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HEPATITIS C (H VARGAS AND S FLAMM, SECTION EDITORS)

Testing for Hepatitis C in Pregnancy: the Time Has Come for Routine Rather than Risk-Based

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Abstract

Purpose of Review The purpose of this review is to discuss the reasons for HCV testing during pregnancy and to review what is known about antiviral treatment during pregnancy.

Recent Findings Hepatitis C virus affects over 3 million persons in the USA and is one of the leading infectious causes of death. While HCV is most commonly transmitted via parenteral exposures, thus affecting people who inject drugs, it is also transmitted from mother-to-child. Due to an expanding opioid crisis, an increasing number of women of childbearing age are now infected, resulting in transmission to infants. Risk-based screening has never been proven effective and thus universal screening of pregnant women for HCV infection has been recommended.

Summary Obstetricians may play a key role in the USA by implementing universal testing for HCV in pregnant women, thereby enhancing the health of mothers and identifying children at risk.

Keywords Hepatitis C virus · Pregnancy · Perinatal transmission · Antiviral treatment · Testing

Introduction

After acute infection with hepatitis C virus (HCV), a proportion of infected individuals clear spontaneously, with higher clearance rates among those who are younger and female [1]. Both the acute phase and chronic phase of HCV infection are usually asymptomatic or minimally symptomatic. Chronic HCV, once established, is associated with a variable rate of liver fibrosis, resulting in future risk of advanced fibrosis and cirrhosis, as well as hepatocellular carcinoma, typically over three or more decades, and is associated with significant lost life expectancy [2]. HCV is the leading single infectious cause of death in the USA, outpacing 60 other reportable infectious conditions (including HIV and tuberculosis) combined [3].

Over the past decade, the epidemiology of hepatitis C (HCV) in the USA has demonstrated a dramatic shift as a result of the opioid epidemic, with an increasing number of new HCV cases reported among young persons who inject drugs (PWID) [4]. Rates of new HCV infections reported among women aged 15–44 have surpassed rates among "baby boomers," born between 1945 and 1965, and are continuing to rise. As a result of a rising burden of HCV reported among women of childbearing age as well as in children nationally, the concern for increasing rates of mother-to-child transmission of HCV has been raised [5••].

As a result of increased prevalence of HCV in reproductive-aged women, more women with HCV will become pregnant and for many of them, obstetrical care will be their primary encounter with the health system. Thus, pregnancy may represent an ideal opportunity to initially diagnose HCV in women, link them to care, and refer them for HCV treatment. Recently, the American Association for the Study of Liver Diseases (AASLD) and the Infectious Disease Society of America (IDSA) have jointly recommended universal screening for HCV among women during pregnancy

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[6•]; however, the Society for Maternal Fetal Medicine still recommends risk-based screening for HCV during pregnancy [7]. In the setting of conflicting recommendations, as well as differing practices across obstetricians, the opportunity to diagnose and treat new HCV cases during pregnancy may be missed, potentially leading to mother-to-child transmission and missed diagnosis of HCV infection among infants, as well as progression of HCV in women. As a result, this missed opportunity would hamper efforts towards the potential elimination of HCV as a public health problem. Here, we advocate for why universal screening during pregnancy should become a universal recommended component of obstetrical care.

An Epidemic of HCV in Women of Childbearing Age

The national opioid crisis has directly shifted the epidemiology of HCV from being largely a disease among baby boomers to becoming a disease of young adults. In an early report from the Centers for Disease Control and Prevention (CDC), the state of Massachusetts reported an overall decline in cases of HCV from 1992 to 2005 [8]. However, on closer look, it was noted that during 2002 to 2006, there was actually an increase among cases in 2002 to 2006 among young adults aged 15 to 24, leading to enhanced surveillance in this age group. From 2007 to 2009, the number of cases continued to increase particularly among non-Hispanic white persons, demonstrating a bimodal age distribution of HCV infection in 2009 (compared with the unimodal age distribution in 2002 pertaining to persons born in 1945–1964). While the timing of the increased incidence in young persons may vary by region, multiple national and state level evaluations have subsequently confirmed similar findings [9, 10].

In 2010, the Wisconsin Division of Public Health identified a 300% increase in HCV cases per year in six rural counties in persons aged < 30 from 2004–2008 to 2009–2010. The majority of the individuals diagnosed with HCV reported injection drug use [11]. This epidemic of increasing HCV cases among young persons particularly in rural settings was investigated on a national scale, and again 34 states reported higher incidence of HCV in 2012 compared with 2006 [4]. Of note, 52% of newly reported HCV infections occurred among women. This is consistent with a shift in demographics of opioids, as the 1960s/1970s disproportionately affected men; however, the current epidemic affects women equally to men [12]. As a result, the CDC examined surveillance date for acute HCV in conjunction with the Treatment Episode Data Set-Admissions (TEDS-A), which contains data on admissions to substance abuse treatment facilities, and again found an increase from 2006 to 2012 in Kentucky, Tennessee, Virginia, and West Virginia, which correlated with an increased number of admissions to substance abuse treatment for opioid dependency programs [13]. Interestingly, in urban settings from these states, there were more cases of acute HCV reported among women then in men, despite similar rates between women and men in nonurban settings.

Women who inject drugs may actually be at higher risk of acquiring HCV then men. In a large systematic review examining HCV incidence among persons who inject drugs (PWIDs), women were 36% more likely to contract HCV from injection drug use then men [14]. Proposed reasons for this difference include behavioral as well as biological factors that may predispose females to higher risks of acquiring HCV. Behavioral risks include increased susceptibility towards stigma and thus lower participation in harm reduction services among women as well as higher risk injection behaviors, such as increased sharing of needles. In a further evaluation of injection behaviors utilizing the InC3 Collaborative cohort, a higher HCV incidence in women was identified in women with reported receptive syringe sharing and ancillary equipment sharing, although these practices did not differ between men and women [15•]. More studies of female PWID are necessary regarding differential access to harm reduction, gender-power dynamics, and/or social networks that account for this finding.

Although some of these data reporting increases in HCV over time may reflect increased testing and reporting on the part of providers, the parallel increase in substance use treatment suggests a true increase in HCV infection rate as a result of injection drug use. In addition, in an evaluation of data from the National Survey on Drug Use and Health (NSDUH) from 2007 to 2014, women were noted to have increasing heroin use over time at a faster rate than men and decreasing nonmedical use of a prescription opioids at a slower rate than men. Thus, gender-specific efforts to address the opioid epidemic need to be developed in order to decrease injection drug use and consequent HCV infection [16].

Given the increased incidence of HCV infection among women of childbearing age, reports have also evaluated HCV infection during pregnancy specifically and found similarly alarming trends. Utilizing state surveillance data in Wisconsin and linking to Medicaid data with birth information, from 2011 to 2015, a 93% increase in HCV diagnosed during pregnancy was noted [17•]. Similarly in a recent report published in Ohio, during a 10-year study period from 2006 to 2015, the rate of maternal HCV infection during pregnancy increased 631% [18]. Utilizing national birth certificate data, HCV infection present at the time of delivery among pregnant women increased by 89% from 2009 to 2014, with rates as high as 22.6 per 1000

liver births in West Virginia and 10.1 in Tennessee [19]. Factors associated with risk of HCV during pregnancy included cigarette smoking, Medicaid insurance, and white, non-Hispanic race. Co-infection with other viruses including hepatitis B and other sexually transmitted infections were also strongly associated.

With increased rates of HCV among pregnant women, increased rates of mother-to-child transmission have also been documented. In the Wisconsin study, although only 34% of infants received recommended HCV testing, 7/31 (22%) of those who actually received appropriate testing had documented HCV transmission (4% of the total number of infants born) [17•]. On a national scale utilizing Quest laboratory data, 0.73% of pregnant women (CI, 0.69 to 0.78%) were estimated to have HCV infection from 2011 to 2014, and with 3.9 million live births annually, and an estimated rate of mother-to-infant transmission of 5.8%, an estimated 1700 infants (CI, 1200 to 2200 infants) were born with HCV infection each year to 29,000 women [5••]. Taken together, the rise in HCV among reproductive-aged women has led to increased infection during pregnancy as well as mother-to-child transmission of HCV. Enhanced detection of HCV during pregnancy with universal screening would allow for increased diagnosis of HCV, improved follow-up of children born to mothers with HCV, and potentially decreased mother-to-child transmission through specialized approaches to obstetrical management to minimize risk of infection. Although the mode of delivery (vaginal versus cesarean birth) does not affect the risk of transmission, and HCV is not transmitted via breastfeeding, obstetricians can minimize the use of amniotomy, fetal scalp electrode monitoring, episiotomy, and/or operative delivery (forceps-assisted or vacuum-assisted vaginal delivery) that may increase the risk of perinatal HCV transmission.

The natural history of HCV following perinatal transmission may be benign, as almost half of infected children will spontaneously clear, and only a minority progress to cirrhosis during childhood [20]. However, a recent study demonstrated that individuals who acquire hepatitis C through mother-to-child transmission develop cirrhosis at younger ages and higher rates than individuals who acquire HCV later in life [21]. For those chronically infected, treatment of children is being studied, with future prospects of application of antiviral treatment as young as age 3. Despite this benign course during childhood, HCV-infected children will be at eventual risk for HCV-related complications and children are unlikely to be proactively identified without knowledge of the status of their mother [22]. In Philadelphia, only 16% of perinatally exposed children had HCV testing [23••]. Another recent study based on billing codes confirmed that only a fraction of infants born to HCV-infected mothers were tested: among 1025 HCV-exposed infants, 323 (31%) had record of receiving well-child services, and among these, only 96 (30%) were properly screened for HCV [24].

Pregnancy and HCV

Liver fibrosis in women generally progresses more slowly than men, possibly related to antifibrotic effects of estrogens or lower rates of alcohol use [25]. Post-menopause, the protective effect of female gender on liver fibrosis appears to be attenuated unless hormone replacement therapy is administered [26, 27]. Given the timeframe until cirrhosis, it is unlikely that HCV-infected women of childbearing age will present with end-stage liver disease during pregnancy. However, women infected with HCV should receive postpartum antiviral treatment regardless of fibrosis stage, which if successful abrogates future risk of HCV-related liver disease and liver cancer as well as the onward risk of transmission.

Identifying more pregnant women with HCV would compel obstetricians to provide appropriate counseling regarding the impact of HCV on pregnancy, especially if specialist help is not immediately available. Key studies regarding the natural history have been recently reviewed [7]. Negative obstetric outcomes were found to be associated with HCV, including cesarean delivery, fetal intolerance of labor, preterm birth, maternal intensive care unit admission, blood transfusion, small for gestational age, and neonatal intensive care unit admission [28, 29]. While a rare event, the potentially serious complication of intrahepatic cholestasis of pregnancy (ICP) may occur up to 20-fold more often in HCV-infected women compared with uninfected women [30]. Therefore, not only has HCV been increasingly recognized among women during pregnancy but also has been associated with worse maternal and fetal outcomes. Although associated features such as injection drug use, socioeconomic status, and other concomitant health risks may be contributing to negative pregnancy outcomes, direct effects of HCV infection on pregnancy likely play a role as well.

Conversely, pregnancy also impacts the natural history of HCV. Nulliparity has been associated with faster fibrosis progression [26]. When following women longitudinally through pregnancy, increases in HCV RNA levels and decreases in ALT have been noted, suggesting a more "relaxed" immune response [31]. Postpartum spontaneous clearance of chronic infection has also been reported, likely due to a surge of immunity following childbirth [32, 33]. The vast majority of women with chronic infection during pregnancy are likely to have ongoing infection postpartum and, if left untreated, are likely to suffer sequelae.

Chronic HCV as a condition exhibits several characteristics that make screening attractive: (1) a long latent period that is largely asymptomatic before severe manifestations, (2) availability of relatively simple testing (blood testing of anti-HCV antibody then confirmatory HCV RNA), (3) determination of its presence is important for the patient's prognosis and informs those at risk for transmission (in this scenario the

infant), (4) patient knowledge of the infection can be improved, and (5) identification of infection leads to an opportunity to intervene and cure the condition.

Prospects for Antiviral Treatment During Pregnancy

As mentioned previously, a prime reason why screening is attractive is the ability to intervene in the natural history of HCV infection. Moreover, the interventions have evolved substantially in recent years, moving from a toxic injectable interferon-based regimen to a safe, oral, interferon-free regimen. During the interferon era, it was difficult to recommend treatment fraught with side effects to postpartum mothers, who were usually decades away from complications. Also, ribavirin conferred teratogenic risk. In contrast, the October 2014 Food and Drug Administration (FDA) approval of the first ribavirin-free directly acting antivirals (DAAs), the fixed dose combination of the NS5B polymerase inhibitor sofosbuvir (SOF), and the NS5A inhibitor ledipasvir (LDV) marked a revolution in HCV therapy and a novel opportunity for treatment of HCV during pregnancy. The fixed dose combination of LDV (90 mg) and SOF (400 mg) has a sustained virologic response (SVR) of approximately 99% and 94%, respectively, when given as a once-a-day pill for either 12 or 8 weeks to treatment-naive HCV genotypes 1, 4, 5, and 6 patients without cirrhosis. For FDA approval, evaluation in pregnancy is not required; however, preclinical studies of pregnant rats and rabbits showed there were no safety concerns for antenatal administration. In fact, LDV/SOF was originally given a pregnancy category B designation [34]. Since 2014, other DAAs have been approved that provide improved coverage of HCV genotypes 2 and 3, specifically, sofosbuvir/velpatasvir, daclatasvir (co-administered with SOF), and glecaprevir/pibrentasvir. None of these medications are known to cause any fetal toxicities in preclinical studies at weight-adjusted doses higher than those administered in humans for HCV treatment, except when the dose was high enough to produce maternal toxicity as well [35–37]. Considering that all the mentioned DAAs are given for only 8 to 12 weeks, it is possible to give a complete course before delivery if started in the late second trimester. This strategy would preclude administration of DAAs during organogenesis, which is completed at 16 weeks of gestation and therefore minimize the risk of teratogenicity, while still giving ample opportunity for maternal HCV cure and prevention of HCV perinatal transmission to the infant. A recent survey of HCV-infected mothers suggested that prevention of transmission to their infants may be a greater motivator to pursue antiviral therapy during pregnancy than their personal cures [38].

The first step towards the evidence-based use of any medical intervention during pregnancy is small phase 1 pharmacokinetic (PK) studies performed under an FDA Investigational New Drug Application. Significant physiologic changes occur during pregnancy that affect drug absorption, distribution, metabolism, and excretion, resulting in PK changes that may have clinical consequences [39]. For example, increased renal clearance of drugs could lead to suboptimal concentrations with standard dosing, leading to potential antiviral resistance or decreased efficacy. The FDA recommends that a phase 1 PK study in pregnancy be conducted for medications if (1) all preclinical and clinical studies to date provide reassuring data regarding the safety of use during pregnancy and (2) this risk to the fetus is not greater than minimal and the purpose of the research is of important biomedical knowledge [40]. These criteria are met for the study of any of the aforementioned HCV DAAs.

The first phase one PK study of LDV/SOF during pregnancy (NCT02683005) initiated a course of LDV/SOF at 23 to 24 weeks' gestation and continued for 12 weeks. Three intensive PK visits occurred between 25 and 27, 29 and 31, and 33 and 35 weeks' gestation. After delivery, the infants will be followed for an entire year with growth assessments, developmental exams, and HCV testing [41]. Nine women were treated with 12 weeks of LDV/SOF, with initial results revealing (1) LDV/SOF was well-tolerated, (2) no significant concerns with efficacy or safety have been detected thus far, and (2) 8 out of 8 women with evaluable data achieved SVR. Pharmacokinetic data are pending [42••]. After ensuring the appropriate dose, larger studies are still needed to determine if antenatal DAA administration and at what gestational age time is safe and effective for both maternal treatment and prevention of perinatal HCV transmission. Although maternal outcome data regarding the phase 1 PK study of LDV/SOF will be available soon, a similar small PK study of a pan-genotypic regimen is needed prior to a larger study of antenatal HCV treatment. A pan-genotypic DAA regimen is preferable to LDV/SOF given the significant prevalence of genotype 3 infection among young persons who use injection drugs [43].

Key points regarding the epidemiology, natural history, and treatment relevant to pregnancy are listed in Table 1.

Risk Factor–Based Screening Versus Universal Screening

Testing for HCV infection involves two stages: an initial screening antibody (anti-HCV) for exposure, if positive, followed by HCV RNA testing typically by real-time PCR. This two-stage testing adds the complexity of a follow-up blood draw; however, many laboratories now offer "reflex" testing—positive anti-HCV results to have automatic HCV RNA from the same specimen. If two visits are required, many patients who are positive by antibody never receive HCV

Table 1 Key points regarding the transmission, epidemiology, natural history, and treatment of hepatitis C virus (HCV) in pregnant women

Transmission/epidemiology
• HCV is associated with bloodborne exposure, predominantly via shared equipment used during injection drug use
• The rate of HCV among women of childbearing age is increasing rapidly
• HCV may be transmitted from mother to child, at a rate of approximately 6%
• The route of delivery (vaginal versus cesarean section) does not influence mother-to-child transmission; decision regarding route of delivery should be made independently of the presence of infection
• Breastfeeding is not associated with HCV transmission; decision to breastfeed should be made independently of the presence of infection
Natural history
• HCV is the leading infectious cause of death in the USA
• HCV-related liver disease progresses more slowly in premenopausal women
• HCV infection is associated with adverse maternal and fetal outcomes
• Cirrhosis and end-stage liver disease is rare among women of childbearing age and children
Treatment
• Cure of HCV greatly reduces future risk of liver disease and abrogates onward transmission
• Women of childbearing age and those actively injecting drugs are prioritized for treatment to prevent transmission
• Antiviral treatment is recommended for virtually all HCV-infected individuals, regardless of ongoing risk factors or fibrosis stage
• Antiviral regimens for HCV have improved in safety and efficacy and now cure > 97% of those treated after 8–12-week courses
• Data regarding treatment during pregnancy are sparse. In a phase 1 study, 8 out of 8 pregnant women with genotype 1 HCV infection achieved SVR after receipt of 12 weeks of ledipasvir/sofosbuvir
• Continuation of antiviral treatment if an infected woman becomes pregnant is an individualized decision that should involve the obstetrician and a specialist
Prevention opportunities
• Those identified with HCV are candidates for vaccination against hepatitis A virus and hepatitis B virus
• Prevention of co-infection with HIV via harm reduction and barrier contraception for high-risk sexual encounters

testing, whereas reflex testing is likely to improve the receipt of important results and enhance subsequent linkage to specialized care [44].

Arguments against maternal testing for HCV based on natural history are that the effects of HCV on pregnancy are not uniform, may be confounded by other factors, or are rare (in the case of ICP). Also, while HCV is ultimately a serious infection, following mother-to-child transmission chronic infection rarely leads to significant liver disease during childhood. Significant liver-related events are generally decades away for both mother and child. An additional argument against maternal testing for HCV may be made based on the lack of data to support antiviral treatment during pregnancy. It is notable that universal screening for HBV for pregnant women was recommended by the CDC prior to the approval of antiviral agents such as lamivudine and well before their antepartum use during pregnancy [45]. Nonetheless, recent SMFM guidance [7] is in agreement with AASLD/IDSA that it is worthwhile to diagnose HCV due to its importance for both the future health of the mother and for the identification of infants who may become infected. There is only discordance regarding the precise approach, namely risk factor–based versus universal screening.

Risk factor–based screening requires ascertainment of past exposures in several categories (Table 2). Some exposures should be rare in women of childbearing age, such as receipt of long-term hemodialysis. Those receiving transfusions before July 1992 and clotting factor concentrates before 1987 should be rare, as many are now beyond childbearing potential; those in this category would likely be limited to those exposed as children who may be unaware of such exposures. Screening based on alanine aminotransferase (ALT) misses HCV-infected women with values within the normal range (up to 46% of infected individuals) [46]; also, ALT is not a routine test during pregnancy. More commonplace would be women who ever injected illegal drugs (even once), women who used intranasal illicit drugs [47•], women with past history of incarceration, and those who have sought evaluation for sexually transmitted infections such as HIV.

If the goal is to apply effective screening, strategies based on risk factor screening unfortunately miss the mark largely because they have never been shown to be successful in the USA. A recent retrospective data analysis of electronic medical records (EMR) for 1426 women presenting for antenatal care in 2016 noted that only 7% were tested for HCV. Of note, 21/40 women with intravenous drug use documented in the EMR were not tested; also, 10% of HCV-positive pregnancies had no evidence of a risk factor [48]. The failure of risk factor–based screening is not at all unique to the obstetrical setting, as the literature indicates that other providers similarly failed to successfully diagnose HCV using this approach [49, 50].

What are reasons for failure of risk factor–based testing? Provider-related barriers include time needed to ask such detailed questions, lack of knowledge regarding HCV risk factors and transmission, and competing priorities. Patients may not wish to report certain behaviors particularly during pregnancy especially surrounding drug use due to stigma, fear of recrimination, and/or because they occurred in the distant past. While it may be obvious to test pregnant women already involved in care for opioid use disorders [51], less obvious and/or past behaviors may not be reliably ascertained especially as self-reporting of smoking, alcohol, and drug use has not proven to be accurate [52, 53]. Use of questionnaires regarding HCV risk factors may reduce provider time and from the patient perspective may reduce stigma, but when applied to pregnant women in a high-risk urban clinic was not sufficient to capture cases [54•].

Table 2 Women in whom prenatal screening for hepatitis C virus is recommended by the Society of Maternal Fetal Medicine (SMFM) [7] and the AASLD-IDSA Guidance Panel [6•]

Recommendations regarding prenatal screening for hepatitis C virus (HCV) in the USA	
SMFM	AASLD-IDSA Guidance
Women who ever used injection or intranasal illegal drugs (even once)*	All pregnant women ideally at the initiation of prenatal care
Women ever on long-term hemodialysis	
Women with percutaneous/parenteral exposures in unregulated setting (e.g., tattoos received outside of licensed parlors or medical procedures done in settings without strict infection control policies)	
Recipients of transfusions or organ transplants before July 1992 and recipients of clotting factor concentrates produced before 1987	
Recipients of blood products from donor who later tested positive for HCV	
Women with history of incarceration	
Women seeking evaluation or care for sexually transmitted infection, including HIV	
Women with unexplained chronic liver disease (including persistently elevated ALT)	

ALT, alanine aminotransferase; *HIV*, human immunodeficiency virus

*Women with ongoing injection or intranasal drug use should have repeat screening in the third trimester

Data regarding universal screening approaches in the context of the recent opioid epidemic are emerging. Recently, Norton Healthcare, centered in Louisville, Kentucky, responded to an increase in opioid use and the attendant risk for infectious complications such as HCV by implementing universal screening of pregnant women, via a standing order in their EMR for prenatal visits. The testing strategy included reflex HCV RNA testing for positive antibody tests. The authors compared in time-series fashion the previous period when risk-based testing was applied to the study period. HCV testing rates rose from 17.9% during risk factor–based screening to 100% during the universal screening. The rate of positive antibodies was not very different (4.3% risk factor–based versus 4.9% universal), but the rate of confirmatory HCV RNA was markedly increased (54.3 to 100%). Ultimately, almost ten times as many women with positive HCV RNA were identified (31 women during risk factor–based screening, 306 during universal screening). It is unlikely that temporal increases in local incidence alone could account for this difference, which is much more easily explained by improvements in the total number of women receiving proper testing [55••].

Issues regarding universal testing and measures that may mitigate these concerns are listed in Table 3. If testing rates rise due to universal application among pregnant women, the number of anti-HCV-positive/HCV RNA-negative individuals will increase in parallel. This pattern generally represents one of three possibilities: (1) false positive; (2) spontaneous clearance; or (3) transient clearance, usually during acute infection. Recombinant immunoblot assays were used in the past to attempt to inform the difference between true- and false-positive anti-HCV but are no longer commercially available. Although anti-HCV testing has excellent sensitivity and specificity, increased testing of lower risk individuals will result in a parallel uptick in the magnitude of false positives. It is safe to counsel that in those with risk factors, the likelihood of

Table 3 Issues with universal screening of pregnant women for HCV

Universal testing issue	Recommendation
Testing characteristics	
False positives	Provider and patient education
Additional visit/blood draw	May be "bundled" with HIV and HCV testing
	Use of "reflex" testing reduces visits
Stigma of testing	Routinizing testing should reduce stigma
Provider time	Routinizing testing reduces provider time spent
Lack of provider knowledge	Education
Added cost	Implementation is within cost-effectiveness thresholds for improving quality-adjusted life-years
Low rate of testing infants	Improved communication between maternal care team and pediatricians, public health follow-up

true positive is increased and in those without risk factors, it is decreased. For those without traditional risk factors listed above, the possibility of childhood exposure from contaminated medical equipment and/or transmission and in utero exposure and subsequent clearance may be considered; the latter is a possibility due to the high prevalence in their mothers' "baby-boomer" generation. In any event, the scenarios of false positive or spontaneous clearance each convey the same message: there is no current infection that requires treatment or confers risk to the newborn.

An argument against universal screening is that increased identification of HCV may lead to incorrect decisions, such as recommending against vaginal birth or breastfeeding. Knowledge gaps regarding HCV have been identified for both patients [56] and providers [57]. Health systems considering universal screening can co-implement education to help prevent these issues [58].

Another concern is that universal prenatal screening may be associated with increased cost. Risk factor–based screening may save costs regarding laboratory testing, reducing the total number of women testing but also increases provider time spent ascertaining risk. The primary screening test for anti-HCV antibodies is relatively cheap, comparable with HIV and HBV testing. Costs of the care of HCV-infected pregnant women include vaccination for hepatitis A virus (considered safe in pregnancy), testing for associated conditions (such as HIV, HBV) [7], and postpartum antiviral treatment. Fortunately, testing for HIV and HBV is already routinely universal for pregnant women. Also, due to competition and negotiations with payors, costs of HCV antiviral regimens are significantly decreasing [59]. A recently published cost-effectiveness model suggests that universal prenatal HCV testing would improve health outcomes, conferring benefits to HCV-pregnant women by their living 1.21 years longer, improved identification of HCV exposure for neonates, and had an incremental cost-effectiveness ratio (ICER) of 41,000 USD/quality-adjusted life year (QALY) gained, well under commonly accepted thresholds [60•]. A separate analysis assumed a lower cost of treatment (25,000 USD) and found that universal antenatal screening had a mean ICER of only $2826 for every QALY gained; this model also projected that for the USA, about 33,000 more women would be identified [61•].

If women with HCV are successfully identified by obstetricians during pregnancy, they may face barriers to receipt of postpartum treatment, which include geographic distance to specialists and insurer restrictions by fibrosis stage and/or sobriety. Novel models of delivering HCV care, including treatment by primary care providers with specialist help via telemedicine or other models, can help overcome geographic barriers [62]. Insurer restrictions in certain regions disproportionately affect Medicaid populations that have higher prevalence of HCV [63]. However, these and other restrictions are steadily being lifted as well as challenged by advocacy and in the courts [59].

Even without postpartum treatment, knowledge of infection confers several benefits, as reviewed above. To maximize follow-up of exposed infants and enhancing the effectiveness of maternal testing, communication between the maternal care team and pediatricians is essential and can be augmented by public health programs similar to those for maternal HBV.

Acknowledging these concerns, the choice to continue risk factor–based screening maintains a status quo of an unproven strategy that apparently is ineffective at identifying HCV-infected mothers and therefore infants at risk. Universal screening of pregnant woman is one proposal that may be bundled with HIV and HBV testing, may be simplified via reflex testing, is cost effective, and ultimately much more efficacious in identifying an important condition that has significant implications for both mother and child.

Conclusion

The opioid epidemic has resulted in rising incidence of HCV in women of childbearing age. Pregnancy represents a unique opportunity to test for HCV, which has potential benefits for maternal, child, and public health. Knowledge of HCV status is a crucial step towards linking the mother to postpartum antiviral treatment and testing of the exposed newborn. Treatment of HCV during pregnancy is not yet recommended. By implementation of universal testing, obstetricians can play major roles in identifying HCV among mothers and their children and linking those with infection to curative treatment, thereby partnering towards the elimination of HCV in the USA.

Compliance with Ethical Standards

Conflict of Interest Catherine A. Chappell has received research funding from Gilead Sciences and Merck though Magee-Womens Research Institute (MWRI) and has served as a consultant for Gilead Sciences. Arthur Y. Kim served as a consultant for Biomarin, Inc. Tatyana Kushner reports personal fees from Gilead Sciences for participation in a scientific advisory board, outside the submitted work.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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