

SPECIAL ARTICLE

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

Conflict of interest: The author declares no competing interests

Received: 1 March 2023

Accepted: 9 March 2023

Online publication: 27 March 2023

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Cite as: Pacheco-Romero J. The coronavirus conundrum - From pandemic to endemic COVID-19 - Should we continue taking care of ourselves? *Rev peru ginecol obstet.* 2023;69(1). DOI: <https://doi.org/10.31403/rpgov69i2478>

The coronavirus conundrum - From pandemic to endemic COVID-19 – Should we continue taking care of ourselves? El enigma del coronavirus – De pandemia a endemia COVID-19- ¿Debemos seguir cuidándonos?

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DOI: <https://doi.org/10.31403/rpgov69i2478>

ABSTRACT

It seems that things are calming down with SARS-Cov-2, as there are no longer daily reports and notes of findings of new variants and subvariants of the virus, as well as clinical changes in symptomatology, hospitalizations, severity, and deaths due to COVID-19. We do not know how we should guard against viral infection during the impending endemic phase of the disease, knowing the complex health problems of prolonged COVID if we contract the virus. In this article we describe the latest known coronavirus mutations, how they affect certain organs and systems, the advantage of a better response to infection in people with healthy lifestyle, the rebound of symptomatology, reinfections at the time of the vaccine, prolonged COVID, excess mortality of physicians who attended the first waves without vaccine, and some news and knowledge about COVID in the pregnant woman and her fetus and newborn; the future of the newborn born to a mother with COVID remains unknown. In the COVID endemic, should we continue to protect ourselves? How?

Key words: Coronavirus infections, SARS-CoV-2, COVID-19, Viral infection, Mutation, Pregnant women, Fetus, Newborn

RESUMEN

Pareciera que se están calmando las cosas con el SARS-Cov-2, pues ya no aparecen comunicaciones y notas diarias de hallazgos de nuevas variantes y subvariantes del virus, así como las modificaciones clínicas en sintomatología, hospitalizaciones, severidad y muertes por COVID-19. No conocemos cómo deberemos cuidarnos de sufrir la infección viral durante la inminente fase endémica de la enfermedad, conociendo los problemas de salud complejos del COVID prolongado si contraemos la virosis. En este artículo hacemos una descripción de las últimas mutaciones conocidas del coronavirus, cómo afectan ciertos órganos y sistemas, la ventaja de una mejor respuesta a la infección en personas con estilo de vida saludable, el rebote de la sintomatología, reinfecciones en la época de la vacuna, el COVID prolongado, el exceso de mortalidad de los médicos que atendieran las primeras olas sin vacuna, y algunas noticias y conocimientos sobre el COVID en la gestante y su feto y recién nacido, quedando la incógnita del futuro del neonato nacido de madre con COVID. En la endemia por COVID, ¿deberemos seguir protegiéndonos? ¿Cómo?

Palabras clave: Infecciones por coronavirus, SARS-CoV-2, COVID-19, Infección viral, Mutación, Gestante, Feto, Recién nacido

INFECTION BY SARS-CoV-2

The origins of COVID-19 have been brought back into the spotlight. Three years into the pandemic that has already killed nearly 7 million people after first being detected in the central Chinese city of Wuhan in late 2019, it is still unclear whether the coronavirus causing the disease leaked from a laboratory or spread to humans from an animal. In the last week of March 2023, the Department of Energy confirmed a classified report that determined, with low confidence, that the virus had escaped from a laboratory. Other members of the U.S. intelligence community disagree, and there is no consensus. Many scientists believe the most likely explanation is that the coronavirus causing COVID-19 jumped from animals to humans, possibly in Wuhan's Huanan Market, a hypothesis supported by multiple studies and reports. The World Health Organization has stated that, although animal origin remains the most likely, the possibility of laboratory escape must be further investigated before it can be ruled out⁽¹⁾.



We have all learned that the Omicron family, descendant of SARS-CoV-2, has a swarm of new subvariants. One of them is XBB, recombinant (fusion) of 2 different BA.2 variants, BJ.1 (BA.2.10.1.1) and BA.2.75. If XBB.1.5 were to spread faster than BQ.1.1, there would be a marked increase in hospitalizations, especially among the elderly. Thus, in New York State, XBB evolved to XBB.1.5, with 3 major mutations (G252V, F486L, and N1012S), and coincided with the increase in hospitalizations there and substantial decline in the other subvariants⁽²⁾. In the first half of January 2023, the Peruvian Ministry of Health identified the presence of XBB.1.5 in three cases residing in Lima, all of which were stable⁽³⁾.

After an average annual decline of 2% from 2014 to 2019, the number of twin births in the United States decreased by 7% from 2019 to 2020 and increased by 2% from 2020 to 2021. In comparison, births of singleton fetuses decreased by 3%. The largest declines occurred in November and December 2019, when they decreased 15% and 19%, respectively, coinciding with a conception period when the coronavirus pandemic began and it was recommended that reproductive medicine practitioners temporarily limit infertility treatment. Twin deliveries are more common among women undergoing infertility treatment and occur at earlier gestational ages than singleton deliveries. The timing of the monthly declines in late 2020 and early 2021 coincides with a conception period when the coronavirus pandemic started and the American Society of Reproductive Medicine recommended that reproductive medicine practitioners temporarily limit infertility treatment. The largest declines in twin birth rates during the November 2020 to January 2021 period occurred among older women, the group most likely to resort to infertility treatment. The decline in twin births from 2019 to 2020 may have contributed, in part, to the reductions in the total number and rate of preterm and low birth weight babies in those 2 years⁽⁴⁾.

A study shows that non-severe SARS-CoV-2 infection alters the plasma proteome for at least 6 weeks, consistent with symptom severity and antibody responses. Differentially abundant proteins are mainly coordinated around pathways of lipid metabolism, atherosclerosis and cholesterol, complement and coagulation cascades, autophagy, and lysosomal function. The

proteomic profile at the time of seroconversion is associated with symptom persistence up to 12 months. The plasma proteomic signature at the time of seroconversion has the potential to identify which individuals are most likely to suffer persistent symptoms related to SARS-CoV-2 infection⁽⁵⁾.

In an analysis of 9 studies with 3,663 patients, the prevalence of dyslipidemia was 18% (4-32%). Dyslipidemia potentially increases mortality and severity of COVID-19. The association was greater in older, male, and hypertensive patients⁽⁶⁾.

In 568 participants with mild to moderate COVID-19 receiving placebo in the ACTIV-2/ A5401 platform trial (Adaptive Platform Treatment Trial for Outpatients With COVID-19), symptomatic rebound was identified in 26% of participants at a median of 11 days after initial onset of COVID-19 symptoms. Viral rebound was detected in 12% and symptom rebound in 27% of participants. Most cases of symptomatic and viral rebound were transient. The combination of symptomatic rebound and high-level viral rebound after initial improvement was observed in only 1-2% of participants⁽⁷⁾.

In a cross-sectional analysis of 77,310 pregnancies (74,663 pregnant women) occurring between January 1, 2019, and December 31, 2020, among Kaiser Permanente Northern California members, there was a 38% increase in unstable and/or unsafe living situations in the first month of the pandemic and a 101% increase in intimate partner violence (IPV) in the first 2 months of the pandemic. These findings suggest that safeguards against IPV are needed in pandemic emergency response plans, such as the need for prenatal screening for unsafe and/or unstable living situations and IPV along with referral to appropriate support services and preventive interventions⁽⁸⁾.

Protection from previous COVID-19 infection against reinfection of the pre-Omicron variants was found to be very high (>82%) and remained high even after 40 weeks. Protection was substantially lower for the Omicron BA.1 variant (45%) and declined more rapidly over time than protection against the earlier variants. Protection against severe disease was high for all variants (>85%). The immunity conferred by past infection should be weighed alongside protection from



vaccination when assessing the future burden of COVID-19 disease, as well as guiding when individuals should be vaccinated and designing policies that mandate worker vaccination or restrict access, based on immune status, to settings where the risk of transmission is high, such as travel and crowded indoor environments⁽⁹⁾. In the long run, most infections will occur in people with strong protection against severe disease because of previous infection, vaccination, or both⁽¹⁰⁾.

Cardiovascular disease is the leading cause of death worldwide, and most deaths from cardiovascular disease are due to myocardial infarction and stroke, according to the World Health Organization. In agreement with a new study, deaths from cardiovascular disease increased during the first two years of the pandemic and peaked during the five waves of COVID-19 in the United States. From March 2020 to March 2022, 90,160 more cardiovascular deaths occurred than expected, nearly 5% more 'excess deaths', with ischemic heart disease, hypertension, cerebrovascular disease, and other diseases of the circulatory system being the most prevalent. Possible explanations for this increase include the pressure that COVID-19 put on the health-care system and, indirectly, emergency cardiovascular care. In addition, people with cardiovascular problems may have been hesitant to seek treatment, or may have avoided treatment, for fear of contracting COVID-19 in a medical setting⁽¹¹⁾. Previous studies on the subject have not provided information on whether the excess in major cardiovascular outcomes was influenced by lack of vaccination, because they were conducted before the vaccines were given. There are two recent studies -one from the South Korean national database and the other from the US NIH Consortium known as N3C (National COVID Cohort Collaborative, National Center for Advancing Translation Sciences)- that show an approximate halving of myocardial infarction and stroke in vaccinated persons compared with unvaccinated matched controls. As for the mechanism of the excess of late (beyond 30 days after COVID) severe cardiovascular outcomes, it has been established that there is inflammation of the endothelial lining of blood vessels and hypercoagulability possibly induced by COVID. COVID or re-infection should be avoided, despite now moving to endemic status in the U.S., with 90% of cases corresponding to variant XBB.1.5 and no increase in hospitalizations or deaths

for many weeks. The virus continues to circulate and will continue to do so for years. Continued caution and better ways to protect against infection, such as nasal vaccinations, are needed⁽¹²⁾.

Researchers at Columbia University in New York examined autopsies of heart tissue from people who had had Covid and found that the infection impaired the regulation of calcium levels in heart cells, a mineral that plays an important role in their contraction and pumping of blood throughout the body. Calcium ions are important messengers that regulate cardiac function; they are stored inside cells, and when needed they are released through channels in the cell membrane in just the right amount. Damage caused by inflammation during a COVID infection appears to open these channels, allowing too much calcium to escape from heart cells, which can reduce heart function and even cause fatal arrhythmias. Although inflammation of the heart is an uncommon but documented side effect of COVID mRNA vaccines, the study only analyzed heart tissue from autopsies that predated the availability of the vaccines⁽¹³⁾.

Hong Kong researchers have found that 4,592 patients hospitalized within 3 days of COVID diagnosis and who received Paxlovid, another antiviral called Lagevrio, or no antiviral drug, rebounded at similar rates, ranging from 4.5% to 6.6%. The study was conducted between February 26, 2022, and July 3, 2022, which is the time when the Omicron BA.2.2 subvariant predominated. In addition, the risk of rebound was found to be associated with being between 18 and 65 years old, having chronic disease, and receiving steroid treatment. Paxlovid did not aggravate rebound⁽¹⁴⁾.

ABOUT LONG COVID

In an evaluation of the electronic medical records of an Israeli health organization, one year after mild COVID-19 infection there was an increased risk of anosmia and dysgeusia (hazard ratio 4.59), cognitive impairment (1.85), dyspnea (1.79), weakness (1.78), palpitations (1.49), streptococcal tonsillitis, and dizziness. Hair loss, chest pain, cough, myalgia, and respiratory disorders increased only during the initial phase. Male and female patients showed minor differences. Most of these problems resolved within one year of diagnosis⁽¹⁵⁾.



New evidence suggests that the SARS-CoV-2 coronavirus attack on the brain may be multiple. The infection can cause memory loss, stroke, and other effects on the brain. Neurological symptoms appeared in 80% of people hospitalized with COVID-19 surveyed in one study. The virus has difficulty crossing the blood-brain barrier and does not significantly attack neurons. In laboratory studies from stem cells, SARS-CoV-2 infected almost exclusively astrocytes, which could explain fatigue, depression and 'brain fog'. SARS-CoV-2 could also infect pericyte-like cells in brain organoids. Finally, some neurological symptoms and damage appear to result from the body's own immune system overreacting and misreacting after encountering the coronavirus⁽¹⁶⁾.

EXCESS MORTALITY AMONG PHYSICIANS

Researchers at Stanford University School of Medicine and the University of Southern California at Los Angeles have used data on deceased physicians aged 45 to 84 years from the American Medical Association to calculate excess deaths between March 2020 and December 2021. In total, 4,511 physicians died during this early phase of COVID-19, 622 more deaths than would have occurred had the pandemic not occurred. Excess active physician deaths peaked at 70 in December 2020, followed by a rapid decline in 2021 when safe and effective vaccines became available. This means that nearly 50 more U.S. physicians than expected died each month during this phase of the pandemic. Physicians who provided direct patient care during the pandemic had excess deaths per 100,000 person-years of 10 in the youngest group and 182 in the oldest group. Non-active physicians had the highest excess deaths per 100,000 person-years compared to physicians who provided direct and non-direct patient care, although this was a substantially lower excess mortality rate than that experienced in the general population^(17,18).

PREVENTION OF DISEASE THROUGH A HEALTHY LIFESTYLE

In a prospective cohort study of 1,981 women (of the 32,249 women in the Nurses' Health Study II cohort) who reported a positive SARS-CoV-2 test between April 2020 and November 2021, adherence to a healthy lifestyle prior to infection (healthy body mass index, never smoking,

high-quality diet, moderate alcohol consumption, regular exercise, and adequate sleep) was inversely associated with the risk of post-COVID infection condition in a dose-dependent manner. Compared with those with no healthy lifestyle factors, those with 5 or 6 factors had half the risk of condition. That is, pre-infection healthy lifestyle was associated with a substantially decreased risk of post-COVID condition⁽¹⁹⁾.

VACCINES

The efficacy of SARS-CoV-2 vaccines in preventing severe disease and death is uncertain because of the paucity of data in individual trials. The extent to which antibody concentrations can predict efficacy is also uncertain. A review included 28 RCTs (n = 286,915 in the vaccination groups and n = 233,236 in the placebo groups; median follow-up 1-6 months after the last vaccination) from 32 publications. The combined efficacy of complete vaccination was 44-5% to prevent asymptomatic infections, 76-5% to prevent symptomatic infections, 95-4% to prevent hospitalization, 90-8% to prevent severe infection, and 85-8% to prevent death. The evidence was insufficient to suggest whether efficacy might differ by vaccine type, age of the vaccinated individual, and interval between doses ($p > 0.05$ for all). The efficacy of SARS-CoV-2 vaccines is greater for preventing severe infection and death than for preventing milder infection. Vaccine efficacy decreases over time but can be improved with a booster. Higher antibody titers are associated with higher estimates of efficacy, but accurate predictions are difficult to make because of large heterogeneity⁽²⁰⁾.

Systematic ethnic inequalities in COVID-19 health outcomes exist, with large differences in exposure risk and some differences in prognosis following hospitalization⁽²¹⁾. And global inequity in vaccine acquisition and administration has been unjust. By February 2022, only 9.5 percent of the population in poor countries had received a dose of vaccine. The pharmaceutical industry did not release the formula so that the vaccines could be mass-produced. At the end of November, the first shipment of the Cuban COVID-19 vaccine called Abdala arrived in Mexico. This was one of the three Cuban vaccines -along with Soberana 2 and Soberana Plus- authorized by the Federal Commission for Protection against Health Risks (Cofepris). They contain a part of the protein that the



coronavirus uses to bind to human cells which, when administered, generates antibodies that block this binding. They are more economical, easy to reproduce and do not require the freezing needed for mRNA⁽²²⁾. Soberana-02 is a COVID-19 conjugate vaccine (recombinant RBD conjugated to tetanus toxoid). Phase 1/2 clinical trials demonstrated high immunogenicity, promoting a neutralizing IgG and specific T-cell response. A third heterologous dose of Soberana-Plus (RBD dimer) further increased neutralizing antibodies. From March 8 to June 24, 2021, a trial evaluating a two-dose schedule of Soberana-02 and a heterologous schedule with an added dose of Soberana-Plus was conducted in Havana, Cuba. A total of 44,031 participants (52.0% women, median age 50 years) were included in a context of initial predominance of VOC Beta, this variant being partially replaced by Delta near the end of the trial. Vaccine efficacy in the heterologous combination was 92.0% against symptomatic disease. There were no severe cases of COVID-19 in the vaccine group versus 6 in the placebo group. Two doses of Soberana-02 were 69.7% and 74.9% effective against symptomatic and severe COVID-19, respectively. The results indicated that the easy-to-manufacture Soberana vaccines are effective in a context of circulating Beta and Delta VOCs, have a favorable safety profile, and may represent an attractive option for use in COVID-19 vaccination programs⁽²³⁾.

Patients with diabetes or obesity are associated with higher severity of COVID-19 and have a higher risk of weak vaccine response one month after a second dose of anti-COVID-19 vaccine compared to control patients. After the second dose of vaccine, seroconversion of IgG antibodies against SARS-CoV-2 spike (Sabs) has been achieved in 94.1% of diabetes patients versus 99.7% of control patients ($p < 0.0001$), and seroconversion of anti-domain receptor-binding antibodies in 93.8% versus 99.1% ($p < 0.0001$), respectively. One month after the second dose, weak response (Sabs < 264 units/mL binding antibody) was significantly more frequent in patients with diabetes than in those with obesity or control patients (12.3% vs. 5.6% and 3.5%, respectively; $p < 0.0001$). Patients with type 2 diabetes and/or obesity may benefit from additional booster doses. Patients with additional comorbidities associated with a weak response, such as chronic kidney disease or elevated HbA1c, should receive post-vaccination serologic monitoring⁽²⁴⁾.

COVID AND THE PREGNANT WOMAN

The COVID-19 pandemic had unique effects on pregnant and postpartum women in the U.S.: maternal deaths from obstetric causes increased by 33% between April and December 2020 compared with previous years. However, that study did not include deaths from non-obstetric causes among pregnant or puerperal persons up to one year. Deaths from drug overdose, suicide, and homicide accounted for large and increasing proportions. In a study of 4,528 pregnancy-associated deaths from April to December 2020, the overall rate was 66.9 deaths per 100,000 live births, a 35.0% increase from 2019. Drug deaths increased 55.3% from 2019 to 2020; homicide deaths, 41.2%; and deaths from obstetric and other causes (mainly motor vehicle accidents), 28.4% and 56.7%, respectively. Only pregnancy-associated suicides decreased from 2019 to 2020⁽²⁵⁾.

The COVID-19 pandemic has turned the health care of pregnant women into a global public health challenge. There are increasing reports showing that not only pregnant women may be at significantly higher risk from COVID-19 than non-pregnant women, but also the fetus. During pregnancy there are adaptive changes, such as reduced residual respiratory capacity, decreased viral immune responses, and increased risk of thromboembolic events⁽²⁶⁾. In 2021, a group of researchers demonstrated an increased risk associated with COVID-19 in pregnancy. Since then, the SARS-CoV-2 virus has undergone genetic mutations. INTERCOVID-2022 is a prospective observational study involving 41 hospitals in 18 countries. To examine the effects of COVID-19 during pregnancy on maternal and perinatal outcomes, and to assess vaccine efficacy when the variant of concern was omicron (B.1.1.529), 4,618 pregnant women were included from November 27, 2021 (the day after WHO declared Omicron a variant of concern) through June 30, 2022: 1,545 (33%) women had a diagnosis of COVID-19 (median gestation 36-7 weeks) and 3,073 (67%) women with similar demographic characteristics did not have a diagnosis of COVID-19. COVID-19 in pregnancy, during the first 6 months of Omicron as the variant of interest, was associated with an increased risk of severe maternal (RRa 1-16) and perinatal (RRa 1-21) morbidity and mortality, especially among symptomatic and unvaccinated women. No in-



creased risk of neonatal morbidity was found (RRa 1-23). Women with full or boosted vaccine doses had a lower risk of severe symptoms, complications, and death. Vaccination coverage among pregnant women remains a priority⁽²⁷⁾. This finding might be due to the intrinsic lower severity of the SARS-CoV-2 Omicron variant than previous variants, population-level immunity from vaccination and previous infection, or both⁽²⁸⁾. To prevent adverse outcomes associated with SARS-CoV-2 infection during pregnancy, pregnant women should stay up to date with recommended COVID-19 vaccines, including a bivalent mRNA booster when they are eligible⁽²⁹⁾. Vaccination during pregnancy becomes a priority and can generate benefits for both mother and newborn. Maternal neutralizing antibodies are transmitted through the placenta and lactation. As for passive immunization, human milk contains other bioactive molecules and cells capable of modulating the immune response of the newborn, which can be amplified after vaccination⁽²⁶⁾. And we believe that in the future we should study how women who became ill with SARS-CoV-2 when they were pregnant evolve, how many develop related diseases and, in parallel, the outcome of children of mothers with COVID-19 during pregnancy or the puerperium, even if they do not present neonatal morbidity.

Preterm birth (PTB) is the leading cause of infant mortality worldwide. After the initial closures due to the COVID-19 pandemic, changes in preterm birth (PTB) rates, ranging from -90% to +30%, were reported in many countries. Reviewing interrupted time series and meta-analyses using harmonized data from 52 million births in 26 countries, with overall PTB rates ranging from 6%-12% and stillbirth rates ranging from 2.5-10.5 per 1,000 births, small reductions in preterm delivery were observed in the first (odds ratio 0.96; p value <0.0001), second (0.96) and third (0.97) months of blockade, but not in the fourth month (0.99), although with some differences between countries after the first month. For high-income countries, there was no association between blockade and stillbirths in the second, third, and fourth months of blockade. There was a higher risk of stillbirth in the first month of lockdown in high-income countries (1.14) and, in Brazil, in the second (1.09), third (1.10) and fourth (1.12; p <0.001) months of lockdown. With an estimated 14.8 million annual PTBs worldwide, the modest reductions observed during the early pandemic

closures translate into a large number of PTBs averted worldwide and warrant further investigation⁽³⁰⁾.

The benefits of facilitating breastfeeding and close mother-newborn contact (family-centred care; FCC) in the perinatal period are well-established. A total of 692 mother-infant dyads (13 sites, 10 countries) were analyzed. 27 (5%) neonates tested positive for SARS-CoV-2 (14 (52%) asymptomatic). Most sites had policies that encouraged FCC during perinatal SARS-CoV-2 infection. 311 (46%) neonates roomed-in with their mother during the admission. Rooming-in increased over time from 23% in March-June 2020 to 74% in January-March 2021 (boreal season). 330 (93%) of the 369 separated neonates had no previous FCC contact with their mother, and 319 (86%) were asymptomatic. Maternal breastmilk was used for feeding in 354 (53%) neonates, increasing from 23% to 70% between March-June 2020 and January-March 2021. FCC was most impacted when mothers had symptomatic COVID-19 at birth⁽³¹⁾.

Finally, all indications are that we have entered an endemic phase of COVID-19. It seems that no new SARS-CoV-2 variants have emerged with a growth advantage over the XBB.1.5 (the recombinant with 2 significant mutations added) that is dominant in much of the world, or its cousin, XBB.1.9.1. But also, genomic and sewage surveillance of the virus and clinical outcomes are being tracked in a more limited way⁽³²⁾. After a quick tour of what has been published about COVID-19 in the last few weeks, comes the question, what will happen to COVID vaccines and drugs licensed for emergency use when the health emergency ends? Will COVID-19 products licensed 'for emergency use' be available after the central pillar of the nation's pandemic response - the national emergency declaration - ends⁽³³⁾. The answer would be, we better continue to take care of ourselves. If we don't get infected with SARS-CoV-2, we won't suffer from long COVID either. Let us particularly protect the pregnant woman and the woman who wants to get pregnant.

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