Evidence Table 10: Key Question 7. Pregnancy Intervention Observational Studies

| **Author, year Country Study Name Overall Quality** | **Study Type** | **Definition of mother-to-child transmission** | **Confounders assessed in analysis** | **Duration of followup** | **Eligibility** | **Exclusion** | **Number screened/ eligible/ enrolled/ analyzed** | **Demographic characteristics of study population** | **HCV genotype HCV viral load HIV infection IV drug use** | **Overall transmission** | **Transmission by labor mgmt: Intra-uterine pressure catheter (IUPC)** |
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| Ceci, 2001156 Italy  Fair | Prospective cohort study | Presence of anti-HCV antibodies beyond 18 months or HCV-positive on two separate tests | HCV maternal risk factors (exposure to blood products and IVDU), HCV viral load, HCV genotype, gestational age, mode of delivery, birth weight | 24 months | HCV-positive, HIV-negative women | HIV-positive | 2447/ 78/ 78/ 78 | **Maternal age (n=78)** Median (range): 30 (21-42)  **\*Characteristics of HCV-RNA positive mothers (n=60) HCV risk factors** Absent: 25 (42%) Blood transfusion: 14 (23%) IVDU: 20 (33%) Blood transfusion and IVDU: 1 (2%) **Mode of delivery** Vaginal: 43 (72%) Cesarean: 17 (28%) **Gestational age** <36 weeks: 9 (15%) >=36 weeks: 51 (85%) **Birth weight** <2500g: 14 (23%) >=2500g: 46 (77%) | **Maternal HCV-RNA status (n=78)** Positive: 60 (77%) Negative: 18 (23%)  **\*Characteristics of HCV-RNA positive mothers (n=60) genotype** 1a: 9 (15%) 1b: 25 (42%) 2a: 20 (33%)  3: 6 (10%)  **Viral load** <0.2X106: 9 (15%) >0.2X106: 51 (85%) | **Overall transmission (n=78)** 2 consecutive positive tests: 8 (10%) 24 month followup: 2 (3%) \*not adjusted | Not reported |
| Conte, 2000157 Italy  Poor | Prospective cohort study | Newborns of anti-HCV positive mothers were tested at birth (on cord blood samples) and infants underwent determination of AST, ALT, anti-HCV and HCV/RNA after 4, 8, 12, and 18 months | Not Reported | First month of pregnancy through 18 months after birth | Anti-HCV positive pregnant women between 1/95 and 12/98 attending Ob/Gyn unit of local Ospedale Maggiore (living in area of about 20 km around Bergamo in northern Italy) | Not Reported | 15,250/370/370/370 | **Maternal age (n=370) mean (SD):** 30.9 (± 5.2) **Mode of delivery (n=370)** Vaginal: 259 (71%) Cesarean: 106 (29%) | **Maternal HCV/RNA status (n=370)** Positive: 266 (72%)  Negative: 104 (28%) **Maternal genotype (n=370):** 1a: 51 (19%) 1b: 82 (31%) 2: 64 (24%) 3a: 53 (20%) 4: 5 (2%) Indeterminate: 11 (4%) **Maternal HIV infection (n=370)**  Yes**:** 15 (4%)  No: 355 (96%) **Past or current IVDU (heroin only) (n=370)** 118 (32%) **Past blood transfusions (n=370)**  68 (18.4%) | **HCV/RNA+**  at birth (n=366): 18 (4.9%) 4 months (n=167): 8 (4.8%) 8 months (n=161): 8 (5%) 12 months (n=155): 8 (5.1%) | Not Reported |
| European Pediatric Hepatitis C Virus Network, 2001158 (Pembrey) Italy, Spain, Germany, Ireland, Scotland, Belgium, Sweden  Good | Multicenter prospective cohort study | Infected: antibody positive beyond 18 months and/or had at least two positive PCR tests (on 2 separate occasions)  Indeterminate: born more than 18 months before data collection, antibody positive before 18 months of age, and either 1) no PCR performed, 2) no positive PCR result, or 3) only a single PCR result | Mode of delivery, breastfeeding, HIV status, maternal age at delivery | At least until 18 months of age | Mother HCV positive at or before delivery or baby identified as HCV positive within 1 month of delivery & maternal infection confirmed Children born on or after Jan 1 1992 (when 2nd generation tests widely used) and at least 18 months at last laboratory assessment (or born more than 18 months before data collection and no longer in followup) | Children with a history of blood transfusion | 1655 mother-child pairs/1474 children/1474/1474 (916 HIV-) | **Maternal age (n=1311)** <20: 219 (17%)  20-25: 563 (43%) 30-39: 495 (38%) >=40: 34 (3%) **Gestational age (n=1248)** <36 weeks: 105 (8%) >=36 weeks: 1143 (92%) **Low birth weight (<2500g) (n=1362)** Yes: 523 (38%) No: 839 (62%) **Fetal scalp monitors (n=724)** Yes: 93 (13%) No: 631 (87%) **Mode of delivery (n=1400)** Cesarean: 382 (27%) Vaginal: 1018 (73%) **Breastfeeding (n=1424)** Breastfed: 351 (25%) Not breastfed: 1073 (75%) **Other infections in pregnancy (n=996)** Yes: 90 (9%) No: 906 (91%) | **Maternal HIV infection (n=1419)** Yes: 503 (35%) No: 916 (65%) **Maternal IV drug use (n=1384)** During this pregnancy: 362 (26%) Yes, but not during pregnancy: 455 (33%) Never: 567 (41%) **Maternal history of hepatitis (n=1038)** Yes: 421 (41%) No: 617 (59%) | **Overall transmission (n=1474)** 136 (9.2%) \*not adjusted | Not Reported |
| European Pediatric Hep C Virus Network, 2005159 (Tovo) Italy, Spain, Germany, Ireland, UK, Norway, Sweden  Good | Multicenter prospective cohort study | Children considered infected if they had >=2 positive HCV RNA PCR test results and/or were anti-HCV antibody positive after 18 months. Children considered uninfected if they had <2 positive HCV RNA PCR test results and <=2 negative HCV RNA PCR rest results and/or were anti-HCV antibody negative after 18 months. | To account for differences between centers in the HCV RNA PCR assays used to determine infection, and to allow for center-associated unobserved differences in background characteristics, the authors incorporated a random effect in the multivariable models at the center level | Children received clinical examinations at birth, 6 weeks, and 3, 6, 9, 12, 18, and 24 months; and thereafter every 6 months if infected or every year if uninfected | HCV infected mothers and their singleton infants or first-born infants from multiple pregnancies with confirmed HCV infection status. | Second-born twins and second- and third-born triplets were excluded. Mother-infant pairs with infants of indeterminate infection status were excluded. | 1787/ 1479/ 1479/ 1220 (1034 HIV-) | **Maternal age (n=1205)** Mean (SD): 31.7 (5.17) Median (range): 32 (17.1-45.1) **Mode of delivery (n=1455)** Vaginal: 764 (52.5%) Emergency CS: 160 (11%) Elective CS: 480 (33%) CS (unspecified): 51 (3.5%) **Infant feeding type (n=1357)** Breast-fed: 452 (32.7%) Formula fed: 930 (67.3%) **Sex of child (n=1470)** Male: 802 (54.6%) Female: 668 (45.4%) **Gestational age (n=1382)** <=34 weeks: 97 (7%) 35-36 weeks: 122 (8.8%) >=37 weeks: 1163 (84.2%) | **Maternal HIV infection (n=1391)** Yes: 208 (15%) No: 1183 (85%) **Child HIV infection (n=1435)** Yes: 10 (0.7%) No: 1397 (97.4%) Indeterminate: 28 (1.9%) **Maternal IV drug use (n=1162)** History: 448 (38.6%) No history: 714 (61.4%) |  |  |
| Garland, 1998160 Australia  Poor | Prospective cohort study | Infants tested at 3, 6 and 12 months for HCV antibodies. Testing included detection of antibody to HCV, and genotyping for presence of 1a, 2a, 2b, 3 a, 4 & 6 HCV genotypes. | NR/Unclear: Collected data on age, parity, type of delivery, time of rupture, drug use, scalp electrodes and breastfeeding but did not indicate if adjustment for confounding was analyzed. | Three years; followup included seropositive women, their newborns & siblings of the newborns. | Women with a history of illicit IV drug use, seen in the Chemical Dependency Unit (CDU) of the Royal Women's Hospital and subject to routine screening for HCV.   Women with positive anti-HCV test results. | Not Reported | Not Reported/ 84/ 83/ 83 women,  91 newborns & 16 siblings of newborns | **Mode of delivery (n=83)**  Vaginal: 61 (74%) | **Maternal HIV infection (n=83)**  Yes: 0 (100%)  **Maternal IV drug use** (n=83) Yes: 83(100%) | 3/91 (3%) | Not Reported |
| Gibb, 2000161  Ireland, UK  Fair | Prospective cohort study | Positive result for HCV antibody within 90 days of birth | adjusted for HIV status, breastfeeding, and mode of delivery | 24 months | Mother known to be HCV infected during pregnancy or if child had positive result for HCV antibody within 90 days of birth | UK children born before 1996 | 499/ 441/ 441/ 441 | **Maternal age (n=441)**  Mean (SD): 27 (6) **Race (n=441)** White: 413 (94%) Non-white: 28 (6%) **Breastfeeding (n=414)** Yes: 59 (14%) No: 355 (86%) **Mode of delivery (n=424)** Vaginal: 339 (80%) Emergency cesarean: 54 (13%)  Elective cesarean: 31 (7%) | **Maternal HIV infection (n=441)** Yes: 22 (5%) No: 328 (74%) Unknown: 91 (21%) **Maternal IV drug use (n=441)** History: 343 (78%)  No history: 98 (22%) | **Overall (n=441)** 6.7% (4.1-10.2) unadjusted | Not Reported |
| LaTorre, 1998162 Italy  Poor | Prospective cohort study | Babies were tested for ALT levels, anti-HCV antibodies by ELISA III and RIBA II and HCV-RNA by RT-PCR. Babies who retained anti-HCV antibodies through 12 months were considered infected | none | Blood test and clinical evaluation of infants within days after birth and then every 4 months for 2 years | Mothers who tested anti-HCV positive before delivery and were HIV negative | Mothers who tested negative for HCV or positive for HIV | 5025/ 5000/ 80/ 80 | **Mode of delivery (n=80)** Vaginal: 66 (82.5%) \*52/66 were HCV-RNA positive cesarean: 14 (17.5%) **Breastfeeding (n=80)** yes: 24 (30%) \*Including 10 HCV-RNA positive and 14 HCV-RNA negative women | **Maternal HCV-RNA status (n=80)** Positive: 56 (70%)  Negative: 24 (30%) **HCV viral load (n=19)** ALT increase>40 U/L: 18 (32.5%) **Maternal IV drug use (n=80)**  Yes:34 (43%) **Blood transfusion (n=80)**  10 (12%) | **Overall transmission (n=80)** 2/80 (2.5%) | Not Reported |
| Lin, 1995163 Republic of China  Poor | Prospective cohort study | Detection of HCV antibodies (serum); detection of HCV RNA in infants tested at 1, 3, 6, 9 or 12 months of age | Not Reported | Up to 12 months | HCV infected mothers | NR | Not Reported/ 40/ 15/+3 healthy controls 15 | Not Reported | **HCV viral load**  (n=15) RNA titers 102 to 2.5 x 108copies/mL  **HIV infection** None | 0/15 (0%) | Not Reported |
| Mast, 2005164 US (Houston & Honolulu)  Good | Prospective cohort study | Infant serum collected at birth and 8 well-child visits. Testing included detection of antibody to HCV, detection of HCV RNA (qualitative and quantitative), and genotyping. | Variables with p<.1 from the univariate analysis and maternal demographic characteristics included in multivariate analysis | Infants born to HCV+ mothers followed from birth to >=12 months, HCV-infected infants followed annually until age 5 | Women presenting for prenatal care (and in Houston, those who didn't receive prenatal care who presented for delivery at 2 county hospitals) were offered testing.   Women with positive anti-HCV test results were invited to enroll (those with indeterminate status were invited to enroll until HCV status was confirmed). | Mothers with serum testing as RIBA indeterminate and HCV RNA negative were excluded from the analysis. | 75,909/ 567/ 332/ 242 women & 244 infants | **Age (n=242)** <20: 7 (2.9%) 20-29: 103 (42.6%) 30-39: 120 (49.6%) >=40: 12 (4.9%) **Race (n=242)** White: 79 (32.6%) Black: 77 (31.8%) Hispanic: 49 (20.3%) | **Mother HCV RNA+ (n=242)** At enrollment or delivery: 194 (79.5%) Both: 179 (77.2%) Delivery: 5 (2.2%)  Enrollment: 4 (1.7%) **Maternal HIV infection (n=242):**  Yes: 11 (4.5%) **HIV and HCV RNA+ (n=242)**  7 (2.9%) **Maternal** **IVDU (n=242)**  126 (52.3%)  **Geometric mean HCV RNA level at delivery (n=194)** HIV-: 2.38\*106 **Maternal HCV genotype (n=116)** Genotype 1a: 76 (66%) Genotype 1b: 16 (14%) Genotype 2b: 10 (9%) Genotype 3a: 13 (11%) Genotype 4a: 1 (.01%) | 9/244(3.7%) | Not Reported |
| McMenamin, 2008165 Ireland  Fair | Retrospective cohort study | Positive neonatal results for HCV antibody after 1 month of age | None | Infant HCV RNA samples tested at median of 6 weeks after delivery, mean 12.5 weeks (range 4-166 weeks) | Mothers who tested positive for HCV antibody antenatally and delivered a liveborn infant, HCV positive mothers identified through the National Virus Reference Laboratory | Mothers who tested negative for HCV antenatally or mothers who tested positive for HCV antenatally and miscarried or had a stillbirth | 26,390/559/559/441 | **Maternal age (n=559)**  Median (range): 26 (16-44)  **Mode of delivery (n=559)**  Vaginal delivery: 443 (79%) Emergency cesarean: 72 (13%)  Planned pre labor cesarean: 44 (8%)  **Gestation (n=559)**  Median (range): 39 (28-42)  **Intrapartum procedures (n=559)**  Intrapartum fetal blood sample: 1 (.002%)  Fetal scalp electrode: 23 (4%) | **Maternal HIV infection (n=559)**  Yes: 18 (3%)  **Maternal HBV status (n=559)**  Positive: 3 (0.5%)  **Maternal HCV RNA status (n=559)**  Positive: 295 (53%)  Negative: 166 (30%)  Missing: 98 (17%) | **Overall transmission (n=441)** 18/441 (4.1%) | Not Reported |
| Moriya, 1995166  Japan  Poor | 2 prospective cohort studies, additional pediatric chart review | Infants testing positive for antibody to HCV | Not Reported | 12 months, up to 24 months | Infants born to mothers who were HCV RNA positive | Not Reported | 16714/ 163/ 100 mothers/  84 mothers, 87 infants | Not Reported | **Maternal HIV infection**  None (n=84)  **Maternal genotype (n=4)** Type 111/2a: n=2 Type 11/1b: n=2 | 2/87 (2.3%) ("during followup period") | Not Reported |
| Okamoto et al, 2000167 Japan (Tottori University & Medical Center)  Poor | Prospective cohort study | Positive test for HCV RNA by RT-PCR analysis with high titers of HCV RNA within 3 months of age. Serum samples of the children born to Ab1 mothers were tested for anti-HCV antibody, HCV RNA, and liver function approximately every 3 months during the first year and biannually thereafter. | Not Reported | Minimum followup period was 6 months | Pregnant women were screened for anti-HCV antibody in Tottori Prefecture, Japan.  None of the mothers had risk factors for HIV infection | Not Reported | 21791/NR Eligible/NR Enrolled/ 59 | **Mode of delivery (n=84)** Vaginal: 56 (66%) Cesarean: 28 (33%) | **Maternal HCV/RNA status (n=84)**  Positive: 50 (60%)  **Maternal viral load (n=84)**  **high (≥ 2.5 x 106 copies/mL):**  21 (25%) | 7/84 (8%) | Not Reported |
| Pipan, 1996168 Italy  Poor | Prospective cohort | HCV/RNA detection in children over a period of 12 months | none | Every three months for one year | Anti-HCV positive pregnant women, no history of Hepatitis B, no apparent source of HCV exposure | History of Hepatitis B, apparent source of HCV exposure | 1338/36/25/25 | **Maternal age (n=25)**  Median (range)26.4 (19-35) | **Maternal HCV/RNA+ (n=25)**  Positive**:**18 (72%) | **Infant HCV/RNA+ at birth** **(n=25)**  None **Infant HCV/RNA+ at 12 months** **(n=25)**  0 | Not Reported |
| Resti, 1998169 Italy  Fair | Prospective cohort study | Children were considered infected when hepatitis C virus RNA was detected or when anti­bodies to the virus persisted beyond age 2 years or reappeared after having disappeared. Alanine aminotransferase concentrations were defined as raised if they were higher than twice the upper limit of normal | Study data suggests that there may be a higher risk of vertical transmission in mothers with a higher viral titre, but the results were not significant. IV drug users were not excluded from analysis, but authors suggest inclusion of these mothers did not significantly impact findings | Median followup in the 403 children who completed the study was 28 (24-38) months | 19 centres participated in the study Women (and their babies) with confirmed hepatitis C antibodies but negative for HIV­1 | History of blood product transfusions or IV drug use was carefully investigated by face to face interviews with experienced pediatricians using standardized questionnaires, but these individuals were not excluded | NR/442/403/ 403 & 403 infants (275 RNA+ mothers) | **RNA+/HIV- mothers (n=275)  Mode of delivery**  Vaginal: 213 (77%) Caesarean: 62 (23%) **Breastfeeding**  Yes: 87 (32%)  No: 188 (68%) | **Maternal IVDU (n=275)** 111 (80%) | 13/275 (4.7%) | Not Reported |
| Spencer, 1997170  Australia  Poor | prospective cohort study | Presence of HCV RNA in serum collected from infant anytime during followup. | Potential maternal risk factors assessed: duration/type of drug use, alcohol, smoking, past HBV infection, age | At least 6 months, up to 6 years when possible | HCV positive and HCV negative pregnant women, IVDU on methadone maintenance program and their infants | Not Reported | Not Reported/ Not Reported/ 131/ 125 anti-HCV+, 63 HCV RNA+ | **Maternal age** mean: 30 | **Maternal HCV RNA status (n=125)**  **Positive:** 63 (62.4%)  **Maternal genotype** **transmitting mothers** Type 1a: 5 (83.3%) Type 3a: 1 (16.7%) **Non-transmitting mothers** Type 1: 1 (1.6%) Type 1a: 36 (57.1%) Type 1b: 4 (6.3%) Type 2a: 1 (1.6%)  Type 2b: 2 (3.2%) Type 3a: 18 (28.6%) Untypeable: 1 (1.6%) **HIV infection**  None  **IVDU**  131 (100%) | 6/63 (9.5%) (at 18 months) | Not Reported |
| Syriopoulou, 2005171 Greece  Poor | Prospective cohort study | HCV/RNA+ more than 2 times after 3 months and/or anti-HCV+ after 18 months | Univariate analysis of IVDU, mother's age, mode of delivery, genotype, type of feeding (but no multivariate analysis) | Every three months until 1 year of age, then every 6 months | Anti-HCV positive pregnant women | Not Reported | NR/86/86/86 mother-child pairs | **Mean age at delivery** (SD): 29.6 (+/- 3 yrs) **Mode of delivery (n=86)** Vaginal: 53 (62%) Cesarean: 33 (38%) | **Maternal HCV genotype (n=54)** 3a: 23 (42%) 1a: 10 (19%) 1b: 7 (13%) 1a/1b: 6 (11%) 2a/2c: 6 (11%) 4c/4d: 2 (4%) **Maternal HCV/RNA status (n=86)**  Positive:56 (65%) **Maternal HIV infection (n=86)**  Yes:1 (1%) **IVDU (n=86)** during pregnancy:  2 (2%) before pregnancy: 6 (7%) | **Overall transmission (n=86):** 2 (2.3%) | Not Reported |
| Tajiri, 2001172 Japan (seven hospitals in the Osaka metropolitan area)  Poor | Prospective cohort study | Babies were tested for serum alanine aminotransferase (ALT) activity, anti-HCV antibodies and HCV RNA at 0, 3, 6, 9, 12 months and every year thereafter.  Babies with repeated positive HCV RNA tests were considered infected. | Not Reported | All infants were followed 9 to 61 months | Pregnant women who tested positive for anti-HCV antibodies | Not Reported | 16800/154/141/114 | **Route of transmission (n=141)** Mother-to-child: 9/141 (6%) Blood transfusion: 31/141 (22%) Accidental needle stick injury: 3/141 (2%) HCV carriers in their families: 11/141 (8%) Other/unidentified: 87/141 (62%)  **Mode of delivery (n=114)** Vaginal: 90 (21%) Cesarean: 24 (79%) | **Maternal IVDU**  None **Maternal HIV infection (n=73)**  Positive: 0  Negative: 73  Not tested: 68  (68 not tested because HIV infection is not endemic in Japan including the areas studied (adult rate of infection, 0.01%) **Maternal HCV viral load** High: 46 (63%) Low: 27 (37%) | 9/114 (7.8%) | Not Reported |
| Tanzi, 1997173 Italy  Poor | Prospective cohort study | presence of antibodies for one or more HCV antigens at birth, 3, 6, 10, and 18 months | None | 18 months | Women admitted to the Maternity Clinic of University of Parma from January to December 1993, those who tested positive for antibodies were invited to submit their children for period checks | Not Reported | 1347/1347/1347/1347 | NR | **Maternal anti-HCV+ (n=1347)** 31 (2.3%) **Maternal** **HCV-RNA+ (n=1347)** 18 (1.3%) **Maternal HIV infection (n=1347)**  4 (.27%) | **Overall transmission (n=32) Infant HCV/RNA+** at birth: 2 (6%) at 3, 6, 10, 18 months: 0 (0%) **Infant anti-HCV+** at birth: 32 (100%) at 18 months: 0 (0%) | Not Reported |
| Zanetti, 1998174 (Intervirology) Italy A prospective Study on Mother-to-Infant Transmission of Hepatitis C virus  Zanetti, 1999175 (Journal of Hepatology) Italy Mother-to-infant transmission of hepatitis C virus  Poor | Prospective cohort study | Detection of HCV-RNA, persistence of anti-HCV beyond 18 months of age or ex novo production of antibody were assumed to represent evidence of infection | Not Reported | For babies born to HCV seropositive mothers, peripheral blood sampling, laboratory and clinical evaluations were scheduled at birth, about every 3 months during the 1st year of life and then every 6 months. | Infants born to HCV-infected mothers, including mothers with history of IV drug use who were screened for HIV antibodies. | Not Reported | 40000+/482/291/291 & 291 infants | Not Reported | **Maternal HIV infection (n=291)**  Yes: 40 (14%)  **Maternal HCV/RNA status**  (n=291)  Positive: 251 (86%)  **Maternal genotype (n=17)** 3a: 6/17  1a: 4/17 2a: 3/17 1b: 2/17 4a: 1/17 4c/4d: 1/17 | HCV+: 17/291 (5.8%) HCV+/HIV+: 3/17 (17.6%) | Not Reported |

| **Author, year Country Study Name Overall Quality** | **Transmission by labor mgmt: Fetal monitoring** | **Transmission by mgmt: Rupture of membranes** | **Transmission by route of delivery** | **Transmission by type of infant feeding** | **Transmission by other risk factors (maternal)** | **Transmission by other risk factors (child)** | **Sub-group analyses** | **Adverse events** | **Funding source** | **(Cont'd) Transmission rate by other risk factors (maternal)** | **(Cont'd) Transmission rate by other risk factors (maternal)** |
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| Ceci, 2001156 Italy  Fair | Not Reported | Not Reported | No association (data NR) | Not Reported | Transmission from women with no known risk of infection was significantly lower (RR=0.17%, 0.04-0.73%; p=0.0063) | Not Reported | Not Reported | Not Reported | Not Reported | **By maternal blood transfusion (n=38) 2+ positive tests vs. 0 positive tests** 3/8 (37.5%) vs. 2/30 (6.7%), p<0.05  **By maternal viremia (n=38) 2+ positive tests vs. 0 positive tests** 6.90 +/- 5.87 x 106 vs. 3.93 +/- 2.94 x 106 |  |
| Conte, 2000157 Italy  Poor | Not Reported | Not Reported | **Cesarean vs. vaginal (n=365)** 1/106 (1%) vs. 7/259 (2.7%)  \*RR: .245 (.275- 49.463) | **Breast vs. formula (n=370)** 2/90 (2%) vs. 6/280 (2%)  \*RR: 1.02 (.305-3.45) | Not Reported | Not Reported | Not Reported | Not Reported | Not Reported |  |  |
| European Pediatric Hepatitis C Virus Network, 2001 (Pembrey)158 Italy, Spain, Germany, Ireland, Scotland, Belgium, Sweden  Good | **Fetal scalp monitoring during delivery (yes vs. no) (n=724)** 11/93 (11.8%) vs. 58/631 (9.2%) OR=1.33 (95% CI 0.63-2.74) \*not adjusted | Not Reported | **Cesarean vs. Vaginal (n=1400)**  28/382 (7.3%) vs. 101/1018 (9.9%) OR: .739 (.467-1.163) \*type of cesarean (CS) or vaginal delivery elective CS: 20/192 (10.4%) Emergency CS: 7/115 (6.1%) Unspecified CS: 1/75 (1.3%) Vaginal, spontaneous: 81/825 (9.8%) Vaginal, instrumented: 12/79 (15.2%) Vaginal, unspecified: 8/114 (7%) **HIV- mothers (n=884)** **Cesarean vs. vaginal** 15/218 (6.9%) vs. 39/666 (5.9%) OR 1.17 (0.59-2.31, p=.66) \*Adjusted for breastfeeding status, maternal age at delivery, and center category \*info on type of CS or vaginal delivery NR for HIV- | **Breast vs. formula (n=1424)** 29/351 (8.3%) vs. 102/1073 (9.5%) **HIV- mothers** **Breast vs. formula (n=887)** 21/319 (6.6%) vs. 36/568 (6.3%) OR 1.07 (0.57-2.02, p=0.83) \*Adjusted for mode of delivery, maternal age at delivery **HIV+ mothers breast vs. Formula (n=497)**  5/13 (38.5%) vs. 64/484 (13.2%) OR 6.41 (1.25-32.94), p=0.03 \*Adjusted for mode of delivery, maternal age at delivery | **Mother HIV positive vs. negative (n=1419)** 70/503 (13.9%) vs. 60/916 (6.6%), OR 2.31 (1.58-3.37) **No** **maternal drug use ever vs. not during pregnancy vs. during pregnancy (n=1384)**  43/567 (7.6%) vs. 49/455 (10.8%) vs. 33/362 (9.1%), OR=0.82 (.50-1.35) vs. OR=1.20 (.74-1.97) **Maternal history of hepatitis (yes vs. no) (n=1038)** 50/421 (11.9%) vs. 55/617 (8.9%), OR=1.38 (0.90-2.10) **Other infections during pregnancy (yes vs. no) (n=996)** 7/90 (7.8%) vs. 84/906 (9.3%), OR=0.83 (0.38-1.81) \*Not adjusted | **<36 weeks gestational age vs. >36 weeks (n=1248)** 7/105 (6.7%) vs. 109/1143 (9.5%), OR 0.68 (0.26-1.50)   **Birth weight <2500g vs. >2500 g (n=1362)** 49/523 (9.4%) vs. 109/1143 (9.5%), OR 1.05 (0.71-1.56) | Not Reported | Not Reported | European Commission DG XII Biomed2 Programme |  |  |
| European Pediatric Hep C Virus Network, 2005 (Tovo)176 Italy, Spain, Germany, Ireland, UK, Norway, Sweden  Good |  |  | **Elective cesarean vs. emergency cesarean or vaginal delivery (n=1220)** OR 1.66 (1.00-2.74) unadjusted, p=.05 OR 1.46 (0.86-2.48) adjusted, p=.16  **HIV- mothers  elective vs. emergency cesarean or vaginal delivery (n=1034)** 1.57 (0.88-2.83) unadjusted, p=0.13 1.59 (0.88-2.86) adjusted, p=0.13  \*adjusted for sex, mode of delivery, prematurity, and infant feeding type | **Breast vs. formula (n=1220)** OR 0.74 (0.42-1.31) unadjusted, p=.30 OR .88 (0.48-1.61) adjusted, p=.68  **HIV- mothers  breast vs. formula (n=1034)** OR 0.88 (0.48-1.61) unadjusted, p=.68 OR 0.92 (0.50-1.70) adjusted, p=.60 | **Mother HIV positive vs. negative (n=1220)** OR 1.89 (1.05-3.40) unadjusted, p=.03 OR 1.82 (0.94-3.52) adjusted, p=.06 | **Female vs. male (n=1220)** OR 2.12 (1.27-3.56) unadjusted, p=.004 OR 2.07 (1.23-3.48) adjusted, p=.006 **Premature vs. term (n=1220)** OR 0.54 (0.23-1.26) unadjusted, p=.15 OR 0.45 (0.19-1.08) adjusted, p=.07 **HIV- mothers female vs. male (n=1034)** OR 1.79 (1.00-3.22) unadjusted, p=.05 OR 1.80 (1.00-3.24) adjusted, p=.07 **HIV- mothers premature vs. term (n=1034)** OR 0.83 (0.32-2.13) unadjusted, p=.69 0.83 (0.32-2.15) adjusted, p=.80 | Not Reported | Not Reported | European Commission Regione Piemonte, Italy; UK Medical Research Council |  |  |
| Gibb, 2000161 Ireland, UK  Fair | Not Reported | Not Reported | **Elective cesarean vs. emergency cesarean vs. vaginal (n=424)** 0% (0-7.4) vs. 5.9% (1.0-17.8) vs. 7.7% (4.5-11.9)  OR elective cesarean 0 (95% CI 0-0.86) vs. OR emergency cesarean 0.84 (95% CI 0.12-3.63) vs.  \*Adjusted for HIV status and breastfeeding  **Elective cesarean vs. vaginal/emergency cesarean (n=424)** 0% (0-7.4) vs. 7.4% (4.5-11.3)  OR 0 (0-0.87) \*Adjusted for HIV status and breastfeeding | **Breast vs. formula (n=414)** 7.7% (2.2-17.8) vs. 6.7% (3.7-10.6)  OR 1.52 (0.35-5.12) \*Adjusted for HIV status and mode of delivery | **HIV positive vs. negative (n=441)** 18.6% (5.8-38.6) vs. 6.4% (3.5-10.3)  OR= 3.8 (0.92-13.2) \*Adjusted for breastfeeding and HIV status | Not Reported | Not Reported | Not Reported | UK Department of Health | Not Reported |  |
| Garland, 1998160   Australia  Poor | Not Reported | Not Reported | **Vaginal vs. cesarean (n=83)** 3/61 (4.9%) vs. 0/22 (0%) | Viral RNA detected in breast milk: 0/18 (0%) | Not Reported | Not Reported | Sibling HCV RNA+: 1/16 (6%) | Not Reported | Not Reported |  |  |
| LaTorre, 1998162 Italy  Poor | Not Reported | Not Reported | **Vaginal vs. cesarean (n=80)** 1/66 (1.5%) vs. 1/14 (7%) | **Breastfed vs. formula fed (n=80)** 0/24 (0%) vs. 2/56 (3.6%)  \*none of the HCV-RNA positive mothers breastfed | **By maternal HCV RNA status (n=80)** mother positive: 2/56 (3.6%) mother negative: 0/24 (0%) \*not adjusted | Not Reported | Not Reported | Not Reported | Not specified, research and testing took place at Careggi Hospital, University of Florence |  |  |
| Lin, 1995163  Republic of China  Poor | Not Reported | Not Reported | Not Reported | Breast feeding transmission rate: (n=11 breast fed) None (0%) | IVDU during pregnancy: 1/12 (8.3%) infants HCV+ | Not Reported | Not Reported | Not Reported | National Science Council, Yuan, China |  |  |
| Mast, 2005164 US (Houston and Honolulu)  Good | **\* Results are for HCV RNA+/HIV- mothers (n=181)  Internal vs. external**  3/16 (18.8%) vs. 4/165 (2.4%), RR 7.7 (1.9-31.6), p=.02  **Internal fetal monitoring** \*Adjusted OR, 6.7 (1.1-35.9) | **\* Results are for HCV RNA+/HIV- mothers (n=182)  Rupture of membranes before onset of labor yes vs. no** 4/45 (8.9%) vs. 3/137 (2.2%), RR 4.1 (0.9-17.5), p=.06  **Duration of membrane rupture**  <1 vs. 1-5 vs. 6-12 vs. >=13 0/53 vs. 1/59 (1.7%) vs. 4/40 (10%) vs. 2/30 (6.7%), p=.02  **Membrane rupture >6 hrs** OR, 9.3 (1.5-179.7) \*adjusted | **\* Results are for HCV RNA+/HIV- mothers (n=181)  Elective cesarean vs. emergency cesarean vs. vaginal delivery** 0/12 (0%) vs. 1/18 (5.5%) vs. 6/151 (4%), elective cesarean RR undefined, emergency cesarean RR 1.4 (0.2-1.1), p=.55  **Elective cesarean vs. emergency cesarean/vaginal**  0/12 vs. 7/169 (4%), RR 0.87 (0.05 to 14) | **\* Results are for HCV RNA+/HIV- mothers (n=182)  Breast vs. formula** 2/62 (3.2%) vs. 5/120 (4.2%), RR 0.8 (0.2-3.9), p=1.0 | **Maternal** **HCV/RNA status at delivery** positive vs. negative 9/190 (4.6%) vs. 0/54, RR undefined  **\*Remaining results are for HCV/RNA+ mothers (n=190) maternal HIV status** positive vs. negative2/8 (25%) vs. 7/182 (3.8%), RR 6.5 (1.6-26.4)  **Maternal HCV RNA level, genome copies/mL**  <=106 vs. >106, <107 vs. >=107 1/61 (1.6%) vs. 2/87 (2.3%) vs. 4/34 (11.8%), p=.03  **Maternal age at delivery, years** >=30 vs. <30 5/100(5) vs. 2/81(2.5), RR 2.0(0.4-10.2), p=0.46 **(results continued in last 2 columns)** | **\*Results for infants born to HCV/RNA+ mothers (n=190)  Sex** Male vs. female 2/85 (2.3%) vs. 5/96 (5.2%), RR 0.45 (0.09-2.27), p=.45  **Gestational age** <37 vs. >=37 0/27 vs. 7/155 (4.5%), RR undefined, p=.6  **Birth weight** <2500g vs. >=2500g 1/22 (4.6%) vs. 6/160 (3.8%), RR 1.2 (0.2-9.6), p=1  **Apgar score at 5 min** <=8 vs. >8 0/21 vs. 7/161 (4.4%), RR undefined, p=1 | Not Reported | Not Reported | Centers for Disease Control | **Prior pregnancies** >4 vs. <=4 2/73 vs. 5/109, RR 0.6(0.1-3.0)  **ALT level at delivery, U/L** >35 vs. <=35 3/45(6.7) vs. 4/137, RR 2.3(0.5-9.8)  **Duration of membrane rupture** <1 vs. 1-5 vs. 6-12 vs. >=13 0/53(0) vs. 1/59(1.7) vs. 4/40(10) vs. 2/30(6.7), (p=.02) adjusted OR for membrane rupture >6h, 9.3(1.5-179.7)  **Duration of labor, h** <=6 vs. 7-12 vs. >=13 2/84(2.4) vs. 4/48(8.3) vs. 1/44(2.3), (p=.78) | **Cigarette smoking during** pregnancy yes vs. no 1/99(1) vs. 6/83(7.23), RR 0.14(0.02-1.1)  **Alcohol intake during pregnancy** yes vs. no 1/42(2.4) vs. 6/140(4.3), RR 0.6(0.1-4.5)  **History of IVDU** yes vs. no 1/94(1.1) vs. 6/88(6.8), RR 0.2 (0.02-1.27)  **Amniotic fluid** clear (ref) vs. meconium vs. bloody 2/129(1.6) vs. 4/40(10) vs. 1/10(10), RR 6.5(1.2-33.9) RR 6.5 (0.6-65.2) |
| McMenamin, 2008165Ireland  Fair | **Fetal scalp electrode (n=23)**  Infant HCV RNA+: 0/11 (0%)infant not tested: 12 | Not Reported | **Elective cesarean vs. emergency cesarean or vaginal delivery (n=441):** 1/33 (3%, 95% CI 0% - 8%) vs. 17/408 (4.2%, 95% CI 2.3%-6.2%) p=NS  \*Not adjusted\*same results if limited to HIV- mothers  **Elective cesarean vs. emergency cesarean or vaginal delivery HCV-RNA+ women (n=295)**  5.3% vs. 7.2%  p=NS  \*Not adjusted  \*Authors didn't provide raw numbers | Not Reported | **HCV RNA positive vs. negative vs. unknown (n=441)**  Positive vs. negative vs. unknown: 18/255 (7.1%, 95% CI 6.3%-7.9%, p<.05) vs. 0/17 (0%, p<.05) vs. 0/69 (0%)\*not adjusted  **HIV positive vs. negative (n=441)**  1/17 (5.9%, 95% CI 0%-17.2%, p=NS)vs. 17/418 (4.1%, 95% CI 2.2%-6.0%, p=NS)  Mother status unknown: 0/6 (0%) | Not Reported | Not Reported | Not Reported | Not specified, retrospective review of data from National Maternity Hospital and Rotunda Hospital |  |  |
| Moriya, 1995166  Japan Poor | Not Reported | Not Reported | Not Reported | Breast feeding transmission rate (n=74): 5/6 infected received breast milk (83%%) vs. 54/68 uninfected (79%)  OR 1.3 (0.14 to 12.0) | Not Reported | Not Reported | Not Reported | Not Reported | Ministry of Health & Welfare, Japan |  |  |
| Okamoto , 2000167  Japan (Tottori University & Medical Center)  Poor | Not Reported | Not Reported | **Vaginal vs. cesarean**  7/41 (17%) vs. 0/18 (0%), p=089 **High Viral Load mothers** (>2.5x106 copies/mL): 7/16 (44%) vs. 0/10 (0%), p=.023 | The sample size was too small to test the effect of breast-feeding. | History of blood transfusion, history of clinical hepatitis NS, data NR | HCV-RNA+ titers of vaginally delivered infants born to RNA+ mothers:  Mothers (Geometric average, 95% CI): Infectious: 5, (7.0, 2.4–20.0) vs. Noninfectious: 31, (1.5, 0.9–2.3), p<.001  Children (Geometric average, 95% CI): Infected: 7, (8.0, 3.8–16.7) vs. Uninfected: 34, (1.4 0.9–2.2), p<.001 | Not Reported | Research on Children and Families of the Ministry of Welfare of Japan | Not Reported |  |  |
| Pipan, 1996168 Italy   Poor | Not Reported | Not Reported | Not Reported | **Breast vs. formula (n=25)** 0/6 (0%) vs. 0/19 (0%) | Not Reported | Not Reported | Not Reported | Not Reported | MURST grant and the FVG Branch of Italian League against Virus Disease |  |  |
| Resti , 1998169 Italy  Fair | Not Reported | Not Reported | **Vaginal vs. cesarean (n=275)** 9/213 (4%) vs. 4/62 (6%), RR 0.65 (0.21-2.05), p=0.498 | **Breast vs. formula (n=275)** 6/87(7%) vs. 7/188(4%), RR = 1.85 (0.64 to 5.35), p=0.358.   3/6 infected breast fed children had hepatitis C virus RNA detected on the day of birth | Transmission from women with no known risk of infection was significantly lower (RR=0.17%, 0.04-0.73%; P=0.0063)   **IVDU during pregnancy** 1/12 (8.3%) infants HCV+  **HCV viral load** No significant difference (z=0.380; P=0.704) in RNA load between mothers who transmitted the virus and those who did not (3.8 (0.02 to 56)×105 RNA copies/ml v 2.4 (0.01 to 92.7)×105 RNA copies/ml) | 6 babies had hepatitis C virus RNA immediately after birth.   The transmission rate was higher in 20 recipients of blood transfusions (RR=10%, 95% CI 3-17%) | Not Reported | Not Reported | Partially supported by grant 394/A from Regione Toscana, III Programma Ricerca Sanitaria and by a grant from Ministero della Ricerca Scientifica | Not Reported |  |
| Spencer,  1997170  Australia  Poor | Not Reported | **Viremic mothers (mean hours ± SD) (n=63)** Transmitted vs. not transmitted: 28±10 vs. 16±4, p=.03 | **Viremic mothers, cesarean (n=63)  transmitted vs. not transmitted** 1/6 (14%) vs. 6/56 (9%), p=.5  **Cesarean vs. vaginal** 1/7 (14%) vs. 5/55 (9%) | **Viremic mothers breastfeeding (n=63)** transmitted vs. not transmitted 2/6 (33%) vs. 31/57 (54%) p=0.4   **Breast fed vs. formula fed** 2/33 (6%) vs. 4/30 (13%)   Viral RNA detected in breast milk: (n= 38) 0% | Viremic mothers transmitting vs. non-transmitting  **Viral load at delivery** 8.9x105 vs. 3.9x105, p=0.04  **Drug use, mean years** 8.8±1.4 vs. 10±0.8, p=0.7  **Past HBV infection** 4/6 (66%) vs. 34/55 (62%), p<0.9  **Heroin use during pregnancy** 2/2 (100%) vs. 38/45 (84%), p<0.9 | **Birth weight (mean g)** 2698 (transmitted n=6) vs. 3020 (no transmission n=57) p= 0.4  **Gestational Age** transmitting vs. non-transmitting: 37±0.9 weeks vs. 39±0.3 weeks, p=0.3 | Not Reported | Not Reported | Not Reported |  |  |
| Syriopoulou, 2005171 Greece  Poor | Not Reported | Not Reported | **Vaginal vs. cesarean (n=56)** 2/39 (5%) vs. 0/17 (0%), p=0.34 | **Breast vs. formula (n=56)** 0/15 (0%) vs. 2/41 (5%), p=0.38 | **HCV/RNA+ vs. HCV/RNA- (n=86)** 2/56 (3.6%) vs. 0/30 (0%) **HIV+ vs. HIV- (n=56)** 1/2 (50%) vs. 1/54 (2%) (p<.001) **IVDU use during pregnancy, yes vs. no (n=56)** 2/3 (67%) \*1 mother was HIV+ vs. 0/54 (0%) (p<.001) **IVDU ever, yes vs. no (n=56)** 2/8 (25%) vs. 0/48 (0%) (p<.001) | Not Reported | Not Reported | Not Reported | Not Reported |  |  |
| Tajiri , 2001172 Japan (seven hospitals in the Osaka metropolitan area)  Poor | Not Reported | Not Reported | **Vaginal vs. cesarean (n=114)** 8/90 (8.8%) vs. 1/24 (4.2%), p = 0.396  \*RR: 2.04 (.284 - 43.42) | **Breast vs. formula (n=114)**  9/98 (9.2%) vs. 0/16, p=0.243 | Maternal HCV Viremia: positive: 9/81 vs. negative: 0/33, p=.040  Maternal viral load: High: 8/46 vs. Low: 0/27, p=0.019 | Not Reported | Not Reported | Not Reported | Not Reported |  |  |
| Tanzi, 1997173 Italy  Poor | Not Reported | Not Reported | Not Reported | HCV RNA+ mothers (n=18) 12/18 HCV/RNA+ mothers breastfed, none infected at 3 month followup | Not Reported | Not Reported | Not Reported | Not Reported | Not Reported |  |  |
| Zanetti , 1998174 (Intervirology) Italy A prospective Study on Mother-to-Infant Transmission of Hepatitis C virus  Zanetti et al, 1999175 (Journal of Hepatology) Italy Mother-to-infant transmission of hepatitis C virus  Poor | Not Reported | Not Reported | **Vaginal vs. cesarean (HCV+)**  7/193 (3.6%) vs. 1/58 (1.7%), p = 0.7 **(HCV+/HIV+)** 0/4(0%) vs. 9/36(25%), p = 0.5 | **HIV- mothers breast vs. formula (n=251)** 3/127 (2.4%) vs. 5/124 (4.0%),  p = 0.5 **HIV+ mothers breast vs. formula** **(n= 40)**  0 vs. 9/40 (22.5%) | Transmission by History of IVDU:  HCV+: Yes: 3/67 (4.5%) vs. No: 5/184 (2.7%), p=0.4 HCV+/HIV+: Yes: 9/40 (22.5%) vs. No: 0  Transmission by History of Chronic Liver Disease or elevated ALT: HCV+: Yes: 3/85 (3.5%) vs. No: 5/166 (3%), p=1 HCV+/HIV+: Yes: 4/10 (40%) vs. No: 5/30 (16.7%), p=0.2 | Not Reported | Not Reported | Not Reported | Not Reported |  |  |

Abbreviations: HCV, hepatitis C virus; SVR, sustained virologic response.