

# Literature Review for Three Centres Antenatal Care Consensus Guidelines

## Hepatitis C

by: Clinical Practice Improvement Unit, The Royal Women's Hospital

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# Hepatitis C

## Conclusion and recommendations

### **Is universal testing for Hepatitis C recommended above selective testing for Hepatitis C?**

The prevalence of hepatitis C in the Australian antenatal population is low (13/1000 women), as are rates of vertical transmission (~6%). At least 40% of cases have no identifiable risk factors. Currently, there is insufficient evidence regarding effectiveness and cost effectiveness of universal screening. There are no available safe treatments in pregnancy. Techniques to reduce vertical transmission such as caesarean section have not yet been adequately evaluated. There is insufficient evidence that antenatal treatment / intervention is of benefit to mother or baby in terms of reduction in disease severity.

### **Recommendation (B)**

In concordance with current international evidence based guidelines, universal testing for hepatitis C is not recommended above selective testing in pregnant women.

### **If selective testing is recommended, what risk factors should be considered during history taking?**

If selective testing is recommended, the risk factors for HCV that should be considered during history taking should include:

#### **High risk**

- Injection drug use (IDU)(~40% of infected mothers)
- A period of incarceration (~67% of women in Victorian prisons being hepatitis C antibody positive)
- A history of transfusion of blood products prior to HCV screening in 1990, particularly in groups who received multiple transfusions. Prevalence of antibodies to HVC in haemophiliacs is 60-80%.
- A history of migration from a country with a high rate on endemic HCV (southern European, African and Asia/Pacific countries).

#### **Moderate risk**

- Newborns of HCV positive mothers
- Persons undergoing chronic haemodialysis
- Recipients of blood from unscreened donors
- Recipients of organ transplants
- Parenteral exposure through the use of contaminated or inadequately sterilized instruments/needles in medical/dental procedures

#### **Low risk**

- Persons engage in high risk sexual activity
- Sexual partners of HCV positive individuals
- Rituals (such as circumcision, scarification, excision), traditional medicine (such as blood letting), other skin breaking activities(such as ear and body piercing)
- Tattoos and body piercing
- Household contact<sup>3</sup>.

However, it is important to note that 40-50% of women infected with HCV have no identifiable risk factors.

### **Does the detection of Hepatitis C during pregnancy assist with long term management?**

In general terms, women with hepatitis C are at increased risk of cirrhosis, hepatocellular carcinoma and autoimmune disorders. Alcohol consumption exacerbates hepatic dysfunction in infected women.

Infants should be followed to 18 months of age to determine HCV infection status.

2/3 of those infants with virus detected after delivery are expected to clear the virus by 2 years of age.

70% of infants in small series demonstrate hepatic dysfunction but the longterm outcomes of this have not been reported.

Pregnancy may worsen liver function in women and this should be discussed with the woman. There is no evidence currently available on whether treatment is advisable prior to, during or after pregnancy.

There is no evidence to suggest that HCV detection during pregnancy assists with longterm management of either mother or baby. However, there is a significant paucity of evidence in this regard.

### **Recommendation (C)**

Based on current evidence the detection of hepatitis C during pregnancy does not assist with long term management.

# Literature Search and Appraisal

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## Literature Search and Appraisal

### 1. Introduction

The Three Centres Collaboration contracted the Royal Women's Hospital (RWH) Clinical Practice Improvement Unit to conduct a comprehensive search and critical appraisal of publications addressing the topic of hepatitis C published between January 2000 and March 2005, to inform the proposed review of the 2001 Three Centres Consensus Guidelines on Antenatal Care.

### 2. Topics to be addressed

- 2.1 Is universal testing for Hepatitis C recommended above selective testing for Hepatitis C?
- 2.2 If selective testing is recommended, what risk factors should be considered during history taking?
- 2.3 Does the detection of Hepatitis C during pregnancy assist with long term management?

### 3. Methods

#### 3.1 Search strategy

- The OVID interface was used to search the following electronic databases:
  - MEDLINE: 2000 – May 2005
  - CINAHL: 2000 – May 2005
  - EBM Reviews: 2000 – March 2005
- Cochrane Database: 2005 Issue 2
- Review of article citations and Cochrane Library references for additional citations
- Guidelines developed by specific Colleges of Obstetricians and Gynaecologists were searched including:
  - Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG)
  - Royal College of Obstetricians and Gynaecologists (RCOG)
  - Society of Obstetricians and Gynaecologists Canada (SOGC), and
  - American College of Obstetricians and Gynecologists.
- Guidelines developed by other groups were searched for via the internet, on the United States National Guidelines Clearinghouse.

#### 3.2 Search terms

Terms used to identify relevant citations are outlined in Appendix I. The search was conducted using and combining various terms for the following:

- Hepatitis C
- Screen
- Pregnancy

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### 4. Search findings

#### 4.1 Initial search

Four of the eight guidelines/statements retrieved for hepatitis C were considered relevant to examine further. The AGREE tool was applied by the project team and as a result three were identified as key citations.

- Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG). College Statement: Hepatitis C (2003)<sup>1</sup>.
- Royal College of Obstetricians and Gynaecologists (RCOG). Clinical Guideline: Antenatal care: routine care for the healthy pregnant woman (2003)<sup>2</sup>.
- Society of Obstetricians and Gynaecologists of Canada Clinical Practice Institute for Clinical Systems Improvement (ICSI). Health Care Guideline: Routine prenatal care (2000)<sup>3</sup>.
- United States Preventive Services Task Force (USPSTF). Screening for Hepatitis C Virus Infection in Adults: Recommendation statement (2004)<sup>4</sup>.

In addition to the guidelines, the initial search applied the following inclusion and exclusion criteria to retrieve 135 citations (Appendix II):

#### Inclusion criteria

Mother – infant transmission  
Clinical course of Hep C

#### Exclusion criteria

Chronic HCV management/treatment  
Hepatitis B  
Children with hepatitis C – management  
Specific treatments/therapies  
Conditions/circumstances associated with contracting hepatitis C including dialysis, incarceration, drug users, health care workers, sexually transmitted diseases, endoscopy, blood transfusions

#### 4.2 Key citation selection

The 135 citations identified in the initial search were triaged into those:

- Possibly containing relevant evidence or authoritative opinion (44 citations), and
- Unlikely to contain relevant evidence or authoritative opinion (91 citations). These citations were either too general or not relevant to the topics to be addressed and were not considered further.

The 44 citations (Appendix III) were retrieved and further screened to identify those studies with respect to quality of methodology and relevance to Australian obstetric practice. As a result of this exercise 26 articles were classified as key citations, and were subjected to systematic critical appraisal by the project team (Appendix IV) and those not meeting the criteria were discarded.

The evidence within these 26 key citations fell into the following levels (see Appendix IV for definitions):

Level I evidence: 0 publications

Level II evidence: 0 publications,

Level III evidence: 14 publications, and

Level IV evidence: 12 publications.

#### 4.3 Grading recommendations

The project team has adapted the Scottish Intercollegiate Guidelines Network (SIGN) system applying the NHMRC Levels of Evidence, to grade recommendations as follows:

- A At least one meta analysis, systematic review, or RCT directly applicable to the target population; or Levels I or II evidence.

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- B A body of evidence including studies rated as Level III-1 or III-2, directly applicable to the target population and demonstrating overall consistency of results.
- C A body of evidence including studies rated as III-3 directly applicable to the target population and demonstrating overall consistency of results.
- D Evidence Level IV.

### 5. Results of the critical appraisal process; Commentary on and interpretation of publications reviewed

#### 5.1 Is universal testing for Hepatitis C recommended above selective testing for Hepatitis C?

- **Reference**

Royal College of Obstetricians and Gynaecologists (RCOG). Evidence based guidelines Antenatal care: routine care for the healthy pregnant woman. 2003 (Level IV)

Hepatitis C (HCV) prevalence ranges from 0.14 to 0.8% in United Kingdom (UK). The risk of mother-to-child transmission in the UK is estimated to lie between 3% and 5%, representing an overall antenatal prevalence of 0.16%<sup>2</sup>. This is consistent with Australian data.

2% of vertically infected children developed hepatomegaly with no other clinical symptoms. Other long-term clinical outcomes are possible. It has also been suggested that a proportion of infected children subsequently become HCV-RNA negative<sup>2</sup>.

RCOG recommend "Pregnant women should not be offered routine screening for hepatitis C virus because there is insufficient evidence on its effectiveness and cost effectiveness"<sup>2</sup>.

- **Reference**

Boucher M, Gruslin A, Society of Obstetricians and Gynaecologists (SOGC) Clinical Practice Guidelines. The reproductive care of women living with Hepatitis C infection. *Journal of SOGC* 2000;96:5-29. (Level IV)

SOGC categorise the sources of acquisition of HCV as follows:

High risk (over 20%)

- Injection drug use (IDU)
- Recipients of unscreened blood products
- Transfusion of blood products that did not undergo viral inactivation

Moderate risk (1-20%)

- Newborns of HCV positive mothers
- Persons undergoing chronic haemodialysis
- Recipients of blood from unscreened donors
- Recipients of organ transplants
- Parenteral exposure through the use of contaminated or inadequately sterilized instruments/needles in medical/dental procedures

Low risk (below 1%)

- Persons engage in high risk sexual activity
- Sexual partners of HCV positive individuals
- Rituals (such as circumcision, scarification, excision), traditional medicine (such as blood letting), other skin breaking activities (such as ear and body piercing)
- Tattooing not carried out in properly regulated premises
- Household contact.

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In Canada, 54% of women with HIV are also infected with HCV<sup>3</sup>.

SOGC reports similar HCV prevalence to the RCOG. Prevalence remains low in both the general (1-3%) and pregnant (0.68-4.5%) populations<sup>3</sup>.

HCV in pregnancy is not associated with an increased risk of congenital malformation, fetal distress, stillbirth or prematurity. Women with HCV and their fetuses are at no greater risk of obstetric or perinatal complications compared with other women. There is no contraindication to pregnancy on the grounds of HCV alone<sup>3</sup>.

SOGC comment there is little reported on the effects of pregnancy on the course of HCV infection. Most women appear to be unaffected with less than 10% displaying elevated transaminases, and in most cases a decrease in ALT during pregnancy has been noted with a rebound postpartum. "It is postulated that endogenous production of interferon by the fetoplacental unit may play a role in the benign course of disease during pregnancy. Cholestasis of pregnancy may be more common among HCV infected women. Rarely women may present with advanced liver disease and complications such as oesophageal varices and coagulopathy, posing risks for bleeding with delivery and the possibility of variceal rupture. These cases should be managed in tertiary care settings"<sup>3</sup>.

SOGC report there has been detection of HCV RNA and anti-HCV antibodies in colostrums and breast milk. However, no case of transmission through breastfeeding has been documented, and therefore, it is generally felt that breastfeeding is not contraindicated<sup>3</sup>.

There is currently insufficient data available regarding the safety of interferon in pregnancy and as such there are no available treatment modalities for HCV in pregnancy<sup>3</sup>.

Therefore universal screening is not currently recommended in Canada in pregnancy, but women falling into the risk categories identified above should be offered testing. SOGC state that even with this approach, between 40 and 60% of infected women will remain unidentified. This is supported by Australian data<sup>5</sup>.

In addition, SOGC state the HCV screening would not meet all of the following key criteria for a screening test to be useful:

- Disease must be of public health importance
- A sensitive and specific test must exist for its detection
- Therapeutic and preventive measures must be available, and
- Direct and indirect screening costs must be acceptable to the individual and society<sup>3</sup>.

- **Reference**

US Preventive Services Task Force. (USPSTF) Clinical guidelines. Screening for hepatitis C virus infection in adults: recommendation statement. *Annals of Internal Medicine* 2004 Mar 16;140(6):462-4. (Level IV)

The USPSTF recommends against routine screening for HCV infection in asymptomatic adults who are not at increased risk (general population) for infection<sup>4,6</sup>.

There is low prevalence of HCV infection in the general population, and most infected do not develop cirrhosis or other major negative health outcomes. In addition, there is

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no evidence that screening for HCV infection results in improved long-term health outcomes<sup>4,6</sup>.

Evidence supports antiviral therapy as it improves intermediate outcomes, such as viraemia. However, potential harms of screening include unnecessary biopsies and labeling, although there is limited evidence to determine the magnitude of these harms. Therefore the potential harms of screening for HCV infection in adults who are not at increased risk for HCV infection are likely to exceed potential benefits<sup>4,6</sup>.

The USPSTF also found insufficient evidence to recommend for or against routine screening for HCV infection in adults at high risk for infection. There was no evidence that screening for HCV infection in adults at high risk leads to improved long term health outcomes, although the yield of screening would be substantially higher in a high-risk population than in an average-risk population<sup>4,6</sup>.

Of those infected with HCV, the proportion who progress to liver disease is uncertain. Limited evidence identifies 10-20% of patients with chronic HCV infection develop cirrhosis within 20 to 30 years<sup>4,6</sup>.

USPSFT also identified risk factors for HCV infection in accordance with those reported in RCOG and SOGC guidelines.

### • Reference

Ferrero S, Lungaro P, Bruzzone BM, Gotta C, Bentivoglio G, Ragni N. Prospective study of mother-to-infant transmission of hepatitis C virus: a 10-year survey (1990-2000). *Acta Obstetrica et Gynecologica Scandinavica* 2003;82(3):229-34. (Level III-2)

This prospective cohort study reported the risk of HCV vertical transmission is very low in HCV-positive/HIV negative women (2% versus 5.4% for HIV positive women coinfecting with HCV) and it is restricted to infants born to HCV viraemic mothers. High maternal viral load is predictive of the vertical transmission. The clearance time of antibodies in non-infected babies is significantly longer if the mother is viremic (9 versus 7 months)<sup>7</sup>.

### Project team comment

This cohort study of 188 babies is in line with current European data.

### • Reference

Saez A, Losa M, Lo Iacono O, Lozano C, Alvarez E, Pita L, et al. Diagnostic and prognostic value of virologic tests in vertical transmission of hepatitis C virus infection: results of a large prospective study in pregnant women. *Hepato-Gastroenterology* 2004;51(58):1104-8. (Level III-2)

This prospective cohort study revealed a prevalence of antenatal HCV of 0.5% by detection of antibodies to HCV. Of note, serum HCV RNA tested positive in 67% of them. The study concluded that vertical HCV transmission is low among HIV-negative HCV-infected mothers. The presence of serum HCV RNA immediately after birth had a high diagnostic and prognostic value, as identified those newborns that developed chronic hepatitis C<sup>8</sup>.

The main risk factor of HCV infection identified was a history of obvious parenteral exposure to blood (transfusion in 45 (38%) and IDU in 5 (4%))<sup>8</sup>.

Additional potential risk factors associated with HCV infection of 119 women in this study, include:

- History of major surgery (20%)

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- Tattooing (8.5%)
- Extensive dental care (7%)
- Sexual anti-HCV positive partner (5%)
- Health care employment (3.5%), and
- Unknown risk factors (14%)<sup>8</sup>.

The rate of mother-to-child transmission was 2.4%. HCV infection occurred in 3.4% of infants born to viraemic mothers by vaginal birth and in none born by caesarean section. Authors found the risk of HCV transmission was not associated with mode of birth ( $p=0.70$ ), and no significant difference of transmission was noted by mode of infant feeding<sup>8</sup>.

### Project team comment

This Spanish prospective cohort study of 20,612 women adds to the body of epidemiological data on HCV in pregnancy. The study includes additional information obtained regarding mode of delivery and breastfeeding as transmission factors, and identifies these as areas for further research.

### • Reference

Tajiri H, Miyoshi Y, Funada S, Etani Y, Abe J, Onodera T, et al. Prospective study of mother-to-infant transmission of hepatitis C virus. *Pediatric Infectious Disease Journal* 2001;20(1):10-4. (Level III-2)

This prospective cohort study of 16,800 pregnant women reported a vertical transmission rate HCV infection of 7.8% in anti-HCV antibody-positive mothers. Transmission was attenuated in women with high viral load<sup>9</sup>.

### Project team comment

This Japanese cohort study conducted from 1993 to 1998 identified 147 infants from 141 women who were HCV antibody positive (from an eligible group of 154 positive women). More than 20% (33 babies) were lost to follow up.

### • Reference

Paternoster DM, Santarossa C, Grella P, Palu G, Baldo V, Boccagni P, et al. Viral load in HCV RNA-positive pregnant women. *American Journal of Gastroenterology* 2001;96(9):2751-4. (Level III-2)

This cohort study undertook HCV screening on 3748 women seen consecutively in their first trimester of pregnancy at the antenatal clinic from 1998 to 1999. Sixty-five women were found to be anti-HCV+/HCV RNA + and were followed up with clinical and serological assessment in their second and third trimesters and 6 months after delivery. All were anti-HIV and hepatitis B surface antigen negative<sup>10</sup>.

The overall rate of vertical transmission was 4.6%. The authors did not detect any meaningful change in transaminases throughout pregnancy and the HCV viral load returned to normal within 6 months postpartum. The study concluded that after initial assessment, repeat testing of transaminases and HCV viral load was unlikely to be of benefit for the remainder of the pregnancy<sup>10</sup>.

### Project team comment

This is a relatively small epidemiological study with only 12 women having abnormal transaminases, raising concerns regarding power of the study to detect meaningful (maternal) morbidities.

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- **Reference**

Spencer JD, Tibbits D, Tippet C, Mead C, Kaldor JM, Dore GJ. Review of antenatal testing policies and practice for HIV and hepatitis C infection. *Australian & New Zealand Journal of Public Health* 2003;27(6):614-9. (Level III-3)

A survey of private obstetricians and general practitioners affiliated with the RANZCOG and directors of obstetric units in public hospitals was undertaken to investigate antenatal HIV and HCV testing policy and practice in Australia. The response rate to postal survey was 85% (847/995), of which 277 (33%) were returned from practitioners or hospitals no longer involved in antenatal care<sup>11</sup>.

The study concluded that HIV and HCV testing policy and practice vary widely. Testing for HIV and HCV was similar, despite differences in ability to treat each infection during pregnancy and reduce vertical transmission<sup>11</sup>.

### **Project team comment**

Despite the response rate of this study of practitioners directly involved in antenatal care being only 57%, this study is directly applicable to current approaches in Victoria. It raises concerns about lack of general perceptions of criteria for effective screening tests, but suggests that practitioners are open to active screening policies.

- **Reference**

Pembrey L, Newell ML, Peckham C. Is there a case for hepatitis C infection screening in the antenatal period? *Journal of Medical Screening* 2003;10(4):161-8. (Level IV)

This review article on available UK evidence reported HCV prevalence and transmission in line with RCOG commentary<sup>2</sup>. The overall HCV prevalence among pregnant women in the UK is estimated to be below 1%. Mothers' country of birth and inner city residence were significant factors influencing seroprevalence. For example seroprevalence was slightly higher in women born Southern Europe, African and Asia-Pacific countries than in those born in UK. The review suggested that high prevalence among IDU users may explain the higher prevalence in inner city populations<sup>12</sup>.

A substantial number of women report no risk factor for acquisition of infection. It is possible that denial of risk factors, such as IDU, occurs in some cases but the possibility of sexual or horizontal transmission cannot be excluded<sup>12</sup>.

In a general population in the UK, the risk of HCV vertical transmission is likely to be between 3% and 5%, rising to about 15% for children born to HIV co-infected women. The risk of vertical transmission of HCV is influenced by the maternal HCV viral load during pregnancy and at birth<sup>12</sup>.

However, currently available therapies, interferon and ribavirin, are contraindicated for use in pregnancy.

The European Paediatric HCV Network is undertaking research to clarify which antenatal interventions are likely to be effective as the development of effective therapies for vertically infected children will be particularly important if safe and effective interventions to reduce mother-to-child transmission are unattainable<sup>12</sup>.

Although routine antenatal screening cannot be recommended at present, it may be important that women with HCV infection are identified early and guidelines developed for the management of those with HCV infection<sup>12</sup>.

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### **Project team comment**

This key review article summarises the available evidence on detection and management of HCV in the pregnant population. The review highlights that in terms of screening HCV does not meet all of the criteria for inclusion in a screening program. Whilst being an important public health problem with a safe, valid and reliable screening test is available neither treatment nor intervention in pregnancy is available, and there are potential harms from screening that may outweigh benefits.

### **• Reference**

Giles M, Hellard M, Sasadeusz J. Hepatitis C and pregnancy: an update.[see comment]. *Australian & New Zealand Journal of Obstetrics & Gynaecology* 2003;43(4):290-3. (Level IV)

This Australian review article identified that antenatal HCV prevalence in Australian women was estimated at 13 per 1000 and up to 40% of pregnant women with HCV have no identifiable risk factor. The advantage of universal antenatal screening for HCV is that it provides an opportunity to identify asymptomatic women with a chronic disease who may be cured with current available treatment of interferon and ribavirin. There is evidence that treatment is more successful if given early, before complications such as cirrhosis develop, and that women identified in this setting are more likely to attend for further follow-up and treatment. However, this treatment is not recommended in pregnancy. The disadvantages of universal screening include the risk of false positive results, potential psychological harm caused by the screening procedure, and the additional costs to the health care system<sup>5</sup>.

Risk factors associated with HCV in the Australian setting include:

- IDU (~40% of infected mothers)
- A period of incarceration (~67% of women in Victorian prisons being hepatitis C antibody positive)
- A history of transfusion of blood products prior to HCV screening in 1990, particularly in groups who received multiple transfusions. Prevalence of antibodies to HVC in haemophiliacs is 60-80%.
- A history of migration from a country with a high rate on endemic HCV
- Tattoos and body piercing<sup>5</sup>.

The risk of contracting HCV through sexual intercourse is controversial. Current evidence indicates the risk of sexual transmission from a person with chronic HCV infection is very low<sup>5</sup>.

The review comments that universal antenatal screening of pregnant women for HCV is not currently recommended by the RANZCOG. However, the RANZCOG does recommend offering testing to pregnant women with a history of risk factors for possible exposure to HCV, and that pretest counseling is given<sup>1</sup>.

### **Project team comment**

This comprehensive, key review article of Australian data is in line with evidence presented in the UK and Canadian context.

### **• Reference**

Roberts EA, Yeung L. Maternal-infant transmission of hepatitis C virus infection. *Hepatology* 2002;36(5 Suppl 1):S106-13. (Level IV)

This review of current evidence identified the prevalence of antibody to HCV (anti-HCV) in pregnant women as 0.1% to 2.4%. Active infection with viraemia is 60% to 70%. Vertical transmission is 4% to 7% per pregnancy. The natural history of mother-to-infant HCV remains uncertain, especially the course in the first year of life when some infants appear to have spontaneous resolution<sup>13</sup>.

### Project team comment

Review article findings are in line with previously reported epidemiological data.

#### • Reference

Conte D, Colucci A, Minola E, Fraquelli M, Prati D. Clinical course of pregnant women with chronic hepatitis C virus infection and risk of mother-to-child hepatitis C virus transmission. *Digestive & Liver Disease* 2001;33(4):366-71. (Level IV)

This review found world prevalence of chronic HCV infection is approximately 3% and the rate of chronicity after primary infection is estimated as being about 85%. The prevalence of chronic HCV infection in pregnant women frequency ranges from 0.58 to 19%. These findings are consistent with those previously reported<sup>14</sup>.

Various factors that could influence the rate of vertical HCV transmission include:

- Maternal HCV viral load and maternal HIV coinfection increase the risk of transmission
- Caesarean section decreases the risk of transmission from 6% to zero in a small 1995 study, and
- HCV is found in breast milk but transmission from breast feeding has not been documented<sup>14</sup>.

### Project team comment

This is a comprehensive and general review paper but no new evidence is presented from within the last 5 years.

### Project team overall conclusion

The prevalence of hepatitis C in the Australian antenatal population is low (13/1000 women), as are rates of vertical transmission (~6%). At least 40% of cases have no identifiable risk factors. Currently, there is insufficient evidence regarding effectiveness and cost effectiveness of universal screening. There are no available safe treatments in pregnancy. Techniques to reduce vertical transmission such as caesarean section have not yet been adequately evaluated. There is insufficient evidence that antenatal treatment / intervention is of benefit to mother or baby in terms of reduction in disease severity.

### Recommendation (B)

In concordance with current international evidence based guidelines, universal testing for hepatitis C is not recommended above selective testing in pregnant women.

### 5.2 If selective testing is recommended, what risk factors should be considered during history taking?

#### • Reference

Boucher M, Gruslin A, Society of Obstetricians and Gynaecologists (SOGC) Clinical Practice Guidelines. The reproductive care of women living with Hepatitis C infection. *Journal of SOGC* 2000;96:5-29. (Level IV)

SOGC categorise the sources of acquisition of HCV as follows:

High risk (over 20%)

- IDU
- Recipients of unscreened blood products
- Transfusion of blood products that did not undergo viral inactivation

Moderate risk (1-20%)

- Newborns of HCV positive mothers
- Persons undergoing chronic haemodialysis
- Recipients of blood from unscreened donors
- Recipients of organ transplants

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- Parenteral exposure through the use of contaminated or inadequately sterilized instruments/needles in medical/dental procedures

### Low risk (below 1%)

- Persons engage in high risk sexual activity
- Sexual partners of HCV positive individuals
- Rituals (such as circumcision, scarification, excision), traditional medicine (such as blood letting), other skin breaking activities (such as ear and body piercing)
- Tattooing not carried out in properly regulated premises, and
- Household contact<sup>3</sup>.

### • Reference

Orton SL, Stramer SL, Dodd RY, Alter MJ. Risk factors for HCV infection among blood donors confirmed to be positive for the presence of HCV RNA and not reactive for the presence of anti-HCV. *Transfusion* 2004 Feb; 44(2): 275-81. (Level III-2)

This case control study of HCV positive blood donors identified recent IDU was independently associated with HCV infection (29.2% cases versus 0% controls  $p < 0.0001$ ). Other potential risk factors include recent history of IDU or incarceration. No risk factor or source for infection was identified for 56% of the HCV positive donors. Sex with someone with hepatitis and history of sexually transmitted disease has been identified as risk factors for HCV infection in previous studies. Analysis showed neither was significant risk factors in this study<sup>15</sup>.

### Project team comment

This study included 116 cases and 694 controls. Follow up was low, with only 56% of cases and 32% of controls, raising internal validity concerns. Only 46% of cases were female, and none specifically referred to vertical transmission. In addition, only 16% of the study population was white non-Hispanic ethnicity. However, the study raises particular concerns for screening in that along with previous reports, 56% of cases had no identifiable risk factor.

### • Reference

Goldberg D, McIntyre PG, Smith R, Appleyard K, Dunlop J, Taylor A, et al. Hepatitis C virus among high and low risk pregnant women in Dundee: unlinked anonymous testing. *BJOG: an International Journal of Obstetrics & Gynaecology* 2001;108(4):365-70. (Level III-2)

A cohort study conducted from January to December 1997 concluded non-injecting partners of injectors may be at considerable risk of acquiring HCV sexually. 23 women were identified as HCV positive in a cohort of 3548 antenatal women. 18 of the 23 women had ongoing pregnancies. Prevalence among IDU, non-injectors who had a sexual partner who injected, and those with neither risk respectively were 41% (7/17) 15% (5/33) and 0.3% (11/3498)<sup>16</sup>.

### Project team comment

The limitations of this study include that other questions of other risk factors such as blood transfusion and tattooing were not asked and details of current injecting and sexual behaviors were not obtained. In addition recall bias may have had a significant role.

### • Reference

Resti M, Azzari C, Galli L, Zuin G, Giacchino R, Bortolotti F, 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. *Journal of Infectious Diseases* 2002 Mar 1; 185(5): 567-72. (Level III-2)

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This prospective multicentre study evaluated whether maternal drug use is a preeminent risk factor for mother-to-child HCV virus transmission. There were 1372 consecutive, unselected HCV antibody positive mothers and their infants studied. Maternal HIV-1 coinfection (crude OR 1.41; 95% CI, 1.16-1.66; P=.007) and maternal IDU (crude OR 1.58; 95% CI, 1.37-1.78; P=.00001) were linked to mother-to-child HCV transmission in unadjusted analysis when all anti-HCV positive mothers were evaluated<sup>17</sup>.

### Project team comment

This large study yielded 98 infected mother-infant pairs for analysis. No significant role was found for breastfeeding perhaps due to the lower number of IDU who breastfeed their infants. It reinforces IDU as a risk factor for HCV transmission. There was an 8% drop out of mother-infant pairs. Of the children lost to follow up 66% were born to viraemic mothers and 31% to IDU mothers, raising concerns of internal validity.

### • Reference

Ceci O, Margiotta M, Mareello F, Francavilla R, Loizzi P, Francavilla A, et al. Vertical transmission of hepatitis C virus in a cohort of 2,447 HIV-seronegative pregnant women: a 24-month prospective study. *Journal of Pediatric Gastroenterology & Nutrition* 2001;33(5):570-5. (Level III-2)

This prospective cohort study examined 78 consecutive HCV-positive/HIV-negative women and their offspring to define the prevalence of and risk factors for HCV vertical transmission<sup>18</sup>.

There was an increased risk of HCV vertical transmission associated with high maternal viral load (P < 0.05), possession of HCV risk factors (blood product exposure prior to 1992, IDU, acupuncture, tattooing, incarceration, body piercing, sexual partner with a history of IDU or of HCV infection) (P < 0.004), and history of blood transfusion (P < 0.05). The study also supports the hypothesis of transient HCV viraemia without infection and vertical transmission without clinical evident disease. In concordance with the previous studies a high maternal viral load and possession of HCV risk factors were the variables predictive of HCV vertical transmission in our patients<sup>18</sup>.

### Project team comment

This is a relatively large cohort study providing confirmatory evidence regarding HCV-related risk factors. High maternal HCV viral load was identified as a risk factor, with no infants of RNA-negative women becoming infected. However, there were only 18 infants in this group and nine were lost to follow-up after 12 months.

### • Reference

Boaz K, Fiore AE, Schrag SJ, Gonik B, Schulkin J. Screening and counseling practices reported by obstetrician-gynecologists for patients with hepatitis C virus infection. *Infectious Diseases in Obstetrics & Gynecology* 2003;11(1):39-44. (Level III-3)

A survey of 1063 American College of Obstetricians and Gynecologists (ACOG) Fellows about HCV screening and counseling practices revealed 70% of respondents always perform HCV screening for women with risk factors, and in particular 49% respondents always screen for HCV infection when women had a history of IDU, and 35% of women who received a blood transfusion before 1992<sup>19</sup>.

Authors conclude that most obstetrician-gynaecologists routinely collect information that can be used to assess HCV infection risk. However, HCV screening practices

## Literature Search and Appraisal

and counseling provided for those with HCV infection are not always consistent with recommendations of the Centers for Disease Control and Prevention and ACOG<sup>19</sup>.

### Project team comment

The response rate to the questionnaire mailout was 56%. This study suggests that risk factors such as IDU and blood transfusion before 1992 are well recognized as risk factors for blood borne viral infections.

#### • Reference

Giles M, Hellard M, Sasadeusz J. Hepatitis C and pregnancy: an update.[see comment]. *Australian & New Zealand Journal of Obstetrics & Gynaecology* 2003;43(4):290-3. (Level IV)

The following risk factors were identified as being associated with HCV in the Australian setting:

- IDU (~40% of infected mothers)
- A period of incarceration (~67% of women in Victorian prisons being hepatitis C antibody positive)
- A history of transfusion of blood products prior to HCV screening in 1990, particularly in groups who received multiple transfusions. Prevalence of antibodies to HVC in haemophiliacs is 60-80%.
- A history of migration from a country with a high rate on endemic HCV
- Tattoos and body piercing<sup>5</sup>.

#### • Reference

Goldberg D, Anderson E. Hepatitis C: who is at risk and how do we identify them? *Journal of Viral Hepatitis* 2004;11 Suppl 1:12-8. (Level IV)

This review identified the following ways in which HCV is transmitted in the populations at risk:

- Inoculation of contaminated blood through the skin
  - Having received a blood/blood product transfusion
  - Having sustained an injury from a sharp implement. (Although no instance of HCV transmission following an accidental needlestick injury outwith the healthcare setting has been documented)
  - Having undergone tattooing or body piercing
  - Having undergone invasive medical procedures including haemodialysis, although the risk of iatrogenic HCV is extremely low.
  - Having injected drugs with reported prevalence ranging from 20 to 90% throughout the world
- Exposure of mucous membranes to contaminated blood or genital secretions
  - Being born – risk of transmission is 5%
  - Unprotected sexual intercourse
  - Exposure to someone else's blood through broken skin or mucous membranes – is rare
- The exposure of the internal body to infected tissue
  - Having received a transplant – has similar implications to those for blood transfusion recipients<sup>20</sup>

### Project team comment

The authors do not outline the methodology for this review.

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### Project team overall conclusion and recommendation (B)

If selective testing is recommended, the risk factors for HCV that should be considered during history taking should include:

#### High risk

- IDU (~40% of infected mothers)
- A period of incarceration (~67% of women in Victorian prisons being hepatitis C antibody positive)
- A history of transfusion of blood products prior to HCV screening in 1990, particularly in groups who received multiple transfusions. Prevalence of antibodies to HVC in haemophiliacs is 60-80%.
- A history of migration from a country with a high rate on endemic HCV (southern European, African and Asia/Pacific countries).

#### Moderate risk

- Newborns of HCV positive mothers
- Persons undergoing chronic haemodialysis
- Recipients of blood from unscreened donors
- Recipients of organ transplants
- Parenteral exposure through the use of contaminated or inadequately sterilized instruments/needles in medical/dental procedures

#### Low risk

- Persons engage in high risk sexual activity
- Sexual partners of HCV positive individuals
- Rituals (such as circumcision, scarification, excision), traditional medicine (such as blood letting), other skin breaking activities (such as ear and body piercing)
- Tattoos and body piercing
- Household contact<sup>3</sup>.

However, it is important to note that 40-50% of women infected with HCV have no identifiable risk factors.

### 5.3 Does the detection of Hepatitis C during pregnancy assist with long term management?

#### • Reference

Boucher M, Gruslin A, Society of Obstetricians and Gynaecologists (SOGC) Clinical Practice Guidelines. The reproductive care of women living with Hepatitis C infection. *Journal of SOGC* 2000;96:5-29. (Level IV)

The SOGC guideline identifies the possible sequelae to HCV as:

- Cirrhosis in about 20% of chronically infected patients. The range of interval from exposure to development of cirrhosis is 3 to 44 years. This appears longer in patients with histologically diagnosed mild activity compared to those with a higher grade of inflammation.
- Hepatocellular carcinoma may develop as a late and infrequent manifestation in patients with cirrhosis. The annual incidence is approximately 1% of those with cirrhosis.
- Extra-hepatic complications possibly the result of triggering an autoimmune response. These include:
  - Cryoglobulinaemia
  - Membranous glomerulonephritis
  - Porphyria cutanea tarda
  - Aplastic anaemia
  - Sjogren's disease
  - Mooren's corneal ulcer
  - B-cell non-Hodgkin's lymphoma
  - Thyroiditis
  - Immune thrombocytopenia.

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One benefit to identification of HCV during pregnancy is related to alcohol consumption. According to the guidelines, consumption of alcohol is the “most important external cofactor for disease progression, both in biochemical and histological severity”. Abstinence is strongly advised as the consumption of two or more units per day increases the rate of progression to cirrhosis threefold<sup>3</sup>.

- **Reference**

US Preventive Services Task Force. Clinical guidelines. Screening for hepatitis C virus infection in adults: recommendation statement. *Annals of Internal Medicine* 2004 Mar 16;140(6):462-4. (Level IV)

This guideline states there is no evidence that screening for HCV infection results in improved long-term health outcomes (such as decreased cirrhosis, hepatocellular cancer, or mortality). However, there is good evidence that anti-viral therapy improves intermediate outcomes including viraemia.

Current treatment is lengthy, expensive and associated with a high drop out rate due to adverse effects. The possible harms of screening are unnecessary biopsies and labeling. The USPSTF conclude that potential harms of screening for HCV infection in adults not at increased risk of HCV infection outweigh the potential benefits.

**Project team comment**

This guideline is pertinent to any adult population without symptoms of HCV infection without specifically referring to pregnancy.

- **Reference**

Mok J, Pembrey L, Tovo PA, Newell ML, European Paediatric Hepatitis CVN. When does mother to child transmission of hepatitis C virus occur? *Archives of Disease in Childhood Fetal & Neonatal Edition* 2005;90(2):F156-60. (Level III-2)

This prospective cohort study of 54 HCV infected children tested within 3 days of birth and their mothers found that approximately 30-50% of infected children acquired infection in utero<sup>21</sup>.

The authors cite other research in over 1400 mother-child pairs from centres of the European Paediatric HCV Network in which mode of delivery was not associated with the risk of vertical transmission in women with only HCV infection. In addition, in most studies no association has been observed between transmission and mode of infant feeding<sup>21</sup>.

The study authors acknowledge that maternal treatment to reduce the risk of vertical transmission, through lowering of viral load, is not currently possible, as interferon and ribavirin are contraindicated during pregnancy<sup>21</sup>.

**Project team comment**

This prospective cohort study adds weight to the window of pregnancy as an important time in transmission of HCV. However, there are currently no available antenatal therapeutic measures to assist with longterm management.

Nevertheless, the 50% or more of neonates infected during or after delivery may be a focus of future research in terms of longterm outcomes.

- **Reference**

Fontaine H, Nalpas B, Carnot F, Brechot C, Pol S. Effect of pregnancy on chronic hepatitis C: a case-control study. *Lancet* 2000 Oct 14; 356(9238): 1328-9. (Level III-2)

## Literature Search and Appraisal

This case control study involved the comparison of liver biopsy samples taken before and after delivery from 12 women HCV positive and 12 non HCV positive women. The results suggest that pregnancy may worsen HCV-related histopathological injury, including fibrosis and cirrhosis<sup>22</sup>.

### Project team comment

This letter raises the question that if pregnancy worsens liver histopathology in HCV, should the woman be treated before or after pregnancy? This is suggested as an area of future research. The study is small but contains important information that is difficult to obtain.

### • Reference

Gibb DM, Goodall RL, Dunn DT, Healy M, Neave P, Cafferkey M, et al. Mother-to-child transmission of hepatitis C virus: evidence for preventable peripartum transmission. *Lancet* 2000 Sep 9; 356(9233): 904-7. (Level III-2)

This cohort study of 441 mother-child pairs found the vertical transmission rate was 6.7% (4.1-10.2) overall, and 3.8 times higher in HIV coinfecting (n=22). In addition, the study found that delivery by elective caesarean section before membrane rupture was associated with a lower transmission risk than vaginal or emergency caesarean section delivery (OR 0 [0-0.87], p=0.04 after adjustment for other factors<sup>23</sup>.

### Project team comment

Whilst not strictly referring to longterm outcomes, this study raises the possibility of caesarean section in HIV-coinfecting women as a preventative strategy for vertical transmission of HCV and therefore prevention of longterm morbidity of the neonate. Antenatal testing would allow possible interventions such as caesarean section to reduce vertical transmission and assist with longterm management.

However, this cohort study was performed between 1994 and 1999. Only 85 out of the 441 children were delivered by caesarean section. This was not a primary endpoint. Therefore, generalisability of this finding is doubtful.

### • Reference

Healy CM, Cafferkey MT, Conroy A, Dooley S, Hall WW, Beckett M, et al. Outcome of infants born to hepatitis C infected women.[see comment]. *Irish Journal of Medical Science* 2001;170(2):103-6; discussion 92-3. (Level III-2)

This cohort study of 314 infants born to 296 HCV positive women found that of 173 infants of defined status, 11 were infected (vertical transmission rate [VTR] 6.4%, 95% CI 2.8-10). Infected infants were diagnosed at a median of three months (range 0.5-10). 40% of infants were small for age and 46% had neonatal abstinence syndrome (NAS). Liver transaminase elevation was documented in 8% of uninfected infants. A negative HCV PCR test before one month of age did not exclude infection but all infected patients had detectable HCV RNA when next tested (range 2-10 months)<sup>24</sup>.

The most common maternal risk factor for infection was IDU (83%). There were 3 deaths in the cohort: one premature infant with severe NAS died of profound apnoea and bradycardia at two weeks of age, one uninfected infant developed a spinal cord astrocytoma and one suffered SIDS<sup>24</sup>.

The suggestion that caesarean section prior to membrane rupture might prevent vertical transmission was not proven in this study. However it is notable that all infected infants were delivered vaginally<sup>24</sup>.

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All infants have remained clinically well to date, three have no clinical or biochemical evidence of compromised liver function. The danger of fulminating hepatitis following superinfection with hepatitis A is largely preventable with early diagnosis and immunization. Long term follow up is required to define the natural history of HCV infection in children but symptomatic disease in infancy appears rare<sup>24</sup>.

8% of uninfected infants had transient elevation of transaminases, suggesting possible reaction to viral clearance.

3/11 infected infants have no biochemical or clinical evidence of compromised liver function.

On the basis of this study, a minimum monitoring schedule for HCV exposed infants is proposed: final testing could be scheduled at 18 months both to confirm seroreversion and detect late seroconversion. Such a schedule would facilitate the prompt initiation of immunization against hepatotropic viruses, and allow more accurate assessment of liver dysfunction in those infected. Poor compliance should be anticipated in those with difficult social circumstances. This study showed that 22% of such women defaulted on follow-up testing of their infants<sup>24</sup>.

### **Project team comment**

This is a small study involving only 11 infected neonates. Larger studies are required to delineate the natural history of outcomes of vertically-acquired HCV in such infants. Less than 30% of infected infants in this study had no evidence of liver dysfunction. A minimum monitoring schedule of 18 months is suggested to detect late seroconverters.

### **• Reference**

Ceci O, Margiotta M, Mareello F, Francavilla R, Loizzi P, Francavilla A, et al. Vertical transmission of hepatitis C virus in a cohort of 2,447 HIV-seronegative pregnant women: a 24-month prospective study. *Journal of Pediatric Gastroenterology & Nutrition* 2001;33(5):570-5. (Level III-2)

This prospective cohort study examined 78 consecutive HCV-positive/HIV-negative women and their offspring to define the prevalence of and risk factors for HCV vertical transmission<sup>18</sup>.

The study shows an overall rate of HCV vertical transmission of 13.3% followed by a spontaneous viral clearance in more than two thirds of the cases within the second year. It also supports the hypothesis of transient HCV viraemia without infection and vertical transmission without clinical evident disease. In concordance with the previous studies a high maternal viral load and possession of HCV risk factors were the variables predictive of HCV vertical transmission in our patients<sup>18</sup>.

### **Project team comment**

This is a relatively large cohort study providing confirmatory evidence regarding HCV-related risk factors of: blood product exposure prior to 1992, IDU, acupuncture, tattooing, incarceration, body piercing, sexual partner with a history of IDU or of HCV infection. High maternal HCV viral load was identified as a risk factor, with no infants of RNA-negative women becoming infected. However, there were only 18 infants in this group and nine were lost to follow-up after 12 months.

The study provides new evidence regarding the prevalence of HCV viraemia without infection after delivery, with viral clearance in over 2/3 of cases within the 2<sup>nd</sup> year.

There were no cases of persistent ALT elevations after 2 years, suggesting that vertically-acquired infection may not be followed by clinically-evident disease.

## Literature Search and Appraisal

- **Reference**

Hupertz VF, Wyllie R. Perinatal hepatitis C infection. *Pediatric Infectious Disease Journal* 2003;22(4):369-72. (Level IV)

This review article comments that the natural history of HCV infection in the mother does not seem to be altered by pregnancy<sup>25</sup>.

HCV antibody in infants is cleared by 18 months of age. Chronic infection is reported in vertically-infected children at rates from 1.5 -80%<sup>25</sup>.

**Project team comment**

This review does not clearly address the issue of longterm morbidity in infected infants but reinforces that infants of infected mothers should be followed for 18 months to determine their HCV status.

- **Reference**

Resti M, Bortolotti F, Vajro P, Maggiore G, Committee of Hepatology of the Italian Society of Pediatric Gastroenterology and H. Guidelines for the screening and follow-up of infants born to anti-HCV positive mothers. *Digestive & Liver Disease* 2003;35(7):453-7. (Level IV)

This review specifically focuses on the management of infants of infected mothers and suggests guidelines for their follow-up. The authors suggest that infants be followed for 18 months to determine their HCV status. Elevated transaminases should be reviewed on a 6-monthly basis in uninfected infants, and HCV status determined again<sup>26</sup>.

**Project team comment**

This review does not specifically address the issue of longterm morbidity in infected infants or mothers but provides confirmatory evidence regarding the length of follow-up required after delivery.

**Project team overall conclusion**

In general terms, women with hepatitis C are at increased risk of cirrhosis, hepatocellular carcinoma and autoimmune disorders. Alcohol consumption exacerbates hepatic dysfunction in infected women.

Infants should be followed to 18 months of age to determine HCV infection status.

2/3 of those infants with virus detected after delivery are expected to clear the virus by 2 years of age.

70% of infants in small series demonstrate hepatic dysfunction but the longterm outcomes of this have not been reported.

Pregnancy may worsen liver function in women and this should be discussed with the woman. There is no evidence currently available on whether treatment is advisable prior to, during or after pregnancy.

There is no evidence to suggest that HCV detection during pregnancy assists with longterm management of either mother or baby. However, there is a significant paucity of evidence in this regard.

**Recommendation (C)**

Based on current evidence the detection of hepatitis C during pregnancy does not assist with long term management.

### 6. Overall conclusions and recommendations following the literature search and appraisal

#### 6.1 Is universal testing for Hepatitis C recommended above selective testing for Hepatitis C?

The prevalence of hepatitis C in the Australian antenatal population is low (13/1000 women), as are rates of vertical transmission (~6%). At least 40% of cases have no identifiable risk factors. Currently, there is insufficient evidence regarding effectiveness and cost effectiveness of universal screening. There are no available safe treatments in pregnancy. Techniques to reduce vertical transmission such as caesarean section have not yet been adequately evaluated. There is insufficient evidence that antenatal treatment / intervention is of benefit to mother or baby in terms of reduction in disease severity.

#### **Recommendation (B)**

In concordance with current international evidence based guidelines, universal testing for hepatitis C is not recommended above selective testing in pregnant women.

#### 6.2 If selective testing is recommended, what risk factors should be considered during history taking?

If selective testing is recommended, the risk factors for HCV that should be considered during history taking should include:

##### **High risk**

- IDU (~40% of infected mothers)
- A period of incarceration (~67% of women in Victorian prisons being hepatitis C antibody positive)
- A history of transfusion of blood products prior to HCV screening in 1990, particularly in groups who received multiple transfusions. Prevalence of antibodies to HVC in haemophiliacs is 60-80%.
- A history of migration from a country with a high rate on endemic HCV (southern European, African and Asia/Pacific countries).

•

##### **Moderate risk**

- Newborns of HCV positive mothers
- Persons undergoing chronic haemodialysis
- Recipients of blood from unscreened donors
- Recipients of organ transplants
- Parenteral exposure through the use of contaminated or inadequately sterilized instruments/needles in medical/dental procedures

##### **Low risk**

- Persons engage in high risk sexual activity
- Sexual partners of HCV positive individuals
- Rituals (such as circumcision, scarification, excision), traditional medicine (such as blood letting), other skin breaking activities(such as ear and body piercing)
- Tattoos and body piercing
- Household contact<sup>3</sup>.

However, it is important to note that 40-50% of women infected with HCV have no identifiable risk factors.

#### 6.3 Does the detection of Hepatitis C during pregnancy assist with long term management?

In general terms, women with hepatitis C are at increased risk of cirrhosis, hepatocellular carcinoma and autoimmune disorders. Alcohol consumption exacerbates hepatic dysfunction in infected women.

## Literature Search and Appraisal

Infants should be followed to 18 months of age to determine HCV infection status.

2/3 of those infants with virus detected after delivery are expected to clear the virus by 2 years of age.

70% of infants in small series demonstrate hepatic dysfunction but the longterm outcomes of this have not been reported.

Pregnancy may worsen liver function in women and this should be discussed with the woman. There is no evidence currently available on whether treatment is advisable prior to, during or after pregnancy.

There is no evidence to suggest that HCV detection during pregnancy assists with longterm management of either mother or baby. However, there is a significant paucity of evidence in this regard.

### **Recommendation (C)**

Based on current evidence the detection of hepatitis C during pregnancy does not assist with long term management.

## Literature Search and Appraisal

### Appendix I

#### Search framework

A structured approach was used to identify an appropriate search strategy for this topic. Using the Patient/Intervention/Compared with/Outcome (PICO) format search terms were listed and entered into the various electronic databases.

P	All pregnant women
I	Universal testing
C	Selective testing / risk factor
O	Detection of Hip C
	Improved long term management of Hepatitis C
	Outcomes for pregnant women

#### Search findings

Term	Medline	Premedline	CINAHL	EBM
Hepatitis C / Hep C / HCV	11956	605	1154	43
Screen\$ / test\$ / diagnosis	1040711	38592	141384	6050
Hepatitis C / Hep C / HCV and screen\$ / test\$ / diagnosis	5847	42/180	40/538	0/37
Hepatitis C / Hep C / HCV and screen\$ / test\$ / diagnosis and pregnan\$ / pregnancy / antenatal / prenatal diagnosis / prenatal	56/113	1/3	6/14	0/11

#### Cochrane

	Systematic Review	DARE	Central Register
Hepatitis C	0/56	3/38	3/1348
Hepatitis C and screening	0/21	1/3	0/40
Hepatitis and screen	0/20	*1/3	*1/25
Hepatitis and pregnancy / antenatal / prenatal	0/20	0/2	0/53

## Literature Search and Appraisal

### Appendix II Results of Initial Search

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## Literature Search and Appraisal

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## Literature Search and Appraisal

### Appendix IV Key Citations

#### Levels of Evidence Ratings

- I** Evidence obtained from a systematic review of all relevant randomised controlled trials.
- II** Evidence obtained from at least one properly-designed randomised controlled trial.
- III-1** Evidence obtained from well-designed pseudorandomised controlled trials (alternate allocation or some other method).
- III-2** Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group.
- III-3** Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group.
- IV** Evidence obtained from case series, opinions of respected authorities, descriptive studies, reports of expert committees and case studies.

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## 2.1 Is universal testing for Hepatitis C recommended above selective testing for Hepatitis C?

Study	Ref.	Population	Intervention	Outcomes	Results	Study type	EL
Ferraro S, Lungaro P et al 2003	7	San Martino Hospital, Italy  170 consecutive anti-HCV positive women and their 188 babies  March 1990 – March 2000	Universal screening  Collection of data regarding mother-infant pairs	Vertical transmission rate  Influences on transmission rate	The vertical transmission rate was 2.7% overall, and it was higher in HIV co-infected women (5.4%, 2/37) than in HIV-negative women (2.0%, 3/151).  All infected infants were born to mothers who had HCV viraemia at delivery. The transmission rate was influenced by maternal levels of viraemia.  Authors conclude that the risk of HCV vertical transmission is very low in HCV-positive/HIV-negative women and it is restricted to infants born to HCV viremic mothers. High maternal viral load is predictive of the vertical transmission. The clearance time of antibodies in non-infected babies is significantly longer if the mother is viremic.	Prospective cohort study	III-2
Saez A, Losa M et al 2004	8	University Hospital Santa Cristina, Madrid, Spain  HIV seronegative pregnant women  January 1992 – December 2000	HCV RNA and viral load were tested at the first and third trimester of pregnancy, birth and subsequently	Vertical transmission rate	Antibodies to HCV were detected in 119 mothers (0.57%), whereas serum HCV RNA tested positive in 67% of them.  HCV RNA was only observed in 2 babies born to 80 HCV RNA-positive mothers (transmission rate: 2.4%), appearing immediately after birth and remaining positive during the entire follow-up (36 months).  Authors conclude that vertical HCV transmission is an infrequent event among HIV-negative HCV-infected mothers.	Prospective cohort study	III-2
Tajiri H, Miyoshi Y et al 2001	9	Faculty of Medicine, Osaka University, Osaka, Japan  16,800 pregnant Japanese women attending seven hospitals in the Osaka metropolitan area  1993 to 1998	Universal screening for anti-HCV antibodies	Incidence of mother-to-infant transmission of HCV in infants born to HCV positive mothers.	<ul style="list-style-type: none"> <li>33 infants were dropped from the study due to failure to follow-up.</li> <li>Of the 114 infants finally evaluated 9 (7.8%) had detectable HCV RNA.</li> <li>Transmission rate was not influenced by the mode of delivery [vaginal delivery, 8 of 90 vs. cesarean section, 1 of 24 (P = 0.396)] or by the type of feeding [9 of 98 for breast-fed infants vs. 0 of 16 for formula-fed infants (P = 0.243)].</li> <li>All infected infants were born to mothers who had HCV viraemia at the delivery (P=0.040) and to those with a high viral load (P=0.019).</li> </ul> <p>Authors conclude that the transmission rate of mother-to-infant HCV infection was 7.8% in anti-HCV antibody-positive mothers. Risk was related to the presence of maternal HCV viraemia at delivery and a high viral load in the mothers.</p>	Prospective cohort study	III-2

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Paternoster DM, Santarossa C et al  2001	10	University of Padua, Padua, Italy  1998 - 1999  3748 women seen consecutively in their first trimester of pregnancy	Universal screen for HCV	HCV viral load during pregnancy in relation to:  HIV coinfection Liver enzymes, and Vertical transmission	<ul style="list-style-type: none"> <li>• 65 anti-HCV+/HCV RNA+</li> <li>• All were anti-HIV and hepatitis B surface antigen negative.</li> <li>• Six months after delivery the viral load returned to the baseline levels; the changes in viral load did not reach any statistical significance.</li> <li>• The overall rate of vertical transmission was 4.6</li> </ul>	Prospective cohort study	III-2
Spencer JD, Tibbits D et al  2003	11	National Centre in HIV Epidemiology and Clinical Research  1999  Obstetricians and GPs affiliated with RANZCOG and public hospitals providing antenatal care.	Postal survey	Type of antenatal policy, proportion of women tested for HCV and number of HCV positive women receiving antenatal care	<ul style="list-style-type: none"> <li>• 570 respondents provide antenatal care.</li> <li>• Universal offer of antenatal testing among private obstetricians, GPs and public hospitals was 54%, 46% and 23% for HCV, respectively.</li> <li>• During 1999, an estimated 37% pregnant women were tested for HCV.</li> <li>• Prevalence rates were estimated at 13 per 1,000, for HCV.</li> </ul>	Obstetrician / GP survey	III-3
Pembrey L, Newell ML et al  2003	12	United Kingdom antenatal women	Universal screening	HCV prevalence  Application antenatal  Influence on management	<p>Overall HCV antenatal prevalence in the UK is estimated to be &lt;1%. High prevalence among injecting drug users. Seroprevalence was:</p> <ul style="list-style-type: none"> <li>• 0.14% for mothers born in the UK</li> <li>• 0.8% for mothers born in Europe</li> <li>• 1.6% for mothers born in Southern Europe</li> </ul> <p>Vertical transmission of HCV in general population is 3-5% and 15% for maternal-to-infant transmission.</p> <p>Current therapies are contraindicated during pregnancy.</p> <p>Large multicentre prospective studies aim to identify possible risk factors for vertical transmission to assist in the identification of interventions likely to be effective.</p> <p>Authors conclude universal antenatal screening for HCV cannot be recommended as it does not meet the key criteria for screening programs:</p>	Review of evidence	IV

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					<ul style="list-style-type: none"> <li>• The condition is an important public health problem</li> <li>• A safe, valid and reliable screening test is available</li> <li>• Treatment or an intervention of proven effectiveness is available</li> <li>• The risk of harm, both physical and psychological, is less than the chance of benefit.</li> </ul> <p>However, they also suggest it is important that women with HCV infection are identified early and guidelines be developed for the management of those with HCV infection.</p>		
Giles M, Hellard M et al	5	Australian antenatal women	Universal screening	Identification of risk factors	1999 estimated prevalence of HCV infection among Australian pregnant women was 13 per 1000.	Review of evidence	IV
2003				<p>Mother-to-child transmission of HCV</p> <p>Management of pregnant women found to be infected with HCV</p>	<p>RANZCOG recommend selective testing of pregnant women with a history of risk factors for possible exposure to HCV.</p> <p>Risk factors associated with HCV include:</p> <ul style="list-style-type: none"> <li>• Injecting drug use</li> <li>• Period of incarceration</li> <li>• Transfusion of blood products pre 1990</li> <li>• Multiple transfusions</li> <li>• Migration from a country with a high rate of endemic HCV</li> <li>• Tattoos and body piercing</li> </ul> <p>There is no evidence that breastfeeding increases the transmission of HCV to the infant.</p> <p>The role of interventions such as elective Caesarean section in the management of women infected with HCV remains uncertain, and further research is recommended.</p>		
Roberts EA and Yeung L	13	Pregnant women			<ul style="list-style-type: none"> <li>• Mother-to-infant transmission of hepatitis C virus (HCV) is comparatively uncommon. However, the rate of mother-to-infant transmission is 4% to 7% per pregnancy in women with HCV viraemia.</li> <li>• Prevalence of antibody to HCV (anti-HCV) in pregnant women is 0.1% to 2.4%, although in some endemic areas it is much higher.</li> <li>• Transmission of HCV occurs only when serum HCV RNA is detectable and may be related to higher levels (above 10(6) copies per mol).</li> <li>• Co-infection with human immunodeficiency virus (HIV) increases the rate of transmission 4 to 5 fold.</li> </ul> <p>Authors conclude that pregnant women at high risk for HCV infection</p>	Review of evidence	IV
2002							

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		should be screened for anti-HCV, and HCV RNA testing should be performed if anti-HCV is positive. However, the natural history of mother-to-infant hepatitis C remains uncertain, especially the course in the first year of life when some infants appear to have spontaneous resolution.			
Conte D, Colucci A et al	14	Prevalence of HCV	Current data on the:	Review of evidence	IV
2001		Relationship with risk factors	<ul style="list-style-type: none"> <li>• World prevalence of chronic HCV infection is approximately 3%</li> <li>• Rate of chronicity after primary infection is estimated at 85%</li> <li>• Prevalence of chronic hepatitis C virus infection in pregnant women as 0.58 to 19%</li> </ul>		
		Rate of mother-to-child HCV	<ul style="list-style-type: none"> <li>• Various risk factors that could influence the rate of mother-to-child hepatitis C virus transmission include HCV related factors, maternal HIV coinfection. However there is no convincing evidence regarding the type of delivery and feeding method.</li> </ul>		

## Literature Search and Appraisal

### 2.2 If selective testing is recommended, what risk factors should be considered during history taking?

Study	Ref.	Population	Intervention	Outcomes	Results	Study type	EL
Orton SL, Stramer RY et al 2004	15	American Red Cross, USA  March 1999 to March 2003  810 blood donors with confirmed NAT results positive for the presence of HCV in the absence of anti-HCV	Extensive demographic and risk questionnaire	Risk factor identification	<ul style="list-style-type: none"> <li>Recent injection drug use (IDU) was independently associated with HCV infection (29.2% vs. 0% of cases vs. controls, <math>p &lt; 0.001</math>).</li> <li>Other sources of infection for three other cases (4.6%) include: <ul style="list-style-type: none"> <li>occupational exposure,</li> <li>sexual contact with an HCV-infected partner (who was an IDU), and</li> <li>perinatal exposure.</li> </ul> </li> <li>Incarceration was independently associated with HCV infection among the group not reporting IDU and after removal of the three donors with likely sources of risk (14.6% vs. 1.3% of cases vs. controls, <math>p &lt; 0.001</math>).</li> </ul>	Case control study	III-2
Goldberg D, McIntyre PG et al 2001	16	Ninewells Hospital, Dundee, UK  January – December 1997  Antenatal clinic attendees and women undergoing termination of pregnancy.	Unlinked anonymous HCV antibody testing linked to non-identifying risk information.	Prevalence of HCV  Risk factor identification	<ul style="list-style-type: none"> <li>Anti-HCV prevalence was 0.6%.</li> <li>Prevalence among injecting drug users, non-injectors who had a sexual partner who injected, and those with neither risk respectively were 41% (7/17), 15% (5/33) and 0.3% (11/3,498).</li> <li>Relative risks for being an injector and a sexual partner of an injector respectively were 131 (95% CI 58-297) and 48 (95% CI 5-32).</li> </ul> <p>Authors conclude that non-injecting partners of injectors may be at considerable risk of acquiring HCV sexually. Selective screening of women who reported high risk behaviour would have failed to detect half the cases.</p>	Cohort study	III-2
Resti M, Azzari C et al 2002	17	24 referral centres in Italy  April 1993 – December 1996  1372 consecutive unselected HCV antibody positive mothers and their infants	Registration and follow-up forms	Significance of risk factors correlated with mother-to-child HCV transmission	<ul style="list-style-type: none"> <li>When all anti-HCV-positive mothers were evaluated, maternal HIV-1 coinfection (crude odds ratios [OR], 1.41; 95% confidence interval [CI], 1.16-1.66; <math>P = .007</math>) and IDU (OR, 1.58; 95% CI, 1.37-1.78; <math>P &lt; .00001</math>) were linked to mother-to-child HCV transmission.</li> <li>Maternal IDU (not maternal HIV-1 coinfection) was significantly associated with mother-to-child HCV transmission when only HCV RNA-positive mothers were evaluated.</li> </ul>	Prospective multicentre study	III-2

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Ceci O, Margiotta M, et al 2001	18	University of Bari, Italy  January 1995 – June 1997  78 consecutive HCV positive/HIV negative women with their offspring	HCV positive mothers' viral load and genotype checked.  Infants tested for ALT and HCV-RNA at birth and at 4,8,12,18,24 months	Prevalence of and risk factors for HCV vertical transmission	<ul style="list-style-type: none"> <li>8 of 60 (13.3%) infants born to HCV-RNA positive mothers acquired HCV infection</li> <li>Only 2 (3.3%) were still infected by the end of follow-up.</li> <li>ALT levels were in the normal range in all study subjects throughout the follow-up.</li> <li>High maternal viral load (<math>P &lt; 0.05</math>), possession of HCV risk factors (<math>P &lt; 0.004</math>), and history of blood transfusion (<math>P &lt; 0.05</math>) were associated with increased risk of HCV vertical transmission.</li> </ul> <p>Authors conclude that vertical transmission from HIV-negative mothers occurred in 13% of cases, however, there is a high rate of spontaneous viral clearance (75%). High maternal viral load and mothers belonging to HCV risk categories were the only variables predictive of the vertical transmission.</p>	Prospective cohort study	III-2
Boaz K, Fiore AE et al 2003	19	American College of Obstetricians and Gynaecologists  2001  ACOG Fellows	Postal survey	Screening and counseling practices for HCV infection	<ul style="list-style-type: none"> <li>&gt;80% of respondents routinely collected drug use and blood transfusion histories from their patients.</li> <li>49% of respondents always screen when patients had a history of injection drug use, and</li> <li>35% screened all patients who had received a blood transfusion before 1992.</li> </ul> <p>Authors conclude that although most obstetrician-gynecologists are routinely collecting information to assess HCV infection risk, HCV screening practices and counseling provided for those with HCV infection are not always consistent with current Centers for Disease Control and Prevention and ACOG recommendations.</p>	Obstetrician Survey	III-3
Resti M, Azzari et al 2002	17	24 referral centres throughout Italy.  April 1993 – December 1996  1372 consecutive, unselected HCV antibody positive mothers and their infants	Registration / follow up forms  Infants screened for HCV RNA	Significance of risk factors considered correlated with mother-to-child HCV transmission	<p>Maternal HIV-1 coinfection (crude odds ratios [OR], 1.41; 95% confidence interval [CI], 1.16-1.66; <math>P = .007</math>) and IDU (OR, 1.58; 95% CI, 1.37-1.78; <math>P &lt; .00001</math>) were linked to mother-to-child HCV transmission in unadjusted analysis when all anti-HCV-positive mothers were evaluated. When only HCV RNA-positive mothers were evaluated, maternal IDU, but not maternal HIV-1 coinfection, was significantly associated with mother-to-child HCV transmission. Multivariable analysis confirmed the link between maternal IDU and HCV transmission (adjusted OR [AOR], 1.51; 95% CI, 1.19-1.92; <math>P = .0006</math>), but no association was found with HIV-1 coinfection (AOR, 0.98; 95% CI, 0.73-1.33; <math>P = .93</math>). IDU, but not HIV-1 coinfection, seems to be a preeminent risk factor for vertical HCV transmission. (C) 2002 Infectious Diseases Society of America</p> <ul style="list-style-type: none"> <li></li> </ul>	Multicentre study	III-2
Goldberg D and	20			Risk factor	<p>Factors influencing the probability of a person acquiring HCV are:</p> <ol style="list-style-type: none"> <li>Those experiencing inoculation of contaminated blood through the skin, having:</li> </ol>	Review of	IV

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Anderson E  2004	identification  Prioritization of HCV screening	<ul style="list-style-type: none"> <li>• Received a blood/blood product transfusion</li> <li>• Sustained an injury from a sharp implement. (No instance of HCV transmission following an accidental needlestick injury outwith the healthcare setting has been documented)</li> <li>• Undergone tattooing or body piercing</li> <li>• Undergone invasive medical procedures including haemodialysis, although the risk of iatrogenic HCV is extremely low.</li> <li>• Injected drugs with reported prevalence ranging from 20 to 90% throughout the world</li> </ul> <p>2. Exposure of mucous membranes to contaminated blood or genital secretions, having:</p> <ul style="list-style-type: none"> <li>• Been born – risk of transmission is 5%</li> <li>• Had unprotected sexual intercourse</li> <li>• Exposure to someone else's blood through broken skin or mucous membranes – is rare</li> <li>• The exposure of the internal body to infected tissue</li> <li>• Having received a transplant – has similar implications to those for blood transfusion recipients</li> </ul> <p>Reasons why HCV case finding might be promoted:</p> <ul style="list-style-type: none"> <li>• To promote harm reduction among HCV-infected individuals</li> <li>• To inform people of their HCV infection status that behaviour to reduce the probability of acquiring or transmitting infection can be promoted</li> <li>• To identify persons who might be eligible for therapy</li> <li>• To monitor HCV infected persons who are currently ineligible for therapy but might become eligible in the future</li> </ul> <p>Authors recommend the following prioritization of HCV screening</p> <p>Very High Priority (testing required)</p> <ul style="list-style-type: none"> <li>• Haemodialysis patients</li> <li>• Blood or blood product, tissue or organ donors</li> <li>• Healthcare workers about to enter an exposure prone procedure training slot or post</li> </ul> <p>High Priority (verbal offer and recommendation of test)</p> <ul style="list-style-type: none"> <li>• Patients with a persistently elevated ALT</li> <li>• Past injecting drug users</li> <li>• Children of a known HCV antibody positive mother</li> <li>• HIV positive persons</li> <li>• Recipients of blood clotting factors prior 1987</li> <li>• Healthcare workers after percutaneous or mucous membrane</li> </ul>	evidence
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## Literature Search and Appraisal

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exposure to HCV infected blood

Intermediate Priority (offer (verbal or in the form of literature) but not recommendation of test)

- Recipients of blood products before 1991
- Current injecting drug users
- People who have had tattoos or body piercing in circumstances where infection control procedure was suspected to be suboptimal
- Persons who have a history of multiple sexual partners, sexually transmitted infections or an HCV positive sexual partner / household contact

Low priority (no offer of test but available if wanted)

- Everyone else including pregnant women not in any of the above categories
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### 2.3 Does the detection of Hepatitis C during pregnancy assist with long term management?

Study	Ref.	Population	Intervention	Outcomes	Results	Study type	EL
Mok J, Pembrey L et al 2004	21	31 centres in 7 countries in Western Europe, European Paediatric Hepatitis C Network  1998  HCV infected children and their mothers	Polymerase chain reaction (PCR) test within first 3 days following birth	HCV RNA PCR results	<ul style="list-style-type: none"> <li>54 children had HCV infection</li> <li>Seventeen of the children (31%, 95% confidence interval 19% to 46%) were positive in the first 3 days of life and could be assumed to have acquired infection in utero.</li> <li>PCR positive was not associated with gender (53% v 49% boys; <math>p=0.77</math>) or mode of birth (29% elective caesarean section in both groups; <math>p=0.98</math>).</li> <li>37 (68%) were negative in the first 3 days of life, 27 of whom were positive when tested again at 3 months, and 9 were first PCR positive after 3 months.</li> </ul> <p>Authors conclude that results suggest at least one third and up to a half of infected children acquired infection in utero.</p>	Prospective cohort study	III-2
Fontaine H, Nalpas B et al 2000	22	Hopital Necker, Paris, France  July 1992 to February 2000  HCV positive women	Liver biopsy	Semiquantitative histopathological measurements	<ul style="list-style-type: none"> <li>12 women with pre and post delivery liver biopsies (cases) and 12 non-pregnant women positive for HCV (control)</li> <li>Necroinflammatory score deterioration 83.3% versus 25.0% and fibrosis score 41.6% versus 8.3%</li> </ul> <p>Authors conclude the findings suggest pregnancy may worsen HCV related histopathological injury.</p>	Case control study	III-2
Gibb, DM, Goodall RL et al 2000	23	3 hospitals in Ireland and British Paediatric Surveillance Unit, UK  January 1994 – April 1999  441 HCV infected mother-child pairs	Survey by single investigator (Ireland) and questionnaire (UK)  Probabilistic model	Vertical transmission rate  Risk factors for transmission	<ul style="list-style-type: none"> <li>6.7% (4.1-10.2) Vertical transmission rate</li> <li>3.8 times higher in HIV coinfecting</li> <li>No effect of breastfeeding on transmission was observed</li> <li>Birth by elective caesarean section before ROM was associated with a lower transmission risk than vaginal or emergency caesarean section birth (OR 0 (0-0.87) <math>p=0.04</math>)</li> </ul>	Prospective cohort study	III-2
Healy CM, Cafferkey MT et al	24	3 main maternity hospitals in Dublin, Ireland	Blood from the umbilical cord /infant sample tested for HCV	Define outcomes for infants born to HCV infected women	<ul style="list-style-type: none"> <li>40% of infants were small for age and 46% had neonatal abstinence syndrome (NAS).</li> <li>Of 173 infants of defined status, 11 were infected (vertical transmission rate [VTR] 6.4%, 95% CI 2.8-10).</li> </ul>	Prospective cohort study	III-2

## Literature Search and Appraisal

2001	1994 – 1999	antibody.	Develop an appropriate infant monitoring schedule	<ul style="list-style-type: none"> <li>• Infected infants were diagnosed at a median of three months (range 0.5-10). Liver transaminases elevation was documented in 8% of uninfected infants.</li> <li>• A negative HCV PCR test before one month of age did not exclude infection but all infected patients had detectable HCV RNA when next tested (range 2-10 months).</li> </ul>			
	314 infants born to 296 HCV positive women	Infant clinical and virologic evaluations every 4-6 months until 18 months old					
Ceci O, Margiotta M, et al	18	University of Bari, Italy	HCV positive mothers' viral load and genotype checked.	Prevalence of and risk factors for HCV vertical transmission	<ul style="list-style-type: none"> <li>• 8 of 60 (13.3%) infants born to HCV-RNA positive mothers acquired HCV infection</li> <li>• Only 2 (3,3%) were still infected by the end of follow-up.</li> <li>• ALT levels were in the normal range in all study subjects throughout the follow-up.</li> <li>• High maternal viral load (<math>P &lt; 0.05</math>), possession of HCV risk factors (<math>P &lt; 0.004</math>), and history of blood transfusion (<math>P &lt; 0.05</math>) were associated with increased risk of HCV vertical transmission.</li> </ul> <p>Authors conclude that vertical transmission from HIV-negative mothers occurred in 13% of cases, however, there is a high rate of spontaneous viral clearance (75%). High maternal viral load and mothers belonging to HCV risk categories were the only variables predictive of the vertical transmission.</p>	Prospective cohort study	III-2
2001	January 1995 – June 1997	78 consecutive HCV positive/HIV negative women with their offspring	Infants tested for ALT and HCV-RNA at birth and at 4,8,12,18,24 months				