Differing presentations of hepatitis C in pregnancy: A case report series supporting universal screening for hepatitis C virus in pregnancy

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ABSTRACT

Introduction: The prevalence of Hepatitis C virus (HCV) infection in women of childbearing age is on the rise. Of people infected, 50–85% develop chronic hepatitis C. Chronic HCV infection is significant because it puts the mother and fetus at risk for well described complications. Conversely, pregnancy alters the natural progression of chronic HCV potentially impacting the long-term health of the mother. Differing presentations of HCV make the identification of patients with HCV infection challenging. Currently, HCV testing for pregnant women is only recommended by the Society for Maternal Fetal Medicine (SMFM) and the American College of Obstetrics and Gynecology (ACOG) for women with preexisting risk factors.

Case Series: In this case series of three obstetric patients with HCV we would like to highlight the varied range of clinical presentations of HCV in pregnancy. The first patient had a known HCV infection prior to pregnancy. Liver function tests and a viral load collected at her first prenatal visit were consistent with viral clearance and she went on to have an uneventful pregnancy. Patient two developed intrahepatic cholestasis of pregnancy (ICP), a well-described complication of chronic HCV infection. Finally, patient three developed transaminitis and a decrease in her viral load: the opposite of expected findings.

Conclusion: This case series illustrates classic and unusual presentations of HCV in pregnancy. Heterogeneity of presentations with inconsistent presence of risk factors on presentation makes predicting who needs screening difficult. Given the availability of new treatments and the serious morbidity chronic hepatitis can inflict on both the mother and baby perhaps universal HCV screening in pregnancy should be reconsidered.

Keywords: Hepatitis C virus, Hepatitis C virus screening, Intrahepatic cholestasis of pregnancy, Pregnancy

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INTRODUCTION

The typical course of chronic hepatitis C virus (HCV) infection during pregnancy appears to be a decrease in alanine aminotransferase (ALT) levels and an increase in HCV ribonucleic acid (RNA) quantitative titers [1–4].
These changes become more pronounced in the second and third trimesters of pregnancy. They are thought to be the result of pregnancy being a state of relative immunosuppression to allow for tolerance of foreign, fetal antigens. This immunosuppression may allow for increased viral replication and decreased immune-mediated hepatic damage, leading to an increase in HCV quantitative titers and a decrease in ALT levels. These values typically return to their pre-pregnancy levels a few months post-partum, which coincide with an increase in the helper T cell type 1 (Th1) immune response [4]. In some patients, the HCV RNA, and ALT levels do not significantly change during pregnancy; these patients have been found to have an elevated Th1 immune response both before and after delivery, suggesting high baseline Th1 expression. Some authors have suggested that the pregnancy-associated decrease in hepatic damage is also responsible for a lower risk of fibrosis progression compared to HCV positive controls with no history of pregnancy, though there is conflicting data regarding this point [1].

Chronic HCV infection is known to affect the course of pregnancy. HCV-infected mothers are at significantly greater risk of developing ICP compared to non-HCV infected controls [5]. It is hypothesized that this is due to alterations in expression of transporter proteins in the liver, hepatocyte, and biliary epithelial cell modification, or increased production of bile acids associated with the ABCB11 genotype [6]. HCV-infected women are at greater risk for gestational diabetes as well. This is possibly due to the same mechanism by which HCV increases the risk of insulin resistance in non-pregnant patients [2]. Other previously documented effects of chronic HCV infection on pregnancy include preterm delivery, low birth weight, small for gestational age, and neonatal intensive care unit (NICU) admission requiring ventilation, though this last finding has not been consistently reproduced [1, 2].

Due to the morbidity associated with HCV for both mother and fetus, screening women for the disease in pregnancy seems reasonable. However, current recommendations only support testing in women with exposure to persistent or new risk factors for HCV [1]. This recommendation could be insufficient in light of the fact that some patients may not disclose risk factors or providers may not ask. Both acute and chronic HCV infections may lack symptoms thus using current recommendations as guidance for HCV screening in pregnancy may lead to a missed opportunity in terms of diagnosing HCV and providing referral for treatment after pregnancy.

Our case series reviews three obstetric patients with HCV infections who had very different clinical presentations. The heterogeneity of these patients supports our position that universal screening for HCV in pregnancy should be reconsidered.

### CASE SERIES

**Patient 1: YE**

Patient 1 is a 29-year-old Hispanic woman G2P1001 (1 prior full-term vaginal delivery) with a known history of HCV who presented at 13 weeks gestation with dichorionic, diamniotic twins confirmed by first trimester ultrasound. Her HCV diagnosis was made in 2016 (approximately one year prior to the current pregnancy) when she presented to her primary care physician complaining of abdominal pain. The patient did not have any identifiable risk factors and she did not have hepatitis in her first pregnancy. However, an ultrasound performed at the time was significant for fatty liver and a subsequent hepatitis panel confirmed the diagnosis of HCV genotype 3. At the time of diagnosis her liver function tests (LFTs) were elevated (AST 470/ALT 647), her bilirubin was within normal limits, and her HCV quantitation was 4,286,570 IU/mL. She tested negative for other strains of hepatitis and for HIV. The patient received treatment and at her new OB visit her HCV RNA was undetectable. Her aspartate aminotransferase (AST) and ALT were both less than 30 well within the normal range. A repeat viral load and liver enzyme panel in the third trimester showed a continued detectable viral load and LFTs within normal limits. She delivered healthy twins at 38 weeks via scheduled primary low transverse cesarean section due to malpresentation of twin B: a female 6 lb 2 oz, and a male 6 lb 7 oz. Both twins had one and five-minute apgars of nine. Neither the mother nor the newborns suffered any complications during the pregnancy, delivery, or during the 6-week postpartum period. Her HCV quantification remained undetectable after pregnancy and she was scheduled to follow up with a hepatologist postpartum.

**Patient 2: LR**

Patient 2 is a 30-year-old African American woman G6P1131 with a prior history of an intrauterine fetal demise (IUDF) at 35 weeks of gestation (IUDF workup was negative) who presented at 15 weeks and 2 days gestation with dichorionic, diamniotic twins diagnosed on a 15 week ultrasound. Her HCV infection was diagnosed prior to the current pregnancy. Of note, she did not have HCV in the pregnancy affected by the IUFD. She did not present with symptoms but was screened to her primary care physician due to high risk sexual behavior. The remainder of her hepatitis and sexually transmitted infections (STI) panel including HIV was negative. On diagnosis her viral load was 5.8 log 10 (high) [630,957 copies/mL] and her LFTs were within normal limits. Her HCV was not genotyped, and she did not receive treatment for her HCV prior to conception. At 20 weeks and 4 days gestation her baseline HCV RNA quantitative titer was 687,330 copies and both her AST and ALT were less than 29 (within normal limits). Then at 24 weeks and 5 days, the patient developed generalized
pruritis. Her exam was significant for an urticarial, macular rash on her extremities and bile acids of 41. She was diagnosed with ICP and pruritic urticarial papules and plaques of pregnancy (PUPPPs). She was started on Ursodiol for symptomatic relief. In addition to HCV, her pregnancy was complicated by a positive group B strep (GBS) vaginal culture and gestational hypertension (GHTN). All of her preeclampsia labs were within normal limits, more specifically her LFTs remained stable, and her urine protein to creatinine ratio was 0.106. Due to the diagnosis of ICP the patient underwent antenatal surveillance consisting of weekly nonstress tests (NST) and biophysical profiles (BPP). At 36 weeks and 1 day of gestation the patient underwent a repeat cesarean section. Preterm delivery was recommended due to worsening ICP in the setting of history of IUFD. The patient delivered two live males via repeat transverse cesarean section due to malpresentation of twin B. Both twins had one and five-minute apgars of nine. Neither the mother nor the newborns suffered any complications during delivery and neither infant required neonatal intensive care unit (NICU) admission.

**Patient 3: HH**

Patient 3 is a 34-year-old Caucasian woman G5P1122 who presented at nine weeks and one day gestation with a single, live, intrauterine pregnancy. The patient had a known history of HCV genotype 1a infection but was treatment naïve. Her HCV RNA quantitative titers and AST/ALT trends are seen in Figure 1. Her past medical history was significant for hypertension, hypothyroidism, asthma, HSV1, HSV2, prior preeclampsia, depression, post-traumatic stress disorder (PTSD), anxiety, and attention deficit hyperactive disorder (ADHD). She additionally had a history of tetrahydrocannabinol (THC) use prior to pregnancy. She discontinued use when she became aware she was pregnant. At 37 weeks and one day of gestation the patient went into labor. She underwent a repeat low transverse cesarean section (she had two prior cesarean deliveries and at our institution was not a candidate for trial of labor after cesarean (TOLAC)) and delivered a live male infant weighing 6 lb with one and five-minute apgars of nine. Neither the mother nor the newborn suffered any complications during labor or delivery.

**DISCUSSION**

Patient 1 had an uncomplicated pregnancy and birth. Based on the negative results of her HCV RNA quantitative titer, she cleared her HCV infection prior to pregnancy [7]. Neither she nor her infant suffered any of the complications associated with chronic HCV infection. Clearance of HCV infection during pregnancy has been described in a case report by Clohessy et al. though this is believed to be a rare occurrence [8]. In the aforementioned case report neither the mother nor the infant suffered any complications attributable to HCV infection similar to Patient 1. This possibly suggests that perhaps the pregnancy of women who have cleared a previous HCV infection may not significantly differ from that of women who have never been infected with HCV.

Patient 2 demonstrated a well-known complication of HCV infection: ICP. A 2017 meta-analysis found that HCV infected patients have an odds ratio (OR) of 20.4 of developing ICP compared to non-HCV infected controls [5]. The association is so strong that if a woman has no history of HCV infection but develops ICP she has an OR of 4.08 of having an HCV infection later in life. This led the authors of the aforementioned meta-analysis to recommend HCV testing for all women who develop ICP. Our patient was diagnosed with both ICP and PUPPPs. Her diagnosis of PUPPPs, in the setting of a twin pregnancy, was not surprising given that the excess abdominal distension associated with multifetal gestation is thought to lead to a higher incidence of PUPPPs [9]. As for her ICP, both twin gestation and HCV infection are risk factors thus we cannot say with certainty that her ICP was directly due to her HCV infection though the literature suggests a strong association between ICP and HCV.

Finally, the classic course of chronic HCV infection during pregnancy is that of increasing HCV titers and decreasing ALT levels however, patient 3 demonstrated the opposite pattern. Previous case reports have shown transaminitis when the virus is contracted acutely during pregnancy or when a chronically infected patient drinks heavily, but neither of those appeared to be the case with patient 3 [10]. There was additionally no evidence of concomitant HIV infection causing an immune response which could potentially account for the paradoxical presentation. Patient 3’s subtype of HCV, 1a, is one of the most common in the United States. If her course could be attributed solely to her viral genotype then this pattern likely would have appeared frequently in the literature [11]. It is unclear what caused this paradoxical reaction. It is also unclear what effect this may have on the course of her HCV infection moving forward. It is possible she lost the protective effects normally associated with pregnancy.

![Figure 1: Trend of Patient 3's LFTs and HCV RNA over the course of her pregnancy.](image-url)
There are limits to what conclusions can be drawn from this report. Patients with HCV infection tend to have many comorbidities leading to confounding outcomes; our patients are no exception. In order to isolate the effect of HCV infection from these comorbidities a study with a large sample size would likely be necessary. However, our case series does raise a couple of considerations.

HCV infection in pregnancy has a wide variety of presentations beyond the usual decrease in ALT and increase in the viral load. As seen here, with patient 1, cleared HCV infections may not negatively impact pregnancy. In fact, the gastroenterology literature suggests that a patient without a viral load should be considered cured [12]. Thus, it begs the question should we counsel our obstetric patients with cleared HCV any different than our patients who were never infected?

As previously stated, ICP is so closely associated with HCV infection that some literature suggests it may be worth testing women with ICP for HCV. Here, we go one step further and postulate that universal HCV screening in pregnancy should be reconsidered. We feel the increasing prevalence of HCV and the varying presentations of HCV in pregnancy, as illustrated by our case series, justifies our recommendation for universal screening during pregnancy. Pregnancy offers an opportunity to screen women who may otherwise not seek medical care either due to lack of symptoms or ignorance of their HCV status/risk factors.

Finally, critics of universal screening site increased healthcare costs as one of the arguments against it [13]. However, without universal screening for HCV in pregnancy we are missing the opportunity to diagnose and treat HCV. Given the increased morbidity of chronic HCV, failure to identify cases and provide treatment may be more costly in the long run [13]. Unidentified cases also increase the risk of vertical transmission. If the care team is unaware, precautions such as avoiding prolonged rupture of membranes, invasive fetal monitoring, and breastfeeding in the setting of cracked/bleeding nipples won’t be taken [14, 15]. Additionally, the opportunity to screen the infant will be missed and may lead to a missed diagnosis in the infant as well.

CONCLUSION

Heterogeneity of presentations with inconsistent presence of risk factors on presentation makes predicting who needs screening difficult. Given the availability of new treatments and the serious morbidity chronic hepatitis can inflict on both the mother and baby perhaps universal HCV screening in pregnancy should be reconsidered.

REFERENCES


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Author Contributions

Daniela Gomez – Analysis of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Sunjay Kumar – Acquisition of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Neeti Misra – Conception of the work, Design of the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Authors declare no conflict of interest.

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All relevant data are within the paper and its Supporting Information files.

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