

# Coxsackie virus B infection and pregnancy

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## ABSTRACT

Frequently, enteroviral infection with Coxsackie virus B (CV-B) goes unnoticed, without or only with mild symptoms. The infection is well known for the gastro-intestinal transmission, but recently, the severe forms of neonate's infection, suggested that vertical transmission should not be neglected and moreover the fetal consequences should be studied. This review relates the most important findings regarding infection with CV-B during pregnancy, most of the information being based on murine studies. It seems that CV-B infection is associated with high rate of abortion and could also impair fertility. Regarding long term effects, CV-B might cause autoimmune diseases, congenital heart defects and neurologic disorders. Severe acute disease in new-born is generally acquired from a symptomatic mother that develop a febrile illness during the last week of pregnancy.

**Keywords:** Coxsackie virus B, pregnancy, abortion, autoimmune diseases

## INTRODUCTION

Since ancient times, one of the greatest problems of human beings was the appearance of infectious diseases. Whether the cause was a bacterium, a virus or a parasite, a key factor in the identification of an infection would be its route of transmission. That is why, people started to classify pathogens depending on this criterion. One of the easiest ways to contact an infection is through gastro-intestinal route, or the so called fecal-oral transmission. On this consideration some viruses were classified for their enteric transmission, forming Enterovirus genus.

Enteroviruses are single-stranded RNA pathogens, that were first classified in four groups based upon the way they grew in experimental animals or in cultured cells: polioviruses, Coxsackie A viruses (CA), Coxsackie B viruses (CB) and echoviruses. Currently, the identified human enteroviruses have been reclassified into five species, according to bio-

logical properties and with the purpose of evolutionary recognition (poliovirus and human enterovirus HE A, B, C, D) [1].

As already mentioned, Coxsackie B viruses are part of Enterovirus genus. Usually, the infection occurs during warm season, and it affects equally males and females. Mostly, CB-V causes asymptomatic and subclinical infections, but when the infection is symptomatic, the manifestations vary, because the viruses have a wide tropism for human organs. It seems that manifestations and their severity are influenced by the age of the patient. Milder disease was observed in children and adults, but severe forms with important complications were seen in neonates [2]. Clinical syndromes caused by Coxsackie B viruses are paralysis, aseptic meningitis, pericarditis, myocarditis, encephalitis, hepatitis, upper respiratory tract disease, pneumonia and undifferentiated febrile illness [1].

## METHODS

PubMed database was searched for studies published from January 2015 to 2021, written in English, that contain any information related to Coxsackie virus B (CV-B) and pregnancy.

## CV-B VERTICAL TRANSMISSION

Apart from fecal-oral mode of transmission and sometimes through respiratory route [3], a possible vertical transmission was suggested by the common cases of CV-B infections among neonates [4]. Severe pathological outcomes associated with maternal-fetal transmission of CV-B include congenital skin lesions, type I diabetes mellitus, later thyroiditis, hydropsfetalis, fetal myocarditis, meningoencephalitis, neurodevelopmental problems, fetal sepsis and miscarriage. Pregnant women are not routinely tested for CV-B detection; therefore, the infection prevalence is not known. However, taking into consideration the fetal pathological consequences of unrecognized and untreated in utero CV-B infection, it is a great need to understand the pathogenesis of this infection [5]. This is the reason why different studies were conducted to demonstrate the route of virus transmission and its effects during pregnancy.

One reason for vertical transmission is the detection of high levels of anti-CV-B antibodies in mothers with infected newborns [6]. Another argument for this hypothesis was the detection of viral genome in both maternal and offspring tissues [7].

Coxsackie B virus infection is dependent on some specific virus-receptor interactions. The known needed receptors are a tight junction (TJ) (localized type I transmembrane protein), called coxsackievirus and adenovirus receptors (CAR) and decay-accelerating factor (DAF), which allow CV-B to enter and infect the target cells. Same receptors were proven to be also involved in vertical transmission of the infection, by mediating infection of CV-B in placental trophoblasts [5].

## EFFECTS OF CVB INFECTION DURING PREGNANCY

In order to investigate the effects of CV-B infection during pregnancy, there were conducted few studies on mice.

### Abortion and preterm birth

A study conducted by Jaidane et al. tried to identify the effect of CV-B4 E2 inoculation in mice dependent on the day of gestation when the virus was inoculated (day 10 of gestation vs. day 17 of gestation). A high rate of abortion, around 53%, was observed when dams (female parent of an animal)

were inoculated at day 10, while an earlier delivery occurred when they were inoculated at day 17. Moreover, the detection of CV-B4 genome in tissues from virus-inoculated dams and their offspring, revealed that virus was vertically transmitted to 18 out of 18 offspring born to dams inoculated at day 10 and to 11 out of 12 offspring born to dams inoculated at day 17. Those observations may suggest that also in human beings, CV-B4 virus infection might be associated with high rate of abortion, if this occurs early in pregnancy or with a preterm birth rate, if it occurs later [8].

A study conducted in Korea also suggest a possible relationship between abortion and CV-B infection. This was a prospective study performed on 51 pregnant women with missed abortion, fetal anomalies, preterm and full-term deliveries. Taking into account that CV-B3 was identified in 8 out of 14 missed abortion patients, and in only 1 of the 27 full-term deliveries and in none of the preterm cases, that means a prevalence of this infection significantly higher in missed abortion. That is why the study concluded that CV-B infection might be a considerable etiological factor for missed abortions [9].

### Autoimmune diseases

Knowing that CV-B are involved in triggering several autoimmune diseases such as Type I Diabetes or Sjogren's syndrome, one study attempted to explore if in utero infection with CV-B affects fetal thymus, the organ responsible for immunological self-tolerance. The study demonstrated viral RNA presence in the thymus and in the thymic T cells of the offspring born to CV-B4 inoculated dams. Also, there were detected significant changes of thymic T-cell populations, changes that might be involved in the pathogenesis of autoimmune disorders [10].

### Congenital heart defects

Being known that CV-B has a great tropism for fetal cardiomyocytes, because of the highly expressed coxsackie and adenovirus receptors in these cells, another study tried to find out if the infection with CV-B3, during critical period of gestation, could be the cause of congenital heart defects. In this murine model conducted study, the authors concluded that various congenital heart defects such as ventricular septal defects, double-outlet right ventricle and ventricular non-compaction, can be caused by maternal infection with CV-B3. The highest incidence of congenital heart defects was observed when the infection occurred during 7<sup>th</sup> and 9<sup>th</sup> embryonic days, with the worst impact detected in 9<sup>th</sup> embryonic day infection. Moreover, the study found a direct relationship between viral load and incidence, respectively severity of pathol-

ogy on the fetus. Even if this virus was previously not known as a cause of congenital heart defects, according to this study, we should now be aware that CV-B3 might be the cause of a significant number of cases with congenital heart defect of unknown cause and we should think that in this context, potential epidemiological measures might be implemented [11].

### CNS disorders

Sometimes, when CV-B infection occurs during pregnancy, the target might be the central nervous system (CNS). One study analyzed brain changes in offspring's brain after pregnant mice CV-B4 inoculation. The vertical transmission was demonstrated through detection of viral particles in offspring's brains. Even if monitoring after birth did not show any cases of death, or neurologic related abnormalities (such as paralysis, asthenia or modified behaviors), histological abnormalities were identified. An inflammatory response was observed, including T-cells infiltrations and reactive microglia at the site of infection and nearby areas in the brain of infected offspring with consequent increased level of cytokines. This detrimental inflammatory environment into the brain is generally associated with some CNS disorders such as psychiatric illness, multiple sclerosis, amyotrophic lateral sclerosis, and Alzheimer disease. Based on those observations, it supposes that in utero transmission of CV-B to CNS and persistence within offspring brain might contribute to the pathogenesis of future CNS disorders [12].

### Neonate pulmonary hemorrhage

There have been reported also situations during pregnancy when CV-B infection was not only a possible cause for future pathologies, as those previous related, but also for urgent decisions. The importance of correct diagnosis of maternal enterovirus infection was highlighted in a series reports of pre-term neonates with pulmonary hemorrhage, as a result of perinatal CV-B infection. After taking the decision to urgent deliver through cesarean section two pairs of twins at 30 weeks gestation because of

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maternal fever, 3 out of 4 newborns died. Meanwhile, it was proven that the cause of newborn's death was CV-B sepsis, with multiple organ system failure, complicated with disseminated intravascular coagulopathy, pulmonary hemorrhage, hypovolemic shock and respiratory failure. The report suggested that an early recognition of maternal CV-B infection would have permitted extension of pregnancy in order to allow protective antibodies to be passively acquired or in case of delivery the necessity of aggressive management would have been anticipated [13].

### EFFECTS OF CVB INFECTION ON FERTILITY

It seems that the CV-B infection might have effects not only during pregnancy but could also impact fertility. Another study conducted on mice showed that CV-B infection leads to an important increase of the number of atretic follicles in the ovaries, decreases levels of estradiol in granulosa cells of the ovaries, reduces aromatase transcript levels in granulosa cells and also significantly decreases the fertility rate. All these changes that disturb the ovarian function during CV-B3 infection could prevent reproduction [14].

### CONCLUSIONS

The current report tries to create a bigger picture of the still poorly known vertical transmission of CV-B. Because there are very few studies performed on human beings, most of them being case reports or prospective studies, most of the information presented is based on studies performed on mice in the laboratory. Based on these studies we could say that, apart from immediately induced symptoms in adults, this virus might be involved in triggering and pathogenesis of some chronic diseases, starting from fetal life, when the infection occurs during pregnancy. According to recent studies, CV-B might be an etiological factor for autoimmune diseases, congenital heart diseases and CNS disorders. Though, further studies are needed in order to better understand the effects of vertical transmission of CV-B.

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