

# COVID-19 AND UPPER LIMB ANOMALIES IN NEWBORNS: A REASON FOR CONCERN?

## COVID-19 E ANOMALIAS DO MEMBRO SUPERIOR EM RECÉM-NASCIDOS: UM MOTIVO DE PREOCUPAÇÃO?

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### ABSTRACT

The relationship between viral infection in pregnancy and congenital anomalies is reported in the medical literature. The risks for the SARS-CoV-2 virus interfering with implantation, growth, and fetal development are not yet known. Many drugs with potential teratogenic risk are being used for treatment. The studies with the vaccine excluded pregnant women from clinical trials, currently preventing high-quality evidence. We present a review of the most common anomalies in the upper extremities caused by congenital viral infection and the risks of anti-COVID-19 therapy and vaccine during pregnancy. We aim to alert orthopedic and hand surgeons to the possibility of these conditions in the future. **Level of evidence V; Narrative review.**

**Keywords:** COVID-19. Infections. Viruses. Musculoskeletal abnormalities. Pregnancy. Newborn.

### RESUMO

A relação entre infecção viral na gravidez e anomalias congênitas é relatada na literatura médica. Os riscos de o vírus SARS-CoV-2 interferir na implantação, crescimento e desenvolvimento fetal ainda não são totalmente conhecidos. Muitos medicamentos com potencial de risco teratogênico estão sendo usados para o tratamento. Os estudos clínicos com a vacina excluíram gestantes, o que tem impedido obter evidências de alta qualidade atualmente. Apresentamos uma revisão das anomalias mais comuns nos membros superiores causadas por infecção viral congênita e os riscos da terapia anti-COVID-19 e da vacina durante a gravidez. Nosso objetivo é alertar os cirurgiões ortopédicos e de mão para a possibilidade desses problemas no futuro. **Nível de evidência V; Revisão narrativa.**

**Descritores:** COVID-19. Infecções. Vírus. Anormalidades musculoesqueléticas. Gravidez. Recém-nascido.

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### INTRODUCTION

The World Health Organization (WHO) declared coronavirus disease (COVID-19) as a pandemic on March 11<sup>th</sup>, 2020. Around the world, the first peak of infection occurred during May and August 2020. Since then, numerous cases of mild to severe complications have been reported in an impactful way.

The relationship between virus infection in pregnancy and congenital anomalies are reported in the medical literature.<sup>1-26</sup> Congenital infections can be transmitted from mother to child via the transplacental route, delivery, or peripartum. Asymptomatic infection of COVID-19 in pregnancy appears to be expected and presents an additional challenge to the medical community worldwide. On the other hand, pregnant women with COVID-19 may have a significantly increased risk of severe symptoms.<sup>27,28</sup>

For the treatment of COVID-19 or its symptoms, many drugs are being used, with potential teratogenic risks, including combined therapy with hydroxychloroquine and azithromycin. However,

it is unclear to what extent these drugs can affect or interfere with the newborn's physiological functions' proper functioning and development.<sup>29</sup> Our concern is related to the possibility of the SARS-CoV-2 virus, interfering with implantation, growth, and fetal development, in addition to the use of drugs for the treatment of COVID-19, or even vaccines, affecting the health of the newborn. In upper limbs, two clinical causes of congenital anomalies can be observed: 1) changes caused during the formation/differentiation process; or 2) changes induced in the central nervous system.<sup>30</sup> We aimed to alert orthopedic and hand surgeons to such future possible conditions and remind them by a brief review, the anomalies in the upper extremity caused by congenital infection virus more common, the risks of anti-COVID-19 therapies and vaccines.

### Congenital virus infection associated with upper limb anomalies

The upper limb anomalies that occur in the most common congenital viral infections.

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## Cytomegalovirus (CMV)

It is the most common cause of intrauterine infection and occurs in approximately 1% of all births. CMV is thought to enter the body by contacting infected secretions such as saliva, urine, blood, or genital secretions. Details of the mechanism by which CMV is transmitted to the human fetus remain unknown.

It affects the central nervous system and causes microcephaly, hydrocephalus, severe mental and motor losses, chorioretinitis, and finger anomalies. Computed tomographic scanning of the brain can demonstrate intracranial calcification. In the CMV infection, the virus may be detected in the urine for five years or longer or in saliva for 2 to 4 years.<sup>1</sup>

Congenital CMV infection has been associated with a wide range of finger anomalies. The previous reports were presented as isolated brachydactyly<sup>2</sup> and short phalanges with rudimentary fingernails.<sup>3</sup> The description of clasped thumb flexion deformity is probably due to the associated hydrocephalus.<sup>4</sup>

## Herpes simplex virus (HSV)

Infection with the neonatal herpes simplex virus (NHSV), although rare, has a wide overlap of symptoms with other neonatal diseases. It usually manifests with skin lesions, eye damage, and brain abnormalities. However, limb hypoplasia is classically described in congenital varicella syndrome. Carola et al. described upper limb hypoplasia in an NHSV.<sup>5</sup> Wine-Davie et al. reported hypoplasia of the left hand without nails, severe skin flaking on the left side of the body, and occasional blisters.<sup>6</sup> Researchers believe that hypoplasia is a consequence of viral damage to the nerve supply to the limb.<sup>5,7</sup>

## Varicella Virus

Chickenpox is an acute disease caused by the varicella-zoster virus. It commonly presents as a benign childhood exanthema. Varicella-zoster virus (VZV) is a teratogen that can cross the placenta if the infection occurs during the first 20 weeks of pregnancy. The congenital malformations and dysfunctions are diverse, with anomalies of the skin, cicatrix in the limbs associated with deformities, ocular abnormalities, brain abnormalities, and mental retardation. Approximately 30% of these children died during the first months of life. Higa et al. believe that the mechanism of congenital varicella syndrome (CVS) malformations can be due not to fetal varicella but the development of herpes zoster in utero and to encephalitis associated with herpes zoster.<sup>8</sup>

In 1987, Alkalay et al. studied 22 children aged between one day and 15 years who had congenital anomalies associated with maternal Chickenpox or zoster-like infection during the first two trimesters of pregnancy. Skeletal abnormalities involved a decrease in the size of an upper or lower extremity in 80% of patients, in addition to bone and muscle hypoplasia. Hypoplasia involved the fingers and toes in 33% of the cases and scapula and clavicle in 13% of the patients.<sup>9</sup> Sauerbrei and Wutzler related hypoplasia of limbs and other skeletal anomalies in 49% of patients.<sup>10</sup>

Savage et al. reported the evidence of denervation of limbs based on electromyography and nerve conduction studies.<sup>11</sup> Alkalay et al. found limb paresis in 65% and phrenic nerve palsy in 12% of the patients.<sup>9</sup> Gupta et al. described a neonate who presented diaphragmatic palsy and brachial palsy associated with bilateral congenital talipes equinovarus.<sup>12</sup>

Neonatal Chickenpox may result from an affected infant's exposure to the virus shortly after birth or if the mother initially contracted Chickenpox more than a week before giving birth. Gangrenous complications occur in 0.05% to 0.16% of patients with varicella infections.

Varicella gangrenous resulted from a postnatal disease. The necrotic area is confined to the region of a previous vesicle. Extensive extremity involvement is rare, and it is believed the gangrene of the

limbs occurs due to arterial thrombosis or bacterial superinfection. The treatment consists of surgical debridement and amputation when is necessary.<sup>13</sup> Ehrbar et al. described a newborn girl with a mummified and hypoplastic arm that died shortly after birth.<sup>14</sup>

## Influenza Virus

There are four types of influenza viruses: A, B, C, and D. Influenza A viruses are the only ones known to cause influenza. Fever caused by influenza during early pregnancy is associated with an increased risk of congenital disabilities. On the other hand, fever can also serve as a marker of more severe infections.<sup>15</sup>

Significant increases in the incidence of some types of defects in children have been reported after influenza A2 epidemics. Defects limited to the thumbs and radius showed a rise, although not statistically, after epidemics in Birmingham, England. Finger-reducing deformities were prevalent among deliveries after the 1963 outbreak in the United States of America.<sup>16</sup> With meta-analysis, limb reductions were associated with influenza exposure in the first trimester.<sup>17</sup>

In a recent meta-analysis, maternal influenza vaccination was not associated with an increased risk of congenital malformations. However, observational studies indicate that it is not possible to exclude adverse effects. Also, additional analyzes are needed for more accurate estimates for results of genetic abnormalities.<sup>18</sup>

## Rubella Virus

Rubella virus (RV) causes a mild rash disease often accompanied by adenopathy and occasional arthralgia. Congenital rubella represents the most important viral cause of fetal harm. During the first trimester of pregnancy, an infection can lead to severe birth abnormalities known as congenital rubella syndrome (CRS). Placental infection occurs during maternal viremia, leading to the spread of the virus throughout the fetus. Spontaneous abortion and fetal death were reported in 40% of the cases analyzed.<sup>19</sup> The involvement of multiple organ systems and common abnormalities include growth restriction, hepatomegaly, hydrocephalus, ventricular septal defect, intracranial calcifications. Anomalies of the musculoskeletal system include weakness in the upper and lower limbs, congenital dislocations, congenital osteogenesis imperfecta, and muscular dystrophies.<sup>20</sup> In a Chinese study to determine the incidence and types of disease in rubella infection, the authors described that 2.09% of children presented limb defects.<sup>21</sup>

## Zika Virus

Initially isolated in 1947, the Zika virus is an arbovirus in the family Flaviviridae. The first documented human outbreak in the Americas occurred in May 2015. Typically, transmission occurs through infected mosquito bites, blood transfusions, and sexual contact and from the mother to the fetus during pregnancy.

In infection during pregnancy, the Zika virus infects the brain cells of the fetus. Most babies die shortly after birth. At birth, congenital Zika syndrome (CZS) was characterized by microcephaly and cerebral calcifications, craniofacial and ocular abnormalities, and defects in the upper and lower limbs congenital joint contracture as contractures consistent with multiple congenital arthrogryposes and hypertonia.<sup>22</sup> In an observational study, eighteen children (21%) had malformations such as arthrogryposis involving > 1 joint contractures of the upper and lower limbs, club feet, and knee flexion contractures. Besides, 3 of the 18 babies had unilateral diaphragmatic paralysis.

Unilateral diaphragmatic paralysis has been described after an infection caused by other viruses such as herpes zoster, poliovirus, West Nile virus, human immunodeficiency virus, and dengue.<sup>23</sup> In a meta-analysis, musculoskeletal disorders, such as arthrogryposis, have been reported as typical. Other reports included clubfoot and hip dysplasia.<sup>24</sup> Matos et al. described that the

treatment of orthopedic sequelae of Zika virus infection could be similar to treating orthopedic sequelae of cerebral palsy.<sup>25</sup> Based on the characteristics of 47 patients, the authors described three groups: Type I - non-spastic, Type II - spastic, and Type III - arthrogryptic. Unfortunately, the authors did not describe the results of orthopedic treatment for these patients.

Serpa et al.<sup>26</sup> described the arthrogryptic alterations in 17 infants diagnosed with CZS. It was noted that the upper limbs' proximal segments were less affected, with a compromised concentration in the distal region of the upper limbs. Hand and wrist bilateral deformities were evident. Severe camptodactyly deformities were commonly found in the long and ring fingers (64.70%), a position similar to the horn hand gesture used by heavy metal fans. Joint contracture in flexion associated or not with wrist ulnar deviation was observed in 35.29% of infants. The authors believe that the patients presented a pattern of impairment particular to congenital Zika virus infection.

### SARS-CoV-2 virus

Thromboembolic events can be multifactorial and of unclear etiology a lot of times. The COVID-19 infection may be associated with increased risk of limb or digital ischemia in adults<sup>(31)</sup>. A study showed an increased rates of placental histopathologic abnormalities, particularly fetal vascular malperfusion and villitis of unknown etiology in asymptomatic women delivering at term.<sup>32</sup> The question is if the fetuses may be at theoretical risk for intrauterine thrombotic events or any other events induced by maternal infection with COVID-19. Pervenn et al. reported a congenital ischemic limb in a neonate born to a COVID-19 mother. The newborn had present purpuric plaques and hemorrhagic bullae of the left forearm, wrist and hand who soon progressed to necrotic plaques and necrosis of all digits on the left hand. Forearm amputation at level of 4 cm distal to the olecranon tip was performed at 19 days of age.<sup>33</sup> The summary of the limb anomalies observed in congenital virus infection can be seen in Table 1.

### Anti-COVID-19 Therapies

Pregnancy is considered a risk factor for COVID-19 severe disease.<sup>27</sup> In a meta-analysis, Diriba et al. stated that none of the studies reported transmission of Coronavirus from the mother to the fetus in the womb during the study period (1,316 pregnant women with symptoms [SARS-CoV-2, MERS-CoV and SARS-CoV]).<sup>30</sup> On the other hand, Khan et al. believe that COVID-19 can result in long-term congenital anomalies due to infection or therapeutic maneuver.<sup>34</sup> Further on, Louchet et al. suggest that there are still many deficiencies in studies on drug efficiency and safety for pregnant women in treating infectious diseases.<sup>35</sup>

Some drugs used in patients during the pandemic already have safety data for pregnant women, although their safety in the context of COVID-19 may be different from conventional use. There are safety data for pregnancy and placental transfer for colchicine, steroids, oseltamivir, and some monoclonal antibodies.<sup>35</sup> A research for study of risk factors for prenatal limb defects in high-risk pregnant women described that 2.1% women took glucocorticoid.<sup>36</sup>

**Table 1.** Virus infections that cause upper limb anomalies following exposures during pregnancy.

Infection	Anomalie
Cytomegalovirus (CMV)	brachydactyly, short phalanges with rudimentary fingernails, clasped thumb
Varicella (Chickenpox)	Upper Limb hypoplasia Limb gangrenous Limb paresis
Herpes simplex virus 2 (HSV-2)	Upper Limb hypoplasia
Influenza Virus	Reduction deformities of the fingers
Rubella (German measles)	Upper limb anomalies
Zika virus	wrist flexion with or not ulnar deviation flexion contracture, camptodactyly.
SARS-CoV-2 virus (COVID-19)	Limb gangrenous

Lopinavir/ritonavir has low placental transfer. Some drugs are banned in pregnancy because of the known teratogenicity like thalidomide or fetal toxicities like blockers of the renin-angiotensin system. Other medications do not have sufficient data on pregnancy outcomes as tocilizumab, interleukin 6 inhibitors, umifenovir, and favipiravir.<sup>35</sup>

Regarding remdesivir, it seems to be safe for use in human pregnancies, as shown in trials conducted in Ebola.<sup>37</sup>

A large retrospective cohort study with UK data showed that prescribing macrolide antibiotics, erythromycin, clarithromycin and azithromycin, during the first trimester of pregnancy was associated with an increased risk of severe malformations. The authors recommended that other antibiotics be prescribed until further research is available.<sup>38</sup>

The study by Huybrechts et al. suggested a small increase in the risk of malformations associated with the use of hydroxychloroquine in the first trimester of pregnancy. The authors indicated that if hydroxychloroquine is useful for COVID-19 in ongoing studies, there is a need to assess potential risks and benefits due to the possibility of malformations.<sup>39</sup>

### Vaccines

Some vaccines serve primarily to protect pregnant women from severe morbidity or mortality. Vaccines against COVID-19 are categorized as molecular and cellular, stimulating the proliferation of immune system memory cells against SARS-CoV-2. The risks associated with the vaccine have led to the exclusion of pregnant women from clinical trials, currently preventing high-quality evidence. However, due to the mass vaccination campaigns, the chances of immunization of women increases. Because of this, pregnant women need to be under improved and adequate safety monitoring conditions.<sup>40</sup> One of the common concerns is the fear of side effects from vaccines. Recently, rare blood clots have emerged after the administration of two vaccines in some patients. The data available shows the available vaccines are better at preventing hospitalization, severe disease and death than they are at preventing symptomatic COVID-19.<sup>41</sup>

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