

HIV and viral hepatitis co-infection in pregnancy: an epidemiological, clinical and diagnostic review

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Abstract. Even though the survival of the population infected with HIV has been increased due to the intensification of antiretroviral therapy, co-infection with hepatitis B or hepatitis C has attracted the attention of doctors and other health professionals regarding the increased incidence of chronic complications resulting from viral hepatitis in HIV-infected population, which differs from that with other opportunistic diseases. Women coinfecting with these viruses have an increased risk of complications during pregnancy, and the vertical transmission of these infections cause significant morbidity and mortality among children. This study aimed to investigate the risks of co-infection with HIV, hepatitis B, and hepatitis C during pregnancy, through a literature review of the last ten years, using the databases LILACS, MEDLINE and SCIELO, which make up the Virtual Health Library. A total of 106 articles were found, by searching in these databases, 46 of which were pre-selected to be read in full, resulting in 15 approved articles. It was noted that most of the accepted studies were carried out in countries of sub-Saharan Africa and Europe, followed by Brazil and the United States. The presence of co-infections made the infection worse and led to disease progression, both in the mother and in the child, compared to infection with only one of these viruses. Therefore, early diagnosis and prevention and treatment are essential to reduce and prevent the vertical transmission of these viruses.

Keywords: Pregnancy; HIV; Hepatitis B; Hepatitis C; Co-infection.

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Introduction

The emergence of AIDS as an epidemic occurred worldwide in the late 1970s, and the first cases were detected in the United States, Haiti, and Central Africa. At the beginning of this pandemic, the cases were restricted to a specific group, so the term “5 H Disease” was temporarily adopted since it was related to homosexuals, hemophiliacs, Haitians, heroin addicts, and hookers. The possible factors of transmission were already known in these groups. In 1983, the first cases arose in women (with an increase in vertical transmission, accounting for more than 80% of the cases in children under 13 years old), children and health professionals (Marques, 2012; Sousa et al., 2012).

HIV is a spherical particle with a diameter between 100 and 120 nm, it belongs to the Family Retroviridae and genus *Lentivirus*, and its nucleus contains two copies of single-stranded RNA, encapsulated by a protein layer or nucleocapsid, capsid, and an outer envelope composed of a phospholipid bilayer (Veras, 2010).

Some studies carried out in the United States and Europe in recent years have shown that hepatopathies (chronic liver failure, cirrhosis, and hepatocarcinoma) have become a significant cause of hospitalization and death among patients, and it is currently the leading cause of death among HIV-infected patients, according to some health centers (Beringer et al., 2012).

Maternal infections can increase the perinatal morbimortality. For this reason, the screening of these diseases during prenatal care is important so that early diagnosis and treatment can be made when it is possible. Numerous maternal infections, which can be transmitted to the fetus, can occur during pregnancy, causing

severe sequelae in the newborn, including AIDS and hepatitis B and hepatitis C. The failure to detect these infections early during prenatal care is a missed opportunity for intervention in the infected pregnant woman, limiting the possibilities of reducing the incidence of pediatric cases of vertical transmission infection (Newton, 1999; Miranda et al., 2009). Intrauterine infections and those acquired during childbirth are important causes of fetal and neonatal mortality and contribute significantly to infant morbidity (Miranda et al., 2012).

In Brazil, 92,210 HIV-infected pregnant women were notified from 2000 to June 2015, most of them in the Southeast region (40.5%), followed by the South (30.8%), Northeast (15.8%), North (7.1%) and Central-West (5.7%) regions. Brazil accounted for 7,668 infected pregnant women identified in 2014, 35.1% in the Southeast, 28.1% in the South, 20.0% in the Northeast, 11.2% in the North, and 5.5% in the Central-West regions. The rate of detection of HIV-infected pregnant women has increased in Brazil in the last ten years; this rate was two cases per thousand live births in 2005 and increased to 2.6 in 2014 (Brasil, 2015a).

Vertical transmission (VT) of HIV-1 can occur in the intrauterine period, in the childbirth or during breastfeeding. The virus can be transmitted within the uterus by transplacental cellular transport, due to a progressive infection of the placental trophoblasts or ruptures in the placental barrier followed by microtransfusion from the mother to the fetus. Transmission during childbirth can occur by the contact of the fetus with the mother's infected secretions as it passes through the vaginal canal, by an infection upward from the vagina to the fetal membranes and the amniotic fluid, or by

absorption into the digestive tract of the newborn. Breastfeeding is the main way of postpartum transmission. The vertical transmission route may be influenced by several factors, such as the type of childbirth, use of antiretroviral therapy, oral inflammation in the newborn, prematurity, and high maternal viral load (Rosa et al., 2015).

Antiretroviral therapy (ART) can be indicated for all HIV-infected pregnant women, regardless of clinical and immunological criteria, and it should not be discontinued after childbirth, irrespective of the level of LT-CD4⁺ at the beginning of the treatment. Permanent treatment for pregnant women living with HIV has a considerable potential to improve the mother's health and prevent transmission to her children and partners (ONUSIDA, 2013; Brasil, 2015b).

At the perinatal exposure, HBV mother-to-child transmission may occur in the childbirth by exposing the newborn to blood or amniotic fluid containing HBV, during passage through the vaginal canal, by the contact with secretions, during breastfeeding and, rarely, by transplacental transmission. Fetal infection with HBV depends on the mother's immune status and viral load (Silva et al., 2015).

According to data from the World Health Organization (WHO), between 130 and 150 million people worldwide have chronic hepatitis C, and a significant number of those who are chronically infected will develop liver cirrhosis or liver cancer. Approximately 500,000 people die each year from liver diseases related to hepatitis C (WHO, 2015).

This study aimed to investigate, through an integrative review, the risks of co-infection with HIV, hepatitis B, and hepatitis C in pregnancy, highlighting the epidemiological, clinical and diagnostic aspects of such infections during pregnancy.

Methodology

Type of study

The present study consists of an integrative review aimed at gathering and synthesizing research results on a given topic or issue, in a systematic and orderly

manner, contributing to the improvement of the knowledge of the subject studied (Mendes et al., 2008). It differs from the traditional review because it tries to overcome possible biases in all the stages, following a method of search and selection; evaluation of the relevance and validity; collection, synthesis, and interpretation of the search data. Moreover, it promotes the updating of health professionals, since it provides them with further knowledge (Galvão et al., 2004).

Guiding question

“What are the possible risks to the mother, fetus or newborn when there is a co-infection associated with hepatitis B, hepatitis C, and HIV?”

Inclusion criteria

The review was performed based on studies that analyzed hepatitis B, hepatitis C and HIV co-infection in pregnancy, considering articles in Portuguese, Spanish or English with full text available in the databases between 2005 and 2015.

Exclusion criteria

Studies that did not analyze hepatitis B, hepatitis C and HIV co-infection in pregnancy were excluded; articles that did not have the full text available or those not published between 2005 and 2015 were not considered for the development of the present study.

Descriptors used

The following Health Sciences Descriptors (DECS) were used: “HIV”, “hepatitis/hepatite B”, “hepatitis/hepatite C” and “pregnancy/gravidez” written in English and Portuguese. The search for the articles was performed through the combination: “hiv AND hepatitis/hepatite b AND hepatitis/hepatite c AND pregnancy/gravidez”.

Database

A bibliographic survey was conducted on the Internet, selecting articles published by researchers in scientific journals indexed in the LILACS, MEDLINE and SCIELO databases, which compose the Virtual Health Library

(BVS/BIREME). The BVS is a network of information management, knowledge exchange and scientific evidence in health, established by the cooperation between institutions and professionals in the production, intermediation, and use of scientific and technical information on health, in open and universal access on the Internet. It differs from other sources of information available on the Internet because it meets criteria for selection and quality control (BVS, 2016).

Selection of articles

The bibliographic search of the studies in the databases was performed at two stages:

- **Initial search:** Potential articles for the present study were identified, respecting the outlined inclusion criteria. The bibliographic search was carried out in the databases considering the years between 2005 and 2015 as a limit period. Articles in Portuguese, Spanish or English, with full text available in the databases, were selected. Then, articles with titles relating to our study were selected by eliminating the repeated ones. Afterwards, the abstracts of all articles were read.
- **Detailed search:** This stage consisted of reading, in full, all articles selected in the initial search for the application of the inclusion and exclusion criteria.

Analysis and presentation of the articles

The articles were read, and the data were collected from an instrument with the following variables: authors, year of

publication, publication period, the country where the study was performed, and possible risks to the mother, fetus or newborn.

Tables contemplating the information previously mentioned were made to better analyze the data extracted from the articles included in the integrative review.

Results and discussion

Once the research is carried out, it is essential to publicize the results to the scientific community and experts, so that there are development and dissemination of knowledge and activities carrying out in a given area. The research begins to exist from the moment it is published, and the renewal of knowledge is driven by this socialization. In this sense, the scientific journals and, consequently, the scientific article itself play a fundamental role in achieving these aims (Curty and Boccato, 2005).

By searching for the descriptors “HIV, hepatitis B, hepatitis C and pregnancy” in Portuguese and in English, 37 and 106 published articles were found, respectively. However, it was observed that the 37 articles found using the descriptors in Portuguese were contained in the 106 articles obtained using these descriptors in English. Then, it was made the initial reading of the 106 articles, and 46 of them were selected for the detailed reading, resulting in 15 approved articles (Table 1).

Table 1. Distribution of the articles found and selected by databases.

Databases	Initial search	Detailed search	Excluded	Approved
LILACS	6	0	0	0
MEDLINE	100	46	31	15
SCIELO	0	0	0	0
Total	106	46	31	15

Regarding the databases, MEDLINE represented the largest number of published articles (Table 1). This finding is justified because it is a medical and biomedical international literature database,

produced by the NLM, which has bibliographical references and abstracts of more than 4 thousand titles of journals published in the United States and in other 70 countries (BVS, 2016).

There were few results from LILACS database (Table 1). It was selected because it is a Latin American database of bibliographical information in health sciences. This database has been produced by Bireme since 1982, with more than 500 titles of journals in 37 countries of Latin America and Caribbean (BVS, 2016). SCIELO was chosen because it is a Brazilian database; however, it showed no articles relating to the present study (Table 1).

The low number of approved articles, as shown in Table 1, can be justified by the fact there are ethical and legal obstacles to performed studies on pregnant women, making difficult a broad analysis of the possible risks caused by HIV/HBV/HCV co-infection in this group. Furthermore, many articles dealt with studies on patients with only one or two of these infections and were therefore excluded from this study.

Most of the studies (26.66%) were carried out in countries of sub-Saharan Africa (Table 2), which accounted for 4 of the 15 studies selected. According to Ezechi et al. (2014), the prevalence of HBV infection is higher in low-income countries of sub-Saharan Africa and in Southeast Asia, where 8-10% of the patients are chronic carriers; these regions account for more than two-thirds of the global load of HIV. However, HCV is more prevalent in Western countries (Andreotti et al., 2014). European countries accounted for 26.66% of the studies, followed by Brazil and the United States with 20% of the studies each (Table 2). According to Mohammadi et al. (2009), in the United States and Europe, the rate of HIV/HBV co-infection varies from 6% to 14%, whereas HIV/HCV co-infection ranges from 25% to 50%.

Table 2. Description of the analyzed articles.

Title	Origin	Journal	Author
Pregnancy is associated with elevation of liver enzymes in HIV-positive women on antiretroviral therapy	UK	Europe PMC	Huntington et al. (2015)
Sero-prevalence and factors associated with Hepatitis B and C co-infection in pregnant Nigerian women living with HIV Infection	Nigeria	The Pan African Medical Journal	Ezechi et al. (2014)
The impact of HBV or HCV infection in a cohort of HIV-infected pregnant women receiving a nevirapine-based antiretroviral regimen in Malawi	Malawi	BMC Infectious Diseases	Andreotti et al. (2014)
Prevalence of HBV, HDV, HCV, and HIV infection during pregnancy in Northern Benin	Benin	Journal Medical Virology	Paschale et al. (2014)
Co-infections associated with human immunodeficiency virus type 1 in pregnant women from southern Brazil: high rate of intraepithelial cervical lesions	Brazil	Memórias do Instituto Oswaldo Cruz	Tomatore et al. (2012)
Prevalence and temporal trends of hepatitis B, Hepatitis C, and HIV/AIDS co-infection during pregnancy across the decade, 1998-2007	USA	Journal of Women's Health	Salihu et al. (2012)
Prevalence of sexually transmitted infections among HIV-infected women in Brazil	Brazil	The Brazilian Journal of Infectious Diseases	Travassos et al. (2012)
Pregnancy outcomes associated with viral hepatitis	USA	Journal of Viral Hepatitis	Reddick et al. (2011)
High rates of active hepatitis B and C co-infections in HIV-1 infected Cameroonian adults initiating antiretroviral therapy	Cameroon	HIV Medicine	Laurent et al. (2010)
Prevalence and risk factors for HIV, syphilis, hepatitis B, hepatitis C, and HTLV-I/II infection in low-income postpartum and pregnant women in Greater Metropolitan Vitória, Espírito Santo State, Brazil	Brazil	Caderno Saúde Pública	Lima and Viana (2009)
Survey of both hepatitis B virus (HBsAg) and hepatitis C virus (HCV-Ab) coinfection among HIV positive patients	Iran	Virology Journal	Mohammadi et al. (2009)
Etravirine in special populations	Spain	Enfermedades Infecciosas y Microbiología Clínica	Gil (2009)
Prevention of mother-to-child transmission of viral infections	USA	Current Problems in Pediatric and Adolescent Health Care	Read et al. (2008)
Viral infections of the fetus and newborn infant	Italy	Medical and Surgical Pediatrics	Tremolada et al. (2008)
Hepatitis B or hepatitis C coinfection in HIV-infected pregnant women in Europe	Spain, Italy, UK, Belgium, Sweden, Germany and Ukraine	HIV Medicine	Landes et al. (2008)

Laurent et al. (2010) report that these co-infections are frequent in Europe and the United States, where the prevalence of HIV, HBV, and HCV in the general population is lower than in Africa. However, the predominant ways of transmission (intravenous drug use and sexual contact) of these infections are

similar in Western countries, whereas in Africa such ways are very different (HIV by heterosexual relationship, HBV by close contact with the family during early childhood and by vertical transmission; regarding the HCV, the ways of transmission are unclear). According to Ezechi et al. (2014) in the Western world,

only 1% of the population is triply infected with HIV, HBV, and HCV.

In Brazil, the prevalence rates of HIV/HCV co-infection obtained from samples from health services are between 9.2% and 54.7%, according to geographic distribution and risk factors for its acquisition. The highest prevalence rates are observed in studies that include injecting drug users in their sample, being the most important risk factor for HCV acquisition. The prevalence rates of HIV/HBV co-infection obtained in Brazilian studies using samples from health services are between 5.3% and 24.3% (Brasil, 2008). The higher prevalence rate of HIV/HCV in comparison to the rate of HIV/HBV co-infection can be attributed to several factors, in particular, the lack of HCV vaccines and the existence HBV vaccines (Brasil, 2011b).

Women during pregnancy are exposed to viral agents that can be transmitted vertically to the fetus or newborn. Some of these viruses, as a result of vertical transmission, may induce clinically relevant damage to the fetus or newborn (Table 3). Pregnant women are at increased risk of sexually transmitted infections due to physiological changes that occur during pregnancy, such as congestion of the cervix, edema of the vaginal mucosa, and changes in the vaginal flora. In addition, they might be less likely to have

partners who use condoms and may find it more difficult to abandon unsafe relationships (Tremolada et al., 2008; Travassos et al., 2012).

In pregnant women infected with HIV and coinfecting with other sexually transmitted diseases (STDs), there may be an increase both in the risk of vertical transmission of HIV and of other pathogens (Table 3). This risk is especially pronounced if HIV infection is acquired during pregnancy. The HCV vertical transmission is increased from three to five times in the presence of HIV co-infection (Read et al., 2008; Travassos et al., 2012).

According to the Clinical Protocol and Therapeutic Guidelines for Prevention of Vertical Transmission of HIV, Syphilis and Viral Hepatitis (Brasil, 2015b), HBV infection in neonates has a higher chronification rate than in adults; in 90% of the infected neonates it evolves to the chronic form, and in the future it can cause cirrhosis and/or hepatocellular carcinoma (Table 3), differently from individuals who acquire this disease throughout life, since these have approximately a 30% chance of developing chronic hepatitis B. Reddick et al. (2011) report that HBV has been associated with preterm birth and antepartum hemorrhage and that HCV has been associated with obstetric cholestasis and low birth weight infants (Table 3).

Table 3. List of possible risks of HIV/HBV/HCV co-infection during pregnancy, mentioned in the analyzed articles.

Risks	
Mother	Antepartum hemorrhage; Elevation in hepatic enzymes; Obstetric cholestasis; Increase in the risk of hepatotoxicity associated with antiretroviral therapy.
Fetus or newborn	Premature birth; Intrauterine growth retardation; Higher possibility of vertical virus transmission; Possible selection of resistant virus.
Both	Increase in immunosuppression; Higher probability of acute or fulminant hepatitis, chronic liver failure, cirrhosis and hepatocellular carcinoma.

According to Gil (2009) and Huntington et al. (2015), hepatotoxicity associated with antiretroviral therapy in

HIV-infected patients is more frequent in HCV/HBV-coinfecting patients, since all classes or families of antiretroviral drugs

can cause hepatotoxicity. In patients with chronic hepatitis without hepatocellular insufficiency, antiretroviral drugs can be used at usual doses. However, in patients with hepatocellular insufficiency, these drugs may change the metabolism and their bioavailability, which can increase toxicity. Huntington et al. (2015) highlight that the pregnancy itself may cause hepatotoxicity during antiretroviral therapy, with a 70% risk of increasing the number of hepatic enzymes (from mild to moderate) and a 260% risk of severely increasing this number (Table 3).

Current guidelines in the United States and Europe recommend the use of combined antiretroviral drugs for HIV/HBV coinfecting individuals. Such treatment should consist of a combination of at least two anti-HBV active drugs (including lamivudine, tenofovir, and emtricitabine) to reduce the risk of developing HBV resistance mutations (Landes et al., 2008). However, it was observed by Landes et al. (2008) that, in Europe, most HIV/HBV-coinfecting pregnant women were not using two of the anti-HBV active drugs in their antiretroviral treatment. Thus, the chances of selecting resistant HBV, which can be transmitted to their children, are increased (Table 3).

Regarding the ideal therapy in HIV/HCV-coinfecting pregnant women, it seems there is no consensus on this approach since the use of interferon alfa-2a during pregnancy is associated with abortion and the ribavirin has the potential for teratogenicity in animal models. Until now, according to the Clinical Protocol and Therapeutic Guidelines for Viral Hepatitis C and Coinfections (Brasil, 2011), there are no studies on the use of new drugs in HCV-infected pregnant women.

It was observed that HIV/HBV/HCV co-infection made the infection worse and led to diseases progression. According to Mohammadi et al. (2009), infection with the three viruses causes a higher risk of acute or fulminant hepatitis, chronic liver failure, cirrhosis, hepatocellular carcinoma, and mortality (Table 3) than infection with only one of these viruses. HCV-seropositive women (and those with HBsAg) were significantly more immunosuppressed (Table 3) than HIV-mono-infected women,

based on counts of CD4 cells, of which number were lower in women with anti-HCV antibodies (Landes et al., 2008; Ezechi et al., 2014).

Tremolada et al. (2008) state that, by early diagnosis and appropriate prophylactic and therapeutic measures, it is possible to significantly reduce the risk of vertical transmission of these viruses and also reduce the severity of the damage caused by these infections. However, in developing countries, the availability and effectiveness of diagnostic, prophylactic and therapeutic intervention are much lower than in economically advanced countries. It occurs since vertically transmitted infections in developing countries still cause high morbidity and mortality (Bonney, 2016).

In view of this, the Brazilian Ministry of Health created the Stork Network in 2011, which is a strategy aimed at implementing a network of care to ensure women the right to reproductive planning and humanized attention to pregnancy, childbirth and puerperium, and ensure that children have the right to a safe birth and healthy growth and development (Brasil, 2015b).

Conclusion

Taking into consideration the risks described in several articles, it was evidenced that the early diagnosis of HIV, HBV, and HCV in pregnant women is essential for the effective treatment in the prenatal and postnatal periods so that decisions can be made with the purpose of reducing and even preventing the vertical transmission of these viruses. Thus, it can also be evidenced that the development of strategies and public policies to control and prevent the transmission of these viruses in pregnant women are urgent measures to control these HBV, HCV and HIV infections in Brazil and worldwide. Moreover, there is a need for more epidemiological studies to better found the public policies focused on pregnant women.

Conflict of interest statement

Authors declare that they have no conflict of interests.

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