SPECIAL ARTICLE

The coronavirus conundrum – Part III
La incógnita del coronavirus – Parte III

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ABSTRACT

The new coronavirus pandemic continues with us and will do so for a long time. It has brought a new way of life, with isolation, confinement, personal protection, distancing, use of virtuality and others. The diagnosis of the infected and its management has been improved; there is no cure yet, although there are vaccines approved in haste. The health crisis has exposed the lack of preparation of our health systems, resulting in political and economic crises, with impoverishment, death, and emotional and psychological complications. In these pages we continue writing in a summarized way the new knowledge about SARS-CoV-2 and the COVID-19 disease, its diagnosis, pathophysiology, symptomatic management and the severe disease, re-infection, its sequelae and lethality. But mainly how it affects the infected woman during pregnancy, childbirth and the puerperium, as well as aspects of rooming in and breastfeeding. And what happens when the infection affects the newborn. The future of the mothers and children who suffered the infection remains to be known.
Key words: Coronavirus, SARS-CoV-2, COVID-19, Pregnancy, Neonate.

RESUMEN

La pandemia del nuevo coronavirus continúa con nosotros y lo hará por largo tiempo. Ha causado un nuevo modo de vivir, con aislamiento, protección personal, distanciamiento, empleo de la virtualidad y otros. Se ha mejorado el diagnóstico del infectado y su manejo. No existe cura aún, aunque se cuenta con vacunas aprobadas con premura. La crisis de salud ha desnudado la falta de preparación de nuestros sistemas de salud, y ha devenido en crisis políticas y económicas, empobrecimiento, muerte e inquietud emocional y psicológica. En estas páginas continuamos escribiendo de manera resumida los nuevos conocimientos sobre el SARS-CoV-2 y la enfermedad COVID-19, su diagnóstico, fisiopatología, manejo sintomático y de la enfermedad severa, la reinfección, sus secuelas y letalidad. Pero, principalmente, el compromiso de la mujer infectada durante el embarazo y el parto y puerperio, así como aspectos del alojamiento conjunto y lactancia; y qué ocurre cuando la infección afecta al neonato. Queda por saber el futuro de las madres y niños que sufrieron la infección.
Palabras clave. Coronavirus, SARS-CoV-2, COVID-19, Embarazo, Neonato.

The new coronavirus pandemic is not over yet. It has expanded around the world with cost in lives and economic costs. The "new normal" consists in the use of masks, social distancing, virtualization, new ways of managing daily expenses, increasing automation, and restrictions on individual freedoms[1]. We still know very little about the virus, and the reality is that SARS-CoV-2 will be with us for years to come, even after a vaccine is available. The herd immunity required to end the pandemic would be above 90%[2].

When did the pandemic start?

The first case of coronavirus detected in the world is considered to have occurred one year ago, on November 17, 2019 in Wuhan, China[3]. Now, data from a new US government study indicate the coronavirus may have been silently spreading in America as early as December 2019. Researchers with the Centers for Disease Control and Prevention collected 7 389 blood samples from routine donations to the American Red Cross between December 13, 2019 and January 17, 2020. Of the samples, 106 contained coronavirus antibodies, suggesting those individuals' immune systems battled COVID-19 before those dates. SARS-CoV-2 reactive antibodies were present in sera prior to the first identified case in the U.S. on January 19, 2020. A total of 39 donations carrying coronavirus antibodies came from residents in the western states of California, Oregon and Washington and 67 samples from the more eastern states of Connecticut, Iowa, Massachusetts, Michigan, Rhode Island and Wisconsin[4]. In addition, according to the Milan Tumor Institute and the University of Siena, the virus circulated in Italy in September 2019, that

is, two months before the aforementioned date [3]. In the study, the presence of SARS-CoV-2 receptor-binding domain (RBD)-specific antibodies was investigated in blood samples of 959 asymptomatic individuals enrolled in a prospective lung cancer screening trial between September 2019 and March 2020. SARS-CoV-2 RBD-specific antibodies were detected in 111 of 959 (11.6%) individuals, starting from September 2019 (14% of the total), with a cluster of positive cases (>30%) in the second week of February 2020 and the highest number (53.2%) in Lombardy. This study showed an unexpected very early circulation of SARS-CoV-2 among asymptomatic individuals in Italy several months before the first patient was identified, and clarifies the onset and spread of the coronavirus disease 2019 (COVID-19) pandemic[5].

What proportion of those infected with SAR-CoV-2 are asymptomatic and how contagious are they?

Research early in the pandemic suggested that the rate of asymptomatic infections could be as high as 81%. But a meta-analysis published last month[6], which included 13 studies involving 21 708 people, calculated the rate of asymptomatic presentation to be 17%. Evidence suggests that most people develop symptoms in 7-13 days. Asymptomatic individuals are 42% less likely to transmit the virus than symptomatic people. The risk of an asymptomatic person passing the virus to others in their home is about one-quarter of the risk of transmission from a symptomatic person. And there is evidence that people with severe COVID-19 have a more substantial and long-lasting neutralizing antibody response[7].

The findings of another systematic review suggest that most people who become infected with SARS-CoV-2 will not remain asymptomatic throughout the course of the infection. In a total of 94 studies reviewed, the overall estimate of the proportion of people who become infected with SARS-CoV-2 and remain asymptomatic throughout infection was 20% in 79 studies that addressed this question. There was some evidence that biases in the selection of participants influenced the estimate. In seven studies of defined populations screened for SARS-CoV-2, 31% remained asymptomatic[8] after the follow-up.

Are we better at managing severe COVID-19 patients?

After a few weeks of decreases in the number of infected and deaths in Asia and Europe, coronavirus infections are rising across much of the United States, with the number of new daily cases nearing 200 000, about five times the number of new daily cases the U.S. was reporting in September. But the number of COVID-19 deaths per day has not necessarily followed this tendency. Reasons for this situation would be: a) increased testing – more infections are being identified; b) better treatments that allow more of the sickest patients to survive – including prone positioning, being more judicious about the use of mechanical ventilators, administering dexamethasone or other steroids to help suppress the overactive inflammatory response, using the antiviral drug remdesivir, convalescent plasma, monoclonal antibodies; c) more young people getting infected with the resulting shift in age distribution of those infected with the coronavirus (with latent virus spread to older populations in the near future); d) better-prepared nursing homes (temporarily); and, e) the lag in the trajectory of an outbreak: infections rise as hospitalizations increase – rise in deaths from those who don't survive their hospital stay[9].

SARS-CoV-2 seroprevalence

Several studies have found that the SARS-CoV-2 seroprevalence (the percentage of the population with serum containing antibodies that recognize the virus) has remained below 20% even in the most adversely affected areas globally, such as Spain and Italy. For all but a few USA States, seroprevalence remained below 10% throughout the study period. New York was the only state where seroprevalence increased above 20%. 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[10]. Biweekly nationwide sera testing can play an important role in helping track the spread of SARS-CoV-2 in the US[11] and in other countries. However, molecular tests are essential for the diagnosis of new cases and tracing their contacts. For example, in Peru, the diagnosis of infected people has been managed with rapid serological tests, initially from manufacturers not recognized by the World Health

Organization. So far, the number of molecular tests carried out in Peru is low, so the numbers of those infected by COVID-19 must be higher. In addition, the SINADEF – National Information System of Deaths of the Ministry of Health – has published the number of confirmed and suspected deaths from COVID-19 as of November 29, 2020. Officially there were 35 966 confirmed deaths from COVID-19. But the system considers that there would be 78 476 deaths until then[12]. A few paragraphs later, we will look at more recent records.

How long does immunity last after getting sick with COVID-19?

Much remains to be learned regarding SARS-CoV-2 immunity. Humoral immunity against SARS-CoV-2 may not be long lasting in persons with mild illness, who compose most persons with COVID-19. Results call for caution regarding antibody-based "immunity passports," herd immunity, and perhaps vaccine durability, especially in light of short-lived immunity against common human coronaviruses[13]. In addition, when it comes to immunity, various types of vaccine are likely to be needed for immuneimmature infants, children, pregnant women, immunocompromised individuals, and immunosenescent individuals aged ≥65 years[14].

COVID-19 non-specific symptoms and sequelae

COVID-19 disease is characterized by mild respiratory symptoms in about 85% of cases[15]. Non-specific symptoms that may appear 2-14 days after exposure to the virus include fever, respiratory symptoms (cough with or without sputum production, shortness of breath, or sore throat), muscle pain, fatigue, anosmia, ageusia, anorexia, malaise, nasal congestion, chills, headache, rash; rarely, diarrhea, nausea, and vomiting. Severe symptoms develop in 15% of cases mainly in vulnerable persons over 60 years old and / or suffering of chronic diseases (hypertension, obesity, heart or lung disease, diabetes) and / or immunosuppression[16,17].

Coronavirus can damage the lungs, brain, eyes, nose, heart and blood vessels, kidneys, liver, intestine, and cause neurological malfunction[18,19]. Viral neuroinvasion may be achieved by several routes, including transsynaptic transfer across infected neurons, entry via the olfactory nerve, infection of vascular endothelium, or leukocyte migration across the blood-brain barrier. The most common neurologic complaints in COVID-19 are anosmia, ageusia, and headache, but other diseases, such as stroke, impairment of consciousness, seizure, and encephalopathy[20] also occur. COVID-19 can have a direct and even indirect effect on erectile dysfunction. Men could have long-term issues of erectile dysfunction because coronavirus can affect the vasculature, pro-inflammatory cytokines can injure testicular function and the infection can increase the morbid and mental problems already present[21].

Lethality

Lethality is about 2%[22] to 3.4%[23]. In Peru, the reported fatality rate is 3.72% (36 677 people died from coronavirus) as of December 14, 2020[24]. Acording to the SINADEF, the number of confirmed deaths by COVID-19 as of December 4, 2020 was 36 231. However, if accumulated with suspected COVID-19 deaths and compared to previous years, there would be 78 825 deaths from COVID-19 up to that date[25].

Reinfection

Previously, few reinfections were published[26]. They are now reported more frequently in the world, including one confirmed case in a child and 26 other probable cases in Peru[27]. Using whole genome sequencing (WGS), nucleotide differences in viral samples sequenced from each episode can be found. Implications suggested by some researchers are a) herd immunity from vaccination or natural infection is unlikely to stop COVID-19 transmission; b) the second episode may be milder than the first, potentially due to primed adaptive immunity; c) mutations in the spike protein of the virus are potentially responsible for reinfection; and d) patients who have recovered from COVID-19 should be included in vaccine studies and should still comply with preventive public health measures[26].

Experts warn that getting a vaccine will not immediately eliminate the need for mask-wearing and other safety measures. The COVID vaccine that we have requires two doses to be fully effective. It does not prevent infection to 100%, but there is a 5% potential for infection. In addi-

tion, persons potentially asymptomatic, with low levels of virus in their systems, can be able to spread the virus to others, even if they are vaccinated[28].

COVID-19 DURING PREGNANCY

In an analysis of approximately 400 000 women aged 15-44 years with symptomatic COVID-19 in the US, intensive care unit admission, invasive ventilation, extracorporeal membrane oxygenation, and death were more likely in pregnant women than in nonpregnant women[29].

Among 598 hospitalized pregnant women with COVID-19 in 13 US States, 55% were asymptomatic at admission. Severe illness occurred among symptomatic pregnant women, including intensive care unit admissions (16%), mechanical ventilation (8%), and death (1%). Pregnancy losses occurred for 2% of pregnancies completed during COVID-19-associated hospitalizations and were experienced by both symptomatic and asymptomatic women. Pregnant women and health care providers should be aware of potential risks for severe COVID-19, including adverse pregnancy outcomes. Identifying COVID-19 during birth hospitalizations is important to guide preventive measures to protect pregnant women, parents, newborns, other patients, and hospital personnel[30].

Hispanic and non-Hispanic black pregnant women appear to be disproportionately affected by SARS-CoV-2 infection during pregnancy in the US. Among reproductive-age women with SARS-CoV-2 infection, pregnancy was associated with hospitalization and increased risk for intensive care unit admission, and receipt of mechanical ventilation, but not with death. Pregnant women might be at increased risk for severe COVID-19 illness[31].

In a prospective national population-based cohort study using the UK Obstetric Surveillance System (UKOSS) (including all 194 obstetric units in the UK), there were 427 pregnant women admitted to hospital with confirmed Sars-CoV-2 infection between March 2020 and April 2020. Compared with 694 women who gave birth between November 2017 and October 2018, estimated incidence of hospitalization with confirmed SARS-CoV-2 in pregnancy was 4.9 per 1 000 maternities. The median gestation time at symptom onset was 34 weeks (IQR 29-38). Black or other minority ethnicity (aOR 4.49), older maternal age (aOR 1.35), overweight and obesity (aORs 1.91 and 2.20, respectively) and pre-existing comorbidities (aOR 1.52) were associated with admission with SARS-CoV-2 during pregnancy. 58% of the women gave birth or had a pregnancy loss; 73% of women who delivered gave birth at term; 9% hospitalized women required respiratory support. Twelve infants (5%) tested positive for SARS-CoV-2 RNA, six of these infants within the first 12 hours after birth. The majority of pregnant women hospitalized with SARS-CoV-2 were in the late second or third trimester, most had good outcomes and transmission of SARS-CoV-2 to infants was uncommon[32].

In Turin, Italy, SARS-CoV-2 infection during the first trimester of pregnancy did not seem to predispose to early pregnancy loss; its cumulative incidence did not differ between women with spontaneous abortion and women with ongoing pregnancy[33].

The SARS-CoV-2 preprocedural asymptomatic infection - PAI rate was 15.7 times higher in the obstetrical unit (4.7%) than in the surgical unit (0.3%) in 1 hospital. These results emphasize the need to prioritize testing and personal protective equipment in the obstetrical units in which higher rates of asymptomatic infection increase the potential of spread, particularly during the second stage of labor with prolonged healthcare workers exposure in an aerosol-heavy environment[34]. This situation has also been found in Peruvian women, and has led to the official recommendation that all pregnant women who are hospitalized undergo a rapid test, even if they are asymptomatic (most of them).

On the other hand, pregnant women should be counseled about the risk for severe COVID-19-associated illness including death[29].

It is important to know that pregnant and postpartum women are vulnerable to stress related to COVID-19. Women with pre-existing mental health diagnoses have more mental health symptoms. Health concerns from the COVID-19 pandemic and grief increase the likelihood for mental health symptoms, so they should be targeted in mental health care[35].

The baby born from SARS-CoV-2-infected mothers – Possibility of vertical transmission

Babies differ from older children with regard to their exposure to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). However, data describing the effect of SARS-CoV-2 in this group are scarce, and guidance is variable[36].

In two Philadelphia hospitals, among 86 pregnant patients with test results positive for SARS-CoV-2, the preterm birth rate was 11.6% (n = 10; 6 spontaneous and 4 medically indicated preterm births) and there was 1 stillbirth. According to the authors, these findings differ from a Danish report of decreasing preterm birth rates and higher stillbirth rates in a UK hospital during the pandemic. They say the differences between studies may be due to differences in enforcement of lockdown orders, population heterogeneity, access to health care, or societal stressors[37]. However, a previous UK article noted that there was no evidence of any increase in stillbirths regionally or nationally during the COVID-19 pandemic in England when compared with the same months in the previous year and despite variable community SARS-CoV-2 incidence rates in different regions[38].

The American Academy of Pediatrics (AAP) initially recommended infection control practices that included temporary maternal-infant physical separation to protect newborns from acquiring SARS-CoV-2 infection from mothers with COVID-19 at the time of delivery[39]. Italian researchers from Lombardy evaluated the safety of infection control practices that included rooming-in for infants born to SARS-CoV-2-infected mothers. Only 1 neonate was diagnosed for SARS-CoV-2 infection during follow-up. The findings suggested that mother-to-infant transmission of SARS-CoV-2 during rooming-in practice is rare, provided that adequate droplet and contact precautions are taken[40]. Similar findings were encountered in New York in a study of 120 neonates from 116 mothers who tested positive for SARS-CoV-2. Allowing neonates to room in with their mothers and direct breastfeeding are safe procedures when paired with effective parental education of infant protective strategies[41,42]. In Peru, there is consensus in recommending delayed cord clamping, rooming-in of mother and infant, and breastfeeding[43].

In the UK, a study of 66 babies with confirmed COVID-19 infection (incidence 5.6 per 10 000 live-births) found that infection with neonatal admission following birth to a mother with perinatal SARS-CoV-2 infection was unlikely, and possible vertical transmission rare, supporting international guidance to avoid separation of mother and baby. 24% of these babies were born preterm[44]. And in a large, single-institution cohort study (U Texas Southwestern Med Center Dallas), SARS-CoV-2 infection during pregnancy (252 vs 3 122) was not associated with adverse pregnancy outcomes. Neonatal infection may be as high as 3% and may occur predominantly among asymptomatic or mildly symptomatic women. Placental abnormalities were not associated with disease severity, and hospitalization frequency was similar to rates among nonpregnant women[45].

Relative to controls, COVID-19 placentas have shown increased prevalence of features of maternal vascular malperfusion (MVM), a pattern of placental injury reflecting abnormalities in oxygenation within the intervillous space associated with adverse perinatal outcomes. In the study, only one COVID-19 patient was hypertensive despite the association of MVM with hypertensive disorders and preeclampsia. These changes may reflect a systemic inflammatory or hypercoagulable state influencing placental physiology[46].

In regards to *in utero* transmission of SARS-CoV-2 infection, a case of a preterm infant who developed fever and mild respiratory disease on the second day of life has been presented in a study. The birth weight was 3 280 g and Apgar scores were 7 and 9 at 1 and 5 minutes of life, respectively. Cord arterial blood gas was mildly acidotic (pH 7.18, base deficit −9.6). As part of the labor and delivery protocol for mothers with COVID-19, delayed cord clamping, and skin-to-skin contact were not performed. The infant was immediately separated from the mother, developed severe acute respiratory syndrome and SARS-CoV-2 nasopharyngeal testing was positive at 24 and 48 hours of life. Placenta histopathology revealed SARS-CoV-2 infection by electron microscopy and immunohistochemistry. Ultrastructural examination by transmission electron microscopy showed 89 to 129 nm diameter structures consistent with viral particles clustered within membrane-bound cisternal spaces

in the syncytiotrophoblastic cells. Amniotic fluid and breastmilk PCR, and cord blood antibody testing was not available at the hospital[47].

Summarizing, the SARS-CoV-2 story will continue. In the new year 2021 we will observe the experience of using a vaccine made by many laboratories, with few winners and many questions still to be resolved. We will be able to see the response of people to the invitation to get vaccinated, as well as the best logistics for the distribution and arrival to the users and if people can continue to take care of themselves as long as herd immunity be sufficient. At the moment, there are many people with fear of receiving the vaccine created so quickly and with health and political pressure. In addition, fake-news that border on fantasy, invention and lies are not helping. All of this could prevent the necessary prevention goals for vulnerable populations from being achieved. We must have a good dose of optimism.

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