

Vertical transmission of hepatitis C: towards universal antenatal screening in the era of new direct acting antivirals (DAAs)? Short review and analysis of the situation in Switzerland

Karoline Aebi-Popp^{1*}, Andrea Duppenhaler², Andri Rauch¹, Andrea De Gottardi³ and Christian Kahlert⁴

¹ Department of Infectious Diseases, Inselspital, Bern University Hospital, University of Bern, Switzerland

² Department of Pediatric Infectious Diseases, University Children's Hospital, Bern, Switzerland

³ Department of Hepatology, University Hospital Bern, Switzerland

⁴ Division of Infectious Diseases, Children's Hospital of Eastern Switzerland, St Gallen, Switzerland

Abstract

At present, routine antenatal hepatitis C virus (HCV) screening is not recommended in pregnant women who do not have known risk factors for infection. The main reason for this attitude has been the lack of effective treatment options to avoid mother-to-child transmission (MTCT) during pregnancy or delivery. Hitherto available treatment regimens based on interferon (IFN) and ribavirin (RBV) were associated with sometimes long-lasting and severe side-effects and thus their indication had to be carefully evaluated. In addition, ribavirin has teratogenic and embryocidal effects and is absolutely contraindicated during pregnancy. The situation has substantially changed with the advent of the newly available treatment regimens based on very effective and well-tolerated direct-acting antiviral agents (DAAs). The aim of this viewpoint is to briefly analyse, using the example of Switzerland, how recent developments in HCV therapy might impact prevention of HCV vertical transmission.

Keywords: HCV, prevention of MTCT, direct-acting antivirals

Introduction

At present, routine antenatal hepatitis C virus (HCV) screening is not recommended in pregnant women who do not have known risk factors for infection. The main reason for this attitude has been the lack of effective treatment options to avoid mother-to-child transmission (MTCT) during pregnancy or delivery. Hitherto available treatment regimens based on interferon (IFN) and ribavirin (RBV) were associated with sometimes long-lasting and severe side-effects and thus their indication had to be carefully evaluated. In addition, ribavirin has teratogenic and embryocidal effects and is absolutely contraindicated during pregnancy.

The situation has substantially changed with the advent of the newly available treatment regimens based on very effective and well-tolerated direct-acting antiviral agents (DAAs). Today, the main advantage of knowing the pregnant women's HCV status is that those with HCV can be referred for treatment after delivery and neonates can be closely followed up to rule out vertical infection. Importantly, HCV eradication can be achieved without using ribavirin. Therefore, clearing HCV infection with the new DAA regimens before subsequent pregnancies becomes a realistic strategy to completely eradicate HCV vertical transmission in the future. As recently shown at a London Centre, routine antenatal screening can be cost-effective [1].

Broad variation in worldwide prevalence in pregnant women

HCV infection is a major global health issue causing acute and chronic liver disease, which can lead to cirrhosis and hepatocellular carcinoma. Since the implementation of routine screening of blood products for HCV, the leading route for childhood infection is vertical transmission. The worldwide prevalence of HCV in pregnant women varies: 8.6% in Egypt [2], 3.6% in Benin, 1.5% in Nigeria [3] and 1.5% in France [4]. The estimated number of people in Europe who are HCV antibody positive varies by country from 0.4% to 5.2% [5].

Current situation in Switzerland and estimates of vertically acquired HCV infections

Approximately 1.6% of the Swiss population is estimated to be HCV-antibody-positive depending on age and other characteristics of the population [6]. An estimated number of 17,939 women are chronically infected with HCV and most of whom are of childbearing age. A study performed in 1990–1991 showed that 0.71% of pregnant women were HCV seropositive, more than 75% of whom had chronic HCV infection [7]. If we consider that around 80,000 deliveries take place each year in Switzerland, it is estimated that 568 women are HCV seropositive and among them, about 450 women will have chronic infection. With a vertical HCV transmission rate of 6% [8], 27 infants would acquire congenital HCV per year in Switzerland. The currently available data from the Federal Office of Public Health (FOPH) reports only between seven and 10 HCV cases in children from 1 to 14 years of age over the last 5 years, which is less than 50% of the expected number.

It is very likely that more than half of HCV-infected newborns are not diagnosed as their mothers are not tested during pregnancy and their newborns are asymptomatic after delivery. Even assuming that approximately 10–20% of perinatally infected children will spontaneously clear HCV infection, a larger number of them will have progressive disease that might not be diagnosed for many years.

Adverse events during pregnancy

HCV-positive pregnant women appear to be at risk for adverse maternal and neonatal outcomes including gestational diabetes, pre-eclampsia, growth restriction, antepartum haemorrhage and preterm birth [9–13]. Rates of intrahepatic cholestasis in pregnancy are more common in HCV-RNA-positive women, reaching rates of up to 20% [14–16]. Furthermore, infants of HCV-positive mothers are more likely to be born with low birthweight and to require assisted ventilation or neonatal intensive care unit admission. These findings seem not to be influenced by maternal intravenous drug use [12].

As liver cell necrosis in chronic HCV infection is triggered by immunological processes, pregnancy with 'physiological' immunosuppression seems to have a favourable effect on liver cell

*Corresponding author: Karoline Aebi-Popp, Department of Infectious Diseases, University Hospital Bern, 3010 Bern, Switzerland
Email: mail@aebi-popp.com

necrosis. Several studies have shown a decrease in the level of transaminases during the second and third trimester of pregnancy [17,18].

Prevention of mother-to-child transmission is not yet feasible

MTCT is the leading source of HCV infection in children [19]. As most of these children are asymptomatic at birth and, in the absence of universal HCV screening, the vast majority of them remain undiagnosed. A recent meta-analysis has shown an MTCT rate of 5.8% [20] in HCV-seropositive and RNA-positive women. The pathophysiology is not fully understood with regards to risk factors. Only HCV viral load and HIV co-infection are identified as independent risk factors for vertical transmission. There is no evidence that transmission could be reduced by elective caesarean section or avoidance of breastfeeding. Intravenous drug use (IVDU) seems to be another risk factor for vertical transmission [21]. Other studies have suggested that the duration of membrane rupture, internal fetal monitoring and vaginal lacerations are associated with an increased transmission rate [22,23]. However, a systematic Cochrane database review could not show any effect of elective Caesarean section on HCV transmission rates [24].

Paediatric infection is usually mild but chronic active infection in 30%

The majority of chronic HCV infections in childhood are benign and asymptomatic. Nevertheless, the early stage of vertically acquired infection is characterised by a wide range of alanine transaminase (ALT) abnormalities [25]. The European Paediatric Network describes three outcomes in vertically acquired HCV infection: 20% of neonates are expected to clear the virus; 50% will develop chronic asymptomatic infection (intermittent viraemia, normal ALT levels); and 30% will have chronic active infection with persistent viraemia and frequent abnormal ALT [13]. Among children with chronic infection, progression of liver fibrosis to cirrhosis in adolescence has been reported, which seems to be even faster in HIV/HCV co-infected children. However, a rapid progression to liver cirrhosis and end-stage liver disease can also occur in HIV-negative children [19]. There are descriptions of rare cases with hepatocellular carcinoma that will require liver transplantation during adolescence [26,27]. Furthermore, extrahepatic manifestations including kidney disease, vasculitis, dermatological manifestations and autoimmunity are reported [28]. Thus, prompt diagnosis and vigilant monitoring of paediatric HCV are justified until treatment with DAAs becomes available in children.

Risk group-based screening during pregnancy remains problematic

As mentioned above, an estimated 450 women chronically infected with HCV become pregnant every year in Switzerland. Most of them are not aware of their infection, as HCV is not routinely screened during pregnancy. Moreover, many women do not fit into the classical risk-group categories and thus have never been screened. The FOPH and the Swiss Society of Obstetrics and Gynecology recommend the testing of at-risk pregnant women for HCV only as part of antenatal care (www.sggg.ch). Testing is encouraged for pregnant women with a history of intravenous drug use or those with HIV or HBV infection. Testing is also recommended for women who have received a blood transfusion or a solid organ transplant before July 1992 or clotting factor concentrates before 1987. One of the major reasons for the underdiagnosis of maternal HCV infection with current screening strategies is probably the inaccurate self-reporting of drug use

in pregnant women at the time of antenatal care. Studies have shown that self-reporting is an unreliable method for determining smoking, alcohol and drug use in pregnancy as such habits are frequently stigmatised [29,30].

Advent of universal HCV screening in pregnancy in the light of new treatment options

In contrast to the situation of maternal HIV infection, measures to influence or even prevent transmission of HCV from the mother to her newborn are unknown. Treatment regimens based on interferon with ribavirin have limited efficacy and severe side-effects. As ribavirin exhibits teratogenic and embryocidal effects, it is absolutely contraindicated during pregnancy. The situation has dramatically changed with the availability of new treatment options that became available last year. DAA combination regimens suppress viral replication within a few days of treatment and cure rates above 90% can be achieved. However, the safety and efficacy of DAAs during pregnancy have not yet been studied. Detrimental effects on fetal development during sofosbuvir or ledipasvir treatment have not been seen in animal models. Accordingly, the FDA has classified both antivirals as category B. In consequence, treatment may even become available during pregnancy as soon as these DAAs are proved to be safe and effective in clinical trials. In Europe, both drugs remain currently contraindicated in pregnant and nursing women (EMA). (www.ema.europa.eu/docs/en_GB/document_library/Other/2014/04/WC500164417.pdf).

Universal screening during pregnancy is justified even if treatment cannot yet be provided during pregnancy. The short (8–12 weeks) treatment regimens offer an ideal opportunity to cure HCV before the next pregnancy. This completely removes the risk of subsequent HCV transmission to the newborn and dramatically reduces the risk of liver-related complications in the mother.

Conclusion

Universal screening of HCV during pregnancy should urgently be re-evaluated in the light of the new DAAs. Balancing the benefits for the mother and child against additional costs for the healthcare system remains very important. With successful treatment of the mother, there is the potential for completely eliminating vertical HCV transmission. At present, as treatment is not yet available during pregnancy, only children born from subsequent pregnancies would be protected, following antenatal diagnosis and treatment after delivery. Linkage of HCV-infected women to hepatology care and a well-structured follow-up of newborns as is the case for HIV-exposed children would be essential to allow timely HCV management and treatment for the mother and detection of paediatric HCV infection for their children. In the near future, treatment for HCV during pregnancy may become available and reduce or even eliminate the risk of vertical transmission. Therefore the discussion for introducing a universal HCV screening during pregnancy should be on the agenda in order to reduce the HCV burden in mothers and their children.

References

1. Selvapatt N, Ward T, Bailey H, Bennett H, Thorne C, See L-M, *et al.* Is antenatal screening for hepatitis C virus cost-effective? A decade's experience at a London centre. *J Hepatol* 2015; **63**: 797–804.
2. AbdulQawi K, Youssef A, Metwally MA *et al.* Prospective study of prevalence and risk factors for hepatitis C in pregnant Egyptian women and its transmission to their infants. *Croat Med J* 2010; **51**: 219–228.
3. Ezechi OC, Kalejaiye OO, Gab-Okafor CV *et al.* Sero-prevalence and factors associated with Hepatitis B and C co-infection in pregnant Nigerian women living with HIV Infection. *Pan Afr Med J* 2014; **17**: 197.
4. Roudot-Thoraval F, Pawlotsky JM, Deforges L *et al.* Anti-HCV seroprevalence in pregnant women in France. *Gut* 1993; **34**(2 Suppl): S55–56.

5. Hahné SJ, Veldhuijzen IK, Wiessing L *et al.* Infection with hepatitis B and C virus in Europe: a systematic review of prevalence and cost-effectiveness of screening. *BMC Infect Dis* 2013; **13**: 181.
6. Sagmeister M, Renner EL, Mullhaupt B, Wong JB. Simulation of hepatitis C based on a mandatory reporting system. *Eur J Gastroenterol Hepatol* 2002; **14**: 25–34.
7. Prasad LR, Massery Spicher V, Kammerlander R, Zwahlen M. Hepatitis C in a sample of pregnant women in Switzerland: seroprevalence and socio-demographic factors. *Swiss Med Wkly* 2007; **137**: 27–32.
8. Benova L, Mohamoud YA, Calvert C, Abu-Raddad LJ. Vertical transmission of hepatitis C virus: systematic review and meta-analysis. *Clin Infect Dis* 2014; **59**: 765–773.
9. Connell LE, Salihi HM, Salemi JL, August EM *et al.* Maternal hepatitis B and hepatitis C carrier status and perinatal outcomes. *Liver Int* 2011; **31**: 1163–1170.
10. Reddick KLB, Jhaveri R, Gandhi M *et al.* Pregnancy outcomes associated with viral hepatitis. *J Viral Hepat* 2011; **1**: e394–8.
11. Safir A, Levy A, Sikuler E, Sheiner E. Maternal hepatitis B virus or hepatitis C virus carrier status as an independent risk factor for adverse perinatal outcome. *Liver Int* 2010; **30**: 765–770.
12. Pergam SA, Wang CC, Gardella CM *et al.* Pregnancy complications associated with hepatitis C: data from a 2003–2005 Washington state birth cohort. *Am J Obstet Gynecol* 2008; **199**: 38.e1–9.
13. Huang Q-T, Huang Q, Zhong M *et al.* Chronic hepatitis C virus infection is associated with increased risk of preterm birth: a meta-analysis of observational studies. *J Viral Hepat* 2015; **22**: 1033–1042.
14. Paternoster DM, Fabris F, Palù G *et al.* Intra-hepatic cholestasis of pregnancy in hepatitis C virus infection. *Acta Obstet Gynecol Scand* 2002; **81**: 99–103.
15. Berkley EMF, Leslie KK, Arora S *et al.* Chronic hepatitis C in pregnancy. *Obstet Gynecol* 2008; **112**(2 Pt 1): 304–310.
16. Locatelli A, Roncaglia N, Arreghini A *et al.* Hepatitis C virus infection is associated with a higher incidence of cholestasis of pregnancy. *Br J Obstet Gynaecol* 1999; **106**: 498–500.
17. Gervais A, Bacq Y, Bernuau J *et al.* Decrease in serum ALT and increase in serum HCV RNA during pregnancy in women with chronic hepatitis C. *J Hepatol* 2000; **32**: 293–299.
18. Conte D, Fraquelli M, Prati D *et al.* Prevalence and clinical course of chronic hepatitis C virus (HCV) infection and rate of HCV vertical transmission in a cohort of 15,250 pregnant women. *Hepatology* 2000; **31**: 751–755.
19. Jonas MM. Children with hepatitis C. *Hepatology* 2002; **36**(5 Suppl 1): S173–178.
20. Benova L, Mohamoud YA, Calvert C, Abu-Raddad LJ. Vertical transmission of hepatitis C virus: systematic review and meta-analysis. *Clin Infect Dis* 2014; **59**: 765–73.
21. Resti M, Azzari C, Galli L *et al.* Maternal drug use is a preeminent risk factor for mother-to-child hepatitis C virus transmission: results from a multicenter study of 1372 mother-infant pairs. *J Infect Dis* 2002; **185**: 567–572.
22. Mast EE, Hwang L-Y, Seto DSY *et al.* Risk factors for perinatal transmission of hepatitis C virus (HCV) and the natural history of HCV infection acquired in infancy. *J Infect Dis* 2005; **192**: 1880–1889.
23. Steininger C, Kundi M, Jatzko G *et al.* Increased risk of mother-to-infant transmission of hepatitis C virus by intrapartum infantile exposure to maternal blood. *J Infect Dis* 2003; **187**: 345–351.
24. McIntyre PG, Tosh K, McGuire W. Caesarean section versus vaginal delivery for preventing mother to infant hepatitis C virus transmission. *Cochrane Database Syst Rev* 2006; **4**: CD005546.
25. Resti M, Jara P, Hierro L *et al.* Clinical features and progression of perinatally acquired hepatitis C virus infection. *J Med Virol* 2003; **70**: 373–377.
26. Malik S, Dekio F, Wen JW. Liver transplantation in a child with multifocal hepatocellular carcinoma hepatitis C and management of post-transplant viral recurrence using boceprevir. *Pediatr Transplant* 2014; **18**: E64–68.
27. González-Peralta RP, Langham MR, Andres JM *et al.* Hepatocellular carcinoma in two young adolescents with chronic hepatitis C. *J Pediatr Gastroenterol Nutr* 2009; **48**: 630–635.
28. Indolfi G, Bartolini E, Olivito B *et al.* Autoimmunity and extrahepatic manifestations in treatment-naïve children with chronic hepatitis C virus infection. *Clin Dev Immunol* 2012; **2012**: 785627.
29. Garg M, Garrison L, Leeman L *et al.* Validity of self-reported drug use information among pregnant women. *Matern Child Health J* 2015: epub ahead of print.
30. Chasnoff IJ, Landress HJ, Barrett ME. The prevalence of illicit-drug or alcohol use during pregnancy and discrepancies in mandatory reporting in Pinellas County, Florida. *N Engl J Med* 1990; **322**: 1202–1206.