Bulletin of the *Transilvania* University of Braşov
Series VI: Medical Sciences • Vol. 15 (64) No. 1 – 2022
https://doi.org/10.31926/but.ms.2022.64.15.1.6

PREGNANCY ASSOCIATED SARS-COV-2 AND ZIKA INFECTIOUS CONDITIONS – RECENT DATA AND OUTCOMES

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Abstract: *The effects of SARS-CoV-2 and Zika viruses (ZIKV) on pregnant women are undeniable a health emergency. Both viruses have a general impact on medical system and are an ongoing challenge requiring intense action considering the arising problems generated in the socio-economical system. This paper aims to present an insight into how Zika virus and SARS-CoV-2 virus affect the maternal and fetal outcomes and it includes a summary of the literature using the PubMed database with a selection of studies from 2016 to 2022. Regarding ZIKV infection during pregnancy and the neonatal outcomes, the evidence show that congenital Zika syndrome encompasses several malformations mainly in the neurological and visual systems, although the syndrome can affect other organ systems. ZIKV infection is also associated with several adverse pregnancy outcomes, including fetal loss. Based on our findings, SARS-CoV2 infection has fewer maternal-fetal complications compared to Zika virus but the number of pregnancies affected by COVID-19 is higher compared to ZKIV. The current data are essential for understanding the diseases profile but further studies should focus on analyzing the development of accurate diagnostic tests in both viruses. Nevertheless, further prospective studies with large number of patients with SARS-CoV-2 infection are needed in order to identify a possible disease-pattern in infants related to this virus.*

Key words: *SARS-CoV-2 infection, Zika virus, pregnancy, maternal outcomes, congenital anomalies*

1. Introduction

In recent years much has been learned about Zika and SARS-CoV-2 viruses and it is well known that both are affecting the maternal-fetal outcomes in different ways. Comparing to SARS-CoV-2, Zika virus was first identified in Uganda in 1947, but it was not recognized a cause of birth malformations until 2016, after a large outbreak in Brazil [1]. In contrast, SARS-CoV-2 virus was first reported in Wuhan,

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Hebei Province, China, in December 2019 [2] and shortly the infection spread rapidly to the rest of the world. Both viruses caused a serious public health emergency given their fast and easy transmissibility.

2. Methods

This paper is a systematic review that includes a summary of the relevant literature based on the consequence of Zika and SARS-CoV-2 infections in pregnancy. We selected the studies using PubMed database and the including and excluding criteria are showed in the table below (Table 1).

Table 1

The including and excluding criteria used for this systematic review

Including criteria	Excluding criteria
Studies from 2016-2022	Studies before 2016
MSH: pregnancy, Zika virus, SARS-CoV-2 virus, neonatal outcomes, molecular mechanisms, congenital abnormalities	Non-pregnancy related articles
Free full text	Abstract only
Clinical trials, meta-analysis, systematic review	

The following main searches were used: "pregnancy AND Zika virus OR ZIKV", "pregnancy AND SARS-CoV-2 virus", "pathology of Zika infection", "pathology of SARS-CoV-2 infection". We included only the case reports in which the information about the mother and the fetus were in detail. We included systematic reviews, clinical trials as well as theoretical studies. Our study included the relevant papers published between 2016-2022 as well as the case reports during this period. Manual searches of reference lists from relevant papers were performed to identify additional studies.

3. Results and Discussion

3.1. Epidemiology and etiology data about Zika virus and pregnancy

In February 2016, the World Health Organization's (WHO) emergency committee declared Zika infection a public health emergency of international concern. The new finding of a disease that might have serious effects on expectant mothers and their babies triggered the search for global partnerships in order to elucidate the pathophysiology of the infection and to deal with the outcomes. Zika virus (ZIKV) is a member of the virus family Flaviviridae, genus Flavivirus [3]. It is a 40-nm virus and has icosahedral symmetry and it has a non-segmented, single-stranded, positive sense RNA genome [3]. Since the Zika virus outbreak in the United States, Centers for Disease Control and Prevention (CDC) concluded that among people with confirmed or possible Zika virus infection during pregnancy, Zika-associated birth defects occured in 5% of babies [4]. According to cohorts from Colombia, Puerto Rico, and French Guiana, the cumulative risk of ZIKV infection for pregnant women living in epidemic areas ranged from 21 to 44 percent [5]. However, this risk largely depended on the local incidence of ZIKV, which varied from 1 percent in Brazil following the first epidemic wave to 75 percent on Yap Island during the outbreak in 2007 [5].

When it comes to transmission, ZIKV is primarily spread by infected mosquitoes like other flaviviruses. Aedes spp. mosquitoes, in particular *Aedes aegypti*,

which is extremely common in tropical and subtropical areas, especially in an urban context, are the major vectors of ZIKV. Although other mosquitoes, *Aedes albopictus* have shown to be effective ZIKV vectors,but there have been no reports of ZIKV epidemics caused by *Ae. albopictus* yet. Various contradictory research state that the transmission of the Zika virus may include mosquitoes from other genera, primarily the culex mosquitoes that spread the West Nile and Japanese encephalitis viruses [6]. After viral RNA was found in 28% of asymptomatic blood donors in French Polynesia in 2014, the possibility of Zika virus transfusion-transmitted infection was hypothesized [7]. This suspicion was later verified in Puerto Rico in 2016 when 1% of blood donors were found to be viraemic [7]. Blood donors who were asymptomatic and Zika virus RNA positive were found in Florida and Texas in 2017 [7]. Moreover, Zika virus sexual transmission is possbile from both asymptomatic and symptomatic infections through genital, oral and anal intercourse [7]. The 2013 French Polynesian outbreak was the first time that perinatal Zika virus transmission has been documented [7]. In the Brazilian epidemic, intrauterine transmission was subsequently confirmed. Materno-fetal transmission of the virus has been supported by the discovery of viral RNA in the amniotic fluid of pregnant women with symptoms suggestive of Zika virus infection, as well as subsequently in fetal brains and miscarriage products [7]. In 2014, Besnard et al. [8] had not discovered any evidence in favor of the transplacental transfer of ZIKV from the mother to the fetus. They have proposed that the infection during birth may be passed on through breastfeeding. In their investigation, close contact between mother and infant as a transmission method could not be ruled out. However, Oliveira et al. [9] had demonstrated, by RT-PCR, that amniocentesis samples were RNA-viral positive. Therefore, it's possible that the illness spread throughout pregnancy rather than following birth.

It has been suggested that the distruction of the placental immunological barrier is caused by chronic placentitis [7]. While Zika virus causes serious harm to the developing fetal brain, it does not trigger a significant inflammatory response within the placenta like other TORCH infections do [7]. Similar to CMV and toxoplasmosis, not all Zika virus-infected pregnant women will experience vertical transmission and not all exposed fetuses will show symptoms of congenital infection [10]. It is yet unknown how frequently congenital infections occur vertically. Although harmful virus particles have been found in breastmilk, no case of neonatal transmission by breastfeeding has yet been reported [10].

3.2. Epidemiology and etiology data about SARS-CoV-2 and pregnancy

SARS-CoV-2 is a coated single-stranded RNA (genome size of 30 kb), consisting of four structural proteins (spike-type surface glycoprotein, coat protein, protein membrane and nucleocapsid protein) and nonstructural proteins that are active targets of ongoing vaccine research [11]. Although much of the world focuses on the lethal respiratory effects of COVID-19, especially in the elderly, emerging information suggests that COVID-19 puts young women and their children at increased risk of pregnancy complications. However, limited data has been

documented on the clinical manifestations of COVID-19-positive pregnant women. Pregnant women may be more likely to get infected by SARS-CoV-2 virus and experience more severe clinical events because to the changes in maternal physiology and immune function that occur during pregnancy. In an updated CDC report which included the cases from January to October 2020, 6.6 percent of the 461,825 reproductive-age women with positive SARS-CoV-2 test results were determined to be pregnant. 409,462 (88.7%) of the 461,825 women in reproductive age were symptomatic. 23,434 (5.7 percent) of all symptomatic women reported being pregnant. According to these data, pregnant women in the US are more likely than non-pregnant women of reproductive age to get SARS-CoV-2 infection and accompanying symptoms [12]. In a study conducted in Romania, Brasov, during 2 years and 3 months [13], out of 842 pregnant women, 555 of them where SARS-CoV-2 positive (65,9%).

As ways of transmitting the virus, the main one is the contact of the mucosa (nasal cavity, oral cavity) of people susceptible to respiratory drops caused by coughing or sneezing by those infected [14]. Transmission was also reported through contacts with contaminated objects. Transmission by air is rare, but is possible in medical procedures such as endotracheal intubation, tracheostomy or bronchoscopy [15]. Most infections occur through close contacts that are defined as "face-to-face" contacts of at least 15 minutes and a maximum distance of 2 meters [16]. Placental infection and vertical transmission of SARS-CoV-2 is rare. In a meta-analysis that included 1316 pregnant women infected with SARS-CoV, MARS-CoV and SARS-CoV-2, no mother-to-child transmission of coronaviruses was detected [17]. A study conducted by Di Mascio et al. [18] on a cohort of 41 pregnant women concluded that SARS-CoV2 infection was associated with a higher rate of preterm birth, preeclampsia, cesarean delivery and intrauterine fetal death ascending transmission of the virus has been identified.

SARS-CoV-2 is prone to genetic evolution, resulting in several variants that may have different characteristics compared to its ancestral strains. Periodic genomic sequencing of viral samples is of major importance, especially in a global pandemic, as it helps to detect any new genetic variants of SARS-CoV-2 that may be more virulent.

3.3. Zika virus related maternal complications and fetal outcomes

In 17–56% of cases of Zika virus infection, pregnant women had symptoms. The second day after infection, symptoms may start to show up and might linger for up to two weeks [19]. Maculopapular rash, a low-grade fever, asthenia, pruritus, arthralgia, retro-orbital cephaleas, myalgia, conjunctivitis or conjunctival hyperemia, and/or edema of the limbs are symptoms of an infection [20]. Rarely, serious neurological issues might arise, including Guillain-Barré syndrome, which can be fatal in pregnant women [20]. However, maternal complications are neither more common nor more severe compared to non-pregnant women [20]. An increased risk of birth abnormalities or fetal loss is not linked to the existence or severity of maternal symptoms [20]. Recent studies

have shown that neither a prolonged viral load nor a persistent viremia were risk factors for unfavorable fetal or neonatal outcomes, despite the fact that a persistent viremia was previously linked to a greater risk of birth abnormalities [19].

Congenital Zika virus syndrome (CZS) is defined by CDC as a" proven in utero ZIKV infection associated with severe microcephaly in which the skull has partially collapsed, decreased brain tissue with a specific pattern of brain damage, damage to the back of the eye, congenital contractures, hypertonia or restricted body movements [21]". While the initial findings suggested a link between microcephaly and ZIKV materno-fetal infection, several case-series and cohorts have demonstrated that microcephaly is not always present in CZS and that ultrasound (US) examinations should pay close attention to the brain structure. Atypical skull shape and an occipital excess of skin are typically linked to microcephaly connected to CZS, which suggests a series of prenatal brain disruption sequence [22]. The mechanism underlying microcephaly is still unknown. It has been hypothesized that infection may have an impact on the fast growing human germinal matrix. Subsequent proinflammatory responses at early stages of brain development reduce cerebral volume [23].

Viral ribose nucleic acid (RNA) has been found in placenta, amniotic fluid, as well as brain tissues of stillborn babies with microcephaly [23]. In brain progenitor cells, ZIKV may infect and multiply vigorously. Contrary to progenitor cells, mature nerve cells are less susceptible to infection by ZIKV and because of this, fetal brains but not adult brains are more vulnerable to ZIKV [23]. Other prenatal features of CZS include: asymmetrical or unilateral ventriculomegaly, calcifications, malformations of cortical development and corpus callosum dysgenesis [22].

When it comes to eye disorders, the ones observed on prenatal ultrasonography or MRI can range from the more common unilateral microphthalmia to anophthalmia. Optic chiasm hypoplasia, coloboma of the retina, and cataract are some of the indicators that can be seen on prenatal images, although the spectrum of optical abnormalities detected postnatally is wider [24]. A quarter of CZS patients have abnormalities of the eyes [24].

Extra-cerebral anomalies include signs of placental inflammation such as increased tickness and calcifications. Placental disfunction induced by ZIKV infection may contribute to intrauterine growth restriction (IUGR), pacticularly in cases of early infection, when placental circulation is not yet established [24]. IUGR was observed in 14% of CZS cases and could be the result of both fetal infection and placental insufficiency [22].

Clinical features of CZS at birth include mild anemia, cholestasis and neurological impariments such as swallowing dysfunction, movement abnormalities and epilepsy [22]. The predominant neurologic findings in young infants with suspected congenital ZIKV infection are extreme irritability, hyperreflexia and hypertonia with spasticity, tremors and extra-pyramidal symptoms [22].

Recent report with more extensive investigations of fetuses and newborns, reported CZS in 4% to 9% of pregnancies exposed to ZIKV, when exposure is defined by proven maternal infection [22]. In a recent study examining the rate of negative outcomes in fetuses/newborns with proven ZIKV infection, 45 percent

showed no symptoms or complications, 20 percent had mild-to-moderate symptoms that may have been related to the infection, 21 percent had severe complications consistent with CZS, and 14 percent led to fetal loss [25]. A maternal infection in the first trimester of pregnancy is linked to an increased risk of miscarriage, fetal loss, or CZS, whereas an infection in the second or third trimester of pregnancy seems to have fewer negative effects on the fetus and the newborn, with more general symptoms, similar to other TORCH infections [22].

3.4. SARS-CoV-2 viurs related maternal compliactions and fetal outcomes

The clinical course of infection in pregnant women was generally not complicated according to a meta-analysis that included 24 publications and 1100 pregnant women [26]. Fever and cough were the most prevalent symptoms in pregnant women who tested positive for COVID-19, followed by anosmia, ageusia, myalgia, exhaustion, sore throat, malaise, stiffness, headache, and poor appetite [26]. Another study suggests that the most common symptoms of SARS-CoV2 virus infection in the general population are fever (91%), cough (67%), fatigue (51%) and dyspnea (30%) [27]. In pregnant women, fever (68%) and cough (34%) are the most common clinical manifestations, followed by dyspnea and diarrhea [28]. The clinical symptoms are similar in pregnant and non-pregnant patients. Depending on the severity of the disease, COVID-19 infection is classified as mild (symptomatic or mild pneumonia), moderate (tachypnea $\geqq$ 30 breaths / min or oxygen saturation ≤93% at rest or PaO2 / FiO2 <300 mmHg) or severe (respiratory failure requiring endotracheal intubation, shock or other organ failure requiring intensive care), accounting for 81%, 14% and 5% of cases in the general population [27]. The World Health Organization reported a large cohort study of 147 women pregnant with COVID-19, only 8% and 1% had moderate and severe form of the disease, and 11% had severe 19. In pregnant women who develop COVID-19 19, initial data showed a similar rate of presentation to the intensive care unit (ICU) compared to women who are not pregnant [28].

When it comes to the delivery mode, the same meta-analysis concluded that despite the guidelines and recommendations of experts which suggest choosing vaginal birth wherever feasible, the preferred mode of delivery in pregnant women with COVID-19 was caesarean section [26]. In the study [13] conducted at „Dr. I.A. Sbarcea" Hospital , it could be observed that there was a higher rate of cesarean sections 57% in the group of patients with SARS-CoV-2 infection compared to the control group which recorded 52% births by cesarean section. Among the indications to perform caesarean section was SARS-CoV-2 infection (7%), to improve maternal status in the context of a severe form. Other indications among those studied, with a high weight in the group of patients with COVID infection were the scarred uterus (38%), fetal distress (21%), pelvic presentation in primiparous (12%) and feto-pelvic disproportions (8%).

A recent study [29] attributes SARS-CoV2 infection to the potential for preeclampsia in pregnant women. The study analyzed 42 pregnancies, of which

34 cases presented COVID-19 mild and moderate forms and 8 cases of severe forms. Of the 8 severe cases, 6 of them had a preeclampsia-like syndrome. Another study [30] on a cohort of 2184 patients revealed the presence of SARS-CoV2 virus in 33.2% of subjects, and 123 of them had preeclampsia. Most of them were primiparous patients. The study concluded that the presence of preeclampsia and pregnancy-induced hypertension are independent factors that associate an increased risk of morbidity and mortality caused by the SARS-CoV2 virus.

Regarding fetal death, there was no significant differences during the COVID pandemics and non-COVID era as shown by the study conducted by Wilkinson et al. [31]. In the study carried out within the Clinical Hospital of Obstetrics and Gynecology "Dr.I.A.Sbârcea" [13] similar results were registered regarding fetal death, respectively 0.70% for the control group and 1.26% for pregnant women with SARS-CoV-2 infection.

The association between SARS-CoV-2 infection in the first half of pregnancy and pregnancy loss is still unknown. Infections with other coronaviruses, such as respiratory syndromes, Coronavirus Acute Respiratory Syndrome (SARS-CoV) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) appear to increase the risk of miscarriage. The overall rate of miscarriages before 20 weeks of gestation varies from 10% to 26% [32] ,the rate increasing with the age of the woman, reaching approximately 53% in women aged 45 and over. However, the rate of miscarriages of COVID-19 cases appears to be in the range of the normal pregnant population.

4. Conclusions

The effects of ZIKV on the fetus are more frequent and severe when maternal infection occurs in the first and second trimesters of pregnancy, resulting in spontaneous abortion and therapeutic abortion due to major congenital malformation compared to SARS-CoV-2 infection in which the maternal-fetal outcomes are less severe. Although both, Zika virus and SARS-CoV-2 infection, had a general impact on the medical system and on obstetric patients, there are limited data on the impact of COVID-19 on pregnant women and newborns and limited data on the real number of neonates affected by the Zika virus. Congenital Zika syndrome also impacts the health system and the families' daily lives, requiring collaboration between levels of healthcare and inter-sector cooperation aimed at comprehensive care for these children.

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