

SPECIAL ARTICLE

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The coronavirus conundrum - New Omicron variant - Challenges - The woman

El enigma del coronavirus – Nueva variante ómicron – Desafíos - La mujer

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ABSTRACT

It has been two years since the appearance of SARS-CoV-2, coronavirus which has spread rapidly throughout the world, causing more than 270 million infected people and more than 5 million deaths. This coronavirus has had many variants and mutations, which is its way of getting into humans more easily and producing COVID-19 disease. The result has been a trail of infections and deaths, with lethality around 1%, and has affected the way of life, work, education, the economy of the countries, increased poverty and violence, among others. We still do not have a cure for the disease, but vaccines have reduced the number of severely infected people and deaths. And antiviral drugs are emerging that could prevent severity and death from COVID-19, if used at the onset of infection. In this article we include some of the news and outcomes occurred in the last trimester and what it has meant for women's and pregnant women's health.

Key words: Coronavirus, COVID-19, variants, mutations, viral infectious disease, Vaccines.

RESUMEN

Se cumple dos años de la aparición del coronavirus SARS-CoV-2, que se ha diseminado prontamente en el mundo, causando más de 270 millones de personas infectadas y más de 5 millones de muertes. Este coronavirus ha tenido muchas variantes y mutaciones, que es su manera de conseguir introducirse con mayor facilidad al ser humano y producir la enfermedad COVID-19. El resultado ha sido un reguero de infecciones y muertes, con letalidad alrededor del 1%, y ha afectado el modo de vida, el trabajo, la educación presencial, la economía de los países, aumento de la pobreza y la violencia, entre otros. Aún no tenemos cura para la enfermedad, pero las vacunas han reducido el número de infectados severos y muertes. Y están apareciendo medicamentos antivirales que podrían evitar la severidad y muerte por COVID-19, si son utilizados al inicio de la infección. En este artículo incluimos algunas de las novedades y resultados ocurridos en el último trimestre y lo que ha significado para la salud de la mujer y la gestante.

Palabras clave. Coronavirus, COVID-19, variantes, mutaciones, enfermedad infecciosa viral, Vacunas.

MORBIDITY/MORTALITY CAUSED BY COVID-19 – HYPERTENSION - HLA-C*04:01

COVID-19 is causing morbidities parallel to the infection per se. One of these is hypertension. A longitudinal study included employees and their spouses/partners, from all 50 states and the District of Columbia, participating in an annual employer-sponsored wellness program operated by Quest Diagnostics. Of 533,645 potential participants in 2018, after applying data exclusions, 464,585 (87%) study participants remained for evaluation with valid data for each of the 3 calendar years analyzed. The cohort included 53.5% women, with a mean age of 45.7 years in 2018. Changes from the preceding year in both systolic and diastolic BP showed no differences between 2019 and January to March 2020 ($p=0.8$ for systolic and $p=0.3$ for diastolic BP). In contrast, annual BP increase was significantly higher in April to December 2020 than 2019 ($p<0.0001$ for systolic and diastolic BP). Systolic and diastolic BP increases held true for men and women and across age groups; larger increases were seen in women for both systolic and diastolic BP, in older participants for systolic BP, and in younger participants for diastolic BP (all $p<0.0001$). The systolic BP increase among US adults during the COVID-19 pandemic



could signal a forthcoming increase in incident cardiovascular disease mortality. Reasons for pandemic-associated BP elevations are likely multifactorial, and although weight gain was not the reason, other possible reasons could include increased alcohol consumption, less physical activity, emotional stress, and less ongoing medical care⁽¹⁾.

More people in the United States have died from COVID-19 this year than died last year, before vaccines were available. The U. S. Centers for Disease Control and Prevention has recorded 386,233 deaths involving COVID-19 in 2021 (until November), compared with 385,343 in 2020 (about 13% compared with 11%). The final number for this year will be higher, as a result of a confluence of factors: most crucially lower-than-needed vaccination rates, but also the relaxation of everyday precautions, like masks and social distancing, and the rise of the highly contagious delta variant. Just 59% of Americans are fully vaccinated⁽²⁾. In several parts of the world, the vaccination necessary for the required immunity has not been achieved. In Peru, it is considered that only 60% of the population is vaccinated.

The association between COVID-19 severity and HLAs in 435 individuals from Germany ($n^{\circ} = 135$), Spain ($n^{\circ} = 133$), Switzerland ($n^{\circ} = 20$) and the United States ($n^{\circ} = 147$), who had been enrolled from March 2020 to August 2020, was analyzed. HLA-C*04:01 carrier state was associated with severe clinical course in SARS-CoV-2 and twice the risk of intubation. The findings suggest that HLA class I alleles have a relevant role in immune defense against SARS-CoV-2⁽³⁾.

REINFECTIONS

In a study of 1,304 identified SARS-CoV-2 reinfections, 413 (31.7%) were caused by the B.1.351 variant, 57 (4.4%) by the B.1.1.7 variant, 213 (16.3%) by "wild-type" virus, and 621 (47.6%) were of unknown status. For reinfected persons, the median time between first infection and reinfection was 277 days. The odds of severe disease at reinfection were 0.12 times that at primary infection. Reinfections had 90% lower odds of resulting in hospitalization or death than primary infections. None led to hospitalization in an ICU, and none ended in death. For a person who has already had a primary infection, the risk of having a se-

vere reinfection is only approximately 1% of the risk of a previously uninfected person having a severe primary infection⁽⁴⁾.

COVID-19-like illness hospitalizations among adults aged ≥ 18 years whose previous infection or vaccination occurred 90–179 days earlier, the adjusted odds of laboratory-confirmed COVID-19 among unvaccinated adults with previous SARS-CoV-2 infection were 5.49-fold higher than the odds among fully vaccinated recipients of an mRNA COVID-19 vaccine who had no documented previous infection⁽⁵⁾.

OnCovid is a European registry that collects data on consecutive patients with solid or hematologic cancer and COVID-19. This multicenter case series study included real-world data from 35 institutions across 6 countries (UK, Italy, Spain, France, Belgium, and Germany). This update included 2 795 consecutive patients diagnosed between February 27, 2020, and February 14, 2021, with 2 634 patients eligible for analysis (median [IQR] age, 68 [18-77] years; 52.8% men). The findings of this registry-based study suggest that mortality in patients with cancer diagnosed with COVID-19 has improved in Europe; this improvement may be associated with earlier diagnosis, improved management, and dynamic changes in community transmission over time⁽⁶⁾.

OMICRON VARIANT OF COVID-19

Since the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was detected in China in December 2019, more than 90 million people worldwide have been infected after a year, and over 2 million people have died from the coronavirus disease 2019 (COVID-19). In Peru, Covid-19 infections have exceeded 2 million cases and 200,000 deaths⁽⁷⁾. At present, the world is witnessing the emergence of a new variant in South Africa, the omicron variant, which is rapidly spreading worldwide. Meanwhile, the delta variant could mutate towards extinction⁽⁸⁾. Officially the new variant is B.1.1.529, designated as a variant of concern on November 25 by the World Health Organization⁽⁹⁾. Fifty mutations have been identified in the B.1.1.529 lineage, the most worrisome being more than 30 in the spike protein region, the area that facilitates a virus' entry into the host cell, enhancing its transmissibility as well as the potential for immunoevasion⁽¹⁰⁾. This new strain would have 32 mutations



in the spike protein, while the Delta strain has 7 mutations in the spike protein⁽¹¹⁾. With so many mutations, it raises the possibilities that Omicron has a number of advantages above previous versions of Covid and would dodge vaccines. This variant could force new confinements in countries that were returning to 'normality' and already opened their borders. Previous coronavirus infection appears to give little immunity to the new Omicron variant. But, receiving a booster vaccine, or a third dose, appears to successfully defeat the Omicron variant. More than half of the Omicron cases in England are in people who have been double vaccinated. The U.K. Health Security Agency warned that the mutant variant is transmitted rapidly and successfully. And it has mutations that suggest reduced protection from vaccine-derived immunity⁽¹²⁾.

The three main symptoms of Covid-19 highlighted by the English National Health Systems are a new persistent cough, a high temperature and a loss of taste and smell; these persons should get a PCR test. Experts consider the most common symptoms so far of the Omicron variant are fatigue, body aches, headache, and raise heart rate in children⁽¹³⁾. But app data claim that people who tested positive now most commonly report a headache, runny nose, sore throat and sneezing⁽¹⁴⁾. As scientists gather more data on the super strain, one worrisome sign is that it could be infecting children at a higher rate than before.

LONG TERM EFFECTS OF COVID-19

In previous articles we have published on the worrying long-lasting effects following COVID-19 infection, which is signifying a problem to be addressed as a new post-infection morbidity.

In order to determine individuals' lasting effects after the acute phase of the disease, LitCOVID (PubMed and Medline) and Embase databases were searched by researchers. All articles with original data for detecting long-term COVID-19 published before 1st of January 2021 and with a minimum of 100 patients were included. A total of 18,251 publications were identified, of which 15 met the inclusion criteria. The prevalence of 55 long-term effects was estimated, 21 meta-analyses were performed, and 47,910 patients were included. The follow-up time ranged from 14 to 110 days post-viral infection. The age of the study participants ranged between 17 and 87

years. It was estimated that 80% (95% CI 65–92) of the patients that were infected with SARS-CoV-2 developed one or more long-term symptoms. The five most common symptoms were fatigue (58%), headache (44%), attention disorder (27%), hair loss (25%), and dyspnea (24%)⁽¹⁵⁾.

A study that used data from electronic health records of 273,618 patients diagnosed with COVID-19 and estimated the risk of having long-COVID features in the 6 months after a diagnosis of COVID-19 found that over 1 in 3 patients had one or more features of long-COVID recorded between 3 and 6 months after a diagnosis of COVID-19. This was significantly higher than after influenza. The risk of long-COVID features was higher in patients who had more severe COVID-19 illness, and slightly higher among females and young adults. White and non-white patients were equally affected. The findings in the subgroups, and the fact that the majority of patients who have features of long-COVID in the 3- to 6-month period already had symptoms in the first 3 months, may help in identifying those at increased risk⁽¹⁶⁾.

THE WOMAN – THE PREGNANT WOMAN – VACCINES -THE FETUS AND NEWBORN

Pregnancies that have occurred in clinical trials of ChAdOx1 nCoV-19 (AZD1222) have been analyzed. 121 (1%) of 9,755 participants reported a pregnancy during the trials. Miscarriage was defined as pregnancy loss before 23 weeks of gestation. Fertility was unaffected by vaccination with ChAdOx1 nCoV-19. Furthermore, compared with women who received the control vaccine, there was no increased risk of miscarriage and no instances of stillbirth in women vaccinated before pregnancy in global clinical trials of ChAdOx1 nCoV-19⁽¹⁷⁾.

However, the maternal-fetal/newborn unit is established at risk for COVID-19 infection. Data from health systems (Kaiser Permanente: Washington, Northwest, Northern California, Southern California, and Colorado; Denver Health; Health Partners; and Marshfield Clinic, Wisconsin) over seven 4-week surveillance periods from December 15, 2020, through June 28, 2021, included, ongoing pregnancies between 6 and 19 weeks-gestation were identified. Miscarriages were assigned to a 4-week surveillance period based on their outcome date. The odds of re-



ceiving a COVID-19 vaccine in the 28 days prior to spontaneous abortion compared with the odds of receiving a COVID-19 vaccine in the 28 days prior to index dates for ongoing pregnancies were analyzed. The proportion of women aged 35 through 49 years with miscarriages was higher (38.7%) than with ongoing pregnancies (22.3%). A COVID-19 vaccine was received within 28 days prior to an index date among 8.0% of ongoing pregnancy periods vs 8.6% of spontaneous abortions⁽¹⁸⁾.

Among 1,249,634 delivery hospitalizations during March 2020–September 2021, U.S. women with COVID-19 were at increased risk for stillbirth compared with women without COVID-19 (adjusted relative risk [aRR] = 1.90; 95% CI = 1.69–2.15). Overall, 21,653 (1.73%) delivery hospitalizations had COVID-19 documented. Among deliveries with COVID-19, chronic hypertension, multiple-gestation pregnancy, adverse cardiac event/outcome, placental abruption, sepsis, shock, acute respiratory distress syndrome, mechanical ventilation, and ICU admission were associated with a higher prevalence of stillbirth. The magnitude of association was higher during the period of SARS-CoV-2 B.1.617.2 (Delta) variant predominance than during the pre-Delta period. Prevention strategies, including vaccination before or during pregnancy, is critical to reduce the impact of COVID-19 on stillbirths⁽¹⁹⁾.

COVID-19 carries risk for preterm delivery. Placental vascular compromise must be considered a risk for the fetus during advanced maternal infections. Clinical manifestations of newborn infection have been mild to moderate and relatively uncommon. Proven antiviral therapy is of yet lacking. The mode of delivery is a medical decision that must include patient risk assessment and patient guidelines. Infections of the maternal-fetal-newborn unit must be taken seriously both for the disease so caused and the potential for subsequent spread of disease⁽²⁰⁾.

The rates of cesarean delivery, preterm birth, and neonatal intensive care unit admission all increased in a Delta cohort⁽²¹⁾. The Delta variant has exacerbated the likelihood that someone who is pregnant, unvaccinated and COVID positive will end up in the ICU and need mechanical ventilation, and in the worst cases die. It also

provides us with additional evidence indicating that stillbirth is potentially an adverse outcome for pregnant people who contract COVID-19^(22,23).

When there are millions of users of combined hormonal contraceptives worldwide, a new risk factor for thromboembolic events appears: infection by the SARS-COV-2 virus. Hormonal contraception produces hepatic changes and thromboembolic events. However, adequate use of family planning could prevent 32% of maternal deaths by preventing high-risk births and legal and illegal abortions. Because of the COVID-19 pandemic, spacing of pregnancies is advocated and recommended, reinforcing an easy-to-implement family planning strategy such as immediate postpartum and postabortion contraception, through various methods available for this purpose⁽²⁴⁾.

The COVID-19 vaccine for children between the ages of 5 to 11 years has undergone thorough evaluations by both FDA and CDC. COVID-19 vaccines have and will continue to undergo the most intensive safety monitoring in U.S. history⁽²⁵⁾.

VACCINE EFFECT

The World Health Organization (WHO) has approved the COVID-19 vaccine COVAXIN® (developed by Bharat Biotech) for emergency use, adding to a growing portfolio of validated vaccines. COVAXIN contains inactivated SARS-CoV-2 antigen, administered in two doses, four weeks apart. The vaccine has been shown to have 78 per cent efficacy against COVID-19 of any severity ≥ 14 days after the second dose⁽²⁶⁾. And the Russian Sputnik vaccine is still waiting approval for use.

Vaccine effects are higher in people who mix and match vaccine doses. Most people have received either two doses of Astrazeneca, the Pfizer vaccines, or two of the same. Most frequent side-effects have been fatigue, headache, joint pain and fever⁽²⁷⁾.

Some fundamental aspects regarding complications when applying the vaccine for COVID-19 are that cerebral venous thrombosis events are often severe, causing focal deficit, epileptic seizures, altered mental status, hemorrhagic le-



sions and intracranial hypertension with cerebral herniation syndromes. These cases of cerebral venous thrombosis associated with thrombocytopenia and vaccination correspond to young adults, especially women, but those with other risk factors, such as previous thrombotic events, vascular risk factors, thrombophilia or hormone use do not appear to be at increased risk of developing cerebral venous thrombosis from this cause. Most of the reported cases occurred after the first dose of the AstraZeneca vaccine⁽²⁸⁾.

Since April 2021, reported cases of myocarditis and pericarditis have increased in the United States after mRNA COVID-19 vaccination (Pfizer-BioNTech and Moderna), predominantly in male adolescents and young adults 16 years of age and older. In most cases, patients responded well to medications and rest and had prompt improvement of symptoms. Onset was typically within several days after mRNA COVID-19 vaccination. Cases have occurred more often after the second dose than the first dose⁽²⁹⁾.

BNT162b2 COVID-19 vaccine slightly increases Bell's palsy risk in an Israeli administrative database, especially in older females (≥ 65 years) without a prior medical history, following the first dose⁽³⁰⁾. Emerging reports of rare neurological complications associated with COVID-19 infection and vaccinations include increased risk of Guillain-Barré syndrome and Bell's palsy with ChAdOx1nCoV-19. There was an increased risk of hemorrhagic stroke with BNT162b2. Although there is an increased risk of neurological complications in those who received COVID-19 vaccines, the risk of these complications is greater following a positive SARS-CoV-2 test⁽³¹⁾.

Not everyone has the same risk for death from Covid. Oxford University have pin-pointed a fragment of DNA that blocks lung cells from fighting off the virus. This gene LZTFL1 doubles the risk of Covid death. About 15.7% of British and Europeans could have this gene, but South Asian would have it in 61.2%, while only 2.4% of Africans and 1.8% of Asian would carry the higher risk genotype. But there are several other important factors among ethnic communities. For example, the immune system would not be affected by the gene, as people respond to the vaccines⁽³²⁾.

BOOSTER DOSE

Even with the Delta (B.1.617.2) strain predominant, observational data suggest there is a progressive reduction in protection against any infection or symptomatic infection. The booster shot is currently approved in people for over-18s, and reducing the interval between the second and booster dose is being looked at. The reactogenicity and immunogenicity of seven different COVID-19 vaccines as a third dose after two doses of ChAdOx1 nCov-19 (Oxford-AstraZeneca) or BNT162b2 (Pfizer-BioNTech) has been investigated. All study vaccines boosted antibody and neutralising responses after ChAd/ChAd initial course and all except one after BNT/BNT, with no safety concerns. Serious adverse events were uncommon, similar in active vaccine and control groups⁽³³⁾.

Participants who received a booster at least 5 months after a second dose of BNT162b2 had 90% lower mortality due to Covid-19 than participants who did not receive a booster. However, studies with longer-term follow-up periods to assess the effectiveness and safety of the booster are still warranted⁽³⁴⁾.

Antispikes (anti-S) IgG antibody titers before and after a third BNT162b2 dose was assessed in individuals aged 60 years and older because this population is at high risk of developing severe SARS-CoV-2 disease and was the first to receive authorization for a third dose. The immune response to 2 doses of BNT162b2 is lower in individuals aged 65 to 85 years vs 18 to 55 years. Among 4,868 health care workers receiving 2 BNT162b2 doses, a significant waning of the humoral response (IgG, neutralizing antibodies) within 6 months of the second dose was observed, especially among adults aged 65 years and older. After a fourth SARS-CoV-2 wave in Israel, the Israeli Ministry of Health authorized, at the end of July 2021, a third BNT162b2 vaccine dose for individuals aged 60 years and older, which was subsequently expanded to younger age groups. This study found that a third BNT162b2 dose in adults aged 60 years and older was associated with significantly increased IgG titers after 10 to 19 days, with no major adverse events⁽³⁵⁾. Will a fourth dose be required?



British scientists found that two-dose regimens of the COVID-19 vaccine do not induce sufficient neutralizing antibodies against the omicron coronavirus variant, indicating that infections in previously infected or vaccinated individuals are likely to increase⁽³⁶⁾.

NEW ANTI-COVID DRUGS

A new voluntary licensing agreement signed by the Medicines Patent Pool (MPP) and the pharmaceutical company MSD will facilitate affordable access to molnupiravir, a new medicine being tested in clinical trials for treating COVID-19. Phase 3 clinical trial results suggest molnupiravir reduces the risk of hospitalization in patients with mild-to-moderate COVID-19 by 50 per cent. It is currently being evaluated for inclusion by the World Health Organization's (WHO's). If approved, it will be the first oral medicine for non-hospitalised patients with mild-to-moderate COVID-19. Merck has not specifically tested molnupiravir against the new Omicron variant but said it should have some potency based on its effectiveness against other strains of coronavirus. A second oral medicine from Pfizer, called Paxlovid, is also being considered for authorization by FDA⁽³⁷⁾.

Another new Covid drug that cuts the risk of death by nearly 80 per cent has been approved in the UK amid the fight against Omicron. Xevudy (Sotrovimab) is being deemed safe and effective at reducing the risk of hospitalisation and death in Covid patients. The drug works by binding to the spike protein on the outside of the Covid virus. This in turn prevents the virus from attaching to and entering human cells - so that it cannot replicate in the body⁽³⁸⁾. Sotrovimab is the second monoclonal antibody therapeutic to be approved in England following Ronapreve. Ronapreve was approved for use in UK patients in August and had previously been used to treat Donald Trump. The antibody treatment is most effective during the early stages of coronavirus illness - and should be administered within five days of showing symptoms. Clinical trials showed the drug was able to reduce the risk of hospitalisation and death by 79 per cent among high-risk adults. There are early indications from scientists that the drug retains activity against key mutations.

It remains to be seen how the Omicron variant will affect the lives of the inhabitants. The infectivity seems to be higher than the Delta variant, which affected and affects more European countries and the Americas. But the fear grows because the Omicron variant has 50 mutations identified in the B.1.1.529 lineage, the most concerning being 32 mutations in the spike protein region (the Delta strain has only 7 mutations in that protein), the area that facilitates a virus' entry into the host cell, enhancing its transmissibility as well as the potential for immunoescape.

In other words, we will have to continue using masks, social distancing, hand washing and vaccination. But we must also maintain personal and family health, so as not to fall victim to SARS-CoV-2 and its many known and unknown variants.

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