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VERTICAL TRANSMISSION BY HEPATITIS C VIRUS: A LITERATURE REVIEW

***[1]Vanessa Toshie Sato, [1]Rhaissa Carla Parizotto Deola, [2]Marília da Mata Silva and *[3]Andréa Grano Marques**

[1]Undergraduate student, Department of Medicine, University Center of Maringá – Unicesumar; [2]Psychologist, Master Student of the Postgraduate Program in Health Promotion, University Center of Maringá–Unicesumar. CAPES Scholarship; [3]Professor, Doctor of the Postgraduate Program in Health Promotion, University Center of Maringá - Unicesumar. Researcher at Cesumar Institute of Science, Technology and Innovation - ICETI

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****Corresponding author:*** **Andréa Grano Marques,**

ABSTRACT

Vertical transmission (TV) by the Hepatitis C virus (HCV) is considered a public health problem since there are no possible interventions to prevent or reduce the risks of transmission. Vertical transmission can occur in the intrauterine period and the peripartum in the presence of risk factors. The objective of the research was to analyze the transmission of risk factors from mother to child and recommendations for infection with hepatitis C. The samples were taken from the national and international scientific literature in the databases of Pubmed, MEDLINE, and LILACS. The search was based on the Health Science Descriptors (DeCS), following the publication criteria in the period between 1993 and 2019, totaling 54 scientific articles. The main risk factors are coinfection with the Human Immunodeficiency Virus (HIV), invasive fetal monitoring, rupture of the membrane and lacerations. Cesarean delivery has proven to be a protective factor in cases of coinfection with the Human Immunodeficiency Virus (HIV), being mandatory only when there are associated risk factors. Breastfeeding is widely recommended, except for cases of coinfection with the Human Immunodeficiency Virus (HIV), fissures, and nipple bleeding. Childhood prognosis is benign in most cases, and treatment generally promotes a sustained biological response.

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INTRODUCTION

In Brazil, between 1999 and 2017, there were 331,855 Hepatitis C notifications detected from anti-HCV or HCV-RNA tests (OKUMOTO, 2018). The monitoring of 28,561 pregnant women over two years revealed that the rates of Hepatitis C infection (0.15%) exceeded those of the Human Immunodeficiency Virus (HIV) (0.09%. And also that the advancement of age was directly proportional to the time of viral contact, with a peak of infection among pregnant women over 40 years old (COSTA *et al.*, 2009). Even so, the actual numbers of people affected by Hepatitis C are higher than those described in the literature because the infection is asymptomatic in the first years. Also, it has a delay in diagnosis. It is essential to consider that the infection with the Hepatitis C virus is a significant public health problem, as it is the leading cause of liver disease and can progress to cirrhosis or hepatocarcinoma (SHEPARD *et al.*, 2005).

The control of vertical transmission in childhood is also essential (MADURGA *et al.*, 2012). Transmission from mother to child can occur in the intrauterine, peripartum and postpartum periods. To explain transmission during the intrauterine period, in vitro tests have shown that syncytiotrophoblast cells can be infected by the Hepatitis C virus, leading to changes similar to those found in infected blood cells. Then, the placental barrier can be damaged, which favors viral transmission (NIE *et al.,* 2012). While, in the peripartum period, obstetric factors such as the type of delivery and invasive procedures can influence transmission (TOSONE *et al.,* 2014). It has been shown that the rupture of membranes over 6 hours, lacerations, and fetal monitoring are the main risk factors that increase infection rates (MAST *et al.,* 2005). Concerning the postpartum period, most studies have stated that it is possible to find the HCV virus in both milk and colostrum (MAST *et al.,* 2005; LIN *et al.,* 1995). The

nutritional, immunological, and psychological benefits (mother-infant bond) of breastfeeding are well known (FREITAS *et al.,* 2008), as well as the protection of respiratory and digestive tract diseases (TINOCO *et al.,* 2007). Besides, a study demonstrated that breast milk could favor protection against enveloped viruses through the action of fatty acids against the viral envelope (PFAENDER *et al.,* 2013). The goal of this review was to analyze the risk factors that enable the vertical transmission of infection by the hepatitis C virus, the possible consequences for the child, as well as the current recommendations to guide the conduct of health professionals.

MATERIALS AND METHODS

The work consisted of a bibliographic review of the national and international scientific literature on breastfeeding by lactating women with Hepatitis C virus, from scientific articles selected in the databases of Latin American and Caribbean Literature in Health Sciences (Lilacs), National Library of Medicine (Medline) and United States National Library of Medicine (PubMed). This research was carried out using the Health Sciences Descriptors (DeCS): "Hepatitis C and Vertical Transmission. " Then, the titles were analyzed, and those studies that corresponded to the research objectives were selected for further evaluation of the abstracts. We chose publications in Portuguese, English, or Spanish dated the period between 1993 and 2019, and articles available in full on the internet.

RESULTS

A total of 1,836 articles were identified in the databases searched from the descriptors Hepatitis C and Vertical Transmission, 973 National Library of Medicine (Medline), 832 United States National Library of Medicine (PubMed) and 43 Latin American and Caribbean in Health Sciences (Lilacs). After analyzing the titles, 733 articles were excluded, whose themes did not meet the research objectives, 526 were subsequently excluded because the publication was not carried out between 1993 to 2019. Five hundred twenty-three articles that were not available were also excluded. Therefore, there were included 54 articles in the present research.

Pathogenesis : Throughout pregnancy, immunological changes occur that are modulated to promote maternal-fetal tolerance (LE CAMPION *et al.,* 2012; MOR, 2010). Thus, infections such as hepatitis C during pregnancy will be strongly affected by these changes, leading to an increase in viral load (HCV-RNA) and a decrease in alanine aminotransferase (ALT), especially in the third trimester. This fact can increase the risk of dissemination (LE CAMPION *et al.,* 2012; GERVAIS *et al.,* 2000). After delivery, maternal immunological changes are reestablished by increasing the specific cellular response. And this reflects in hepatocellular damage since maternal viral replication is controlled (LE CAMPION *et al.,* 2012). After pregnancy, there is a worsening of maternal liver disease. A study that evaluated the histological changes by liver biopsy in 12 positive women for HCV before and after birth, and 12 positive women for HCV non - pregnant showed further deterioration in the group of pregnant women when it was compared to the group control (necroinflammatory score: 83.3% vs. 25.0%; fibrosis score 41.6% vs. 8.3%, respectively) (FONTAINE *et al.,* 2000), revealing that pregnancy may have been the worsening of histopathological liver injury to HCV. In another study, neonates exposed to HCV presented suppression of immune activation and proinflammatory markers, which was counterbalanced by the increase of IFN-γ, suggesting virus transmission in the uterus, which alters fetal immunology and balance between suppressive and proinflammatory responses (BABIK *et al.,* 2010). In the early years of a child's life, there are abnormal variations in ALT levels, demonstrating the interaction of immune and viral factors. And these high levels at the beginning offer a more significant opportunity to decrease viremia during follow-up in the following months. Although the incidence of chronic HCV progression is high, the liver disease usually has mild symptoms (RESTI *et al.,* 2003). Chronic infection is generally asymptomatic in childhood. Only a few cases have hepatomegaly and hepatic fibrosis. These changes do not cause damage to the growth and child's quality of life.

Severe liver disease or liver failure is rare, although it can occur during chronic progression (TOVO, 2016). A European study that evaluated 663 infants with chronic hepatitis C, cirrhosis was reported in 17, and 6 underwent liver transplantation. Also, since chronification occurs after a few years, at preschool age, antiviral treatment is often postponed until that age (INDOLFI *et al.,* 2019). The clinical evolution was described in a study carried out with 34 children infected by vertical transmission, 25% had a spontaneous clearance of the virus in up to 7.3 years of age, and children with lower age and lower ALT levels obtained a higher clearance rate (YEUNG *et al.,* 2007). In another research, it was reported that children usually have few symptoms up to the age of 15. And that in 20% spontaneous virus clearance occurs with an average of 14.9 months (when there are two consecutive negative CRP, absence of clinical manifestations and ALT within normality), 50% are asymptomatic, and 30% have chronic hepatitis. It has also been shown that viremia and elevated ALT levels may be associated with hepatomegaly, being the only sign shown in the children monitored in the study appearing in 10%.

A survey carried out in Europe observed 104 cases of infection in children from birth to 4 years and described that 51% were positive for viral RNA, 42% had sporadic positive results, and 5.7% had negative tests. The vast majority of positive results showed an elevation in ALT, which was the only manifestation. Only two cases showed hepatomegaly. After 24 months, ALT levels have substantially regressed, but most tests have remained positive for infection (TOVO *et al.,* 2000). Another study followed 62 children for two years, in which increased ALT levels in the first year were seen by 93%. After the thirtieth month, ALT levels begin to decline, and the amount of viral RNA was negative in 19% of children. However, 81% of cases had chronic disease progression, but with a mild or asymptomatic manifestation (RESTI *et al.,* 2003). Childhood evolution is mostly benign, with the first ten years being a slowly progressive disease without symptoms (RERKSUPPAPHOL *et al.,* 2004). Although the incidence of chronification is high, the liver disease generally has few signs or is asymptomatic (RESTI *et al.,* 2003; INDOLFI *et al.,* 2019). And in the rare cases in which there are hepatomegaly and liver fibrosis, there are no critical changes in child development (INDOLFI *et al.,* 2019). Finally, the mode of transmission does not seem to have much influence on viral clearance and levels of anti-HCV antibodies in serum (RERKSUPPAPHOL *et al.,* 2004).

Vertical Transmission: Vertical transmission of HCV is still considered a public health problem since there are no interventions to prevent or reduce it other than anti-HIV therapy in co-infected mothers (TOVO, 2016). In general, the rate of vertical infection by the HCV virus is between 3.7% and 13% (CONTE *et al.,* 2000; GARDENAL *et al.,* 2011; RESTI *et al.,* 2002). In the prevalence of HIV coinfection, the rate is much higher, equivalent to 25% to 50% more than the value of non-co-infected mothers. (MAST *et al.,* 2005; GARDENAL *et al.,* 2011; GIBB, 2000). Transmission from mother to child can occur during intrauterine, peripartum and postpartum. To explain transmission during the intrauterine period, in vitro tests could demonstrate that the syncytiotrophoblast cells can be infected by HCV, leading to changes similar to those found in infected blood cells. Then, the placental barrier can be damaged, which favors viral transmission (NIE *et al.,* 2012). While in the peri-delivery period, obstetric factors such as the type of delivery and invasive procedures can influence transmission (TOSONE *et al.,* 2014). It was demonstrated in a study that the rupture of membranes lasting more than 6 hours, lacerations, and fetal monitoring are risk factors that increase the rates of infection (MAST *et al.,* 2005). Regarding the type of delivery (surgical or transvaginal), a study was carried out in Japan with 188 HIV positive women who analyzed the vertical transmission rate. It was found that the high viremia in the Polymerase Chain Reaction (CRP) quantitative (high viral load: ≥ 6.0 × 10 5 IU / mL) enabled a higher rate of transvaginal transmission (MURAKAMI *et al.,* 2012). However, this study is contrary to the metanalysis that evaluated eight studies totaling 641 pairs of mothers and children who compared the rate of perinatal transmission of HCV in elective or emergency cesarean section with vaginal delivery in HCV-RNA + / HIV mothers. This fact shows that vaginal delivery has little influence on increasing HCV transmission (MAST *et al.,* 2005; RESTI *et al.,* 1998; GHAMAR *et al.,* 2010). However, it has been shown that HIV-positive women who have had a surgical delivery have 60% less risk of having an infected child. The immunobiological mechanisms by which HCV transmission is favored are not well established. The propitiation of a higher viral load due to immunosuppression is pointed out as one of the causes, but this cannot be proven (CONTE *et al.,* 2000). It has been reported that HIV infection appears to favor HCV entry into maternal blood mononuclear cells, undifferentiated hematopoietic cells, and bone marrow cells. Therefore, maternal mononuclear cells can be transmitted to the fetus acting as reservoirs of the virus, which contributes to the evolution of the disease in the child (AZZARI *et al.,* 2000). The chorioamnionitis generated by HIV infection can also favor the breaking of the physical placental barrier (KWIEK *et al.,* 2005).

Some authors have also classified the highest viral RNA levels (HCV RNA> 10 6 copies of the genome / mL) in mothers as a risk factor (MAST *et al.,* 2005; OKAMOTO *et al.,* 2000; DAL MOLIN *et al.,* 2002). However, a study demonstrated that viral levels do not seem to interfere with transmission, and it was reported that even among studies that proved the relationship between RNA levels and the highest transmission, entitlement differed. There were difficulties in quantifying viral RNA in samples. The author concludes that RNA quantification should not be used for risk counseling for vertical transmission (MAST *et al.,* 2005). The quantification of the serum level of alanine transaminase (ALT), in the presence of maternal hepatitis C, was pointed out as a tool to assess the chance of greater transmissibility. High values would be related to more significant viral replication, consequently higher transmission. However, inconsistent data were demonstrated in the articles found, as a study that measured the serum ALT levels of 82 women at the time of delivery detected levels above 110 IU/L and a transmission rate of 10.8% compared to 4.3% in the group with levels below this value.36 However, in another study, 105 mother-child couples were analyzed, and infection occurred in 6.6% of babies. In these, the mothers' abnormal ALT levels had no significant relationship with the highest percentage of transmission (DAL MOLIN *et al.,* 2002). Another study showed that mothers with elevated ALT had lower viremia than others with ALT within the normal range and that five transmitting mothers had normal ALT (RUIZ-EXTREMERA *et al.,* 2000).

Vertical Transmission through Breastfeeding: Due to the benefits of breast milk, breastfeeding has been accepted in cases of lactating women infected with the HCV virus. However, most studies have stated that it is possible to find the HCV virus in both milk and colostrum. Breastfeeding was not shown to be a statistically significant risk factor for postnatal transmission (MAST *et al.,* 2005; LIN *et al.,* 1995; GARDENAL *et al.,* 2011; GHAMAR *et al.,* 2010; HAYASHIDA *et al.,* 2007). However, it is essential to consider that some risk factors may predispose to the transmission through breastfeeding (HIV coinfection, bleeding, or nipple fissures) and that in these cases, breastfeeding must be suspended (TOSONE *et al.,* 2014). Breastfeeding time was also not an essential factor for vertical transmission. Multivariate analysis carried out in a United Kingdom study showed that the number of infected children did not increase with the extension of the breastfeeding period for another four weeks, and the values were statistically equivalent. The mechanisms that make vertical transmission unfeasible by this route are not well defined. It is suggested that the low viral title in milk and the inactivation by the infant's digestive tract may make viral progression in the child unfeasible (TOSONE *et al.,* 2014). However, it has been described in the literature that breast milk seems to favor protection against infections by enveloped viruses (PFAENDER *et al.,* 2013).

The study was carried out from an in vitro system capable of demonstrating the ability of breast milk to neutralize the HCV virus regardless of the genotype. It was seen that as there was no interference either in viral replication or in the production of capsid proteins, the changes would be related to loss of integrity of the viral envelope. After centrifuging the milk, to know which milk component is responsible for the antiviral activity, it was observed that only the fat of the milk would have this property. Interestingly, the milk tested underwent a cooling process at 4º C, a fact that would increase the amount of free Monounsaturated Fatty Acids (MUFA) and Polyunsaturated (PUFA) in the sample by increasing the activity of endogenous lipases. Thus, the author defended the hypothesis that lipoprotein Lipase and Lipase stimulated by bile salt break down triglycerides releasing free fatty acids that would lead to damage to the viral envelope resulting in less infection (PFAENDER *et al.,* 2013). In the same study, it was tried, without success, to confirm that the low pH of gastric juice would quickly destroy low concentrations of HCV in milk. However, in vitro samples, after 24 hours of pre-incubation of infected milk in gastric juices of healthy children

and adults, it was observed that the virus remained stable, contrary to the most accepted hypotheses until then (PFAENDER *et al.,* 2013). Therefore, understanding the mechanisms by which the virus is not transmitted through this route can help in the formulation of preventive measures and possible treatments (JHAVERI, 2013). However, because of vertical transmission low rate through breastfeeding, the low viral RNA detection in the majority of studies, breastfeeding is widely encouraged in the presence of maternal hepatitis C. It is essential to consider other factors risk already mentioned. The leading international and national guidelines, including the recommendation of the Brazilian Society of Pediatrics, the American Academy of Pediatrics, theCenters for Disease Control and Prevention (2019) recommend breastfeeding, except in cases of HIV coinfection and nipple fissures or bleeding (LAMOUNIER *et al.,* 2004).

Treatment and SVR (Sustained Virologic Response): During pregnancy, antiviral treatment is not recommended due to side effects, so women should undergo drug therapy before pregnancy to decrease the viral RNA load. And, after delivery, being under treatment, breastfeeding should be suspended. In children, antiviral treatment must be started after two years of age (TOSONE *et al.,* 2014). Therefore, child treatment should be sought to prevent the possibility of progression of the liver problem related to hepatitis C (BRUIX, SHERMAN, 2011). It is recommended by the Centers for Disease Control and Prevention test antibodies anti-HCV in positive children by vertical transmission after one year after delivery because the antibodies acquired passively by breastfeeding decreased (SMITH*et al.,* 2012). The infant diagnosis aims to investigate liver diseases, through the testing of alpha-fetoprotein annually, liver ultrasound, in case of an increase in transaminases (in the absence of therapy) or biopsy, which is not recommended casually. In cases of fibrosis, cirrhosis, extrahepatic manifestations, and diseases that can progress rapidly to liver disease, they are monitored every year with alpha-fetoprotein and ultrasound. Then the therapy is immediately proposed (SMITH *et al.,* 2012; INDOLFI *et al.,* 2018). After treatment, the final result is demonstrated by undetectable RNA (limit≤ 15 IU / mL for 24 weeks after treatment with Interferon Alfa Pegylated (IFN Pegylated) and ribavirin (TOSONE *et al.,* 2014). The recommendation to initiate treatment is individualized according to the severity of liver disease by biopsy, potential adverse effects, and the presence of other conditions. In these cases can be considered the use of direct antiviral off- label (Indolfi*et al.,* 2018) Therapy is usually planned after breastfeeding, lasts between 8 and 12 weeks, and SVR can appear in up to 12 weeks of follow - up, totaling six months after the completion of breastfeeding (ROBERTS *et al.,* 2010).

Children between 3 and 17 years old are recommended pegylated IFN alpha and ribavirin, previously restricted only to adults (MACK *et al.,* 2012; WIRTH 2011). This fact is demonstrated by the low rates of pediatric severe hepatic complications, in which children are at lower risk than an adult, as therapy with INF and ribavirin shows Sustained Virological Response (equivalent to cure) after 24 months in 98 to 100% of children (HABER *et al.,* 2017; KELLY *et al.,* 2011). In recent studies, new drugs such as sofosbuvir/daclatasvir had mild adverse effects without interruptions, being safe in the therapy of children infected with hepatitis C of genotype four from the age of 8 (ABDEL GHAFFAR *et al.,* 2018). The combined IFN and ribavirin therapy has SVR in 100% in genotype 2 and 3, but only 45 to 55% in genotypes 1 and 4 (GRANOT *et al.,* 2015).

DISCUSSION

Vertical transmission of Hepatitis C is the main route of childhood infection. Statistically breastfeeding does not have a risk of vertical infection, except in cases of associated risk factors (fissures, nipple bleeding, and HIV/HCV coinfection). The overall rate of vertical transmission through this route is meager, but the virus can be found in samples of milk and colostrum. The immunobiological and physiological mechanisms that prevent viral transmission through breastfeeding are not well established. However, statistical data and knowledge about the pathogenesis of hepatitis C in children seem to favor the indication of breastfeeding, since the prognostic course in infants tends to reduce liver damage, with less chance of cirrhosis and hepatocellular cancer than in adults. Children also have high rates of spontaneous viral clearance, and most remain asymptomatic until approximately ten years of age. Although the chance of chronificationis high and viral RNA can be identified for many years in the blood, liver symptoms are mild in the child, unlike in the mother after delivery. As for screening in infants, anti-HCV antibodies in infants positive for RNA by vertical transmission is done after one year, as this is when antibodies transmitted from mother to child disappear. The treatment is individualized and can be started after breastfeeding with IFN Alpha Pegylated and ribavirin from 8 to 12 weeks, or it can be postponed until 12 years of age, depending on the degree of liver damage evidenced. In the mother, treatment during pregnancy is contraindicated due to the teratogenic potential of the drugs. During breastfeeding, if there is severe liver damage, it is necessary to suspend breastfeeding due to complications caused by the medication to the infant.

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