

SPECIAL ARTICLE

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Financing: The author did not receive specific financing for this paper

Conflict of interest: The author declares no conflict of interest

Received: 24 May 2023

Accepted: 29 May 2023

Online publication: 5 July 2023

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Cite as: Pacheco-Romero J. The coronavirus conundrum - Consequences of the SARS-CoV-2 infection in humans - The brain - Pregnant women and newborns. *Rev peru ginecol obstet.* 2023;69(2). DOI: 10.31403/rpgo.v69i2513

The coronavirus conundrum - Consequences of the SARS-CoV-2 infection in humans – The brain – Pregnant women and newborns

El enigma del coronavirus – Consecuencias de la infección por el SARS-CoV-2 en el ser humano – El cerebro – Gestante y recién nacido

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DOI: 10.31403/rpgo.v69i2513

ABSTRACT

The SARS-CoV-2 virus continues to replicate. Its new variants would not be causing the deaths and serious hospitalizations of the years 2020-2022, so the World Health Organization (WHO) has declared the end of the state of health emergency. Until May 24, 2023, the WHO coronavirus dashboard shows more than 766 million confirmed cases, and about 7 million deaths in the world, with greater concentration in Europe, Western Pacific, and America (especially the U.S.A. and Brazil). Europe and China prepare for new virus breakthroughs. Therefore, health precaution is recommended, as well as compliance with vaccination and boosters, and the development of new vaccines. We comment on the fragility of randomized trials published in the first two years of the pandemic, as well as recent findings of which patients with COVID could develop long COVID. It is important to know the new scopes on the affectation of the coronavirus on the pregnant woman, the fetus and the neonate and the initial follow-up of the latter.

Key words: Coronavirus infections, SARS-CoV-2, COVID-19, Viral replication, SARS-CoV-2 vaccines, Cerebrum, Pregnant woman, Fetus, Newborn

RESUMEN

El virus SARS-CoV-2 sigue replicándose. Sus nuevas variantes no estarían causando las muertes y hospitalizaciones graves de los años 2020 a 2022, por lo que la Organización Mundial de la Salud (OMS) ha declarado el final del estado de emergencia sanitaria. Hasta el 24 de mayo de 2023, el tablero de coronavirus de la OMS señala más de 766 millones de casos confirmados, y cerca de 7 millones de muertes en el mundo, con mayor concentración en Europa, Pacífico Occidental y América (especialmente en los E.E. U.U. y Brasil). Europa y China se preparan para los nuevos avances del virus. Por ello se recomienda precaución sanitaria y cumplir con la vacunación y refuerzos, así como elaborar nuevas vacunas. Se comenta sobre la fragilidad de los ensayos aleatorios publicados en los primeros dos años de la pandemia, así como los recientes hallazgos de cuáles enfermos con COVID podrían desarrollar COVID prolongado. Es de importancia conocer los nuevos alcances sobre la afectación del coronavirus sobre la gestante, el feto y neonato y el seguimiento inicial de los últimos.

Palabras clave. Infecciones por coronavirus, SARS-CoV-2, COVID-19, Replicación viral, Vacunas SARS-CoV-2, Cerebro, Gestante, Feto, Recién nacido

First peer-reviewed analysis of the Chinese swabs confirms animal DNA was present in samples from Wuhan market that tested positive for SARS-CoV-2⁽¹⁾. After viral replication into thousands of thousands of variants and subvariants, the new COVID-19 subvariant named XBB.1.16 by the World Health Organization (WHO) was first detected in the Indian subcontinent in late January 2023, and then in 29 countries. It was informally dubbed as 'Arcturus', a variant of concern or interest to WHO. XBB.1.16 is a product of the mixture of the subvariants BA.2.10.1 and BA.2.75. XBB.1.16 has not been reported to have increased intensive care unit admissions or deaths, even in countries where it has increased the number of cases⁽²⁾.



Until May 24, 2023, the WHO coronavirus dashboard indicates more than 766,000 confirmed cases and about 7 million deaths from the virus worldwide, with the highest concentration in Europe and the Western Pacific, somewhat less in the Americas, especially in the USA and Brazil⁽³⁾. In Peru, more than 220,000 people have died⁽⁴⁾.

There are now new outbreaks of COVID-19 across Europe with persistent circulation of the virus and of new Omicron subvariants, even during this summer, a notable difference from influenza virus or other seasonal respiratory infections. It is difficult to assess the extent of the most recent waves of COVID-19 because of the sharp reduction in diagnostic testing. Excess mortality remains high as 467,921 people died in Europe during 2022. Hospital admissions continue and infections persist in immunocompromised people with comorbidities. Between 3-20% of those affected suffer from prolonged COVID. New strategies and investments are needed to tackle COVID-19 and develop greater resistance to future respiratory pathogens⁽³⁻⁵⁾. The latest surge in COVID-19 cases in China is not surprising to researchers, who say that China will see an infection cycle every six months now that all COVID-19 restrictions have been removed and highly infectious variants are dominant. But they caution that rolling waves of infection carry the risk of new variants emerging.

Now, Chinese authorities are rushing to distribute vaccines to combat a new wave of coronavirus cases that is expected to peak in June and infect up to 65 million people a week. This will occur as the new XBB.1.5 variant of the virus evolves to overcome the immunity built up after China's abrupt exit from its strict 'zero covid' regime last winter, resulting in up to 85% of the population becoming infected at that time. In the United States, the new variant caused a spike in infections, but the public health emergency was still declared over on May 11, although experts do not rule out new variants triggering another wave of infections in the coming years. Although Chinese authorities say the new wave will be less severe, public health experts say an aggressive program of vaccine boosters and immediate supply of antivirals in hospitals is needed to prevent another spike in deaths among China's large elderly population⁽⁴⁻⁶⁾.

The COVID-19 public health emergency may be over, but certain protocols still remain. Experts say people should still isolate for at least 5 days if they test positive for COVID-19. People who test positive for the virus should follow other health protocols, such as wearing masks and notifying close contacts⁽⁵⁻⁷⁾. The elderly, the immunocompromised and persons with comorbidities and those who are not fully vaccinated should wear masks, wash their hands, and practice distancing in crowded environments.

ABOUT THE TREATMENT

Regarding the treatment of the viral disease, there have been a multitude of proposals for medical treatment and drug testing, most of which were changed or withdrawn due to lack of obvious positive results. The recommendation of the WHO and the U.S. Federal Drug Administration for the use of Paxlovid (nirmatrelvir and ritonavir) is highlighted. An emulated trial with molnupiravir and nirmatrelvir-ritonavir included hospitalized patients with COVID-19 aged 18 years or older between March 16 and July 18, 2022 (n = 7,119). Molnupiravir and nirmatrelvir-ritonavir reduced all-cause mortality in both vaccinated and unvaccinated hospitalized patients. Admission to intensive care or need for ventilatory support was not significantly reduced⁽⁶⁻⁸⁾. New data suggest that antivirals against SARS-CoV-2 may be effective in preventing prolonged COVID. Studies have suggested that nirmatrelvir in combination with ritonavir reduced the risk of prolonged COVID by 26% and molnupiravir by 14%. In exploratory analyses, ensitrelvir also reduced the risk of prolonged COVID. Taken together, these data on nirmatrelvir, molnupiravir and ensitrelvir point in the direction that the use of antivirals in the acute phase of COVID-19 could be an important strategy to prevent prolonged COVID⁽⁷⁻⁹⁾.

ANTIBIOTIC RESISTANCE

Frequent antibiotic use in patients with COVID-19 may exacerbate antimicrobial resistance. One study did a systematic review and meta-analysis in the WHO COVID-19 research database of studies of bacterial co-infections (identified within ≤48 h of presentation) and secondary infections (>48 h after presentation) in outpatients or hospitalized patients with COVID-19. They included



148 studies of 362,976 patients between December 2019 and May 2021. The prevalence of bacterial coinfection was 5.3%, while the prevalence of secondary bacterial infection was 18.4%. Among those with bacterial infections, the proportion of antimicrobial-resistant infections was 60.8% and the proportion of resistant strains was 37.5%, findings that should be taken into consideration⁽⁸⁻¹⁰⁾.

VACCINES

The WHO Strategic Advisory Group of Experts (SAGE) on immunization reviewed at the end of March 2023 the roadmap to prioritize the use of COVID-19 vaccines because of the impact caused by the Omicron variant and the high level of population immunity due to infection and vaccination. The high priority group includes the elderly, young adults with comorbidities such as diabetes and heart disease, persons with immunodeficiency conditions such as HIV/AIDS and transplant recipients, children aged 6 months and older, pregnant women, and front-line health care workers. SAGE recommends administering an additional booster dose 6-12 months after the last dose, depending on factors such as age and immunodeficiency conditions. Children with immunodeficiency conditions and comorbidities are at increased risk for the severe form of COVID-19. Vaccination of pregnant women protects both mother and fetus, and in turn tends to reduce the likelihood of infants being hospitalized for COVID-19⁽⁹⁻¹¹⁾.

Current trends suggest that only about 73% of the European Union's inhabitants (15 years of age and over) were immunized, with more than 104 million people yet to be immunized. Reluctance to vaccinate is a key impediment to conducting pandemic immunization programs⁽¹⁰⁻¹²⁾.

Several B.1.1.529 (Omicron) subvariants of coronavirus 2 have emerged as dominant strains, such as BF.7, BQ.1, BQ.1.1, BQ.1.1, and XBB. These variants contain more mutations in the receptor binding domain of the spike protein than the BA.2 and BA.5 strains. Such Omicron subvariants have shown escape to humoral immunity elicited by vaccines based on prototype strain sequences, such as the inactivated vaccine and ZF2001. So new generation and updated Covid-19 vaccines are needed to improve protection and control of the pandemic⁽¹¹⁻¹³⁾.

FRAGILITY OF PUBLISHED RANDOMIZED CLINICAL TRIALS FOR COVID-19

Interpreting the results of randomized clinical trials (RCTs) for COVID-19, which have been published rapidly and in large numbers in medical journals through early August 2021, represents a challenge during a pandemic. Investigators have reviewed certain characteristics of 47 RCTs for COVID-19: 36 (77%) were studies of treatment drug effects, 5 (11%) studies of vaccines, and 6 (13%) studies of other interventions, with a total of 138,235 participants. The median (IQR) frailty index of the included trials was 4 (1-11). The median (IQR) frailty indexes of RCTs of treatment drugs, vaccines, and other interventions were 2.5 (1-6), 119 (61-139), and 4.5 (1-18), respectively. The frailty rate of more than half of the studies was less than 1% of each sample size, although the frailty rate as a proportion of events needing to change would be much higher. That is, a relatively small number of events (a median of 4) would be required to change the results of the COVID-19 RCTs from statistically significant to nonsignificant. Most of the COVID-19 vaccine trials had a large frailty index, whereas most of the RCTs studying treatment drugs and other interventions had a very small frailty index. Furthermore, the frailty index among most studies was less than 1% of each sample size. These findings suggest that health care professionals and policy makers should not rely too much on individual RCT results for COVID-19⁽¹²⁻¹⁴⁾.

LONG COVID – POST-ACUTE SEQUELAE OF SARS-CoV-2 INFECTION (PASC) - POST-COVID-19 CONDITION

As a first step to provide a framework for further research, a definition of post-acute sequelae of SARS-CoV-2 infection (PASC) was developed based on symptoms from a prospective cohort study. A total of 9,764 participants from the RECOVER adult cohort (89% SARS-CoV-2 infected; 71% female; 16% Hispanic/Latino; 15% non-Hispanic black; median age, 47 years [IQR, 35-60]) met the selection criteria. Adjusted odds ratios were 1.5 or higher (infected vs. uninfected participants) for 37 symptoms. Symptoms contributing to the PASC score included post-exertional malaise, fatigue, brain fog, dizziness, gastrointestinal symptoms, palpitations, changes in sexual desire or ability, loss of or changes in smell or taste, thirst, chronic cough, chest pain, and



abnormal movements. Among the 2,231 participants first infected on or after December 1, 2021, and enrolled within 30 days of infection, 224 (10%) were PASC-positive at 6 months⁽¹³⁻¹⁵⁾.

More than 3 years after the onset of the COVID-19 pandemic, the mechanisms elucidating the occurrence of persistent disease symptoms (prolonged COVID) in 10%-30% of individuals remain unclear. They may be related to abnormalities in the immune system and the persistent presence of the virus in the mucous membranes of the body. This picture of SARS-CoV-2 post-acute sequelae of COVID-19 persists for months. The immune response in convalescent individuals with PASC has been evaluated in comparison to asymptomatic, uninfected convalescent participants six months after their diagnosis of COVID-19. The study indicates that PASC is defined by persistent immune dysfunction up to six months after SARS-CoV-2 infection, including altered mucosal immune parameters, redistribution of mucosal CD8+ β 7Integrin+ T cells and IgA, indicating possible viral persistence as well as mucosal involvement⁽¹⁴⁻¹⁶⁾.

According to data from the UK CircCOVID study, poor sleep quality and irregular sleep could be important factors in dyspnea in patients previously hospitalized for COVID-19. The study conducted jointly by researchers from the University of Leicester (UK), 20 other UK institutes and the University of Helsinki (Finland) also showed that sleep disturbance after hospitalization for COVID was associated with dyspnea and reduced lung function. Further analysis revealed that the effects of sleep disturbance on dyspnea were partially mediated by anxiety and muscle weakness⁽¹⁵⁻¹⁷⁾.

Since the UK Biobank study which showed brain atrophy, gray matter loss and cognitive impairment in some 400 people who had contracted COVID compared to matched controls, by baseline pre-COVID MRI scans and ~3 years later, there has been great concern about the impact of this virus on the brain. Two new studies, the Munich study (marked accumulation of SARS-CoV-2 spike protein in skull meninges and brain tissue, not found in controls) and the Hamburg study (MRI findings related to two important neuroinflammatory markers of brain white matter: extracellular free water and mean diffusivity), show persistent inflammatory mechanisms

in brain tissue, even in patients with mild COVID. These are studies of people with COVID, not specifically of patients with prolonged COVID. Though, numerous studies document the brain effects of long COVID, from the loss of supportive cells in the brain called glial cells (microglia, astrocytes, and oligodendrocytes) to the premature death of our neurons leading to signs of early dementia in too many patients with long COVID, even young people who had mild symptoms⁽¹⁸⁾.

Data from the COVID-2 electronic survey suggest that people with a rheumatic disease are twice as likely as non-rheumatic disease sufferers to experience long-term effects after contracting COVID-19. The prevalence of post-COVID-19 condition, the term advocated by WHO to describe long-term COVID, was 10.8% among people with autoimmune rheumatic diseases (AIRD's) versus 5.3% of those without an autoimmune condition (designated as 'healthy controls'). The OR was 2.1 and the p -value=0.002⁽¹⁶⁻¹⁹⁾.

MATERNAL-PERINATAL OUTCOMES

During the COVID-19 pandemic, emergency department utilization for obstetric and gynecologic reasons was reduced. A systematic review has included all studies that evaluated women presenting to the obstetrics and gynecology emergency department during the COVID-19 pandemic for any reason. During the confinement, there was an increase in the proportion of hospitalizations for obstetric and gynecologic reasons, especially for labor symptoms and hypertensive disorders⁽¹⁷⁻²⁰⁾.

From the start of the COVID-19 pandemic in mid-March 2020 through mid-February 2023, nearly 103 million cases and 1.1 million deaths were reported in the United States. During the early period of the pandemic, 45,425 (17.6 per 1000) pregnant women had a diagnosis of COVID-19 at delivery and 1,704 hospitals (63.3%) cared for pregnant women with COVID-19 infection at delivery. Characteristics associated with COVID-19 infection were younger age, later study period, black and Hispanic race, lower family income, obesity, medical comorbidity, homelessness, northeastern region, earlier gestational age, and admission to larger urban hospitals. These pregnant women at delivery were more likely to develop severe maternal morbidity com-



pared to those without (46.4 vs. 18.8 per 1000; aOR: 2.60). They were at increased risk of tracheostomy, respiratory distress syndrome, ventilation, acute myocardial infarction, sepsis, shock, cardiac arrest, and coagulopathy, with a 14-fold increased risk of mortality compared to those without (64.0 vs. 4.3 per 100,000 deliveries), with median time to death of 16 days. The COVID-19 case fatality rate decreased over time from 232.9 to 79.1 per 100,000 deliveries⁽¹⁸⁻²¹⁾.

A report updates an earlier one that showed maternal mortality rates for 2018-2020. In 2021, 1,205 women died from maternal causes in the United States, compared with 861 in 2020 and 754 in 2019. The maternal mortality rate for 2021 was 32.9 deaths per 100,000 live births, compared with a rate of 23.8 in 2020 and 20.1 in 2019. In 2021, rates for black women were significantly higher than those for white and Hispanic women. The rate for women aged 40 years and older was 6.8 times higher than that for women under 25 years of age⁽¹⁹⁻²²⁾.

In a large retrospective cohort study, receipt of the primary vaccination series with COVID-19 mRNA was associated with a lower rate of adverse pregnancy outcomes, such as perinatal death, preterm delivery, very low birth weight infants, and NICU admission⁽²⁰⁻²³⁾.

In determining the association between symptoms of COVID-19 infection and adverse maternal-perinatal outcomes in 272 pregnant women in a referral hospital, 50.3% had symptoms of infection. Of these, 35.7% of the pregnant women and 16.5% of the newborns had an adverse outcome. The risk of maternal complications as a whole, premature rupture of membranes and preeclampsia, as well as the risk of perinatal complications and acute fetal distress, were increased⁽²¹⁻²⁴⁾.

In an Israeli study from February 1, 2020, to January 31, 2022, 84 patients were analyzed: 34 patients in the non-delivery group, four in postpartum, 32 in critical delivery and 14 in noncritical delivery. In patients who underwent delivery during their ICU stay, maternal outcome deteriorated after delivery among critical post-partum patients compared with non-critical post-partum women, who improved after delivery⁽²²⁻²⁵⁾.

According to a recent study published in Cureus,

COVID-19 infection may be associated with maternal mortality during pregnancy, but not with infant morbidity and mortality. Risks in pregnancy were highest during the COVID-19 pandemic. Pregnancy was previously considered an immunocompromised state but now it is considered an immune modulated state. Of the 3,421 obstetric admissions and 2,132 deliveries recorded during both waves, there were 123 admissions and 85 COVID-positive deliveries during wave 1, compared with 101 admissions and 73 deliveries during wave 2, with an incidence of COVID infection in pregnancy of 6.54. Obstetric comorbidities were 46% in wave 1 and 78% in wave 2, especially anemia with 16% and pregnancy-induced hypertension with 19%. In wave 2, 21 ICU admissions were recorded, 90% of which required ventilatory support, 76% inotropic support and 71% anticoagulation. In this cycle, 20 deaths were recorded in the ICU, while only one death was recorded during cycle 1. COVID-19 infection was observed in 1 neonate in wave 1 and in 4 neonates in wave 2, indicating a low risk of compromise for the neonate⁽²³⁻²⁶⁾.

Since the initial outbreak of COVID-19, a new population of infants exposed in utero to maternal infection has emerged, the health outcomes of which are largely unknown. A longitudinal cohort study has taken advantage of a prospective perinatal biological registry of 149 infants exposed in utero to COVID-19 and 127 unexposed controls. Infants with in utero exposure to COVID-19 showed lower birth weight and accelerated weight gain in the first year of life, which may be a precursor to later cardiometabolic pathologies⁽²⁴⁻²⁷⁾.

Previous studies on maternal and placental immune response have found sex-specific responses to COVID-19. However, data have been limited due to a lack of information on maternal and placental immune response. To determine the sex-specific risks of exposure to COVID-19 in utero, investigators conducted a study using data from 8 hospitals in eastern Massachusetts. One pandemic cohort consisted of live births from March 1, 2020, to May 31, 2021, while the comparison cohort consisted of live births from January 1, 2018, to December 31, 2018. A third cohort consisting of live births from March 1 to December 31, 2019, was also analyzed for sensitivity analysis. This cohort study of 18,355 infants born after February 2020 found that sons,



but not daughters, of mothers with a positive SARS-CoV-2 polymerase chain reaction test result during pregnancy were more likely to receive a diagnosis of neurodevelopmental impairment in the first 12 months after delivery, even after taking into account preterm delivery⁽²⁸⁾. In another study, researchers have evaluated two infants with seizures, small head and developmental delay born to mothers who had contracted COVID-19 during pregnancy⁽²⁶⁻²⁹⁾.

Meanwhile, during the pandemic, many fertility clinics experienced a surge of interest in egg freezing procedures. According to a recent report by the American Society for Reproductive Medicine, the number of eggs freezing cycles in the United States increased by more than 31% one year after the onset of the COVID-19 pandemic, from 16,786 cycles in 2020 to 24,558 in 2021. Egg freezing cycles soared 31% in 2021. 89,208 babies were born with assisted reproductive technology according to the latest data from the Society for Assisted Reproductive Technology (SART) and multiple birth rates continue to decline⁽²⁷⁻³⁰⁾. It is interesting to know that since the birth of the first test-tube child in 1978, more than 10 million children have been born by in vitro fertilization (IVF) worldwide; it is estimated that up to 7.7% of children in Europe and 4.7% in the USA are born by IVF. IVF pregnancy rates have improved greatly since the 2010s because of better cryopreservation and culture of blastocysts. And perinatal risks to children have decreased because of the indication for single embryo transfer during the procedure, which has declined the incidence of multiple births⁽²⁸⁻³¹⁾.

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