportive treatment.
- Early delivery?

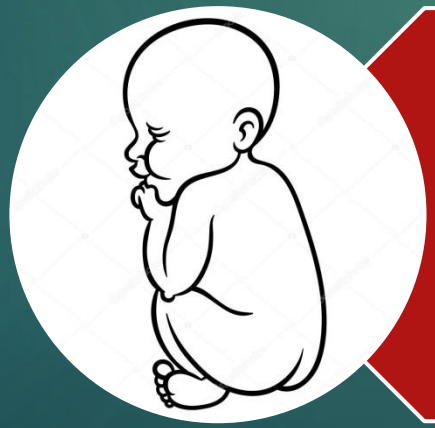
Fulminant hepatic failure

- Early delivery?
- Treat complications of fulminant hepatic failure.
- Emergency liver transplantation

Infants born to mothers infected with HEV



No specific treatments or recommendations exist.



Close observation of the infant advised.

Prevention

Hecolin Vaccine

- Expressed in E. coli derived from HEV-1 Chinese strain.
- Induces a vigorous T cell-dependent antibody response.
- Commercially available in 30-µg doses to be administered at 0-, 1- and 6-month regimens
- At 4.5 years, vaccine efficacy 86.8%; 16 to 65 year-olds
- Cross-protective efficacy as HEV-4 is the predominant genotype in the region of study.

Zhang Jun, Zhang Xue-Feng, Long-term efficacy of a hepatitis E vaccine N Engl J Med 2015
Kamili S. Towards the development of a hepatitis E vaccine. Virus Res 2011; 161: 93–100.

Should HEV vaccine administered during pregnancy?

Safety in Pregnant Women

- Retrospective analysis of participants, who were of pregnant and were inadvertently vaccinated, suggested that the vaccine is safe for mother and fetus.
- Only one pregnant woman reported grade 1 local AE.

Group	Doses	No. adverse event / no. vaccine doses					P
		Time of gestation				Non-pregnant control	
		1st trimester	2nd trimester	3rd trimester	Total		
Vaccine (n=37)	1st dose	0/14	0/5	0/2	0/21	3/42	-
	2nd dose	1/12	0/1	0/6	1/19	1/38	>0.05
	3rd dose	0/11	0/1	0/1	0/13	0/26	-
	Total	1/37	0/7	0/9	**1/53**	**4/106**	>0.05
Placebo (n=31)	1st dose	1/14	0/2	0/2	1/18	0/36	-
	2nd dose	0/9	0/3	0/2	0/14	1/28	-
	3rd dose	0/10	0/1	0/3	0/14	0/28	-
	Total	1/33	0/6	0/7	**1/46**	**1/92**	>0.05

All adverse events < grade 3 severity

Wu et al. Hepatology 2012

SAGE Review Dec 2014 vs. Nov 2021

World Health Organization

Weekly epidemiological record
Relevé épidémiologique hebdomadaire

In December 2014 the Strategic Advisory Group of Experts on immunization (SAGE) concluded that

*"… without additional data, at this stage it **is not possible to make any recommendation concerning the introduction of this vaccine in routine national programmes** in populations where epidemic and sporadic hepatitis E disease is common. However, national authorities may decide to use this vaccine based on the local epidemiology…"*

Gaps identified in the SAGE report:

- Disease burden
- Long-term protection
- Efficacy against different genotypes
- Vaccine target: *High-risk groups versus general population*
  - Children (<16 years) and older age (>65 years)
  - Persons with liver disease or immunosuppression
  - Pregnant women
  - Outbreak settings

In Nov. 2021 SAGE meeting Major Proposed action:

- Accepting gaps identified in 2015 being completed in Ph. IV studies.
- Recommending to put HE on WHO **vaccine preventive infectious disease priority list**.
- Emphasizing **protecting pregnancy by vaccinating** childbearing age women.

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doi:10.1002/jgh3.12646

REVIEW ARTICLE

Hepatitis E: Genotypes, strategies to prevent and manage, and the existing knowledge gaps

Lubna Kamani,*,† Zahra Ali Padhani‡ and Jai K Das§

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J Ayub Med Coll Abbottabad 2015;27(1)

ORIGINAL ARTICLE

MORBIDITY AND MORTALITY ASSESSMENT IN ACUTE HEPATITIS-E

Lubna Kamani, Saeed Sadiq Hamid, Faisal Wasim Ismail, Syed Waqas Haider, Safia Awan, Ashfaq Ahmed,Wasim Jafri

Gastroenterology Section, Department of Medicine, Aga Khan University Hospital, Karachi-Pakistan

Pregnancy in Advance Liver Disease

Pregnancy in Advance Liver Disease

- Pregnancy is uncommon (but not rare) because of reduced fertility in advanced liver disease.
- Pregnancy is not contraindicated in this group of patients.
- Poor fetal outcome is increased and includes fetal demise, intrauterine growth retardation, prematurity, and high cesarean rate.
- Poor pregnancy outcome is correlated to a model for end-stage liver disease (MELD) score greater than 10.
- High maternal mortality (upto 7.8%)
- Preconception endoscopy for variceal surveillance and eradication is advised.
- Primary prophylaxis with endoscopic band ligation (EVL) may be performed at 28 weeks.

Pregnancy in Patients with Advanced Chronic Liver Disease. Esposti S. Clinical Liver Disease, Vol 4, No 3, September 2014

Mode of Delivery in Advanced CLD.

- Coagulopathy is a major concern at this time.
- Correct coagulopathy and plan delivery.
- It requires an individualized plan depending degree of liver function, presence/treatment of oesophageal varices as well as patient and obstetrician preferences.
- If prophylactic EVBL is not done then elective C-section is usually preferable.
- For vaginal deliveries, consideration should be given for early epidural anesthesia, shortening of the second stage, and assisted delivery.
- General anesthesia and surgery is poorly tolerated in cirrhotic patients.

Pregnancy in Patients with Advanced Chronic Liver Disease. Esposti S. Clinical Liver Disease, Vol 4, No 3, September 201

Successful pregnancy outcome in decompensated chronic liver disease with portal vein thrombosis: Case report and review of literature

Article *in* European journal of gastroenterology & hepatology 23(7):617-9 · July 2011 *with* 29 Reads
DOI: 10.1097/MEG.0b013e328346969f · Source: PubMed

Abstract

Pregnancy is rare in women with decompensated chronic liver disease. In this case report, we describe a case of a young woman who presented with hepatitis B-related decompensated chronic liver disease with portal vein thrombosis having successful full-term uneventful pregnancy.

Endoscopy in pregnancy

- Limited data on the safety and effectiveness of endoscopy in pregnancy
- Should be deferred until the second trimester if possible
- Ensure hemodynamic stability and oxygenation- aggressive hydration
- Left lateral position to avoid vascular compression
- Meperidine (category C) and propofol (category B) can be used for endoscopic sedation
- Benzodiazepenes are category D in pregnancy and should be avoided

Glosten B et al. Anesthesia for Obstetrics Miller RD (ed). Anesthesia Churchill Livingstone : New York, NY, USA , 2000 , 2025 – 68.
Qadeer MA et al. Clin Gastroenterol Hepatol 2005 ; 3 : 1049 – 56 .

Safety of Endoscopy and Its Outcome in Pregnancy

Lubna Kamani [1] , Muhammad S. Achakzai [2], Faisal Wasim Ismail [3] , Farhana Kayani [2]

1. Gastroenterology, Liaquat National Hospital & Medical College, Karachi, PAK 2. Gastroenterology, Bolan Medical College, Quetta, PAK 3. Gastroenterology, Aga Khan University Hospital, Karachi, PAK

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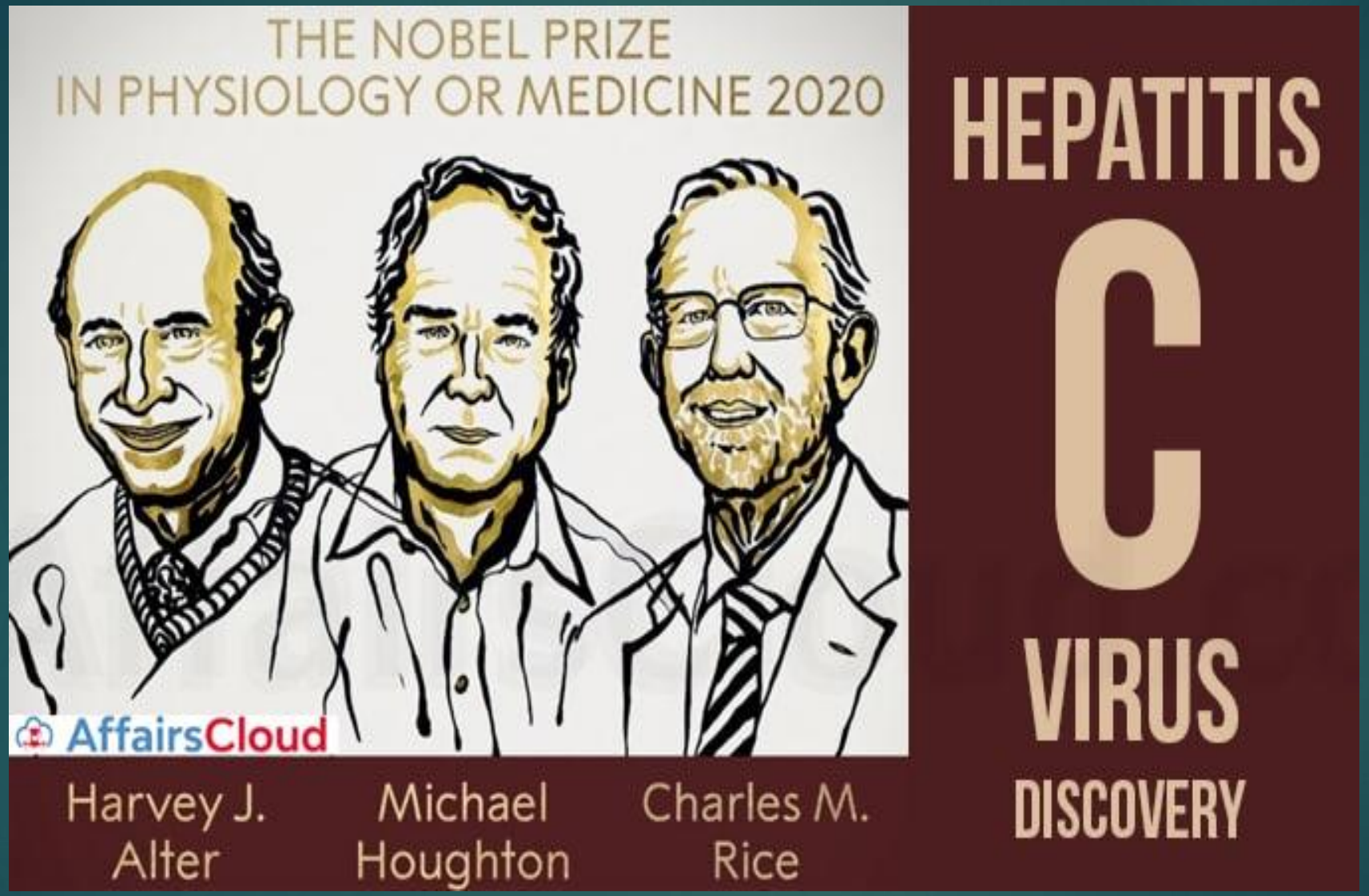
Take home points…….

- Guidelines have been updated to **recommend HBV/HCV screening for all pregnant women**
- Initiating Hepatitis B treatment at 28 weeks of pregnancy with high maternal viral load to reduce MTCT.
- More data required on safety of TAF during pregnancy.
- Availability of birth dose HBV vaccine esp. in developing countries.
- HCV treatment recommended before pregnancy for women of childbearing age
- HCV treatment during pregnancy is not currently recommended by guidelines.
- Lactation is safe in these patients.

Take home points.....

- Multidisciplinary approach required in pregnant women with advanced CLD patients.
- Screening endoscopy if indicated can be done safely in second trimester.
- HEV in endemic areas is still the leading cause of FHF in pregnancy.
- Safe and effective vaccine is required worldwide for women with child bearing age and pregnant females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