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The coronavirus conundrum, the pregnant woman, her child. Part 2

La incógnita del coronavirus, la gestante, su niño – Continuación

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ABSTRACT

When COVID-19 appeared, we did not expect its rapid expansion throughout the world nor the serious consequences it would bring. We currently understand more about the virus' morphology and its activity in the environment and within the human body, as well as its greater predisposition to affect vulnerable populations, such as the elderly and persons with comorbidities like obesity, diabetes, hypertension and immunosuppression. This virus shows a predilection for men, and a higher prevalence in countries with greater poverty, promiscuity and economically depressed areas, among others. Various treatments have been tested and discarded in patients with moderate and severe disease. The frequency of deaths is decreasing due to personal protection measures, social distancing, emergency quarantine, and combination of medications and supplemental oxygen. However, there is still no cure, and we are waiting for the appearance of the vaccine. Women are less frequently and less severely affected; however, they should follow preventive measures, especially if frail with comorbidities. Preventive medical consultations and non-emergency surgical procedures have been temporarily postponed. Pregnant women are experiencing an increase in prematurity, fetal deaths, placental lesions and presence of the virus in placental adnexa, with cases of severe morbidity and maternal death. This article is an update on the situation of COVID-19 in the world and in Peru, emphasizing the care of women and pregnant women.
Key words: Coronavirus infection, SARS-CoV-19, COVID-19, Pregnancy, Infectious complications of pregnancy, Preeclampsia, Premature birth, Maternal death, Fetal death.

RESUMEN

Cuando apareció la enfermedad por el coronavirus SARS-CoV-2, no esperábamos su rápida expansión en el mundo y las graves consecuencias que traería. Se ha ido conociendo al virus morfológicamente y su accionar en el ambiente y en el organismo del ser humano, su mayor predisposición de enfermar a poblaciones vulnerables, como el adulto mayor, poblaciones con comorbilidad como obesidad, diabetes, hipertensión e inmunodepresión, predilección por el sexo masculino, mayor prevalencia en países con mayor pobreza, promiscuidad, zonas deprimidas económicamente, entre otros. Se ha tenido que improvisar y descartar diversos tratamientos en aquellos pacientes con enfermedad COVID-19 moderada y severa. Eventualmente se está disminuyendo la frecuencia de muertes con medidas de protección personal, distanciamiento social, cuarentena de emergencia, y combinación de medicamentos y administración de oxígeno. Pero aún no hay cura, y se está a la expectativa en la aparición de la vacuna. Con relación a la mujer, ella es comprometida en menor proporción y severidad por la enfermedad COVID-19, pero debe cumplir las medidas de prevención, especialmente si es frágil y tiene comorbilidades. Se ha postergado temporalmente su evaluación preventiva y las intervenciones quirúrgicas si no son de emergencia. En la gestante se está encontrando aumento de prematuridad, gestaciones frustras, lesiones placentarias y presencia del virus en anexos placentarios, con casos de morbilidad severa y muerte maternas. En este artículo se hace una puesta al día resumida sobre la situación de la enfermedad COVID-19 en el mundo y el Perú, enfatizando el cuidado de la mujer y de la gestante.
Palabras clave. Infección por coronavirus, SARS-CoV-19, COVID-19, Gestante, Complicaciones infecciosas del embarazo, Preeclampsia, Parto prematuro, Muerte materna, Muerte fetal.

In the last issue of the Peruvian Journal of Gynecology and Obstetrics, we stated "A potentially respiratory disease has suddenly appeared and disrupted the life of people around the world'. 'SARS-CoV-2 is not only here to stay; it has revolutionized our way of living and thinking of our future"[(1)].

During the second half of 2020, we are learning just a little more about how the virus spreads and infects people, its symptoms, clinical findings, the higher vulnerability of older age and certain comorbidities, the need for face masks, social distancing, staying at home and avoiding dangerous locations, the weakness of health systems, the vulnerability of people in the front line – medical teams, police, sanitary workers –, the profound damage of unprepared health systems and economies,

especially in developing countries, the economy crisis, the increase in poverty and the reduction of the middle class... However, it is concerning that we still do not know how to combat the virus and COVID-19 effectively, nor how to treat severe disease, the duration of symptoms and immunity, disease recurrence, genetic variations of the virus, and the effectivity, safety and duration of a vaccine. In short, we don't have a cure yet and the vaccine is in phase 3, in the middle of a scientific and political competition.

The disease

COVID-19 may have appeared in Los Angeles, California as early as December 2019[2,3], practically at the same time that it presented in China and Asia. SARS-CoV-2 has infected millions of people in Europe, mainly Italy, Spain, Belgium and the United Kingdom; then, it attacked the USA and Latin America, with Brazil, Mexico, Ecuador and Peru among the most affected countries. Since August 2020, Peru leads the list of deaths per million inhabitants in the world[4]. As of September, the World Health Organization has confirmed more than 27 million COVID-19 cases around the world and almost 1 million deaths[5].

In this paper, we will present the new knowledge and challenges since the publication of our article in the second quarter of 2020[1].

Epidemiology and transmission

Our knowledge about SARS-CoV-2 behavior, infectivity, complications and sequelae has greatly increased as a consequence of its intense transmission in various Latin American countries and territories, as well as the generation of evidence by the scientific community[6]. The outbreaks in Wuhan and Beijing were both linked to seafood markets, but further investigation is required to determine the root cause. Although the epidemic abated in China, a second outbreak began in June 2020 in Beijing[7].

SARS-CoV-2 transmission is person-to-person and takes place when an infected person coughs, sneezes or exhales, via respiratory droplets and aerosols that may remain in the air up to three hours[8]. Along with dissemination by mouth, nose and eye mucosa, the virus has been found in the ear mucosa and tympanic membrane[9]. The virus has also been detected in saliva, tears, blood, cerebrospinal fluid, semen, conjunctival secretions, and stool[8]. More SARS-CoV-2 RNA copies have been detected in saliva specimens than in nasopharyngeal swab specimens, and a higher percentage of saliva samples were positive up to 10 days after COVID-19 diagnosis[10]. Collection of saliva samples by patients themselves would alleviate demands for supplies of swabs and personal protective equipment. Infections have also been consistent with the vertical spread of virus-laden aerosol particles via buildings' stacks and vents[11].

The incubation period is 1 to 14 days, with a median of 4 to 5 days[12]; this interval is possibly longer in children.

In general, this coronavirus affects persons 30 to 79 years old more often and is less frequent among people under 20.

The most important finding regarding contagion is that asymptomatic persons, as well as persons in the first two to three days of infection who have not developed symptoms yet, may be more infectious than symptomatic persons[8]. Infectivity lasts approximately 7 to 10 days in asymptomatic persons and 5 to 10 weeks in infected subjects.

A Korean study reported a median time from diagnosis to the first negative conversion of 17 days for asymptomatic patients and 19.5 days for symptomatic (including presymptomatic) patients ($p = .07$). The viral load from diagnosis to discharge tended to decrease more slowly in asymptomatic patients than in symptomatic (including presymptomatic) patients[13]. Therefore, isolating asymptomatic patients may be necessary to control the spread of SARS-CoV-2. On the other hand, Brazilian studies have found persistence of active SARS-CoV-2 virus for 152 days (5 months) in a female health professional who initially presented with mild disease and became afterwards asymptomatic but with ability of transmission[14].

Children under 5 years old with mild to moderate COVID-19 have high amounts of SARS-CoV-2 viral RNA in their nasopharynx compared with older children and adults. Thus, young children can potentially be important drivers of SARS-CoV-2 spread in the general population[15].

Clinical presentation

COVID-19 continues being considered a respiratory infection with a presentation that varies from common cold-like to severe pneumonia[16]. Nevertheless, compromise is multisystemic and potentially fatal. About 40% of COVID-19 cases develop mild symptoms (fever, cough, dyspnea, myalgia or arthralgia, odynophagia, fatigue, diarrhea and headache), 40% present moderate symptoms (pneumonia), 15% severe clinical manifestations (severe pneumonia) that require oxygen support, and 5% develop a critical clinical status that includes one or more of the following: respiratory insufficiency, acute respiratory distress syndrome (ARDS), sepsis and septic shock, thromboembolism and coagulation disorders and multiorganic failure, including acute renal failure, liver failure, heart failure, cardiogenic shock, myocarditis and cerebrovascular accident, among others. Besides, there are reports of complications attributed to invasive or non-invasive procedures performed during the clinical management of the case[6].

Severely ill patients tend to have a high concentration of pro-inflammatory cytokines, such as interleukin (IL)-6, compared to those who are moderately ill. The high level of cytokines, called "cytokine storm", indicates a poor prognosis and may contribute to mortality from COVID-19. Excessive infiltration of pro-inflammatory cells, mainly involving macrophages and T-helper 17 cells, has been found in lung tissues of patients with COVID-19 in the postmortem examination[17]. However, recent research finds critically ill patients with COVID-19 and ARDS had lower circulating cytokine levels compared with patients with bacterial sepsis and similar levels in comparison to other critically ill patients. These findings are in line with lower leukocyte counts observed in patients with COVID-19, despite the presence of severe pulmonary injury. These reports suggest that COVID-19 may not be characterized by cytokine storm. Whether anticytokine therapies will benefit patients with COVID-19 remains to be determined[18].

Secondary hemophagocytic lymphohistiocytosis (sHLH) is an under-recognized hyperinflammatory syndrome characterized by fulminant and fatal hypercytokinemia ("cytokine storm") with multiorgan failure; cardinal features include unremitting fever, cytopenia, and hyperferritinemia, as well as pulmonary involvement[19].

Severe symptoms appear in 15% of cases, mainly in vulnerable persons over 60 years old or people suffering from chronic diseases (heart disease, hypertension, obesity, lung disease, diabetes, smokers and/or immunosuppressed people[6,20-22].

The most common neurologic complaints in COVID-19 are anosmia, ageusia and headache, but other problems, such as stroke, impairment of consciousness, seizure, and encephalopathy, have also been reported. Viral neuroinvasion may be achieved by transsynaptic transfer across infected neurons, entry via the olfactory nerve, infection of vascular endothelium, or leukocyte migration across the blood-brain barrier[23].

Disease severity would depend on the amount of the SARS-CoV2 receptor molecule angiotensin I-converting enzyme 2 (ACE2) on the surface of cells throughout the body, including bowels, lungs, heart and nose; a higher number of ACE2 receptors correlates with a higher risk of severe coronavirus infection. This would be a gene-dependent phenomenon. Lethality has increased from about 2% (95% CI 0.5-4%) (24) to 5% (0.5-15%)[25]. In addition to respiratory compromise, cardiovascular complications are rapidly emerging as a key threat in COVID-19. ACE2 receptors are also expressed by endothelial cells, and in a series of patients with COVID-19, endothelial cell involvement across vascular beds of different organs has been shown[16].

An intriguing finding is that COVID-19 seems to preferentially have worse outcomes in males versus females. The authors of a systematic review and meta-analysis have studied whether this relationship holds true for cancer patients. They show that the OR for experiencing a composite endpoint including severe illness and all-cause death was 1.6 (95% CI 1.38 to1.85) in males versus females. For severe illness and mortality separately, the OR was 1.47 (1.16 to 1.85) and 1.58 (1.18 to 2.13), respectively[26].

Infection in children is reported less frequently than among adults, with rates of 1 to 5%[8]. Clinical manifestations are usually mild. However, since May 2020, a hyperinflammatory syndrome leading to multiorganic failure and shock has

been observed. It is called the multisystemic inflammatory syndrome (MIS), and affects children and adolescents[6]. Symptoms, such as high, sustained fever (above 38.9 degrees Celsius), conjunctivitis, rash, abdominal pain and diarrhea, seem to overlap with two existing conditions: toxic shock syndrome and Kawasaki disease[27]. In these children, hyperinflammatory syndrome with dermatologic, mucocutaneous, and gastrointestinal manifestations was associated with cardiac dysfunction[28]. They also presented new neurological symptoms involving both the central and peripheral nervous systems and splenial changes on imaging, in the absence of respiratory symptoms[29].

Regarding the experience of pregnant women with COVID-19 in Wuhan, China, the median age was 31 years, 52% were nulliparous, and 64% were infected with SARS-CoV-2 in the third trimester. The most common symptoms were fever (in 75%) and cough (in 73%); lymphopenia was present in 44% of patients, and 79% of women who underwent chest tomography had infiltrates in both lungs[30]. Compared with the risk of severe disease in the general population across mainland China (15.7%), the risk of severe disease was lower in pregnant women (8%). No positive results were reported in neonatal throat swabs of 8 newborns and breast milk samples from 3 mothers.

Prevention and treatment

Throughout the year 2020, there have been advances in prevention strategies and pandemic control[31]. General prevention measures have not varied, and include: avoiding exposure to the virus, washing hands often, with soap and water for at least 20 seconds, or with a 60% alcohol-based sanitizer, avoiding coughing or sneezing and touching the eyes, nose, and mouth with unwashed hands, avoiding contact with people (distance over 2 meters), and shaking hands. If symptoms appear, seek medical care early, stay at home, clean and disinfect frequently touched surfaces[8]. Wear facial masks, especially in public settings where social distancing measures are difficult to maintain. Compliance with this recommendation has been ignored, especially by young people and low-income people. Isolate all suspected and confirmed cases, implement recommended infection prevention and control procedures, and report all cases to local health authorities.

In relation to the new coronavirus, variation in the viral genome is clinically important. Among 131 patients hospitalized in Singapore, 70% had wild-type virus, 22% had delta 382-variant virus, and 8% had mixed infection. Compared with the group infected with wild-type virus, those infected with the delta 382-variant alone were younger (median age, 37 vs. 47 years), had a longer duration of symptoms (6 vs. 4 days), and had lower virus levels on initial nasopharyngeal polymerase chain reaction assays. Also, patients infected with the delta 382-variant were less likely to develop hypoxia than those infected with wild-type virus, and had lower plasma levels of pro-inflammatory cytokines and higher concentrations of interferon-gamma than those with wild-type virus[32].

Currently, there is no specific treatment for COVID-19, and no cure is available. The coronavirus pandemic is forcing clinicians, health care institutions and public officials to develop crisis standards of care that differ radically from ordinary care services[33].

Management of a patient with coronavirus is overall symptomatic. Antibiotics are not effective against viral infections such as COVID-19. The FDA has granted emergency use authorization for the antiviral drug remdesivir to treat patients with this disease. The U.S. National Institutes of Health recently recommended the corticosteroid dexamethasone for people with severe COVID-19 who require supplemental oxygen or mechanical ventilation. The FDA has also granted emergency use authorization for convalescent plasma therapy to treat COVID-19[34].

In a survey to 852 physicians from 44 different specialties and 29 countries, it was determined that the heterogeneity of therapeutic decisions increased as the COVID-19 clinical scenario worsened. Factors associated with aggressive therapeutic decisions were higher self-perceived expertise (high vs. null, OR 1.95, 95%CI 1.31–2.89), perceived quality of COVID-19 publications (high vs. null, OR 1.92, 95%CI 1.17–3.16), and female sex (OR 1.17, 95%CI 1.02–1.33). Conversely, using less aggressive therapies was associated with being a specialist in infectious diseases, Latin American and North American origin, lower confidence in the treatments chosen, and having published articles indexed in PubMed as the first-author[35].

Sequelae to COVID-19

Recovered COVID-19 patients may have a residual cough or fatigue and reduced lung function. However, an intense inflammatory response of infected persons leads to pulmonary, cardiovascular, central and peripheral nervous system, psychiatric and psychologic sequelae[6]. Severe lung involvement results in pulmonary fibrosis, frequently bilateral, in the inferior lobes. Viral infection-related myocarditis reduces systolic function and arrhythmias due to cardiomyocyte damage, interstitial myocardial fibrosis and hypoxia[36]. SARS-CoV-2 would reach the central and peripheral nervous system by either hematogenous propagation or direct viral neurotropism. Neurological sequelae include long-term cognitive deterioration affecting memory, attentiveness and diffuse neuronal loss[37]. Neuropsychiatric manifestations would include encephalopathy, mood changes, psychosis, neuromuscular dysfunction and demyelinating processes[6]. Finally, psychological sequelae should be considered in individuals at all ages, as well as in health professionals and workers.

Reinfection

The World Health Organization (WHO) informed that there is currently no evidence of protection from a second infection in people who recovered from COVID-19 and have antibodies against it[38]. Levels of antibodies against SARS-CoV-2 vary widely in patients after recovery; some of them would recover without developing high titers of virus-specific neutralizing antibodies. These patients would be at risk of reinfection[39]. Some recovered patients may still be virus carriers, and potentially infectious. Current criteria for hospital discharge or discontinuation of quarantine and continuity of care may need to be reevaluated[40]. In South Korea, it has been reported that 260 patients thought to have recovered from the disease have tested positive again. Rather than viral reactivation or patient reinfection, the likely cause of positive results for SARS-CoV-2 would be fragments of dead viruses, days and even weeks after full recoveries[41].

Recently, epidemiological, clinical, serological and genomic analyses confirmed that a patient had a reinfection instead of persistent viral shedding from the first infection. SARS-CoV-2 may continue to circulate around the world despite herd immunity due to natural infection or vaccination. Further studies of re-infected patients will shed light on protective correlates, important for vaccine design[42].

SARS-CoV-2 vaccines

At this time, there are no vaccines proven to protect the body against COVID-19. About 140 vaccines are in early development, and around two dozen are now being tested on people in clinical trials[43]. These vaccines would be in the following development phases: 135+ preclinical, 19 in phase 1, 12 in phase 2, 8 in phase 3, and 2 approved in Russia[44].

The U.S. Food and Drug Administration announced that a public meeting of the Vaccines and Related Biological Products Advisory Committee will be held on October 22, 2020, to discuss the general matter of the development, authorization, and/or licensure of vaccines indicated to prevent COVID-19[45].

In the following lines, we summarize the recommendations of important medical institutions and journals related to the practice of gynecology and obstetrics that will help to make decisions about women's care.

Gynecologic patients and COVID-19

The American College of Obstetricians and Gynecologists (ACOG) advises that determining the best management options for patients in the COVID-19 pandemic depends on the patient's signs and symptoms, their comorbidities and underlying medical condition, type of presentation (acute versus chronic) and available health resources, along with other factors[46]. Preventive visits, routine screenings, contraceptive counseling and prescribing, management of asymptomatic ovarian cyst, menopausal symptoms, routine gynecologic or postoperative follow-up, and mental or behavioral health screening may be addressed by telehealth or deferred until after the COVID-19 outbreak[46].

Elective surgeries should be postponed; however, obstetric and gynecologic procedures for which a delay would negatively affect patient health and safety should not be delayed[46]. Regarding endoscopic procedures, all forms of contagion are found in endoscopy units: aerosols from vomiting, retch-

ing, belching, and flatus; fecal matter, close contact, and contamination of the environment. Hysteroscopy is considered the gold standard procedure for the diagnosis and management of intrauterine pathologies. It is frequently performed in an office setting without the use of anesthesia. The recommendation is to limit hysteroscopic procedures to patients in whom delaying the procedure could result in adverse clinical outcomes[47]. In general, all diagnostic endoscopies should be discontinued, and only urgent and therapeutic endoscopies should be performed. All endoscopy personnel must have strict protection measures[48].

Assisted reproduction during the COVID-19 pandemic

In the earliest stages of the pandemic, the American Society for Reproductive Medicine (ASRM) and the European Society of Human Reproduction and Embryology (ESHRE), independently recommended discontinuing reproductive care except for the most urgent cases. More recently, with successful mitigation strategies in some areas and emergence of additional data, the societies have endorsed gradual and judicious resumption of delivery of full reproductive care[49]. For patients who started assisted reproduction treatment, elective oocyte or embryo freezing for later embryo transfer (freeze-all) is recommended. In cases of urgent fertility preservation in oncology patients, the cryopreservation of gametes, embryos or tissue should still be considered[50].

However, apart from the undoubtedly important considerations of the effect of SARS-CoV-2 infection on pregnancy and the fetus, we should also direct our attention to ovarian physiology and consider the theoretical risks that IVF treatment may pose on fertility patients, during the COVID-19 pandemic[51].

Pregnant women during the COVID-19 pandemic

Pregnancy itself alters the body's immune system and response to viral infections in general, which can occasionally cause more severe symptoms. Pregnant patients with comorbidities may be at a higher risk for severe illness, consistent with the general population with similar comorbidities[52].

Current data and data from early in the pandemic show low rates of maternal and neonatal mortality and vertical transmission of SARS-CoV-2. A study reported a preterm birth rate of 20% and a cesarean delivery rate exceeding 80%, which seem to be related to geographic practice patterns. No vertical transmission and no maternal deaths were reported. The neonatal death rate was 0.3%[53].

However, the CDC published two reports in the Morbidity and Mortality Weekly Report on COVID-19 regarding pregnant women. In one report[54], the agency calls for pregnant women and healthcare providers to be aware of the risks of severe COVID-19, which include serious birth outcomes. Main signs and symptoms at hospital admission among 272 symptomatic hospitalized pregnant women with COVID-19 were fever/chills, cough, shortness of breath, myalgias, nausea/vomiting, headache, sore throat, abdominal pain and chest pain. 16% of these patients required admission to the ICU, 8% required mechanical ventilation, and 1% died. 448 of 458 (97.8%) women completed their gestation resulting in a live birth and 10 (2.2%) suffered pregnancy loss. Identifying COVID-19 in women during birth hospitalizations is important to guide preventive measures to protect pregnant women, parents, newborns, other patients, and hospital personnel.

In the other report, prevalences of prepregnancy obesity and gestational diabetes were higher among pregnant women hospitalized for COVID-19–related illness (e.g., worsening respiratory status). The agency encouraged pregnant women to wear face masks, wash their hands often and maintain social distance to prevent COVID-19[55].

In hospitalized mothers infected with SARS-CoV-2, over 90% of whom also had pneumonia, preterm birth was the most common adverse pregnancy outcome. COVID-19 infection was also associated with preeclampsia, C-section, and perinatal death[56].

In another study among patients with mild symptoms at presentation, all patients with a vaginal delivery had good outcomes. In contrast,

13.5% of women undergoing cesarean section had severe maternal outcomes and 21.6% had clinical deterioration. C-section was also associated with an increased risk of NICU admission[57].

The COVID-19 epidemic needs a global bioethics reflection and response. A bioethics and ethics of science and technology approach, rooted in human rights, should play a key role in the context of this challenging pandemic. On both national and international levels, health and social policies should be based on solid evidence, taking into account the uncertainties that exist during epidemics, especially in the case of a novel pathogen. Epidemics clearly expose the strengths and weaknesses of healthcare systems in different countries, as well as the obstacles and inequities of access to healthcare[58].

Pregnant women are particularly susceptible to morbidity and mortality, especially by a highly pathogenic virus[58]. Severe maternal complications need admission to the intensive care unit and use of mechanical ventilation; they also present perinatal deaths[59], preterm birth, abortion, preeclampsia and/or indication for preterm cesarean section[31].

Pregnant women with severe COVID-19 can develop a preeclampsia (PE)-like syndrome that might be distinguished from actual PE by sFlt-1/PlGF, LDH and uterine artery pulsatility index (UtAPI) assessment. Healthcare providers should be aware of this syndrome's existence and monitor pregnancies with suspected pre-eclampsia with caution[60]. Similar findings are occurring in Peru. Cases presenting both at sea level and at altitude are published in the current number.

COVID-19 has led to broad societal changes that will not be fully reversed after the pandemic subsides. These changes include less frequent physical contact, fewer opportunities for informal interactions, increased telework, and new ways of interacting online[61]. Remote consultations and self-monitoring of blood pressure may be recommended in healthy women whenever possible to reduce the number of hospital visits. Remote follow-ups for monitoring diabetes, hypertension, mood disorders and other conditions should be considered[52].

In medicine, especially in obstetrics and gynecology, face-to-face consultations have become minimal; primary care physical examination has disappeared and its future implementation has to be considered very seriously[62]. However, it has been reported that there would be no difference between the number of prenatal visits among women with versus women without COVID-19, which provides reassurance that healthcare settings are unlikely places of exposure to the virus[63].

Routine antenatal care appointments should be delayed in patients with suspected or confirmed COVID-19 until after the recommended period of self-isolation. Appointments can be deferred until 7 days after the start of symptoms, unless they worsen[52]. More urgent appointments require a senior decision on urgency and potential risks and benefits.

When possible, antenatal fetal surveillance and ultrasonography should continue as medically indicated. Elective ultrasound examinations should not be performed[4 8].

Following delivery and in order to limit the risk of inadvertent exposure and infection, it may be appropriate to expedite discharge when mother and infant are healthy; this should be linked to home telehealth visits for both[52]. Maternity services should offer a combination of face-to-face and remote postnatal follow-up, according to the needs of mother and newborn, for example in cases of hypertensive diseases of pregnancy, low birth weight, prematurity or if there are any concerns about feeding.

Pregnant women with COVID-19

The clinical characteristics of pregnant women with COVID-19 are similar to those reported in non-pregnant adults. Symptoms due to physiological adaptations of pregnancy or adverse pregnancy events (e.g. dyspnea, fever, gastrointestinal symptoms, fatigue) may overlap with COVID-19 symptoms[9]. Most of the women (85–86%) contracting SARS-CoV-2 will exhibit mild disease; the rates of severe disease vary between 9.3 and 11.1%, and those of critical disease, between 2 and 6.9%, which are just as similar to the general population[64]. Treatment

should be symptomatic. Pre-existing comorbidities, high maternal age, and high body mass index are risk factors for severe COVID-19[65].

There is a recent publication from the UK that addresses the characteristics and outcomes of pregnant women with confirmed SARS-CoV-2 infection who were admitted to a hospital. Median gestation time at admission was 34 weeks; 10% required ICU admission and 1.2% died. Regarding the deliveries, 75% were term births and 15% were preterm deliveries (7% due to COVID-19 complications). 59% of women had a cesarean delivery, most for non-COVID-19–related reasons. Two neonates died and three were stillborn, but the relation to SARS-CoV-2 infection was unclear. Twelve infants tested positive for SARS-CoV-2, including 6 within 12 hours of birth. Advanced maternal age (over 35 years) and obesity carried higher risk for hospitalization[66].

Pregnancy seems to have worsened the course of COVID-19 in Spanish patients, who had a longer hospital stay, higher rate of renal failure, sepsis, disseminated intravascular coagulation, intensive care unit use, mechanical ventilation and higher lethality[24].

Miscarriage, intrauterine growth restriction, preterm birth and stillbirth have been reported, and seem to be increasing in many regions and in Peru. Corticosteroid therapy may be considered in women who are at risk of preterm birth between weeks 24 and 37 for fetal lung maturation.

Consider home care in women with asymptomatic or mild illness, provided that the patient is able to care for herself, that monitoring and follow-up are possible and that the patient has no signs of potentially severe illness (e.g. breathlessness, hemoptysis, new-onset chest pain or pressure, anorexia, dehydration, confusion), no comorbidities and no obstetric issues[52].

Patients should be managed in a hospital setting when possible; however, home care may be suitable for selected patients with mild illness unless there is concern about rapid deterioration or an inability to promptly return to the hospital if necessary. Patients should remain in isolation for 2 weeks after symptoms disappear, and visitors should not be allowed until the end of this period[8]. Pregnant women should be managed by a multidisciplinary team, including obstetric, perinatal, neonatal, and intensive care specialists, and they should also receive mental health and psychosocial support[8]. Health care practitioners should promptly notify infection control personnel at their facility of the anticipated arrival of pregnant patients with confirmed COVID-19 or under investigation[67].

Suspected and confirmed cases should be managed with appropriate maternal and fetal monitoring whenever possible. Women with severe illness or complications may require admission to an intensive care unit.

It has been reported that, between January 22 and September 1 in the United States, the total cases of pregnant women with COVID-19 were 20 216, and total deaths were 44. There were more cases in women aged 20 to 39 years; regarding ethnicity, there were almost double as many cases in Hispanic or Latino than in White, non-Hispanic and Black non-Hispanic women[68].

Samples required for an initial nucleic acid test in a pregnant woman with COVID-19 are a single swab used for throat and nose (nasopharyngeal secretions), and sputum, if available[69]. Saliva specimens may be an alternative diagnostic sample, because there would be more SARS-CoV-2 RNA copies in saliva specimens than in nasopharyngeal swab specimens. In addition, a higher percentage of saliva samples than nasopharyngeal swab samples were positive up to 10 days after COVID-19 was diagnosed[10]. Samples should be processed in an appropriate laboratory.

Results from RT-PCR suggest that a high viral load may be detected soon after illness onset, also in minimally symptomatic persons[70]. One or more negative results do not rule out the possibility of infection. Test results may be false positives, false negatives or ambiguous. The rate of false negative results in non-pregnant patients ranges from 17 to 63% for NP SARS-CoV2 RT-PCR[71]. False-negative testing of NP SARS-CoV2 RT-PCR is a clinically relevant problem with multiple implications, especially in pregnant women with suspicion for severe or critical COVID-19 infection[72]. Improper sampling accounts for some false negative results.

In suspected patients with negative nucleic acid tests, one can use as diagnostic criteria positive serum-specific lgM or specific lgG antibody titer

in the recovery phase approximately 4 times higher than that in the acute phase[73].

Lung ultrasound seems a clinically useful tool to assess pulmonary compromise. Chest imaging and CT scan are considered safe in pregnant women. Multiple bilateral lobular and subsegmental areas of ground-glass opacity or consolidation are found in most patients, usually with a peripheral or posterior distribution, mainly in the lower lobes. Crazy paving, air bronchograms, reversed halo sign and perilobular pattern, all patterns of organizing pneumonia, may also appear[8]. Abnormalities can rapidly evolve from focal unilateral to diffuse bilateral ground-glass opacities that progress to or co-exist with consolidations within 1 to 3 weeks.

Treatment for severe COVID-19 includes admission to critical care, prone position, appropriate monitoring and supportive therapies such as oxygen and airway management, fluids, prevention of complications (acute respiratory distress syndrome (ARDS), sepsis, and septic shock), antimicrobials within 1 hour of initial patient assessment for suspected sepsis, and management following institutional guidelines of fever (consider paracetamol), cough and breathlessness, anxiety, delirium, and agitation. Consider intubation and mechanical ventilation in patients who are acutely deteriorating. Pregnant women may benefit from lying in the lateral decubitus position[8]. Nitric oxide at 160–200 ppm might be beneficial for pregnant patients with COVID-19 with hypoxic respiratory failure[74].

Administration of systemic corticosteroids, compared with usual care or placebo, was associated with lower 28-day all-cause mortality in critically ill patients with COVID-19[75].

Choice of delivery and timing should be individualized based on gestational age and maternal, fetal and delivery conditions. Induction of labor and vaginal delivery is preferred in pregnant women with confirmed COVID-19 infection to avoid unnecessary surgical complications; however, emergency cesarean delivery may be required if medically justified (e.g., maternal sepsis or fetal distress). If possible, a negative pressure isolation room is recommended for labor, delivery and neonatal care in confirmed cases[52].

Following delivery, families should be provided with guidance about how to identify signs of illness in their newborn or worsening of the woman's symptoms, as well as with appropriate contact details if they have concerns or questions about their baby's wellbeing. All families are recommended to self-isolate at home for 14 days after birth of a baby to a woman with active COVID-19 infection[52].

Planning delivery in patients with COVID-19

The New England Journal of Medicine (NEJM) has published the following suggestion from Columbia University Irving Medical Center, after their experience with pregnant women hospitalized for delivery in this pandemic: use universal SARS-CoV-2 testing in all pregnant patients presenting for delivery because most patients positive for SARS-CoV-2 at delivery were asymptomatic, and over one in eight asymptomatic patients admitted to the labor and delivery unit were positive for the virus. This would help to determine hospital isolation practices and bed assignments, inform neonatal care, and guide the use of personal protective equipment[76]. In Peru, all pregnant women who are hospitalized or come for delivery are tested with rapid tests in order to adopt necessary measures for the attending personal. In women 24 weeks pregnant or more, fetal wellbeing is established and the patient remains in observation awaiting the diagnostic test results. Ultrasound examination and cardiotocography are performed according to weeks of pregnancy[24].

When a pregnant patient with suspected or confirmed COVID-19 is admitted and birth is anticipated, the obstetrician, midwife-in-charge, neonatologist, neonatal nurse, pediatric or family medicine and anesthesia teams should be notified in order to facilitate care and the use of personal protective equipment (PPE). For women with suspected or confirmed COVID-19 in the third trimester who have recovered, it is reasonable to attempt to postpone delivery (if no other medical indications arise) until a negative test result is obtained or quarantine status is lifted, in an attempt to avoid transmission to the neonate[77]. Many hospitals are banning partners from births during the pandemic. Efforts should be made to minimize the number of staff members entering the room and units.

Inductions of labor and cesarean deliveries should continue to be performed as indicated. Due to the possibility of fetal compromise, continuous electronic fetal monitoring in labor is currently recommended for all women with COVID-19[52]. Fever should be investigated and treated accordingly[52].

Delivery in patients with COVID-19

Mode of birth should be discussed with the pregnant woman, considering gestational age, her preferences and medical, obstetric or pediatric indications for intervention. This decision should not be influenced by the presence of COVID-19, unless the woman's respiratory condition demands urgent intervention for birth[24,52]. It is suggested to attend vaginal deliveries in the patient's conditioned room or in a special delivery room for COVID-19 infected people.

Management of labor is not altered in women giving birth during the COVID-19 pandemic or in women with confirmed or suspected COVID-19. Labor, and particularly pushing, often causes loss of feces, where the virus can be present, thus spreading the infection[78].

Elective instrumental birth may be considered in a symptomatic woman who is becoming exhausted or hypoxic[52]. Cesarean delivery should be based on obstetric (fetal or maternal) indications and not on COVID-19 status alone. Epidural analgesia may be recommended in labor to women with suspected or confirmed COVID-19, to minimize the need for general anesthesia if urgent intervention for birth is required.

Current evidence-based guidelines for delayed cord clamping should continue to be followed. If an adequate mother-child isolation is warranted, skin to skin contact after birth could be possible[24].

Pregnant women with severe illness should be monitored with pulse oximetry, arterial blood gas analysis, full blood count, comprehensive metabolic panel, coagulation screen, inflammatory markers (serum procalcitonin and C-reactive protein), serum troponin, serum lactate dehydrogenase and serum creatine kinase. These patients can present leukopenia, lymphopenia, leukocytosis, elevated liver transaminases, elevated lactate dehydrogenase and elevated C-reactive protein, neutrophilia, thrombocytopenia, decreased hemoglobin, decreased albumin, renal impairment, and low oxygen saturation[8].

Emerging evidence suggests that individuals with COVID-19 admitted to a hospital are in a hypercoagulable state; since there is an increased risk of maternal venous thromboembolism (VTE), women should be assessed for this condition after birth[52]. For women receiving postpartum anticoagulation, the optimum duration of therapy is unclear. Some recommend discontinuing prophylaxis upon discharge, and others, to continue prophylaxis for 10 to 14 days. Patients at high risk of VTE receive a longer course, depending on the indication for prophylaxis[79].

The fetus

An increase in the stillbirth rate during the pandemic has been noticed, also in Peru. A direct link with SARS-CoV-2 infection is possible. Although none of the stillbirths in the pandemic period were among women with COVID-19, surveillance studies in pregnant women reported that as much as 90% of SARS-CoV-2–positive cases were asymptomatic. The increase in stillbirths may be a result of indirect effects, such as reluctance to go to the hospital when needed for fear of contracting COVID-19 or reduced antenatal visits, ultrasound scans and referrals. Hypertension in pregnancy may have been underdiagnosed during the pandemic since women had fewer face to face antenatal visits[80].

It is suggested that the virus can be passed to fetuses and newborns. In Italy, genetic material of SARS-CoV-2 has been found in samples of umbilical cord blood, placenta, and, in one case, breast milk. Researchers also found specific anti-coronavirus antibodies in umbilical cord blood and in mother's milk. No current data suggest a higher risk of miscarriage or early pregnancy loss in relation to COVID-19, nor that the virus is teratogenic[52]. Some case reports of preterm birth in women with COVID-19 may be due to a medical indication. However, other studies propose that the most remarkable effect of COVID-19 infection in the third trimester would be preterm delivery[64]. To date, there is no conclusive evidence of vertical transmission of COVID-19[77]; nevertheless, it is probable[52]. Causes for transplacental transmission of SARS-CoV-2 in a neonate born to an infected mother would

be:[1] maternal viremia,[2] placental infection, placental inflammation, and[3] neonatal viremia much higher in placental tissue than in amniotic fluid and maternal or neonatal blood[81,82].

A possible explanation would be that the placental membranes that contain the fetus and amniotic fluid lack the messenger RNA (mRNA) molecule required to manufacture the ACE2 receptor, the main cell surface receptor used by SARS-CoV-2 to cause infection. Placental tissues also lack the mRNA needed to create the TMPRSS2 enzyme, which the virus needs to enter a cell[83].

The newborn

Rates of SARS-CoV-2 infection in neonates do not appear to be affected by mode of delivery, method of infant feeding, or contact with a mother with suspected or confirmed SARS-CoV-2 infection. Current recommendations regarding the neonate include delayed cord clamping -more than one minute- and immediate skin-to-skin care. The risk of a neonate acquiring SARS-CoV-2 from the mother is low. Transmission of SARS-CoV-2 to neonates is thought to occur primarily through respiratory droplets during the postnatal period when neonates are exposed to mothers or other caregivers infected with SARS-CoV-2. This is why the use of masks by the mother is so important. Limited reports in the literature have raised concern of possible intrauterine, intrapartum, or peripartum transmission, but the extent and clinical significance of vertical transmission, which appears to be rare, remains unclear[84].

SARS-CoV-2 infections in neonates are uncommon. Reported signs among neonates with COVID-19 include fever, lethargy, rhinorrhea, cough, tachypnea, increased work of breathing, vomiting, diarrhea, and poor feeding. If neonates do become infected, the majority have either asymptomatic infections or mild symptoms. Severe illness in neonates, including illness requiring mechanical ventilation, appears to be rare. Neonates with underlying medical conditions and preterm infants (<37 weeks gestational age) may be at higher risk of severe illness from COVID-19. Testing and isolating is recommended for all neonates born to mothers with suspected or confirmed COVID-19. Isolating infants in a neonatal intensive care unit (NICU) should be avoided unless the neonate's clinical condition warrants NICU admission[84].

The WHO recommends that mothers and infants should remain together when possible, and breastfeeding should be encouraged while applying appropriate infection prevention and control measures (e.g., hand hygiene before and after contact with the baby, wearing a mask while breastfeeding). A newborn with documented infection requires close outpatient follow-up after discharge[8].

Breastfeeding

Allowing neonates to room in with their mothers and direct breastfeeding are safe procedures when paired with effective parental education of infant protective strategies[85].

Breast milk is an unlikely source of transmission of SARS-CoV-2 from mothers to infants[86].

The majority of the data has not demonstrated presence of SARS-CoV-2 in breastmilk. Therefore, suspected or confirmed maternal COVID-19 is not considered a contraindication to infant feeding with breastmilk at this time[77]. There are rare exceptions when breastfeeding or feeding expressed breast milk are not recommended. The mother, in coordination with her family and health care practitioners, should make the decisions about starting or continuing breastfeeding and how to do so. Currently, the primary concern is not whether the virus can be transmitted through breast milk, but rather whether an infected mother can transmit the virus through respiratory droplets during breastfeeding.

A mother with confirmed COVID-19 or who is a symptomatic patient under investigation should take all possible precautions to avoid spreading the virus to her infant, including washing her hands before touching them and wearing a face mask while breastfeeding. If expressing breast milk with a manual or electric breast pump, the mother should wash her hands before touching any pump or bottle parts and follow recommendations for proper pump cleaning after every use. If possible, consider having someone without disease feed the expressed breast milk to the infant[67].

Kangaroo mother care must follow all safety protocols for COVID-19. Provide oral colostrum care to all hospitalized newborns and limit feeding with breast-milk substitutes unless medically justified[87].

Contraception

Considering all the new knowledge about COVID-19 and its repercussion on mother and infant, future parents should discuss postponing pregnancy in some geographic areas until there is treatment and/or a vaccine to protect people from SARS-CoV-2. However, the supply, provision, use, and supervision-guidance of contraception has decreased in the Americas.

The novel coronavirus, SARS-CoV-2, has proven unusual regarding the spectrum of its pathological effects. In addition to damage inflicted on the lungs, kidneys, heart and other organ systems, there are reports of hypercoagulable states in patients hospitalized with COVID-19[88]. Conversations between clinicians and basic researchers and between endocrinologists and hematologists should be nurtured to explore potential interactions between SARS-CoV-2 and pregnancy or estrogen therapy that could guide clinical management[89].

The immediate future

Researchers modelled how COVID-19 is unfolding in 86 countries and found that official figures significantly understate infections and deaths so far. Epidemiologists, in cooperation with health officials, have estimated that, in some communities, for every confirmed case, there are five to ten people with undetected infection, and at least one estimate suggests there are far more. In Peru, by September 4 there were officially 29 405 deaths; however, when compared to the number of deaths registered in 2019, there would be almost two thirds more deaths attributable to COVID-19 that had not been counted yet. Projections to March 2021 are that these 86 countries will have experienced nearly 300 million infections and over 2 million deaths. By mid-September, over 30,3 million infections had occurred globally-15 million in America-, with 2 million additional cases each week, according to data from Johns Hopkins University. World deaths approach 1 million losses, with the addition of 40 to 50 thousand each week. Peru is the fifth country with the highest numbers of COVID-19 infected persons, with more than 750 000 cases and more than 31 000 deaths (fatality rate is 4.1%). Peru is also first regarding deaths per million inhabitants[90]. Currently, there is a re-emergence of COVID-19 in Europe, which raises concern regarding a new home confinement in times of a global economic and labor crisis.

It is estimated that 55 to 80% of a population must be immune through infections or a vaccine to end the pandemic. Estimates indicate that only a small proportion of people have been infected. According to the CDC of the United States, antibody prevalence ranged from 1% to 6,9%[91]. In Lima, Peru, 1 of every 4 persons would have been infected with COVID-19[92].

Little is known about the nature and duration of the humoral immune response to infection with SARS-CoV-2. Antibodies against SARS-CoV-2 do not appear to decline 4 months after diagnosis. Additional observations confirmed elevated antibody levels in older adults and in persons who were hospitalized. Conversely, antibody levels were lower in smokers and in women who had milder forms of disease[93].

If immunity to the virus lasts less than a year, for example, as is the case of other human coronaviruses, there could be annual surges in COVID-19 through to 2025 and beyond. The protective role of antibodies against SARS-CoV-2 is unknown. Early antibody decay after acute viral antigenic exposure is quasi exponential, and studies have found that antibody loss is quicker than that reported for SARS-CoV-1[94].

There is information of two SARS-CoV-2 infections in one same individual. Through nucleic acid sequence analysis, the viruses associated with each infection were found to possess a degree of genetic discordance that cannot be explained reasonably through short-term in vivo evolution. Thus, it is possible for humans to become infected multiple times by SARS-CoV-2, but the generalizability of this finding is not known[95]. Another case in Nevada, USA, happened just 3 months after the first infection, and it was more severe. The cases suggest that a vaccine may need to be reapplied periodically[96].

We hope we will have antiviral treatment and a vaccine within this or next year. There is great expectation regarding the safety and outcomes of remdesivir as an antiviral drug therapy in severe disease. A 5-day course of remdesivir was associated with a small, but significant, clinical improvement compared with standard care in patients with moderate COVID-19[97]. Convales-

cent plasma therapy (passive immunotherapy) has been reported to reduce deaths (OR 0.43) when administered within 3 days of infection or 72 hours of admission and monoclonal antibodies[98]. Besides, the National Institutes of Health of the United States recently recommended the corticosteroid dexamethasone for people with severe COVID-19 who require oxygen or mechanical ventilation[34].

Ongoing clinical trials and investigations still have many unanswered questions about the virus and its behavior. In many countries, severe disease and deaths have decreased; in others, it seems to have returned with certain aggressiveness. In America and some developing countries, the COVID-19 curve is not flattening or is erratic. Epidemiologists expect resurgent waves of infection that could last into 2022.

In Italy, a large proportion of patients with COVID-19 presented with symptoms (71.4% of 31 845 confirmed cases as of June 3, 2020). A study found that, in patients who had recovered from COVID-19, 87.4% reported persistence of at least 1 symptom, particularly fatigue and dyspnea[99].

While cognitive, physical, psychological, and medical impairments are common after sepsis, clinical presentation varies considerably and may not be limited to those who experience critical illness. Some patients develop predominantly cognitive symptoms (memory deficits, difficulty concentrating), whereas others experience predominantly physical limitations (exercise intolerance, fatigue, dysphagia) or psychological sequelae (anxiety, depression, nightmares). A study of 143 COVID-19 survivors found that nearly 90% were experiencing persistent symptoms (the most common were fatigue, dyspnea and joint pain) 2 months after onset of COVID-19[100].

Mental stress and mental disorders in people have more than doubled. Prevalence of depression symptoms in the US was more than 3 times higher during COVID-19 than before the COVID-19 pandemic[101]. Younger adults, racial/ethnic minorities, essential workers, and unpaid adult caregivers reported having experienced disproportionately worse mental health outcomes, increased substance use, and elevated suicidal ideation[102]. Clinicians are finding that COVID-19 patients suffer of telogen effluvium weeks after recovering from the infection; this hair loss may follow infections, medications, high fever, prolonged hospitalization, metabolic or physiologic stress. Hospitals must prepare for a wave of mental health disorders including anxiety, depression or post-traumatic stress, confusion, and anger among their workers.

Regarding vaccines, on January 10, Chinese researchers posted the novel coronavirus' RNA sequence on a preprint server. Immediately, scientists who study genetic vaccines turned their efforts to the emerging pathogen that causes COVID-19. On July 27, based on encouraging early results, mRNA-1273 and another mRNA vaccine candidate, BNT162b2, from BioNTech and Pfizer, both entered phase 3 trials. Current antiviral vaccine designs can be described as falling into 2 groups: protein based or gene based. Protein-based vaccines deliver an immune system–stimulating antigen to the body, and include whole-inactivated (killed) vaccines, as in polio and flu shots, as well as subunit vaccines and virus-like particles. Gene-based vaccines carry the genetic instructions for the host's cells to make the antigen, which mimics a natural infection. In newer gene-based designs—viral vector, DNA, and mRNA vaccines—, scientists synthesize and insert genetic instructions from the pathogen of interest to induce immune responses; these vaccines are chemicals catalyzed in a test tube or a tank. However, genetic approaches have a potential immunological advantage. In addition to eliciting antibodies and CD4+ helper T cells, they recruit CD8+ cytotoxic T cells, also known as killer T cells, through the major histocompatibility class I pathway[103]. As of September 20, thirty five potential vaccines against COVID-19 were in clinical trials: nineteen in phase 1, twelve in phase 2, eight in phase 3 and two approved in Russia[44], with another 145 in preclinical development, including both gene- and protein-based candidates[104].

In an April 2020 survey of approximately 1 000 adults representative of the U.S. population, it was found that only about 6 in every 10 respondents said "yes" when asked whether they will get vaccinated when a vaccine for coronavirus becomes available[105].

Latin America has registered 2 479 doctors who died from COVID-19. This figure is led by Mexico, whose number of deceased physicians is 1 410,

followed by Brazil, with 238, and Peru, which ranks third with 166 white-coat heroes deceased due to coronavirus[106].

The current recommendation is that the first group to receive a vaccine should be high risk workers in healthcare facilities and first responders, because they are at significantly higher risk of contracting severe COVID-19, as well as older adults living in long-term care facilities or overcrowded settings. The groups that should be prioritized next would be workers in industries, teachers and school staff, older adults, people in homeless shelters or group homes and those in prisons, as well as staff who work there. In the third phase, the vaccine would be provided to young adults and children, as well as workers at increased risk of exposure not included in previous phases. Lastly, the fourth phase would include everyone else, which should happen no later than 12 to 18 months after the initial roll-out[107].

The World Health Organization and its appointed Strategic Advisory Group of Experts on Immunization, or SAGE, have released a worldwide vaccine distribution plan. "The first priority must be to vaccinate some people in all the countries, rather than all the people in some countries," WHO Director-General Dr. Tedros Adhanom Ghebreyesus said. "Vaccine nationalism will prolong the pandemic, not shorten it."[108].

Finally, the recommendations endorsed by the CDC for people going out remain the same[109]:

- Wear a cloth face covering when doing any in-person exchanges.
- Wash your hands for at least 20 seconds.
- Interacting with more people increases your risk of contagion.
- The closer you are to other people who may be infected, the greater your risk of getting sick.
- Spending more time with people who may be infected increases your risk of becoming infected.

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