Lancet Gastroenterology & Hepatology

Commentary on "Global prevalence of hepatitis C virus in women of childbearing age in 2019: A modeling study"

Title: Labour pains: eliminating HCV in women and children

Authors: Ali Judd,[1*] Intira Jeannie Collins,[1] Sarah Pett,[1,2] Di M. Gibb[1]

Affiliations:

1 MRC Clinical Trials Unit at UCL, University College London, London, UK

2 Institute for Global Health, University College London, London, UK

* Corresponding author: a.judd@ucl.ac.uk

Text: (779 words)

Hepatitis C is a major global public health problem, and a leading cause of death worldwide.[1] However it is a problem which, with enough public health investment, has the potential to go away. Curative treatment, with safe, short course direct acting antivirals (DAAs), has been available for several years, and elimination is in reach.[2] Thus the priority now is to identify and treat ***all*** those infected, to reduce morbidity and mortality, and prevent new infections, including those which are acquired through mother-to-child transmission.

Dugan *et al* provide an important contribution to the field with their modelled estimates of the global prevalence of HCV in women of childbearing age.[3] They find that around 71 million women aged 15-49 years may be living with HCV, accounting for one-fifth of the global population with viremic HCV. Importantly they estimate prevalence at a national and regional level. The huge burden of infections in predominantly low and middle income countries (LMIC) is striking, with China, Pakistan, Russia and India containing nearly half of the global HCV infections in women of childbearing age. This wealth imbalance in the global distribution of infections has implications for how we target women for testing, treatment, and prevention of onward transmission to infants. There are also implications for prevention of re-infection, given that in many LMIC settings, the primary driver of transmission is unsafe healthcare practices.[2]

The authors recommend pre-conception test and treat strategies, suggesting that routine gynaecological visits for the general population of women are a way to identify those with HCV. While this approach may be feasible in high income countries, with delivery through established cervical screening programmes, it may not be feasible or cost-effective in many LMIC, where gynaecological access is rarely available. For example, some of the countries estimated to have the highest burden of HCV also have a high burden of cervical cancer,[4] reflecting failures in rolling out cervical screening and HPV vaccination. Even in high income settings with concentrated HCV epidemics like the USA, HCV testing linked to gynaecological visits is likely to miss women at most risk of HCV, namely those who inject drugs.[5] Other universal health interventions include community-based mass HCV screening and treatment programmes, as in Egypt, although these efforts exclude pregnant and lactating women due to the lack of treatment options available to them.

In high income countries, universal antenatal (or prenatal) HCV testing has been shown to be cost effective,[6] and is now recommended in the USA.[5] However, as DAA treatment has yet to be approved in pregnant or lactating women, due to a lack of safety data, these groups have been completely left out of the treatment cascade, creating a huge gap in treatment access. Small studies suggest that ribavirin-free DAA regimens, given in the second and third trimester of pregnancy, are safe, with high prevalence of maternal cure, no vertical transmissions, and no adverse effects,[7,8] but much larger trials are needed to confirm these findings. In the meantime, the strategy is to keep women linked into care post-partum, and be treated after they stop breastfeeding. Unfortunately, all evidence to date (mainly from high income settings) shows very poor engagement in the post-partum care cascade,[9] and it may be worse in many LMIC like Pakistan, where women breastfeed for a median of two years. This treatment gap serves as a gender imbalance and effectively obstructs women from benefitting from the advantages of cure; aside from the harmful effects of HCV on maternal and infant outcomes, there is also the risk of vertical transmission to

successive offspring.[10] Importantly, there are no treatment options for infants and young children aged under three years, and the net result is that few women and children with HCV are receiving timely treatment, and so they remain at risk of progressive liver disease.

Dugan et al's paper is important as it clearly demonstrates how women of childbearing age do now need to be recognised as a key risk population for hepatitis C prevention, treatment and cure, if we are serious about elimination. Multiple approaches are needed to diagnose and treat all women of child-bearing age, including mass community-based screening and treatment programmes as well as universal antenatal screening, which is the cornerstone of maternal and child health. Additionally risk of re-infection needs to be reduced through continued focus on improving safety in medical practices. However these efforts will have limited benefit without well conducted large clinical trials to ascertain the safety of DAAs in pregnancy and during the lactation period, which have the potential to cure the mother and prevent HCV in the baby. Such trials are critical in paving the way for equitable access to treatment for all women living with HCV.

Declaration of interest:

AJ reports grants from ViiV Healthcare, grants from Gilead Sciences, grants from MRC, grants from Abbvie, grants from NHS England, grants from International AIDS Society, outside the submitted work. IJC reports grants from ViiV, grants from Gilead, grants from AbbVie, outside the submitted work. SP reports grants from Gilead Sciences, grants from MRC, outside the submitted work. DG reports grants from ViiV Healthcare, grants from Gilead Sciences, grants from MRC, grants from Janssen Pharmaceuticals, grants from European and Developing Countries Clinical Trials Partnership (EDCTP), outside the submitted work.

References

1. Cooke GS, Andrieux-Meyer I, Applegate TL, et al. Accelerating the elimination of viral hepatitis: a Lancet Gastroenterology & Hepatology Commission. *Lancet Gastroenterol Hepatol* 2019; **4**(2): 135-84.
2. World Health Organization (WHO). Global hepatitis report, 2017. Geneva: WHO, 2017.
3. Dugan E, Blach S, Biondi M, et al. Global prevalence of hepatitis C virus in women of childbearing age in 2019: A modeling study. *Lancet Gastroenterol Hepatol* In press.
4. Arbyn M, Weiderpass E, Bruni L, et al. Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. *The Lancet Global Health* 2020; **8**(2): e191-e203.
5. Schillie S, Wester C, Osborne M, Wesolowski L, Ryerson AB. CDC recommendations for hepatitis C screening among adults — United States, 2020. *MMWR Recomm Rep* 2020; **69**(RR-2): 1-17.
6. Chaillon A, Rand EB, Reau N, Martin NK. Cost-effectiveness of universal hepatitis C virus screening of pregnant women in the United States. *Clin Infect Dis* 2019; **69**(11): 1888-95.
7. Chappell CA, Scarsi KK, Kirby BJ, et al. Ledipasvir plus sofosbuvir in pregnant women with hepatitis C virus infection: a phase 1 pharmacokinetic study. *Lancet Microbe* 2020; **1**(5): e200-e8.
8. Yattoo GN. Treatment of chronic hepatitis C with ledipasvir/sofosbuvir combination during pregnancy. Abstract number O-HCV-38. 27th Annual Conference of Asian Pacific Association for the Study of the Liver. New Delhi, India: Hepatol Int; 2018. p. S293.
9. Bhardwaj AM, Mhanna MJ, Abughali NF. Maternal risk factors associated with inadequate testing and loss to follow-up in infants with perinatal hepatitis C virus exposure. *J Neonatal Perinatal Med* 2020: 10.3233/NPM-190264.
10. Kushner T, Terrault NA. Hepatitis C in pregnancy: a unique opportunity to improve the hepatitis C cascade of care. *Hepatol Commun* 2019; **3**(1): 20-8.