Published in final edited form as:
Am J Obstet Gynecol. 2008 July ; 199(1): 38.e1–38.e9.

Pregnancy Complications Associated with Hepatitis C: Data from a 2003–2005 Washington State Birth Cohort

Steven A. PERGAM, MD[1], **Chia C. WANG, MD, MS**[1], **Carolyn M. GARDELLA, MD, MPH**[2], **Taylor G. SANDISON, MD, MPH**[1], **Warren T. PHIPPS, MD**[1], and **Stephen E. HAWES, PhD**[3]

1 *University of Washington, Department of Medicine*

2 *University of Washington, Department of Obstetrics and Gynecology*

3 *University of Washington, Department of Epidemiology*

Abstract

Objective—To determine the effect of HCV on selected maternal and infant birth outcomes.

Study Design—This population-based cohort study using Washington State birth records from 2003–2005 compared a cohort of pregnant women identified as HCV-positive from birth certificate data (n=506) to randomly selected HCV-negative mothers (n=2022) and drug-using HCV-negative mothers (n=1439).

Results—Infants of HCV-positive mothers were more likely to be low birth weight (OR, 2.17; 95% CI, 1.24, 3.80), small for gestational age (OR, 1.46; 95% CI, 1.00, 2.13), need assisted ventilation (OR, 2.37; 95% CI, 1.46, 3.85), and require NICU admission (OR, 2.91; 95% CI, 1.86, 4.55). HCV-positive mothers with excess weight gain also had a greater risk of gestational diabetes (OR, 2.51; 95% CI, 1.04, 6.03). Compared to the drug-using cohort, NICU admission and need for assisted ventilation remained associated with HCV.

Conclusions—HCV-positive pregnant women appear to be at-risk for adverse neonatal and maternal outcomes.

Keywords

Hepatitis C; Gestational Diabetes; Drug use; Pregnancy complications

Introduction

Approximately four million people in the US are infected with Hepatitis C virus (HCV).[1,2] In pregnant women, the prevalence of HCV is estimated to range between 0.7 and 4.4%.[3–8] With 4.1 million annual births in the US, up to 200,000 pregnant women per year would be expected to have a history of HCV infection.

Corresponding Author: Steven A Pergam, MD, Fred Hutchinson Cancer Center, 1100 Fairview Ave. North, D3-100, P.O. Box 19024, Seattle, WA 98109, Phone: (206) 667-6702, Fax: (206) 667-4411, Email: spergam@fhcrc.org.

Presentation of material in submitted manuscript: Some of the data in this manuscript will be presented at the Infectious Disease Society of America Conference in San Diego, October 4–10, 2007.

Condensation: Maternal HCV is associated with gestational diabetes and adverse neonatal outcomes regardless of drug use history.

Although HCV affects a significant number of pregnant women, there is little research regarding the impact of HCV on pregnancy outcomes. Prior studies of HCV and pregnancy have focused on vertical transmission of HCV infection, without examining the potential effects of chronic HCV infection on maternal health, complications during delivery, and neonatal health. Since identification of adverse outcomes could effect current screening recommendations, such information could have widespread public health implications.

In 2003, Washington State added maternal HCV status to its birth certificate data collection form, providing an opportunity to assess the potential effects of HCV on pregnancy. The objectives of this study were to evaluate associations between maternal HCV infection, maternal pregnancy complications, and neonate health in Washington State from 2003–2005.

Materials and Methods

Study population

We conducted a population-based cohort study, using Washington State singleton birth records from 2003 to 2005. Birth certificate data for mothers and infants were linked to the Comprehensive Hospital Abstract Reporting System (CHARS), created by the Washington State Department of Health, which contains hospital discharge records of inpatients in non-federal facilities in the state. Birth certificates use a check-box format to collect information on demographic characteristics, complications, procedures, and on newborn conditions. Birth certificates are completed by trained medical records staff with information abstracted from patient records.[9]

The exposed cohort consisted of women noted to be HCV-positive on a birth certificate check-box (n=506). The unexposed cohort consisted of four HCV-negative mothers per exposed, and were randomly selected from the same dataset and frequency matched by birth year (n=2024). Two women in this comparison group were excluded after CHARS data indicated they were HCV-positive (n=2022). A second comparison group consisted of HCV-negative mothers identified from birth certificate data with a history of drug use identified in CHARS using the methods described below (n=1439). HCV-positive mother's drug-using status was determined using similar methods.

Defining drug use and prenatal care

Maternal drug use was ascertained by reviewing CHARS data and identifying all ICD-9 codes associated with a history of opioid, cocaine, and methamphetamine use as has been demonstrated in other studies.[10,11] Drug use was considered positive if the following ICD-9 codes were assigned to the mother: 304.0 (opioid dependence), 304.2 (cocaine dependence), 304.4 (amphetamine dependence), 304.7 (combinations of opioid type drug and any other), 304.9 (unspecified drug dependence), 305.5 (opioid abuse), 305.6 (cocaine abuse), 305.7 (amphetamine or relating acting sympathomimetic abuse), and 292 (drug withdrawal syndromes), or the neonate: 760.72 (Noxious influences on fetus or newborn via placenta or breast milk, narcotics – excludes anesthetic and analgesic drugs administered during labor and delivery), 760.75 (Noxious influences on fetus or newborn via placenta or breast milk - cocaine), and 779.5 (drug withdrawal syndrome in newborn). Prenatal care was assessed using the Adequacy of Prenatal Care Utilization (APCU) index, which uses trimester at first prenatal visit and number of visits to determine a patient's level of care (inadequate, intermediate, adequate, adequate-plus).[12]

Defining maternal and neonatal outcomes

Maternal pregnancy complications of gestational diabetes (GDM) and premature ruptured membranes (PROM) were determined from birth certificate and CHARS data.[13] Mothers were

classified by Body Mass Index (BMI), using their pre-pregnancy weight, as underweight (<18.5), normal (18.5 to 24.9), overweight (25.0 to 29.9) and obese (>30).[14] Pregnancy related weight gain was described using the Institute of Medicine's guidelines, which are based on kilograms of weight gained and mother's baseline BMI. These guidelines recommend pregnancy weight gain of 28 to 40 lbs for women with a BMI of less then 19.8, 25 to 35 lbs for women with a BMI of 19.8 to 26, and 15 to 25 lbs for women with a BMI of 26.1 and to 29.0.[15] Studies suggest that weight gain of 15 to 25 lbs is also appropriate for women with a BMI greater then 29.0.[16] Patients under recommended levels were considered as insufficient, those who gained above recommended guidelines as excess, and those within guidelines as appropriate.

Neonatal outcomes determined from birth certificate data included: having low birth weight (LBW) (< 2500 grams), being small for gestational age (SGA), prematurity (< 37 weeks), neonatal jaundice, low apgar score (< 7 at 5 minutes), Neonatal Intensive Care Unit (NICU) admission, and any need for assisted ventilation. Neonatal jaundice data was collected using the ICD-9 code 774 (neonatal jaundice) from CHARS data. We also reviewed ICD-9 diagnostic codes for to evaluate reasons for NICU admission. Using CHARS data, reasons were classified as due to respiratory, infectious, cardiac, metabolic/gastrointestinal, hematologic, congenital abnormalities, or drug use/withdrawal causes. All reasons were non-mutually exclusive.

Statistical methods

Multivariate logistic regression methods were used to calculate odds ratios (OR) and 95% confidence intervals (95% CI) for outcomes associated with maternal HCV infection. *A priori* confounders included: maternal age, race (White, Black, Hispanic, Asian/Pacific Islander, Native American), tobacco use, alcohol use, drug use, and prenatal care usage. Due to missing prenatal care data in the HCV-negative drug-using cohort, this variable was removed from the model when comparing drug-using cohorts.

Other factors including mother's insurance status, occupation, educational level, pregnancy weight gain, parity, and maternal infections [hepatitis B virus, *Chlamydia trachomatis*, *Neisseria gonorrhea*, Herpes simplex-2 virus, group B streptococcus, syphilis and chorioamnionitis] were also considered potential confounders. We adjusted for these confounders if they altered the OR for the outcomes of interest by 10% of more. In sub-analysis involving drug-using cohorts, mother's occupation and maternal pregnancy weight gain were not included in the model due to significant missing data.

To explore factors associated with NICU admission, Mantel-Haensel stratified analysis was used to determine condition-specific ORs and 95% CIs between children born to HCV-positive mothers stratified by drug use and those in the other cohorts. Due to small numbers, we adjusted only for maternal smoking and prenatal care utilization when comparing the non-drug-using cohorts. In the drug-using cohorts we adjusted for maternal smoking only, due to the large percentage of missing data in prenatal care usage in the HCV-negative drug-using cohort. The University of Washington Institutional Review Board approved of this study. All statistical analysis was performed using STATA 9.0 (College Station, TX).

Results

Demographics

During 2003–2005, 506 mothers (0.2%) of 240,131 singleton deliveries were reported to have HCV, and 2022 women were randomly selected to be HCV-negative controls. In addition, 1439 (0.6%) HCV-negative women and 124 (25%) of the HCV-positive mothers were identified as drug users.

As shown in Table 1, HCV-positive women were similar to HCV-negative drug users in many respects, and less similar to the randomly selected comparison group. Drug-using women, regardless of HCV status, were more likely to be unmarried, have less education, have inadequate prenatal care, have received Medicaid, and smoke than their randomly selected HCV-negative counterparts. The lowest rates of prenatal care and highest rates of Medicaid use were found in the HCV-negative drug-using group.

Maternal outcomes

HCV-positive women were somewhat more likely to have GDM than HCV-negative women (OR, 1.53; 95% CI, 0.85, 2.27) (Table 2). However, among women with excess weight gain during pregnancy, HCV infection was strongly associated with GDM (OR, 2.51; 95% CI, 1.04, 6.03). This association was not observed in women with insufficient or adequate weight gain, (OR, 0.89; 95% CI, 0.28, 2.80 and OR, 1.14; 95% CI, 0.38, 3.39). There was also a trend toward an association between HCV and PROM (OR, 1.66; 95% CI, 0.93, 2.96).

To determine the impact of drug use, a stratified analysis was performed based on drug use history (Table 3). Among non-drug-using mothers, HCV-positivity (n=382) remained associated with GDM in women with excess weight gain (OR, 3.09; 95% CI, 1.29, 7.42). In addition, a similar trend toward an association between HCV infection and PROM (OR, 1.74; 95% CI, 0.98, 3.25) was observed.

Similarly, when the analysis was limited to HCV-positive (n=124) and HCV-negative (n=1439) mothers with a history of drug use, HCV remained somewhat associated with increased risk of PROM (OR, 1.33; 95% CI, 0.60, 2.95) (Table 3). Due to the small number of HCV-positive drug users with GDM (n=2) no comment could be made in regard to this outcome.

Neonatal outcomes

HCV infection was associated with an increased risk of the infant being LBW (OR, 2.17; 95 % CI, 1.24, 3.80), SGA (OR, 1.46; 95% CI, 1.00, 2.13), requiring NICU admission (OR, 2.91; 95% CI, 1.86, 4.55), and needing assisted ventilation (OR, 2.37; 95% CI, 1.46, 3.85) (Table 2). There were non-significant trends for low apgar score (OR, 1.53; 95% CI, 0.93, 2.54), prematurity (OR, 1.54; 95% CI, 0.97, 2.43), and neonatal jaundice (OR, 1.25; 95% CI, 0.82, 1.90) being associated with HCV.

Analyses stratified by drug use again yielded similar findings for non-drug-using mothers (Table 3). HCV was associated with increased risk of being LBW (OR, 2.15; 95% CI 1.19, 3.90), SGA (OR, 1.62; 95% CI, 1.07, 2.43), requiring NICU admission (OR, 3.00; 95% CI, 1.85, 4.86), needing assisted ventilation (OR, 2.25; 95% CI, 1.40, 3.63), and prematurity (OR, 1.69; 95% CI, 1.04, 2.73). Neonates born to HCV-positive mothers were somewhat more likely to have a low apgar score (OR, 1.42; 95% CI, 0.85, 2.37), but this association did not reach statistical significance. In non-drug-using mothers, HCV was not associated with neonatal jaundice (OR, 1.06; 95% CI, 0.67, 1.69).

Finally, when analysis was restricted to mothers with a history of drug use, maternal HCV remained strongly associated with NICU admission (OR, 2.80; 95% CI, 1.83, 4.29) and with need for assisted ventilation (OR, 1.82; 95% CI, 1.03, 3.22) (Table 3). Neonates born to HCV-positive drug-using mothers did not have an increased risk of being LBW (OR, 1.19; 95% CI, 0.74, 1.91), prematurity (OR, 1.03; 95% CI, 0.66, 1.61), SGA (OR, 0.97; 95% CI, 0.57, 1.64), or having a low apgar score (OR, 1.12; 95% CI 0.60, 2.08). There was a non-significant trend toward an association between HCV and neonatal jaundice (OR, 1.50; 95% CI, 0.94, 2.41).

Reasons for NICU admission

Children born to HCV positive mothers were admitted to the NICU (n=93) for a variety of reasons, most commonly with respiratory problems (38.7%), due to maternal drug use/withdrawal (35.5%), early gestational age/prematurity (37.6%), and infections (26.9%). When stratified by drug use, HCV status in non-drug-using mothers was associated with admission to the NICU for respiratory (OR 3.25; 95% CI, 1.62, 6.51) and congenital reasons (OR 4.17; 95% CI, 1.18, 14.8) (Table 4). In these same two cohorts there were also non-significant trends toward an association between maternal HCV status and gestational age/prematurity (OR 1.71; 95% CI, 0.83, 3.56), infectious (OR 2.08; 95% CI, 0.92, 4.72), cardiac (OR 1.41; 95% CI, 0.49, 4.01), metabolic/gastrointestinal (OR 1.24; 95% CI, 0.49, 3.18), and hematologic reasons (OR 3.41; 95% CI, 0.87, 13.3) for NICU admission.

In drug-using women, similar findings were seen (Table 4). Maternal HCV status was associated with admission to the NICU for respiratory (OR 1.91; 95% CI, 1.05, 3.46), infectious (OR 2.41; 95% CI, 1.31, 4.44), and metabolic/gastrointestinal reasons (OR 2.80; 95% CI, 1.49, 5.28). For the remaining outcomes in the drug-using cohorts there were again non-significant trends in all other reasons for admission. Due to small numbers, no conclusions could be drawn in NICU admissions due to congenital abnormalities.

Comments

This study demonstrates that HCV infection in pregnant women is associated with several poor pregnancy and neonatal outcomes. We found that women with HCV may be at higher risk for PROM, and those with excess weight gain during pregnancy have an increased risk of GDM. Likewise, infants born to HCV-infected women were more likely to be LBW, SGA, require NICU admission, and need assisted ventilation. NICU admission and need for assisted ventilation remained strongly associated with maternal HCV regardless of drug use.

This large, population-based cohort demonstrates a previously unreported association between HCV and gestational diabetes. Studies have demonstrated an association between type II diabetes mellitus (DM) and HCV.[17–24] HCV has also been shown to be directly involved in the development of insulin resistance, particularly in individuals with genotype 3 HCV infection.[25–27] Although the mechanism is unknown, HCV has been detected in the pancreas and may cause β-cell dysfunction.[18,28] Risk for GDM is also thought to be due to increases in insulin resistance and BMI[29], and it is possible that by working through similar pathways that HCV could be associated with an increased risk of GDM.

Few studies of HCV and pregnancy have ascertained pregnancy outcomes. Increased risks for obstetric complications associated with HCV infection have not been noted in previous studies, but these were limited by small sample sizes.[30–32] In one study, viremia in HCV seropositive mothers was associated with PROM.[33] In this study, we also report evidence for a possible association between maternal HCV infection and PROM.

In neonates, the paucity of data coupled with the relative infrequency of many adverse outcomes has made it difficult to quantify risk associated with maternal HCV. In previous literature, apgar scores for children born to HCV exposed and unexposed women appear to be similar.[31,32,34] Studies evaluating prematurity however have been contradictory; two studies found no difference in HCV-positive women[31,34], while another found high rates of prematurity and spontaneous abortion in acute disease.[35] Absent data regarding maternal drug use, socio-economic status and other risk factors for HCV acquisition and poor neonatal outcome limit these cross-sectional analyses.

Our findings demonstrate greater risks of neonatal morbidity than have been previously reported, even when adjusting for socio-economic correlates and maternal drug use. We found that HCV was associated with having LBW, prematurity and SGA. Additionally, NICU admission and assisted ventilation were associated with HCV. Drug use has a strong association with poor neonatal outcomes[10,11,36] and has the potential to be a major driving force behind these results. In order to evaluate the role of drug use, drug-using members of the HCV cohort were compared to a HCV-negative drug-using cohort. While being LBW, prematurity, and SGA were not associated with HCV infection in maternal drug users, need for assisted ventilation and NICU admission remained strongly associated with HCV.

HCV appears to be associated with multiple adverse outcomes, yet mechanisms for this increased risk are unknown. Epidemiologically, HCV exposure may be a surrogate marker for other high risk behaviors or factors which could increase the risk of poor outcomes. Physiologically, vascular compromise of the placenta can lead to poor neonatal outcomes.[37,38] Since HCV can cause vasculitis, involvement of the placental vasculature could explain the growth retardation and higher risk of complications post delivery. Pathologic examination of placental changes in women with HCV exposure and further prospective evaluation of other co-factors may help elucidate reasons for increasing pregnancy risk associated with HCV.

This analysis does have limitations imposed by the data. Because universal HCV testing is not mandatory during pregnancy, patients noted to be HCV positive may have significant risk factors that initiated provider screening - introducing an ascertainment bias. While this is unavoidable due to the limitations of birth certificate data collection, if our outcomes of interest were associated with an increased rate of screening mothers for HCV we may be overestimating the risk associated with exposure. Missing data also limits our analysis when analyzing our drug-using HCV-negative cohort.

Given the low prevalence (0.2%) of HCV noted in the birth certificates, it is likely not all exposed mothers were included in the HCV-positive cohort, and that some HCV-positive mothers may have been included in our unexposed groups. Regardless, the low prevalence of HCV infection in the general population means that these issues should not have altered our results substantially. Mothers documented with HCV in the birth certificates were also most likely a combination of those with and without viremia, and whether replicating virus had any effect on these outcomes could not be determined.

Although we tried to evaluate associations between maternal drug use and outcomes of interest, we cannot rule out continued confounding. Similarly, underreporting may have occurred with respect to maternal smoking and alcohol use during pregnancy, resulting in misclassification and the potential for residual confounding. However, since more accurate assessment tools of self-reported drug use have been shown to be inadequate, prospective data may not help to limit further confounding.[39–41]

Finally, Human Immunodeficiency Virus (HIV) status is not included in the dataset. Approximately 6% of HCV infected individuals in the United States are believed to be co-infected with HIV.[2] If these numbers are similar in the present study cohort, then confounding due to HIV infection should not have greatly impacted our results.

Testing at-risk mothers for HCV is advocated by both the Centers for Disease Control[42] and the American College of Obstetricians and Gynecologists[43], but routine HCV screening of all pregnant patients is not considered cost-effective.[44] Still, guidelines may miss at-risk women, as up to 40% of pregnant women with HCV have no identifiable risk factor[5] and HCV risk factors remain under-ascertained by health care providers during pregnancy.[45,46] At-risk screening may only detect half of women exposed to HCV, indicating this method of screening

may be inadequate.[7] Pregnancy also is an opportunity to identify early HCV infection as many who are found to be positive during pregnancy are unaware of their serologic status.[32]

HCV exposure may have a much greater effect on pregnancy and neonatal outcomes then previously reported, indicating that routine HCV screening in pregnant women may need to be reconsidered. In this study, HCV exposure in women with excess weight gain was strongly associated with gestational diabetes. Further studies are needed to clarify this association and to evaluate the additional potential role of HCV on development of gestational diabetes. HCV was also associated with poor neonatal outcomes including being low birth weight, being small for gestational age, the need for assisted ventilation, and NICU admission. Future prospective studies evaluating placental involvement with HCV, role of viral genotype and HCV viremia, and further emphasis on drug use and socio-economic status are warranted.

Acknowledgements

Sources of Financial Support: Dr. Pergam is supported by NIAID grant # T32 AI007044. Drs. Phipps and Sandison are supported by NIH grant #T32 AI007140. Dr. Gardella is supported by NIAID grant # AI-30731. Dr. Wang supported in part by NIH grant #5 K23 AI51523.

We are grateful to Anna Wald, MD, MPH for her assistance in reviewing early results and suggesting additional analyses. We are also indebted to Beth Mueller, PhD for her assistance in the early analysis plan for the project, and to William O'Brien for his assistance with data abstraction. None of those acknowledged were compensated for their contribution.

References

1. Global surveillance and control of hepatitis C. Report of a WHO Consultation organized in collaboration with the Viral Hepatitis Prevention Board, Antwerp, Belgium. J Viral Hepat 1999;6:35–47. [PubMed: 10847128]
2. Alter MJ, Kruszon-Moran D, Nainan OV, et al. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. N Engl J Med 1999;341:556–562. [PubMed: 10451460]
3. Marranconi F, Fabris P, Stecca C, et al. Prevalence of anti-HCV and risk factors for hepatitis C virus infection in healthy pregnant women. Infection 1994;22:333–337. [PubMed: 7531180]
4. Marcellin P, Bernuau J, Martinot-Peignoux M, et al. Prevalence of hepatitis C virus infection in asymptomatic anti-HIV1 negative pregnant women and their children. Dig Dis Sci 1993;38:2151–2155. [PubMed: 8261814]
5. Conte D, Fraquelli M, Prati D, et al. Prevalence and clinical course of chronic hepatitis C virus (HCV) infection and rate of HCV vertical transmission in a cohort of 15,250 pregnant women. Hepatology 2000;31:751–755. [PubMed: 10706568]
6. Baldo V, Floreani A, Menegon T, et al. Hepatitis C virus, hepatitis B virus and human immunodeficiency virus infection in pregnant women in North-East Italy: a seroepidemiological study. Eur J Epidemiol 2000;16:87–91. [PubMed: 10780348]
7. Silverman NS, Jenkin BK, Wu C, et al. Hepatitis C virus in pregnancy: seroprevalence and risk factors for infection. Am J Obstet Gynecol 1993;169:583–587. [PubMed: 7690523]
8. Leikin EL, Reinus JF, Schmell E, et al. Epidemiologic predictors of hepatitis C virus infection in pregnant women. Obstet Gynecol 1994;84:529–534. [PubMed: 7522312]
9. Baeten JM, Bukusi EA, Lambe M. Pregnancy complications and outcomes among overweight and obese nulliparous women. Am J Public Health 2001;91:436–440. [PubMed: 11236410]
10. Burns L, Mattick RP, Cooke M. The use of record linkage to examine illicit drug use in pregnancy. Addiction 2006;101:873–882. [PubMed: 16696631]
11. Kennare R, Heard A, Chan A. Substance use during pregnancy: risk factors and obstetric and perinatal outcomes in South Australia. Aust N Z J Obstet Gynaecol 2005;45:220–225. [PubMed: 15904448]
12. Kotelchuck M. An evaluation of the Kessner Adequacy of Prenatal Care Index and a proposed Adequacy of Prenatal Care Utilization Index. Am J Public Health 1994;84:1414–1420. [PubMed: 8092364]

13. Lydon-Rochelle MT, Holt VL, Cardenas V, et al. The reporting of pre-existing maternal medical conditions and complications of pregnancy on birth certificates and in hospital discharge data. Am J Obstet Gynecol 2005;193:125–134. [PubMed: 16021070]

14. Centers for Disease Control. BMI - Body Mass Index: About BMI for Adults. 2006. accessed at http://www.cdc.gov/nccdphp/dnpa/bmi/adult_BMI/about_adult_BMI.htm on 5/10/06

15. Institute of Medicine, Food and Nutrition Board. Committee on Nutritional Status During Pregnancy, part I: Nutritional Status and Weight Gain. National Academy Press; Washington, DC: 1990.

16. Edwards LE, Hellerstedt WL, Alton IR, et al. Pregnancy complications and birth outcomes in obese and normal-weight women: effects of gestational weight change. Obstet Gynecol 1996;87:389–394. [PubMed: 8598961]

17. Fraser GM, Harman I, Meller N, et al. Diabetes mellitus is associated with chronic hepatitis C but not chronic hepatitis B infection. Isr J Med Sci 1996;32:526–530. [PubMed: 8756978]

18. Caronia S, Taylor K, Pagliaro L, et al. Further evidence for an association between non-insulin-dependent diabetes mellitus and chronic hepatitis C virus infection. Hepatology 1999;30:1059–1063. [PubMed: 10498660]

19. Gray H, Wreghitt T, Stratton IM, et al. High prevalence of hepatitis C infection in Afro-Caribbean patients with type 2 diabetes and abnormal liver function tests. Diabet Med 1995;12:244–249. [PubMed: 7538925]

20. Allison ME, Wreghitt T, Palmer CR, et al. Evidence for a link between hepatitis C virus infection and diabetes mellitus in a cirrhotic population. J Hepatol 1994;21:1135–1139. [PubMed: 7699240]

21. Ozyilkan E, Arslan M. Increased prevalence of diabetes mellitus in patients with chronic hepatitis C virus infection. Am J Gastroenterol 1996;91:1480–1481. [PubMed: 8678039]

22. Grimbert S, Valensi P, Levy-Marchal C, et al. High prevalence of diabetes mellitus in patients with chronic hepatitis C. A case-control study. Gastroenterol Clin Biol 1996;20:544–548. [PubMed: 8881566]

23. Mehta SH, Brancati FL, Strathdee SA, et al. Hepatitis C virus infection and incident type 2 diabetes. Hepatology 2003;38:50–56. [PubMed: 12829986]

24. Mehta SH, Brancati FL, Sulkowski MS, et al. Prevalence of type 2 diabetes mellitus among persons with hepatitis C virus infection in the United States. Ann Intern Med 2000;133:592–599. [PubMed: 11033586]

25. Shintani Y, Fujie H, Miyoshi H, et al. Hepatitis C virus infection and diabetes: direct involvement of the virus in the development of insulin resistance. Gastroenterology 2004;126:840–848. [PubMed: 14988838]

26. Hui JM, Sud A, Farrell GC, et al. Insulin resistance is associated with chronic hepatitis C virus infection and fibrosis progression [corrected]. Gastroenterology 2003;125:1695–1704. [PubMed: 14724822]

27. Lonardo A, Loria P, Adinolfi LE, et al. Hepatitis C and steatosis: a reappraisal. J Viral Hepat 2006;13:73–80. [PubMed: 16436124]

28. Laskus T, Radkowski M, Wang LF, et al. Search for hepatitis C virus extrahepatic replication sites in patients with acquired immunodeficiency syndrome: specific detection of negative-strand viral RNA in various tissues. Hepatology 1998;28:1398–1401. [PubMed: 9794927]

29. Kaaja RJ, Greer IA. Manifestations of chronic disease during pregnancy. JAMA 2005;294:2751–2757. [PubMed: 16333011]

30. Jabeen T, Cannon B, Hogan J, et al. Pregnancy and pregnancy outcome in hepatitis C type 1b. Qjm 2000;93:597–601. [PubMed: 10984554]

31. Jaffery T, Tariq N, Ayub R, et al. Frequency of hepatitis C in pregnancy and pregnancy outcome. J Coll Physicians Surg Pak 2005;15:716–719. [PubMed: 16300710]

32. Floreani A, Paternoster D, Zappala F, et al. Hepatitis C virus infection in pregnancy. Br J Obstet Gynaecol 1996;103:325–329. [PubMed: 8605128]

33. Latt NC, Spencer JD, Beeby PJ, et al. Hepatitis C in injecting drug-using women during and after pregnancy. J Gastroenterol Hepatol 2000;15:175–181. [PubMed: 10735542]

34. Bohman VR, Stettler RW, Little BB, et al. Seroprevalence and risk factors for hepatitis C virus antibody in pregnant women. Obstet Gynecol 1992;80:609–613. [PubMed: 1407881]

35. Medhat A, el-Sharkawy MM, Shaaban MM, et al. Acute viral hepatitis in pregnancy. Int J Gynaecol Obstet 1993;40:25–31. [PubMed: 8094346]

36. Ludlow JP, Evans SF, Hulse G. Obstetric and perinatal outcomes in pregnancies associated with illicit substance abuse. Aust N Z J Obstet Gynaecol 2004;44:302–306. [PubMed: 15282000]

37. Redline RW. Severe fetal placental vascular lesions in term infants with neurologic impairment. Am J Obstet Gynecol 2005;192:452–457. [PubMed: 15695986]

38. Sander CM, Gilliland D, Akers C, et al. Livebirths with placental hemorrhagic endovasculitis: interlesional relationships and perinatal outcomes. Arch Pathol Lab Med 2002;126:157–164. [PubMed: 11825110]

39. Colon HM, Robles RR, Sahai H. The validity of drug use responses in a household survey in Puerto Rico: comparison of survey responses of cocaine and heroin use with hair tests. Int J Epidemiol 2001;30:1042–1049. [PubMed: 11689520]

40. Colon HM, Robles RR, Sahai H. The validity of drug use self-reports among hard core drug users in a household survey in Puerto Rico: comparison of survey responses of cocaine and heroin use with hair tests. Drug Alcohol Depend 2002;67:269–279. [PubMed: 12127198]

41. Buchan BJ, M LD, Tims FM, et al. Cannabis use: consistency and validity of self-report, on-site urine testing and laboratory testing. Addiction 2002;97 Suppl 1:98–108. [PubMed: 12460132]

42. Centers for Disease Control and Prevention. Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. MMWR Recomm Rep 1998;47:1–39.

43. American College of Obstetricians and Gynecologists. ACOG Technical Bulletin No. 246. Washington, DC: American College of Obstetricians and Gynecologists; 2000. Primary and Preventive Care: Periodic Assessments; p. 1-7.

44. Plunkett BA, Grobman WA. Routine hepatitis C virus screening in pregnancy: a cost-effectiveness analysis. Am J Obstet Gynecol 2005;192:1153–1161. [PubMed: 15846195]

45. Boaz K, Fiore AE, Schrag SJ, et al. Screening and counseling practices reported by obstetrician-gynecologists for patients with hepatitis C virus infection. Infect Dis Obstet Gynecol 2003;11:39–44. [PubMed: 12839631]

46. Giles ML, Sasadeusz JJ, Garland SM, et al. An audit of obstetricians' management of women potentially infected with blood-borne viruses. Med J Aust 2004;180:328–332. [PubMed: 15059052]

Table 1

Selected maternal characteristics of pregnancies from within specific cohorts, Washington State 2003–2005

	HCV-positive n = 506 number (%)	Random HCV-negative n = 2022 number (%)	HCV-negative with drug use n = 1439 number (%)
Mean Age (SD)	29.6 (6.4)	27.8 (6.4)	26.2 (6.1)
<20	19 (4)	190 (9)	177 (12)
20–24	112 (22)	486 (24)	454 (32)
25–29	120 (24)	544 (27)	415 (29)
30–34	127 (25)	496 (25)	220 (15)
35–39	99 (20)	244 (12)	142 (10)
>40	29 (5)	62 (3)	31 (2)
Race			
White	388 (77)	1438 (71)	1007 (70)
Black	27 (5)	87 (4)	116 (8)
Hispanic	22 (4)	214 (11)	58 (4)
Asian/PI	22 (4)	189 (9)	39 (3)
Native American	36 (8)	56 (3)	187 (13)
unknown	11 (2)	38 (2)	32 (2)
Marital status			
married	182 (36)	1377 (68)	252 (18)
unmarried	313 (62)	636 (31)	1168 (81)
unknown	11 (2)	9 (<1)	19 (1)
Mother's education Mean years (SD)	11.7 (1.9)	13.1 (2.8)	11.1 (1.7)
high school or less	334 (66)	885 (44)	1089 (76)
beyond high school	152 (30)	1110 (55)	289 (20)
unknown	20 (4)	27 (1)	61 (4)
Mother's occupation			
employed	293 (58)	1451 (71)	844 (59)
homemaker	95 (19)	336 (17)	255 (18)
unemployed/disabled	36 (7)	84 (4)	153 (11)
unknown	82 (16)	151 (7)	187 (13)
Number Pregnancies Mean (SD)	1.79 (1.66)	1.07 (1.33)	1.8(1.8)
primaparous	116 (23)	805 (40)	383 (27)
multiparous	384 (76)	1168 (58)	980 (68)
unknown	6 (1)	49 (2)	76 (5)
APCU index *			
inadequate	127 (25)	164 (12)	627 (44)
intermediate	81 (16)	263 (19)	137 (10)
adequate	142 (28)	512 (37)	160 (11)
adequate plus	76 (15)	176 (13)	89 (6)
unknown	80 (16)	257 (19)	426 (30)
Mother's weight gain **			
insufficient	113 (22)	442 (22)	347 (24)
appropriate	111 (22)	504 (25)	235 (16)
excess	179 (35)	733 (36)	398 (28)
missing	103 (20)	343 (17)	459 (32)
Insurance status			
Medicaid	335 (66)	736 (36)	1077 (75)
Private insurance	105 (21)	1046 (52)	158 (11)
Self-pay	13 (3)	23 (1)	59 (4)
other governmental	32 (6)	104 (5)	85 (6)
unknown	21 (4)	113 (6)	60 (4)
Smoking			
yes	286 (57)	226 (11)	817 (57)
no	211 (42)	1775 (88)	591 (41)
unknown	9 (2)	21 (1)	31 (2)
Alcohol use			
yes	12 (2)	2 (<1)	66 (5)
no	494 (98)	2020 (100)	1373 (95)
Drug Use			
yes	124 (25)	17 (<1)	1439 (100)
no	382 (75)	2005 (99)	- - -

Percentages may not equal 100 due to rounding. All values given as n (%) unless indicated

* Adequacy of Perinatal Care Utilization index

** According to Institute of Medicine guidelin

Table 2

Risk of selected maternal and infant outcomes in HCV pregnant mothers relative to randomly selected HCV-negative mothers

	All Mothers		
Outcome	**All HCV-positive n/total (%)**	**Random HCV-negative n/total (%)**	**Adjusted OR† (95% CI)**
Maternal			
Gestational DM	37/497 (7)	113/2017 (6)	1.53 (0.85, 2.27),[ab]
Insufficient wt gain	9/111 (8)	38/442 (9)	0.89 (0.28, 2.80)
Appropriate wt gain	5/104 (5)	18/310 (6)	1.14 (0.38, 3.39)
Excess wt gain	17/178 (10)	28/730 (4)	2.51 (1.04, 6.03)
Premature ruptured membranes	38/448 (8)	65/2011 (3)	1.66 (0.93, 2.96)
Infant			
Low birth weight (<2500 grams)	63/501 (13)	73/2019 (4)	2.17 (1.24, 3.80)[b]
Prematurity (<37 wks)	82/500 (16)	127/2016 (6)	1.54 (0.97, 2.43)
Small for Gestational Age	81/496 (16)	176/2015 (9)	1.46 (1.00, 2.13)
Neonatal jaundice	61/506 (12)	177/2022 (9)	1.25 (0.82, 1.90)
Low apgar score (< 7)	44/506 (9)	99/2022 (5)	1.53 (0.93, 2.54),[cd]
NICU admission	93/485 (19)	96/2005 (5)	2.91 (1.86, 4.55)[a]
Assisted ventilation (any)	69/485 (14)	115/2005 (6)	2.37 (1.46, 3.85)[c]

Percentages may not equal 100 due to rounding. All values given as n (%) unless indicated

Multivariate logistic regression methods used to calculate OR and 95% CI.

† All outcomes adjusted for mother's age, mother's race, maternal smoking, maternal drug use, maternal alcohol use, and prenatal care usage (see details in methods section).

Outcomes also adjusted for:

a – insurance status,

b – mother's occupation,

c – mother's education,

d – weight gain during pregnancy

Table 3

Risk of selected maternal and infant outcomes in HCV-positive mothers relative to HCV-negative mothers stratified by drug use

	Mothers without drug use			Mothers with drug use		
Outcome	**HCV-positive without drug use n = 382**	**Random HCV-negative without drug use n = 2005**	**Adjusted OR† (95% CI)**	**HCV-positive with drug use n = 124**	**HCV-negative with drug use n=1439**	**Adjusted OR‡ (95% CI)**
Maternal						
Gestational DM	35/379 (9)	111/2000 (6)	1.65 (0.92, 2.99),[ab]	2/118 (2)	50/1431 (3)	- - - -
Insufficient wt gain	9/86 (10)	38/438 (9)	0.89 (0.29, 2.82)	- - - -	- - - -	- - - -
Appropriate wt gain	5/89 (9)	28/500 (6)	1.13 (0.38, 3.35)	- - - -	- - - -	- - - -
Excess wt gain	16/143 (11)	27/725 (4)	3.09 (1.29, 7.42)	- - - -	- - - -	- - - -
Premature ruptured membranes	27/374 (7)	63/1994 (3)	1.74 (0.98, 3.25)[a]	11/114 (10)	77/1402 (5)	1.33 (0.60, 2.95),[ae]
Infant						
Low birth weight (<2500 grams)	36/382 (9)	71/1931 (4)	2.15 (1.19, 3.90)[b]	27/119 (23)	249/1390 (17)	1.19 (0.74, 1.91)
Prematurity (<37 wks)	48/378 (13)	122/1999 (6)	1.69 (1.04, 2.73)	34/122 (28)	338/1413 (24)	1.03 (0.66, 1.61)
Small for Gestational Age	61/378 (16)	174/1998 (9)	1.62 (1.07, 2.43)[c]	20/118 (17)	225/1369 (16)	0.97 (0.57, 1.64)
Neonatal jaundice	35/382 (9)	177/2005 (9)	1.06 (0.67, 1.69)[d]	26/124 (21)	228/1408 (16)	1.50 (0.94, 2.41)
Low apgar score (< 7)	31/382 (8)	97/2005 (5)	1.42 (0.85, 2.37)	13/124 (10)	135/1439 (9)	1.12 (0.60, 2.08)
NICU admission	49/377 (13)	92/1988 (5)	3.00 (1.85, 4.86)[a]	44/108 (41)	269/1363 (20)	2.80 (1.83, 4.29)
Assisted ventilation (any)	51/377 (14)	112/1988 (6)	2.25 (1.40, 3.63)[c]	18/108 (17)	127/1364 (9)	1.82 (1.03, 3.22)

Percentages may not equal 100 due to rounding. All values given as n (%) unless indicated

Multivariate logistic regression methods used to calculate OR and 95% CI.

† All outcomes adjusted for mother's age, mother's race, maternal smoking, maternal alcohol use, and prenatal care

‡ All outcomes adjusted for mother's age, mother's race, maternal smoking, and maternal alcohol use.

Outcomes also adjusted for:

a – insurance status,

b – mother's occupation,

c – weight gain during pregnancy,

d – marital status,

e – genital herpes

Table 4

NICU admission reason and risk in HCV-positive and HCV-negative mothers stratified by drug-using status

NICU Admission Reasons (not mutually exclusive)	HCV-positive without drug use n (%)	Random HCV-negative without drug use n (%)	Adjusted OR† (95% CI)	HCV-positive mothers with drug use n (%)	HCV-negative mothers with drug use n (%)	Adjusted OR‡ (95% CI)
Respiratory	22/382 (6)	42/2005 (2)	3.25 (1.62, 6.51)	14/124 (11)	97/1439 (7)	1.91 (1.05, 3.46)
Gestational Age or Prematurity	19/382 (5)	39/2005 (2)	1.71 (0.83, 3.56)	16/124 (13)	125/1439 (9)	1.69 (0.96, 2.96)
Infectious	11/382 (3)	18/2005 (<1)	2.08 (0.92, 4.72)	14/124 (11)	72/1439 (5)	2.41 (1.31, 4.44)
Metabolic/Gastrointestinal	9/382 (2)	32/2005 (2)	1.24 (0.49, 3.18)	13/124 (10)	64/1439 (4)	2.80 (1.49, 5.28)
Cardiac	6/382 (2)	19/2005 (1)	1.41 (0.49, 4.01)	3/124 (2)	15/1439 (1)	2.24 (0.66, 7.60)
Hematologic	5/382 (1)	9/2005 (<1)	3.41 (0.87, 13.3)	3/124 (2)	18/1439 (1)	2.03 (0.57, 7.21)
Congenital Abnormalities	4/382 (1)	4/2005 (<1)	4.17 (1.18, 14.8)	0/124 (0)	4/1439 (<1)	

Percentages may not equal 100 due to rounding. All values given as n (%) unless indicated

Mantel-Haensel stratified analysis were utilized to determine OR and 95% CI.

† All outcomes adjusted for maternal smoking and prenatal care utilization

‡ All outcomes adjusted for maternal smoking