

SPECIAL ARTICLE

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The coronavirus conundrum – A third wave? - Vaccines and viral variants - The pregnant woman and her child

La incógnita del coronavirus – ¿Una tercera ola? – Vacunas y variantes virales -La gestante y su niño

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ABSTRACT

The SARS-CoV-2 virus continues to reproduce rapidly and is showing more infectious variants. The second wave of the pandemic is subsiding in Europe and the United States of North America, but not in South America. In Peru, the number of deaths has more than doubled, with a higher mortality rate in men and in those over 70 years of age. It has been corroborated worldwide that pregnant women suffer a more severe disease -sometimes with a process similar to preeclampsia- with a greater possibility of death than non-pregnant women and greater fetal death and prematurity. Initial vaccines developed in the USA and Europe are proving effective in reducing infections, hospitalizations and deaths in countries where vaccination has advanced more rapidly. It is being administered in pregnant women without major side effects, and they are recommended to be vaccinated to avoid severe infection. As of now, the duration of immunity given by COVID-19 infection and by the vaccine is not known. A third booster dose and rebranding of vaccinees is being considered. And a third wave of infections is expected due to the emergence of the Brazilian and Indian (Delta) variants.

Key words: Coronavirus infections, SARS-CoV-2 virus, Pregnancy, complications, Newborn.

RESUMEN

El virus SARS-CoV-2 sigue reproduciéndose velozmente y muestra variantes más infecciosas. La segunda ola de la enfermedad va apaciguándose en Europa y Estados Unidos de América del Norte, menos en América del Sur. En el Perú, las cifras de fallecidos han sido muerdadas a más del doble, encontrándose mayor mortandad en los hombres y en los mayores de 70 años. Se ha corroborado en el mundo que la gestante sufre una enfermedad más severa -a veces con un proceso similar a la preeclampsia-, con más posibilidad de muerte que la mujer no gestante y mayor muerte fetal y prematuridad. Las vacunas iniciales elaboradas en los EE UU y Europa están siendo efectivas en disminuir las infecciones, hospitalizaciones y muertes en los países donde la vacunación ha avanzado más rápido. Está siendo administrada en gestantes sin efectos secundarios mayores, recomendándoseles se vacunen para evitar la infección severa. Mientras tanto, no se conoce la duración de la inmunidad dada por la infección COVID-19 y por la vacuna. Se está considerando una tercera dosis de refuerzo y el cambio de marca en los vacunados. Y se está en espera de una tercera ola de infecciones debido a la aparición de las variantes brasilera e india (delta).

Palabras clave. Infecciones por coronavirus, Virus SARS-CoV-2, Complicaciones del embarazo, Recién nacido.

DEATHS FROM COVID-19 IN PERU

According to The Johns Hopkins statistics, on June 1, 2021, there were 171 million cases of COVID-19 and 3,553,113 deaths worldwide. The USA topped the list with 33 million cases and nearly 500,000 deaths. In South America, Brazil (third in the world ranking) led with 16.5 million cases and 462,000 deaths. Peru was 17th in the ranking, with nearly 2 million cases and 69,342 deaths, and was fourth in South America, after Brazil, Argentina and Colombia. However, when the real death toll figures were published, Peru had 180,764 deaths up to that date, more in men than in women. In other words, the fatal figure increased by 260%, when incorporating cases with virological, serological, radiological, epidemiological nexus, epidemiological investigation, clinical and/or Sinadef (National Computerized Death System) criteria of death certificate with cause of



death by COVID-19⁽¹⁾. About 90 thousand deaths occurred in the first COVID-19 wave and about 190 thousand during the second wave, which has not yet ended. This makes Peru the leader in the percentage of COVID-19 deaths with 0.59%, followed by the USA, Brazil, Spain and Chile, with the highest number of COVID-19 deaths in the world in relation to the size of its population, that is 5 551 COVID-19 deaths per million⁽²⁾.

It has been reported that the first death from the virus in Peru occurred on March 3, 2020 in Saposoa, San Martín (Peruvian jungle), and there were up to 20 cases before the first three deaths from COVID-19 in Peru were officially reported on March 19, 2020⁽³⁾. In other words, the virus would have been circulating in Peru since February 2020. In the US, out of 24,079 study participants with blood specimens in all 50 US states from January 2 to March 18, 2020, nine were seropositive to SARS-CoV-2, seven of whom were seropositive weeks prior to the first confirmed case in the states of Illinois, Massachusetts, Wisconsin, Pennsylvania, and Mississippi⁽⁴⁾.

THE TWO WAVES OF COVID-19 -- SARS-CoV-2 DELTA VARIANT SPREADING AROUND THE WORLD

The second wave of COVID-19, from 2020 to 2021, has produced more infections than the first wave, apparently due to more aggressive variants of the virus, such as Bristol, Kent, California, New York, Brazilian, South African, Indian (Delta). Health institutions and intensive care units were overwhelmed and, in some countries, there were more deaths than could be cremated or buried. In others, on the contrary, the rapid administration of vaccines to the population has reduced severe cases and deaths, and may be an important cause of the decline of the virus second wave. Europe and the USA are preparing for a possible third wave, with the return of restrictions and protests from the population. The COVID-19 Delta (Indian) variant has been identified in 60 countries -including Peru-, and United Kingdom scientists have said it may be 40% to 60% more contagious than the Alpha variant. The Delta variant is becoming the most common form of the virus in the UK. The existing vaccines appear to be less effective against the Delta variant, with the Pfizer-BioNTech vaccine about 88% effective and the AstraZeneca vaccine about 60% effective in preventing symptomatic COVID-19⁽⁵⁾. Partially vaccinated people who have had only

their first dose of two-dose vaccines appear to be especially vulnerable to the strain⁽⁶⁾. At the moment, the United Kingdom, Germany and Russia are experiencing a spike in infections by the Delta variant which, in the first of these countries, reaches 80% and could overtake the Alpha variant within weeks⁽⁷⁾. In Peru, infections are increasing in the south of the country.

In the United Kingdom, it is estimated that there could be 100,000 cases of COVID-19 infection every day by July 2021. According to the ZOE COVID Symptom Survey, the infection is attacking adults under 40 years of age, causing headache, sore throat, runny nose and fever, while those over 40 years of age have a milder headache, runny nose, sneezing and sore throat due to being vaccinated. In either case, they are not the classic symptoms of cough, fever or anosmia⁽⁸⁾.

COVID-19 DISEASE SEQUELAE

Many patients recover from COVID-19 within a few weeks, but 10-30% exhibit persistent or new symptoms more than four weeks -even nine months- after first being diagnosed⁽⁹⁾. In a descriptive analysis of 1,959,982 patients with COVID-19 without a control group, FAIR Health, Inc. drew on longitudinal data from its database of more than 34 billion private healthcare claim records from 2002 to the present. All patients in the longitudinal dataset who had been diagnosed with COVID-19 from February to December 2020 were included, except for those with certain preexisting conditions (such as cancer and chronic kidney disease) that might have acted as confounders. The remaining 1,959,982 patients were studied for their case characteristics. The persistent conditions found included fatigue, cognitive difficulties ("brain fog"), headache, numbness/tingling, loss of smell or taste, dizziness, heart palpitations, chest pain, shortness of breath, cough, sore throat, joint or muscle pain, excessive sweating, insomnia, depression, anxiety and fever⁽¹⁰⁾. Patients with COVID-19, after the first 30 days of illness, are at higher risk of death than people who have not had COVID-19⁽¹¹⁾. The causes of long-haul COVID are still unknown. Theories include persistent immune activation after the acute phase; initial damage from the virus, such as damage to nerve pathways, that is slow to heal; and persistent presence of low-level virus⁽¹²⁾.



More attention is now being paid to this serious post-Covid problem, which can disrupt the health, work and well-being of a large part of the world's population. The Spanish Society of General and Family Physicians and patient groups LONG COVID ACTS has published a Clinical Guide for the care of the Long COVID/ persistent COVID patient, a collaborative project agreed upon by 48 scientific societies⁽¹³⁾. They propose as etiopathogenic hypotheses the persistence of the virus, the inflammatory storm and alteration of immunity, and antibodies, with prevalence of long COVID in 10% of those infected. The most frequent symptoms at the national level in women were asthenia, general malaise, lack of concentration, memory lapses (average between 88 and 95%), while in the international population were fatigue, post-exertional malaise and cognitive dysfunction (average around 70%). In both groups there were general symptoms in more than 96%, neurological symptoms in more than 86%, psychological/emotional symptoms in 87%, locomotor, respiratory and digestive symptoms between 70 and 94%. In the first 7 days, experiencing more than five symptoms should alert to a high probability of the development of symptom persistence. It is emphasized that the approach to these patients should be comprehensive and multidisciplinary, bio-psycho-social, and include speech therapy, physiotherapy, rehabilitation, occupational therapy; it is recommended not to stigmatize the patient. Apart from symptomatic therapies (they are described in the Guidelines), potential systemic treatments with antiviral drugs, monoclonal antibodies, corticosteroids and others are not yet authorized for use.

The absence of objective findings or positive results on laboratory or imaging studies must not negate patients' symptoms. The medical community must learn from its experience with other postviral conditions, and avoid clinical approaches that have greater potential for harm than for healing. Coordinated, multidisciplinary efforts are essential both for clinical care and for research to better understand the pathophysiology, epidemiology, and effective management of persistent symptoms after SARS-CoV-2 infection⁽¹⁴⁾.

VACCINES AGAINST SARS-CoV-2

Among the vaccines against SARS-CoV-2, those prepared with mRNA (Pfizer/BioNTech and Moderna) -which trigger an immune response con-

sisting of antibodies against the 'spike' protein on a portion of the surface of the virus- have been most efficient (> 95%)⁽¹⁵⁾. The World Health Organization - WHO has licensed the two AstraZeneca/Oxford versions (recombinant chimpanzee adenovirus; efficacy 79%) -SKBio and Serum Institute of India-, the Janssen vaccine (recombinant vector Ad.26.COVS.2.S) and the Chinese Sinopharm and Sinovac vaccines. With the AstraZeneca and Janssen vaccines (efficacy 67%), cases of neurological system involvement were reported⁽¹⁶⁾, with some cases of transverse sinus thrombosis⁽¹⁷⁾. The BIBP/Sinopharm (efficacy about 75%) and Sinovac (prevents symptomatic COVID-19 in 51% of vaccinees and severe disease and hospitalization in 100% of vaccinees) vaccines are inactivated virus or virus fragment vaccines⁽¹⁸⁻²⁰⁾.

A study found new COVID-19 Novavax vaccines to be about 90% effective against the coronavirus and also protect against variants in a large U.S./Mexico study⁽²¹⁾. A pivotal study conducted in 10 countries by CureVac N.V. (Nasdaq: CVAC), of transformative medicines based on messenger ribonucleic acid ("mRNA"), announced results of the second interim analysis in 40,000 subjects. CVnCoV demonstrated an interim vaccine efficacy of 47% against COVID-19 disease of any severity and did not meet prespecified statistical success criteria⁽²²⁾.

The efficacy of all these vaccines has been studied in adult populations over 18 years of age, and not in children under 18 years of age, pregnant women, nursing mothers and older adults. However, initial experiences in these population groups not included in the trials have had favorable results. We will refer to the vaccination of pregnant and lactating women later on.

Children in the US and Israel have been allowed to have the vaccination. Pfizer has found that the vaccine appeared 100 per cent effective with no serious side effects on them⁽²³⁾. Moderna, AstraZeneca and Janssen are all being tested on under-18s. However, there is a recommendation that children should not be vaccinated against COVID until there is more information about the risks⁽²⁴⁾.

Although the vaccines approved by WHO and national health agencies are safe and effective, there is a follow-up on such safety and effective-



ness, as licensure has been on an emergency basis. There is a greater risk of serious illness and death in unvaccinated populations, especially in those with morbidities such as obesity, diabetes mellitus, hypertension, as well as in populations with fewer resources and certain races.

A variable but important percentage of the population does not wish to be vaccinated, which can be negative for herd immunity. In the U.S., a Gallup poll found that 60% of U.S. adults have already received full vaccination. But, 78% of adult Americans who have not yet received the COVID-19 vaccine have said they do not want to be vaccinated, with 51% definitely not wanting to be vaccinated⁽²⁵⁾.

IMMUNITY TO COVID-19 DISEASE FROM INFECTION AND FROM THE VACCINE

It remains to be elucidated how long the immunity given by the vaccine and by COVID-19 disease *per se* lasts, and whether it is possible to switch vaccine brands.

A previous history of SARS-CoV-2 infection has been associated with an 84% lower risk of infection, with median protective effect observed 7 months following primary infection. This period is the minimum probable effect because seroconversions were not included. The study shows that previous infection with SARS-CoV-2 induces effective immunity to future infections in most individuals⁽²⁶⁾.

The findings of the authors suggest that infection and the development of an antibody response provides protection similar to or even better than currently used SARS-CoV-2 vaccines. Although antibodies induced by SARS-CoV-2 infection are more variable and often lower in titre than antibody responses induced after vaccination, this observation does make sense considering current SARS-CoV-2 vaccines induce systemic immune responses to spike proteins while natural infection also induces mucosal immune responses and immune responses against the many other open reading frames encoded by the approximately 29,900 nucleotides of SARS-CoV-2. The SIREN study adds to a growing number of studies, which demonstrate that infection does protect against reinfection, and probably in an antibody-dependent manner⁽²⁷⁾.

Vaccine companies are studying better vaccines that prevent the disease due to the new variants that are appearing, and to be applied in a single dose. Scientists are expanding efforts to evaluate when fully vaccinated people will need booster shots - and, if so, whether people can switch brands. It is also possible to use different vaccines in the same country⁽¹⁷⁾. And a third dose to the two-dose vaccines is possible in about 8 to 12 months⁽²⁸⁾. What is essential is to vaccinate the population as soon as possible, maintaining the use of double masks and even covering with a plastic shield, as well as social distancing and hand washing.

COVID-19 VACCINE IN THE PREGNANT WOMAN, THE LACTATING WOMAN, THE NEONATE

Available data suggest that symptomatic pregnant patients with COVID-19 are at an increased risk of more severe illness than non-pregnant patients. The absolute risk for severe COVID-19 is low; however, data suggest an increased risk of ICU admission, need for medical ventilatory support (ECMO) and death reported in pregnant women with symptomatic COVID-19 infection when compared to symptomatic non-pregnant women⁽²⁹⁾. However, the study of a large geographically diverse cohort database from 853 hospitals, in reproductive-aged patients hospitalized with COVID-19, in-hospital mortality was found low in pregnant patients⁽³⁰⁾. In another multinational cohort study of 2,130 pregnant women in 18 countries, women diagnosed with COVID-19 were at increased risk of a composite index of maternal morbidity and mortality, including preeclampsia and preterm delivery, compared with pregnant persons without a diagnosis of COVID-19. Newborns born to women diagnosed with COVID-19 had a significantly higher severe neonatal morbidity index and severe perinatal morbidity and mortality index compared to newborns born to women without a COVID-19 diagnosis^(31,32).

Early COVID-19 infections are associated with hypertensive diseases of pregnancy - HDP, even when accounting for differential exposure and delivery times, suggesting that COVID-19 infection may alter pregnancy physiology and increase the risk of HDP development over time. Infection closer to term is not associated with HDP, which likely reflects the high proportion



of asymptomatic infections found at the time of delivery from a universal testing policy and insufficient time to develop HDP in these cases. Emerging evidence suggests that COVID-19 modulates placental angiotensin-converting enzyme 2 expression, which may be related to HDP development⁽³³⁾.

These findings should alert pregnant women and physicians to strictly implement all recommended preventive measures for COVID-19, including vaccination during pregnancy.

Regarding neonates, in a nationwide, prospective cohort study that included 88 159 infants from Sweden, SARS-CoV-2 infection in pregnancy was significantly associated with higher risk of any neonatal respiratory disorder (2.8% vs 2.0%; odds ratio, 1.42) and some other neonatal morbidities, but not neonatal mortality (0.30% vs 0.12%; odds ratio, 2.55)⁽³⁴⁾. In another cohort study of 255 neonates born to women with positive SARS-CoV-2 test results within 2 weeks before and 72 hours after delivery, 88.2% of newborns were tested for the virus during the birth hospitalization and 2.2% had positive results. A main risk factor for neonatal test result positivity was maternal social vulnerability, and the burden of SARS-CoV-2 exposure on newborn health was associated with preterm delivery, which was prompted by worsening maternal COVID-19 illness. The findings emphasize the importance of both biological and social factors in perinatal SARS-CoV-2 infection outcomes. Newborns exposed to SARS-CoV-2 were at risk for both direct and indirect adverse health outcomes, supporting efforts of ongoing surveillance of the virus and long-term follow-up⁽³⁵⁾.

Pregnant and postpartum women face unique challenges during the COVID-19 pandemic that may put them at elevated risk of mental health problems. Of the 6,894 participants in an anonymous, online, cross-sectional study in 64 countries, substantial proportions of women scored at or above the cut-offs for elevated posttraumatic stress (2,979 [43%]), anxiety/depression (2,138 [31%]), and loneliness (3,691 [53%]). The most commonly reported worries were related to pregnancy and delivery, including family being unable to visit after delivery (59%), the baby contracting COVID-19 (59%), lack of a support person during delivery (55%), and COVID-19 causing changes to the delivery plan (41%)⁽³⁶⁾.

Two new studies show that the two COVID-19 mRNA vaccines now available in the United States appear to be completely safe for pregnant women. The women had good responses to the vaccines, producing needed levels of neutralizing antibodies and immune cells known as memory T cells, which may offer more lasting protection. The research also indicates that the vaccines might offer protection to infants born to vaccinated mothers^(37,38).

Unfounded claims linking COVID-19 vaccines to infertility have been scientifically disproven. ACOG recommends vaccination for all eligible people who may consider future pregnancy. Women under age 50 including those who are pregnant can receive any FDA-authorized COVID-19 vaccine available to them. However, they should be aware of the rare risk of TTS (thrombosis with thrombocytopenia syndrome) after receipt of the Janssen COVID-19 vaccine and that other FDA-authorized COVID-19 vaccines are available (i.e., mRNA vaccines)⁽³⁹⁾.

Coronavirus disease 2019 (COVID-19) vaccination in pregnancy induces a robust maternal immune response, with transplacental antibody transfer detectable in cord blood as early as 16 days after the first dose⁽⁴⁰⁾. Also, robust secretion of SARS-CoV-2 specific IgA and IgG antibodies have been found in breast milk of breastfeeding women for 6 weeks after the first of 2 vaccinations against COVID-19. IgA secretion was evident as early as 2 weeks after vaccination, followed by a spike in IgG after 4 weeks, or the equivalent of 1 week after the second vaccine. In spite of the lack of information, breastfeeding women should be vaccinated⁽⁴¹⁾.

The American College of Obstetricians and Gynecologists ACOG recommends that pregnant individuals have access to COVID-19 vaccines and that COVID-19 vaccines should be offered to lactating individuals. A discussion with their health care provider can help them make an informed decision. Important considerations include: the potential efficacy of the vaccine; the risk and potential severity of maternal disease, including the effects of disease on the fetus and newborn; and the safety of the vaccine for the pregnant patient and the fetus. While a conversation with a clinician may be helpful, it should not be required prior to vaccination, as this may cause unnecessary barriers to access⁽⁴²⁾. The Pe-



ruvian Society of Obstetrics and Gynecology and the International Federation of Gynecology and Obstetrics joined together to provide these recommendations in Peru.

COVID-19 AND MATERNAL MORTALITY AND PERU

In Peru, the maternal mortality ratio (MM) decreased during the present century, and this achievement had been reached among the Sustainable Development Goals of the United Nations. But due to the pandemic, in 2020, MM increased 47.3% with respect to 2019, and the trend predicts that it could increase even more in 2021. This has been correlated with the higher incidence of virus infection in pregnant and postpartum women. The causes of maternal death have been hypertension and hemorrhage, with COVID-19 being the leading cause of indirect maternal mortality, accounting for 38.6% of all maternal deaths. It is known that poverty, marginalization, poor care of the pregnant woman, and lack of health sector response capacity have contributed to these deaths.

Peru has moved back at least five years on its road to reducing maternal mortality due to the profound impact COVID-19 has had on the capacity of health services. The health system needs urgent reengineering, and the pregnant woman should be included in the COVID-19 risk groups. Peru swiftly implemented strict measures to control the spread of the virus, such as closing borders, restricting freedom of movement nationwide, banning crowds, and closing schools, universities, and churches. It also restricted all non-essential activities or services, including non-emergency primary health services. Despite these actions, it is among the countries with the highest COVID-19 incidence and mortality rates in Latin America and the Caribbean, as well as globally⁽⁴³⁾.

In a new survey data from the Guttmacher Institute that advocates for reproductive rights, more than a third of respondents said they planned to either put off having children or have fewer because of the pandemic, which was devastating to reproductive-age women despite being far more deadly to older men⁽⁴⁴⁾.

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