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# Responsible Inclusion of Pregnant Individuals in Eradicating Hepatitis C Virus

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**Abbreviations**

HCV-Hepatitis C virus; DAAs-direct-acting antivirals; CDC-Centers for Disease Control and Prevention; USPSTF-United States Preventive Services Task Force

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**Abstract**

Hepatitis C virus (HCV) infections have increased in recent years due to injection drug use and the opioid epidemic. Simultaneously, HCV cure has become a reality, with the advent of direct-acting antivirals (DAAs) and expansion of treatment programs. As a result, HCV screening recommendations now include all adults, including pregnant individuals, and many countries have endorsed widespread DAA access as a strategy to achieve HCV eradication. However, almost universally, pregnant individuals have been systematically excluded from HCV clinical research and treatment programs. This omission runs counter to public health strategies focused on elimination of HCV but is consistent with a historical pattern of exclusion of pregnant individuals from research. Our systematic review of publications on HCV treatment with DAAs in pregnancy revealed only one interventional study, which evaluated sofosbuvir/ledipasvir in 8 pregnant individuals. Given the paucity of research on this issue of great public health importance, we aimed to appraise the current landscape of HCV research/treatment and analyze the ethical considerations for responsibly including pregnant individuals. We propose that pregnancy may be an opportune time to offer HCV treatment given improved access, motivation, and other health care monitoring occurring in the antenatal period. Moreover, treatment of pregnant individuals may support the goal of eliminating perinatal HCV transmission and overcome the established challenges with transitioning care after delivery. The exclusion of pregnant individuals without justification denies them and their offspring access to potential health benefits, raising justice concerns considering growing data on DAA safety and global efforts to promote equitable and comprehensive HCV eradication. Finally, we propose a path forward for research and treatment programs during pregnancy to help advance the goal of HCV elimination.

The epidemiology and treatment of Hepatitis C virus (HCV) infection has been transformed over the last decade. Newly identified cases have increased dramatically, driven by injection drug use and the opioid epidemic(1-3) and HCV screening recommendations have expanded to include all adults.(1, 4-6) In 2020, some guidelines in the United States (US) have included pregnant individuals in universal HCV screening recommendations for the first time.(5, 6)

However, pregnant individuals have been excluded from most HCV clinical research and treatment programs around the world. Thus, we aimed to assess data on HCV treatment in pregnancy – including via a systematic review – and analyze ethical considerations for the responsible inclusion

of pregnant individuals. Finally, we offer a proposal for the responsible inclusion of pregnant individuals in research and treatment programs.

**The Global Goal of HCV Eradication**

While HCV treatment once consisted of a year-long, partially efficacious regimen requiring subcutaneous injection with many side effects, it now involves 6-8 weeks of a once-daily oral regimen that cures >95% patients with HCV infection.(7-9) These highly efficacious direct-acting antivirals (DAAs) have enabled public health authorities globally to employ different strategies for "microelimination" of HCV.(10) Such strategies generally involve first expanding screening efforts to identify all patients with HCV then streamlining treatment access to achieve cure. A lower prevalence of people with HCV would translate to reduced transmission, which ultimately will lead to eradication of HCV. The World Health Organization has embraced this approach, setting global targets for HCV elimination by 2030, and these goals are aligned with U.S. Health and Human Services Healthy People 2030 targets.(11-13)

Various strategies can achieve eradication. For example, Iceland and Egypt have enacted national plans for widespread testing and "universal" access to DAAs,(14) and persons living with HCV in Egypt have declined substantially.(15) In the US, many states have lifted insurance restrictions on publicly-funded access to DAAs and have attempted "universal" access after simple criteria for testing and evaluation are met. Louisiana and Washington are implementing novel strategies for financing universal DAA access, negotiating fixed-price agreements with pharmaceutical companies regardless of how many patients are treated (or "Netflix models").(16-18) Australia has used this model to great effect across the country to dramatically reduce the population burden of HCV.(19) Nevertheless, these efforts all systematically exclude one population with a potentially high prevalence of HCV infection: pregnant individuals.

**Pregnant Individuals and HCV Screening**

Pregnant individuals have been part of the wave of HCV infections among young adults primarily related to the opioid epidemic.(20-23) A high prevalence within pregnant individuals has

been documented in many states in which the opioid epidemic has been rampant, prompting Kentucky to mandate universal screening for HCV during pregnancy.(20-26)

This changing epidemiology of HCV first drove the American Association for the Study of Liver Diseases/Infectious Diseases Society of America (AASLD/IDSA) in 2018 to recommend universal screening of all pregnant individuals(27), which was ultimately taken up by both the USPSTF and CDC in their recommendation for universal screening of all adults.(5, 6) However, recommendations still defer treatment for pregnant individuals with HCV until after giving birth, a strategy that captures only a fraction of those who could benefit. While there may be some off-label treatment of pregnant patients being undertaken by providers, no individual or group has reported their experience and only the AASLD/IDSA include discussion on a case by case basis among existing professional guidelines regarding HCV treatment in pregnancy.

**A Paucity of Data: Systematic Review**

To evaluate the evidence on HCV DAA treatment in pregnancy, we conducted a systematic review of the literature, conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Briefly, a search of the MEDLINE (via PubMed), EMBASE, Cochrane Library, clinicaltrials.gov, CINAHL, and Global Health databases for relevant studies was first performed during October and November 2019 and refreshed in July 2020. A separate clinicaltrials.gov search was performed again in January 2021. The reference lists of the reports selected for inclusion were screened for further potentially relevant articles. Any comparative studies such as randomized controlled trials, quasi-experimental designs, and observational studies that assessed the effectiveness of therapy were included. No language restriction was applied. The search strategy is provided in Supplemental Table 1 and was uploaded in PROSPERO. Two investigators (SA and RJ) independently screened all citations by title and abstract. The same investigators then screened the studies retrieved independently. Disagreements regarding inclusion were resolved by discussion.

Our systematic review abided by PRISMA guidelines (Supplemental Figure 1) and identified 1987 unique references, of which 1783 were potentially relevant. Of these, 31 references addressed treatment for HCV in pregnancy. Only one of these described an interventional treatment study; a

study of sofosbuvir/ledipasvir initiated during pregnancy in 8 individuals.(28) The remaining 30 papers discussed HCV treatment during pregnancy generally and/or called for further study, including a pharmacokinetic study of sofosbuvir/velpatasvir treatment during pregnancy that is currently recruiting with a target enrollment of 10 participants and a target completion date of June 2023(29).

In summary, the scarcity of publications on this topic demonstrates the exclusion of pregnant people from research.

**Ethical Considerations for the Responsible Inclusion of Pregnant Individuals**

These results are consistent with the historical pattern of excluding pregnant individuals from research by default.(30, 31) Perhaps the most important reason for this exclusion is the desire to protect pregnant individuals and fetuses classified as "vulnerable,"(30) which was in response to unethical studies in which researchers exploited vulnerable populations. In the 1990s, however, the HIV epidemic shifted the paradigm of research oversight away from regulatory paternalism towards greater participant access to research benefits.(32) In 1994, NIH's Office of Research on Women's Health called for pregnant individuals to be "presumed eligible" for clinical research participation, which was later echoed by international guidelines.(33) Recent guidelines now recommend that research with pregnant individuals be "promoted."(34) Moreover, the 2019 revision of the US Federal regulations governing research removed pregnant individuals from the list of groups classified as vulnerable to coercion or undue influence, given there is no reason to question the decision-making capacity of pregnant individuals as a group.(35)

Despite this increasing recognition of the importance of greater inclusion of pregnant individuals in research, change has been slow. In 2011, there were no safety data in pregnancy for 73% of drugs approved by FDA in the prior decade, and "very limited" safety data in pregnancy for 19.2% of treatments.(36) Pregnant individuals also largely were excluded from trials conducted during the Ebola epidemic of 2013-2016 and in the COVID-19 pandemic.(37, 38)

Although exclusion from research may be appropriate in some cases, exclusion without justification unjustly denies pregnant individuals and fetuses access to potential health benefits. Paradoxically, while pregnant individuals are not more vulnerable to coercion or undue influence than other groups, a substantial source of vulnerability for pregnant individuals is greater exposure to risk

from important interventions due to a lack of scientific knowledge.(39) Information about pharmacokinetics, fetal safety, and the maternal risks and benefits are all critical evidence gaps that should be addressed through research but are often neglected.(40)

There are three generally accepted scientific considerations for inclusion of pregnant individuals in research: (1) basic clinical safety data should be available in the general population, (2) clinical efficacy should be established for the general population, and (3) sufficient preclinical and early clinical data relevant for use in pregnancy should be available.(41). The first two considerations have been met for HCV treatment, as it is well-established that treatment with DAAs is both safe and efficacious for achieving sustained virologic response in non-pregnant individuals with HCV infection. Additionally, the pilot treatment study of sofosbuvir/ledipasvir has begun to satisfy the third consideration.(28)

Additionally, the US Code of Federal Regulations Section 46.204 permits approval of research in pregnancy if the research offers a prospect of direct benefit for the pregnant individual and/or the fetus, and risks are minimized. Examining the risks and benefits of HCV treatment in pregnancy reveals that research could meet these conditions.

*Potential benefits and risks from HCV treatment during pregnancy*

There is clear potential benefit for initiating HCV treatment during pregnancy rather than delaying it until after pregnancy. In addition to curing HCV in pregnant individuals, treatment during pregnancy could markedly reduce, if not eliminate, perinatal HCV transmission and associated risks to the fetus. Viremia is the only absolute requirement for perinatal transmission and the current DAA regimens all rapidly reduce HCV RNA levels to undetectable within 2 weeks of initiation.(42, 43) While the precise window of transmission in unknown, it is possible that rapid and potent suppression of viremia will virtually eliminate the risk.(44)

There are potential risks from HCV treatment during pregnancy, such as possible teratogenic effects as well as unique toxicity during pregnancy. Teratogenic risks remain theoretical worries, but review of product label information with both pan-genotypic regimens did not demonstrate any notable toxicities in pregnant animals or their offspring.(45, 46) Since DAA regimens are as short as 6 to 8 weeks, and therapy could be started in the middle of the 2nd trimester after organogenesis is

complete and still conclude before delivery, potential teratogenic effects would be minimized while utilizing the window of opportunity for treatment in pregnancy. In the absence of teratogenicity, however, fetal exposure to DAAs could still have other long-lasting other effects, requiring further research in pregnant individuals and their offspring. As for toxicity, DAAs have been exceptionally well tolerated in medically complex patients such as those with uncompensated cirrhosis, end-stage renal disease requiring dialysis, and HIV. Aside from drug-drug interactions, side effects are rare. There is no *a priori* reason to believe administration in pregnancy would be different. Ultimately, the best way to evaluate these largely theoretical risks of HCV treatment during pregnancy would be to conduct research to generate more evidence about the risks and benefits.

*Other considerations regarding HCV treatment during pregnancy*

HCV treatment during pregnancy offers many advantages compared with delaying treatment until after pregnancy is complete. Pregnancy is a window of opportunity in which current DAA regimens could be integrated into prenatal care. Studies of HIV treatment during pregnancy demonstrate comparable or higher adherence with antiretroviral therapy than treatment outside of pregnancy, and pregnancy has been established to be a period of increased engagement in care.(47)

With the lifting of Medicaid restrictions on treatment with DAAs and expansion of health care coverage to all pregnant people through at least 6 weeks postpartum, HCV treatment during pregnancy could be provided while a patient still has coverage and avoid the potential deficit in care that could arise with interruptions of coverage. Even when coverage remains available, transitioning individuals after pregnancy to providers who address non-obstetric and longer-term issues is often challenging. Indeed, several studies have documented very follow-up low rates when pregnant individuals are referred for HCV treatment after delivery.(25, 48-50)

While the high cost of DAAs is frequently mentioned as a reason against treatment during pregnancy, the cost is no different than for anyone else. A study of cost-effectiveness has demonstrated that treatment initiated during pregnancy is a high value proposition.(51)

Finally, liability concerns may lead sponsors to avoid conducting research in pregnancy or seeking labeling for the use of their products in pregnancy.(52) Ultimately, the legal culture surrounding research in pregnancy may be a more important barrier than existing laws, but may also

be more flexible and easier to change.(52) For instance, public recognition of the great need for research in pregnancy and advocacy could begin to shift institutional attitudes.

Some may reflect and ask, "What do pregnant patients think?" about HCV treatment during pregnancy. Our research indicates that patients are largely supportive of these concepts and want more open discussions with their providers on the subject.(53)

**Looking Forward**

The currently recruiting sofosbuvir/velpatasvir in pregnancy study is a necessary first step to accelerate the inclusion of pregnant individuals in HCV treatment programs, but with only 10 patients, it will not address the unresolved questions of safety that require larger scale studies. What is needed is a clinical trial to study the current HCV pan-genotypic DAA regimens with the National Institutes for Health (NIH) as the sponsor. Ideally, NIH could lead a public-private partnership, in coordination with the FDA, which is designed to study the 2 most common pan-genotypic regimens using the same study infrastructure, the same enrollment criteria and the same clinical outcomes. Study sites should be part of an established network accustomed to performing clinical studies during pregnancy related to maternal infectious diseases (e.g. International Maternal Pediatric Adolescent AIDS Clinical Trials Network [IMPAACT]). Since most trials used for initial licensure of DAAs were open-label and enrolled 100-300 individuals, a target of 100 pregnant individuals could receive each regimen. If the safety and efficacy are consistent with those seen in non-pregnant individuals and in the phase 1 trial in pregnancy, the FDA label would be expanded for use during pregnancy.(28)

Since initial studies do not identify rare adverse events, mandatory pregnancy registry should be established for post-approval treatment to evaluate effectiveness and safety in a real-world setting. Treatment could be linked to data registry enrollment and reporting requirements, and private payors would be required to cover treatment in the same manner as for non-pregnant patients. A safety monitoring committee would review all outcomes of HCV treatment during pregnancy and immediately alert providers of any sentinel events. After several years of data were collected and major safety concerns abate, the registry would then shift to a post-marketing model like the Vaccine Adverse Events Reporting System (VAERS).

This proposal is one clear way to achieve equitable inclusion of pregnant patients in HCV treatment programs, and it highlights the important work remaining to be done. Until the injustice of exclusion of pregnant patients from HCV research and, by extension, treatment programs, is addressed, we will not be able to move together equitably in a global endeavor to eliminate HCV.

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