



Informe de **Recomendación**

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Universal testing for hepatitis C in pregnant women in antenatal care

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Technology: Universal testing for hepatitis C in pregnant women in the first trimester of pregnancy during antenatal care.

Indication: To intensify efforts to expand hepatitis C testing, treatment and prevention of vertical transmission with the aim of eliminating the disease as a public health problem.

Applicant: Department of Diseases of Chronic Conditions and Sexually Transmitted Infections of the Secretariat of Health Surveillance of the Ministry of Health of Brazil.

Background: The prevalence of hepatitis C among pregnant women in Brazil is estimated to be around 0.2% to 1.4%, but, in 2014, the detection rate among women of childbearing age doubled after the incorporation of direct-acting antivirals with high effectiveness and safety in the scope of the Brazilian Public Health System (SUS). The risk of vertical transmission varies depending on factors such as the correct planning of obstetric procedures, maternal viremia, and HIV coinfection. Hepatitis C in pregnancy is associated with adverse health outcomes for pregnant women and newborns, and, in the long term, an increase in the incidence of hepatocellular carcinoma, cirrhosis, need for liver transplantation, use of health services, and mortality. Currently, the approach to detect hepatitis C in pregnant women depends on the identification of pre-existing risk factors, which has been evaluated to be ineffective in identifying the actual number of cases. Screening is proposed as an alternative to risk-based testing in order to increase the detection rate, decrease vertical transmission, and increase treatment coverage, taking into account the public policies to eliminate hepatitis C implemented by SUS.

Question: Is the hepatitis C screening strategy among pregnant women, in the first trimester of pregnancy during antenatal care, effective, safe and cost-effective when compared with the risk-based testing strategy currently recommended in the Clinical Protocol and Therapeutic Guidelines for Hepatitis C and Coinfections of the Ministry of Health of Brazil?

Scientific evidence: Observational and descriptive cross-sectional studies indicated that the risk-based testing strategy is associated with low diagnostic yield and low sensitivity, or with a low detection of pregnant women effectively diagnosed with hepatitis C during antenatal care. In a study carried out in Canada, where the prevalence of hepatitis C virus (HCV) in pregnant women was estimated at 0.6%, a positive answer (to a structured questionnaire) to at least one risk factor was associated with sensitivity of 67%, specificity of 28%, positive predictive value of 0.4%, and negative predictive value of 99% for identification of pregnant women with HCV. The positive predictive value would depend on the risk factors evaluated. This variability could result in different detection rates of hepatitis C with the risk approach strategy, with a number of true positive cases not identified ranging from 2.5% to 27%, but reaching up to 50%. In fact, in most studies, no statistically significant association was found between the presence of risk factors and a positive HCV diagnosis in pregnant women. With respect to the criteria of Wilson and Jungner used in the evaluation of screening strategies, most criteria would be met, however, there are still no studies evaluating relevant short-term health outcomes (obstetric outcomes and vertical transmission) and long-term health outcomes (disease progression and transmissibility) associated with the implementation of a screening program for hepatitis C in pregnant women. A criterion that has not been met is that there is currently no approved antiviral treatment for use in pregnancy.

Economic evaluation: A cost-effectiveness analysis from the perspective of SUS was conducted to compare the two strategies using a static decision tree model combined with Markov chains. The screening strategy was associated with incremental costs of BRL 288.78, and an incremental increase in Quality Adjusted Life Years (QALY) of 0.18 per pregnant woman screened, compared to risk-based testing strategy, with an incremental cost-effectiveness ratio of BRL 1,617.95 per QALY for screening versus risk-based testing.

Budget impact analysis: The annual budget impact associated with the implementation of a screening program for hepatitis C in pregnancy from the perspective of SUS was estimated to be BRL 49 million, and BRL 250 million after five years. Direct costs associated with diagnosis, complementary tests and medical procedures, and treatment were considered. Variation in parameters, such as coverage rate of pregnant women tested in the

public health system compared with the supplementary health system, rate of pregnant women tested in the first trimester of pregnancy, number of pregnant women coinfecting with HIV, and rate of treatment provided, could reduce the budget impact from 41 to 55%.

International recommendations: The National Institute for Health and Care Excellence - NICE (England), the Canadian Agency for Drugs and Technologies in Health - CADTH (Canada), and the European Association for the Study of the Liver recommend testing based on the detection of risk factors. In the United States, the Centers for Disease Control and Prevention (CDC), the U.S. Preventive Services Task Force (USPSTF), the American Association for the Study of Liver Diseases, and the Infectious Diseases Society of America recommend hepatitis C screening in pregnancy. The American College of Obstetricians and Gynecologists (ACOG) is currently reviewing the recommendations published in 2017. In Australia and New Zealand, The Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) has recommended hepatitis C screening in pregnancy in 2020.

Considerations: Moderate quality evidence showed that the strategy of selecting pregnant women for testing based on identification of risks is ineffective, with low positive predictive value and low sensitivity. Although there are no randomized controlled trials or observational studies with a comparator arm evaluating health outcomes and risks associated with both strategies, it is possible that the number of women not detected by the risk-based testing strategy is significant with serious consequences for the health of both mother and child. From the perspective of SUS, the screening strategy was shown to be more effective than risk-based testing with an increase of BRL 288 per pregnant woman tested. Some global health authorities have been reviewing the recommendations for hepatitis C diagnosis in pregnant women to recommend screening, especially in view of the increasing rates of HCV detection among women worldwide and in Brazil. The implementation of the screening program would meet most criteria of Wilson and Jungner, except by the fact that there is no HCV treatment approved for use in pregnancy. It would result in an annual increment of BRL 49 million to the budget of the Ministry of Health of Brazil, mainly due to the high cost of treatments.

Initial Recommendation: The CONITEC's members present at its 87th Ordinary Meeting, on June 3rd, 2020, unanimously decided to recommend the incorporation of universal testing for hepatitis C in pregnant women in antenatal care.

Public consultation: The Public Consultation No. 19/2020, published in the Official Gazette of the Federal Executive on June 15th, 2020, was held from June 16th to July 6th, 2020. A total of 50 contributions were received, of which eight were technical-scientific contributions, and 42 were experience or opinion contributions. After analysing them, four technical-scientific contributions were included in this report, which agreed with CONITEC's preliminary recommendation. Two organizations and also the Drugs for Neglected Diseases initiative (DNDi) – Latin America and the Brazilian Society of Infectious Diseases took part in the public consultation. The studies submitted reinforced the importance of accurate detection of pregnant women infected with hepatitis C in view of adverse outcomes in pregnancy in this clinical context, as well as the possibility of referral and follow-up of high-risk pregnant women, better planning of obstetric procedures, timely treatment for both mother and child after birth, and alignment with the goals for the elimination of the disease in Brazil, reducing vertical transmission. The risk-based testing strategy was considered to be ineffective. All 42 contributions about the experience of this technology or opinion on its incorporation agreed with CONITEC's preliminary recommendation, including those submitted by the Optimism Support Group for Hepatitis Patients and the Brazilian Society of Hepatology. It was noticed that there was a great convergence between the experience or opinion contributions and the technical-scientific ones. Therefore, CONITEC decided to maintain the preliminary recommendation in favour of the incorporation of universal testing for hepatitis C in pregnant women in antenatal care.

Final Recommendation: The CONITEC's members present at the 89th Ordinary Meeting considered the risk-based testing strategy to be ineffective, based on the studies analysed in this report, even though most evidence

evaluating universal testing for hepatitis C in pregnant women in antenatal care were considered of low methodological quality. It was also taken into consideration the knowledge of the natural history of hepatitis C and the risks of hepatitis C infection in pregnancy for both mother and newborn, as well as the possibility of a better planning of obstetric procedures, follow-up, and care of these patients when there is an accurate case identification. In addition, confirmatory Polymerase Chain Reaction (PCR) and viral load after positive serologic results were considered necessary. Therefore, the CONITEC's members present at the Ordinary Meeting unanimously decided to recommend the incorporation of universal testing for hepatitis C in pregnant women in antenatal care, according to the Clinical Protocol and Therapeutic Guidelines of the Ministry of Health. The Deliberation Record No. 537/2020 was signed.

Decision: To incorporate universal testing for hepatitis C in pregnant women in antenatal care, according to the Clinical Protocol and Therapeutic Guidelines of the Ministry of Health of Brazil, in the scope of SUS, according to Ordinance No. 32, published in the Official Gazette of the Federal Executive No. 160, Section 1, page 118, on August 20th, 2020.

