

SPECIAL ARTICLE

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The coronavirus conundrum – Variants and vaccines – The pregnant woman and her child

La incógnita del coronavirus – Variantes y vacunas - La gestante y su niño

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ABSTRACT

In late 2020, vaccines developed in the Western world against the SARS-CoV-2 virus were approved and are currently being inoculated, together with Chinese and Russian vaccines. In the meantime, we are in a second wave of the disease and the new coronavirus has been transforming to allow for better propagation, harboring and replication in humans. The disease now manifests itself with new symptoms, greater contagiousness, severity and variation in the number of deaths. Coronavirus infection of pregnant women is occurring with harshness and maternal and perinatal consequences. Vaccination has been initiated in pregnant women and nursing mothers, after discussion with their gynecologists about risks and benefits. This article provides a brief account of the events that took place during the transition from 2020 to 2021.

Key words: Coronavirus infections, SARS-CoV-2 virus, COVID-19

RESUMEN

A finales de 2020 se aprobaron las vacunas desarrolladas en el mundo occidental contra el virus SARS-CoV-2, que ya están siendo inoculadas, conjuntamente con vacunas chinas y rusas. Mientras tanto, estamos en una segunda oleada de la enfermedad y el nuevo coronavirus se ha ido transformando para permitirse una mejor propagación, alojamiento y replicación en el ser humano. La enfermedad se manifiesta ahora con nueva sintomatología, mayor contagio, inclemencia y variación en el número de fallecimientos. La infección de la gestante por coronavirus se está presentando con severidad y consecuencias materno perinatales. Ya se inició la vacunación en gestantes y madres lactantes, previa conversación con su ginecólogo sobre los riesgos y beneficios. Este artículo ofrece un breve relato de los acontecimientos que tuvieron lugar durante la transición de 2020 a 2021.

Palabras clave. Infecciones por coronavirus, Virus SARS-CoV-2, COVID-19

HOW IS CONTAGION GOING IN THE COVID-19 PANDEMIC?

The first known transmission of COVID-19 occurred on November 17, 2019 in Wuhan, China. In June 2020, the epicenter of the pandemic moved to the Latin American and Caribbean region. At the beginning of March 2021, we are in the second wave of the disease caused by the SARS-CoV-2 virus and, among the countries currently most affected by the contagions, after the United States (about 30 million), are India and Brazil, with 11 million; Russia and the United Kingdom with 4 million; France with about 4 million and Spain with 3 million. In Latin America, Colombia, Argentina and Mexico have surpassed 2 million infections, while Peru is approaching 1.5 million infections⁽¹⁾.

TENDENCY IN FATALITY BY COVID-19

In terms of deaths, after the United States, with more than half a million, the countries with the most deaths in Latin America are Brazil with 260,000, Mexico with close to 200,000, Colombia with 60,000, Argentina with 52,000 and Peru with close to 50,000⁽¹⁾. However, the figures in Peru could be above 125,000 deaths officially⁽²⁾, and we would be after Brazil and Mexico in number of casualties.



Results from data provided by the Italian National Institute of Statistics indicate opposing age-related trends among women in infection and death rates due to COVID-19. The prevalence of COVID-19 infection was 3.6% higher in women than in the general population from 20 to 59 years of age, then decreased to -13.3% below that of the general population between 60 and 89 years of age. Death rates among infected women showed the opposite age-related trend. In infected women, the mortality rate was -77.4% lower than that of men aged 20 to 59 years. Between 60 and 89 years of age, the difference in women decreases to -34.5% below that of men⁽³⁾.

Among 192 550 adults hospitalized with COVID-19 who were discharged from 555 US medical centers, 53% were men, 43% were White, and 65% had Medicare or Medicaid insurance. The most common comorbidities included hypertension (61.5%), diabetes (38.4%), and obesity (27.4%). 28.9% were admitted to the ICU, 13.6% died during the hospitalization. In-hospital mortality increased in association with increasing age; 179 of 12 644 patients (1.4%) aged 18 to 29 years died, and 8 277 of 31 135 patients (26.6%) 80 years or older died. Of the patients admitted to the ICU, 27.8% died. The median hospital length of stay among patients who were not admitted to the ICU was 6 days, with a median cost per admission of \$10 520. The median hospital length of stay for those admitted to the ICU was 15 days, with a median cost per admission of \$39 825. The highest mortality was in March (22.1%), and then decreased each month until August (6.5%) (χ^2 for trend, 3592.3; $p < .001$)⁽⁴⁾.

HAVE THE SYMPTOMS CHANGED?

The three main symptoms of Covid-19 are a new persistent cough, a high temperature or a loss of taste and smell (anosmia). It is important then to get a test and isolate. Less common complaints are tiredness, aches and pains, sore throat, diarrhea, conjunctivitis, headache, skin rash, difficulty breathing, chest pain or pressure.

Transmission from asymptomatic individuals is estimated to account for more than half of all transmissions. In addition to identification and isolation of persons with symptomatic COVID-19, effective control of spread will require reducing

the risk of transmission from people with infection who do not have symptoms. Measures such as wearing masks, hand hygiene, social distancing, and strategic testing of people who are not ill will be foundational to slowing the spread of COVID-19 until safe and effective vaccines are available and widely used⁽⁵⁾.

SARS-CoV-2 MUTATIONS AND VARIANTS

Although the terms mutation, variant, and strain are often used interchangeably in describing the epidemiology of SARS-CoV-2, the distinctions are important. Mutation refers to the actual change in sequence, for example, of the spike glycoprotein. Genomes that differ in sequence are often called variants, that is a strain when it has a demonstrably different phenotype (e.g., a difference in antigenicity, transmissibility, or virulence). Mutations arise as a natural by-product of viral replication. Coronaviruses make fewer mutations than most RNA viruses because they encode an enzyme that corrects some of the errors made during replication. There is interest in whether mutations in the spike glycoprotein mediate escape from host antibodies and could potentially compromise vaccine effectiveness, since spike is the major viral antigen in the current vaccines. If a variant has one or more mutations in spike that increase transmissibility, it could quickly outcompete and replace other circulating variants. Because current vaccines provoke an immune response to the entire spike protein, it is hoped that effective protection may still occur despite a few changes at antigenic sites in SARS-CoV-2 variants⁽⁶⁾.

There are around 4,000 coronavirus variants now in circulation around the world. Only a very small minority are likely to be important and to change the virus in an appreciable way. The mutations scientists are most concerned about are those with a change in the spike protein, particularly one known as E484K. It can bind to human cells quickly and infect them more easily, and it may also be resistant to current vaccines. The E484K mutation was initially found in both the South African variant (B1351) and the Brazilian variant (P1). But, the E484K mutation has now been found in the UK variant (B117) as well. It means the variant, which first emerged in Kent late last year, has mutated once more to become more similar to the other dangerous variants⁽⁷⁾.



It is not unexpected that new variants have developed - all viruses mutate as they make copies of themselves to spread and thrive and maximize the replication of its genome. Most of these differences are inconsequential. A few can even be harmful to the virus's survival. But some can make it more infectious or threatening. Apart from the Brazil variant (also known as P.1), concerns focus on a few. The UK or Kent variant (also known as B.1.1.7) is up to twice as deadly compared with the original strain. This strain is the most dominant in Britain, has spread to more than 50 countries and appears to be mutating again. And the South Africa variant (B.1.351) has been found in at least 20 other countries, including the UK. All three have undergone changes to their spike. A recent study suggests the Brazilian variant may be resisting antibodies in people who should have some immunity because they have caught and recovered from an earlier version of coronavirus⁽⁸⁾. The Brazilian variant P.1 has already entered Peru, having been found in two neighboring regions of Brazil and in Lima⁽⁹⁾.

Variants in the S-protein that increase the amount of virus shed from an infected person or that increase its affinity for the ACE2 receptor are likely to increase virus transmission, an important problem in the context of a pandemic. These "escape mutations" typically arise when the virus is put under selective pressure by antibodies that limit but do not eliminate viral replication. Under these conditions, the virus might then find a way to escape this pressure and restore its ability to reproduce more efficiently⁽¹⁰⁾.

All leading vaccine companies are now redesigning their S-protein components to counter new variants, particularly B.1.351. Although it is unknown whether, when, and what additional variants might arise in the future, the E484K sequence change may represent a common solution as the virus adapts to neutralizing antibody-selection pressures⁽¹¹⁾.

ANTIBODIES AND IMMUNITY – COVID-19

Several studies have found that the SARS-CoV-2 seroprevalence has remained below 20% even in the most adversely affected areas globally, such as Spain and Italy. The U.S. has been one of the countries most affected by the coronavirus. When testing of more than 130,000 samples from all 50 US states plus Washington, DC and

Puerto Rico, the highest level of seroprevalence was in New York, which surged from 6.9% in March to a peak of approximately 25% before mid-August 2020. For all but a few states, seroprevalence remained below 10% throughout the study period; New York was the only state where seroprevalence increased above 20%. In several states, seroprevalence stayed below 1%. That is, seroprevalence tended to wane over time. Thus, despite the pandemic raging across the US, most people do not have evidence of prior COVID-19 infection by antibodies to SARS-CoV-2. More than 60%, and perhaps up to 80%, of the population may need immunity for the viral replication rate to drop below 1, enabling a modest level of disease control. There is though a limited number of reinfections of SARS-CoV-2 to date⁽¹²⁾. Although there is recent research suggesting that if you have had COVID-19 disease and have beaten it, this would be better than vaccinating, there is an important place for vaccines to gain herd immunity.

As an example, in Manaus, Brazil, a study of blood donors indicated that 76% (95% CI 67–98) of the population had been infected with SARS-CoV-2 by October, 2020. High attack rates of SARS-CoV-2 were also estimated in population-based samples from other locations in the Amazon Basin—e.g., Iquitos, Peru 70%. The estimated SARS-CoV-2 attack rate in Manaus would be above the theoretical herd immunity threshold (67%), given a basic case reproduction number (R0) of 3. In this context, the abrupt increase in the number of COVID-19 hospital admissions in Manaus during January, 2021 (3,431 in Jan 1–19, 2021, vs 552 in Dec 1–19, 2020) is unexpected and of concern.

There are at least four non-mutually exclusive possible explanations for the resurgence of COVID-19 in Manaus. First, the SARS-CoV-2 attack rate could have been overestimated during the first wave. The 76% estimate of past infection might have been biased upwards due to adjustments to the observed 52.5% seroprevalence in June, 2020, to account for antibody waning. However, even this lower bound should confer important population immunity to avoid a larger outbreak. Second, immunity against infection might have already begun to wane by December, 2020, because of a general decrease in immune protection. Third, SARS-CoV-2 lineages might evade immunity generated in response to previous infection. Two of



these variants are circulating in Brazil (B.1.1.7 and P.1) and one (P.1) was detected in Manaus on Jan 12, 2021. One case of SARS-CoV-2 reinfection has been associated with the P.1 lineage in Manaus that accrued ten unique spike protein mutations, including E484K and N501K. Fourth, SARS-CoV-2 lineages circulating in the second wave might have higher inherent transmissibility than pre-existing lineages circulating in Manaus. Contact tracing and outbreak investigation data are needed to better understand relative transmissibility of P.1 lineage⁽¹³⁾.

There is growing optimism and hope that by virtue of ongoing immunization efforts, seasonality (declining infections through August), and naturally acquired immunity, by spring and early summer 2021 in the US there will be a substantial decline in the number of deaths and hospitalizations related to COVID-19. However, this optimism must be tempered by several important factors. The likelihood of achieving herd immunity against SARS-CoV-2 is low simply because not all individuals in the US are eligible to be vaccinated and a quarter of eligible individuals will likely decline to be immunized. Moreover, the vaccines do not provide full immunity against infection, and the currently available vaccines are less effective against variant B.1.351, and possibly other variants. Recurrent seasonal COVID-19 could require both health system change and profound cultural adjustment for the life of high-risk individuals in the winter months. There is an urgent need to prepare for such a scenario by aligning surveillance, medical response, public health response, and socioeconomic programs⁽¹⁴⁾. These are the strategies that should also be adopted by our countries.

REINFECTIONS

Thirty-one confirmed cases of covid-19 reinfection have been recorded worldwide until January 2021, although that could be an underestimate from delays in reporting and resource pressures in the ongoing pandemic. To date, most of the SARS-CoV-2 reinfections that have been reported have been milder than first encounters with the virus, although some have been more harmful—and two people have died as a result. Those who experience the mildest symptoms in their initial infection have a higher likelihood of reinfection, perhaps because they didn't develop an immune response the first time. If anyone has recovered from SARS-CoV-2, it is not an excuse

to forget about social distancing and not to wear a mask. We know we can have COVID-19 twice⁽¹⁵⁾.

SEQUELAE OF COVID-19

A study has found that one in eight recovered COVID-19 patients die within 140 days - with a third readmitted to hospital within weeks. Of 47,780 people discharged from hospital in the first wave, 29.4 per cent returned in less than five months. Of those readmitted, 12.3 per cent of them died, according to research from Leicester University and the Office for National Statistics (ONS). The long-term effects of COVID-19 can cause survivors to develop heart problems, diabetes and chronic liver and kidney conditions. Experts say that people who have been discharged should be monitored in the months afterwards⁽¹⁶⁾.

In an ambidirectional cohort study of patients with confirmed COVID-19 who had been discharged from Jin Yin-tan Hospital (Wuhan, China) between Jan 7, 2020, and May 29, 2020, a total of 1 733 of 2 469 discharged patients with COVID-19 were enrolled. At 6 months after acute infection, COVID-19 survivors were mainly troubled with fatigue or muscle weakness, sleep difficulties, and anxiety or depression. Patients who were more severely ill during their hospital stay had more severe impaired pulmonary diffusion capacities and abnormal chest imaging manifestations, and are the main target population for intervention of long-term recovery⁽¹⁷⁾. As part of the pathophysiological process of COVID-19, an intense inflammatory response is generated, with the respiratory tract and mainly the lung as the first organ affected. However, several studies point out that the sequelae of this infection are not only limited to the respiratory tract, and that sequelae have been reported in the cardiovascular system and in the central and peripheral nervous system, as well as psychiatric and psychological sequelae⁽¹⁸⁾.

Out of 81 patients included in a study of whom 34 (41%) had been admitted to the ICU, New York Heart Association class II-III heart failure symptoms was present in 62% of the patients. Left ventricular function was normal in 78% of patients. ICU patients had a lower diffusion capacity (mean difference 12.5% $p = 0.01$), lower forced expiratory volume in one second and forced vital capacity (mean difference 14.9%;



$p < 0.001$; 15.4%; $p < 0.001$; respectively). Risk of depression, anxiety and post-traumatic stress disorder were 17%, 5% and 10% respectively and similar for both ICU and non-ICU patients. Overall, most patients suffered from functional limitations. Dyspnea on exertion was most frequently reported, possibly related to pulmonary fibrosis. In addition, mechanical ventilation, deconditioning, or pulmonary embolism may play an important role⁽¹⁹⁾.

The brain cortex is richly vascularized with capillaries. If some proportion of capillaries are blocked or occluded by megakaryocytes during the immune system reaction, it blocks some level of blood flow and oxygen delivery leading to impaired cognitive function⁽²⁰⁾. A UK study also suggested that in the worst cases the infection can cause mental decline equivalent to an 8.5-point fall in IQ or the brain ageing a decade. Scientists suggest that the "brain fog" reported by many people weeks and months after recovering may be a sign of more serious cognitive deficits. Many people with long COVID have difficulty concentrating and thinking and some have even experienced short-term memory loss as a result of the virus. In a handful of cases, some patients have also reported psychosis and delirium. They could be a result of the coronavirus directly impacting the brain, oxygen deprivation during COVID-19, medications, or the stress of having COVID-19 - a deadly disease⁽²¹⁾.

We knew that SARS-CoV-2 can be detected in saliva, urine, and semen in a small percentage of men who recovered from COVID-19. New publications find that one-quarter of men who recovered from COVID-19 demonstrated oligo-crypto-azoospermia, indicating that an assessment of semen quality should be recommended for men of reproductive age who are affected by COVID-19⁽²²⁾.

THE PREGNANT WOMAN, THE FETUS AND NEONATE

Whether pregnancy increases susceptibility to COVID-19 remains unknown. Many hospitals instituted universal SARS-CoV-2 screening for individuals presenting for labor and delivery, providing information on the frequency of asymptomatic infection among pregnant individuals, and seroprevalence studies of pregnant individuals confirmed that, as with the nonpregnant population, asymptomatic infection is com-

mon⁽²³⁾. Among more than 450,000 symptomatic women of reproductive age with COVID-19 for whom pregnancy status was known, admission to an intensive care unit, invasive ventilation, extracorporeal membrane oxygenation, and death were all more likely among pregnant individuals than among nonpregnant women of reproductive age. Some but not all studies have suggested that stillbirths occur more often among SARS-CoV-2-infected individuals or during the pandemic. For example, in an analysis from the UK, the rate of stillbirths was 2 to 3 times higher among pregnant individuals during vs before the pandemic, with rates of 9.3 vs 2.4/1000 births, respectively, although whether the increase is related to SARS-CoV-2 infection or other pandemic-related factors is unknown^(24,25).

Since the first reported cases of COVID-19 in the Americas until 14 January 2021, there were 139,016 SARS-CoV-2 positive cases among pregnant women, including 802 deaths (1%), in 19 countries/territories for which information was available. Compared to the data in the 11 December 2020 PAHO/WHO Epidemiological Update, this represents an increase of 18,065 new cases and 105 new deaths. During the same period, the highest relative increases in confirmed cases and deaths were observed in Venezuela⁽²⁶⁾. In Peru, more than 40,000 pregnant women tested positive for the virus and 76 died. The closure of the first level of care was a key factor, and it was not given priority in its reopening. On January 15, the Pan American Health Organization (PAHO) published its epidemiological update on COVID-19 in which it states that, per million inhabitants, Peru is the country with the highest number of pregnant women with COVID-19 in Latin America. Our country has 49% of infected pregnant women in the region. According to figures from the Ministry of Health (MINSA), Lima, Piura, La Libertad and Cajamarca account for half of the infected pregnant women. Between 2019 and 2020, maternal mortality increased by 42.3% (from 302 to 430 maternal deaths), with complications such as preterm birth, preeclampsia, and preterm labor⁽²⁷⁾.

Preterm delivery, abortion, preeclampsia, perinatal death and/or indication for preterm cesarean section have occurred in pregnant women infected with SARS-CoV-2 who developed pneumonia. At the moment, there are reports of possible vertical transmission from mother to child, which seems to occur in the third trimester of



gestation, without being able to rule out the potential and consequent risk of fetal morbidity and mortality⁽²⁸⁾.

An Israeli hospital has reported the case of a 36-week stillborn fetus carrying the virus in a woman infected with the coronavirus; the intrauterine infection would have occurred via the placenta. It was the first such reported instance in Israel. The 29-year-old woman, in her 25th week of pregnancy, arrived at the hospital after two days of fever and COVID-19 symptoms, having realized that there was no fetal movement. The woman tested positive for the coronavirus when she was admitted to the hospital and the baby was found to be carrying the virus in tests after the stillbirth. The head of the Infectious Disease Department at the Assuta Hospital in Ashdod, Israel said there were only a few recorded cases in the world of a mother infecting an unborn child, with some cases reported in Brazil⁽²⁹⁾. Another case of a fetus that died with complications linked to COVID-19 had been previously seen in Israel⁽³⁰⁾.

There is a great deal of information related to the special conditions for the care of the pregnant woman, delivery and puerperium⁽³¹⁾. There is current consensus to prefer vaginal delivery, umbilical cord section within three minutes of birth, rooming-in and breastfeeding in women diagnosed with COVID-19, always with mother-to-child viral transmission precautions and professional personnel protection⁽³²⁾. Neonatal SARS-CoV-2 infection is uncommon in babies admitted to the hospital. Infection with neonatal admission following birth to a mother with perinatal SARS-CoV-2 infection was unlikely, supporting international guidance to avoid separation of mother and baby⁽³³⁾.

Pregnant and postpartum women are vulnerable to COVID-19-related stresses. Women with pre-existing mental health diagnoses have elevated mental health symptoms. Among a group of pregnant women respondents to a survey, 36.4% reported clinically significant levels of depression, 22.7% for generalized anxiety, and 10.3% for post-traumatic stress syndrome (PTSD). Women with pre-existing mental health diagnoses based on their self-reported history were 1.6-to-3.7 more likely to score at clinically significant levels of depression, generalized anxiety, and PTSD. Approximately 18% reported

high levels of COVID-19-related health worries and were 2.6-to-4.2 times more likely to score above the clinical threshold for mental health symptoms. Approximately 9% reported high levels of grief and were 4.8-to-5.5 times more likely to score above the clinical threshold for mental health symptoms⁽³⁴⁾. Gynecologists must develop within their practice strategies to address mental health-related worry and distress in this pandemic time.

Within implications for public health practice, pregnant women and their families should be counseled on measures to prevent infection with SARS-CoV-2 as well as the risk for severe COVID-19-associated illness including death⁽³⁵⁾.

SARS-CoV-2 VACCINES

Efficacy of vaccines currently available worldwide is as follows: Pfizer-BioNTech (mRNA, RNA template for the spike protein) 94.6%; Moderna (mRNA, RNA instructs our cells to produce the SARS-CoV-2 spike protein to trigger an immune response) 94.1%; Oxford-AstraZeneca (viral vector, a harmless virus is engineered to contain the gene for the SARS-CoV-2 spike protein) 70.4%; Sinopharm (inactivated virus, SARS-CoV-2 virus is rendered inert through a chemical process that preserves the structure of the virus) 79.3%; Gamaleya (viral vector, a harmless virus is engineered to contain the gene for the SARS-CoV-2 spike protein) 91.1%; Johnson & Johnson (viral vector, a harmless virus is engineered to contain the gene for the SARS-CoV-2 spike protein) 72%^(36,37).

The recent authorization by the US Food and Drug Administration (FDA) of vaccines against COVID-19 has raised hopes for an end to the pandemic, but given the many challenges with vaccine availability, distribution, and hesitancy as well as the emergence of variants that might result in lower vaccine efficacy or overcome natural immunity, it is likely that SARS-CoV-2 will continue to circulate. The Pfizer, Moderna (both messenger RNA vaccines), and AstraZeneca vaccines work by instructing the body's own cells to produce spike proteins found on the surface of the virus. The immune system develops killer antibodies against these proteins, and when the SARS-CoV-2 virus comes along, the immune system has a memory of the "spike" on the surface, and is primed to at-



tack it. However, a change in the shape of the spike protein (variants) makes it more difficult for the immune system to recognize the virus. Up to mid-January 2021, 71 deaths related to the Pfizer/BioNTech vaccine were recorded, including 23 in Norway, 16 in the UK, 12 in Germany, 5 in France, all in people over 75 and very elderly with comorbidities, possibly due to their high frailty⁽³⁸⁾. We should be aware though that a single shot of the available two-dose COVID-19 vaccines can prevent serious illness and death.

After administration of 13.8 million doses of Pfizer-BioNTech and Moderna COVID-19 vaccines to the U.S. population during the first month of the vaccination program, the postauthorization safety profiles for both vaccines are reassuring. Most (90.9%) Vaccine Adverse Event Reporting System (VAERS) reports were for nonserious events and involved transient local and systemic symptoms - injection site pain, fatigue, headache, and myalgia, with a higher frequency after the second dose. VAERS received 113 reports of death after COVID-19 vaccinations; two thirds of these deaths occurred among long-term care facility (LTCF) residents, where underlying medical conditions are common and consistent with background all-cause mortality and no unexpected pattern that might suggest a causal relationship with vaccination. V-safe monitoring will be able to provide information on vaccination during pregnancy through follow-up in the v-safe pregnancy registry. Mass vaccination with highly effective vaccines is critical to controlling the COVID-19 pandemic. These initial findings should provide reassurance to health care providers and to vaccine recipients and promote confidence in the safety of COVID-19 vaccines⁽³⁹⁾.

VACCINATION DURING PREGNANCY AND LACTATION

Recent publications demonstrate that symptomatic pregnant individuals with COVID-19 are at increased risk of more severe illness and death compared with nonpregnant peers. Many pregnant individuals have medical conditions known to put them at further increased risk of severe illness and complications. ACOG and SMFM recommend that pregnant individuals be free to make their own informed decisions regarding COVID-19 vaccination. While pregnant individuals are encouraged to discuss vaccina-

tion considerations with their clinical care team when feasible, documentation of such a discussion should not be required prior to receiving a COVID-19 vaccine^(40,41).

Data on pregnancy outcomes of the small number of pregnant individuals inadvertently exposed during the clinical trials are not yet available because pregnancies are ongoing. Nearly all vaccines are allowed during pregnancy if the benefits are expected to outweigh potential risks. In the last year much has been learned about the effects of COVID-19 on persons who are pregnant or postpartum; however, many questions remain. Clinicians will need to follow updates from CDC, ACOG, and SMFM for the latest information related to COVID-19 during pregnancy and approaches for prevention and treatment⁽⁴²⁾.

Issues to be considered when counseling pregnant persons include data from animal studies and inadvertently exposed pregnancies during vaccine clinical trials when available, potential risks to pregnancy of vaccine reactogenicity, timing of vaccination during pregnancy, evidence for safety of other vaccines during pregnancy, risk of COVID-19 complications due to pregnancy and the pregnant person's underlying conditions, and risk of exposure to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and vaccine potential for risk mitigation⁽⁴³⁾.

COVID-19 VACCINE AND COUPLES WHO ARE PLANNING TO CONCEIVE

As recent studies have suggested that pregnancy is a risk factor for severe COVID-19 disease, the American Society for Reproductive Medicine (ASRM) recommends patients undergoing fertility treatment and pregnant patients should be encouraged to receive vaccination based on eligibility criteria⁽⁴⁴⁾.

The question posed by this author is, -if there is evidence that pregnant women who develop COVID-19 disease do so with greater severity and a higher probability of death than an infected non-pregnant woman of reproductive age; if the pregnant woman affected by the virus develops a condition similar to dangerous preeclampsia; if infected mothers would have more fetal deaths and prematurity; if placental lesions caused by SARS-CoV-2 have been reported; if more cases of probable vertical transmission are emerg-



ing; if the pregnant woman is more affected by mental stress and other related problems that persist after delivery; if we do not yet know the results of the application of the SARS-CoV-2 vaccine in pregnant women; if the pregnant woman is more affected by mental and other stresses that last after delivery; if we still do not know how children who were infected with COVID-19 at birth evolve; if men infected with the virus have sperm problems, among others - would it not be preferable to couples who are thinking of conceiving to wait until we know more about how the viral disease affects the pregnant woman and her product?

PROBABLE DECLINE IN U.S. BIRTHS DURING THE PANDEMIC

The COVID-19 pandemic would lead to a decline in U.S. births of about 8 percent, that will be added to the downward trend in annual births, resulting in 300,000 fewer births this year than would otherwise be expected. There is a well-documented cycle to the nation's birthrate: When the labor market is weak, aggregate birthrates decline; when the labor market improves, birthrates improve⁽⁴⁵⁾.

IVERMECTIN

Although several clinical trials are now underway to test possible therapies, the worldwide response to the COVID-19 outbreak has been largely limited to monitoring/containment. The antiparasitic drug ivermectin has been approved by the Food and Drug Administration (FDA) for use in the United States. This drug has broad-spectrum antiviral activity *in vitro*, reducing SARS-CoV-2 viral RNA, 5 000-fold at 48 hours. If the drug were administered to patients at the onset of infection, it could help limit viral load, prevent severe disease progression and limit person-to-person transmission^(46,47).

In a new randomized clinical trial that included 476 patients in Colombia, the duration of symptoms was not significantly different for patients who received a 5-day course of ivermectin compared with placebo (median time to resolution of symptoms, 10 vs 12 days; hazard ratio for resolution of symptoms, 1.07). The findings do not support the use of ivermectin for treatment of mild COVID-19, although larger trials may be needed to understand effects on other clinically relevant outcomes⁽⁴⁸⁾.

Let us hope to achieve a suitable vaccination in our countries and the world, so that, adding this population to the one already infected by SARS-CoV-2, we can achieve the herd immunity necessary to gradually enter a post-pandemic life.

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