



COVID-19 in pregnancy: Italian experience

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Abstract

It has been happened a significant increase of critically severe pneumonia cases in northern Italy by the end of February 2020 with consequent overcrowding of intensive care units (ICU). Due to the COVID-19 fast outbreak, a strict quarantine was imposed in the areas with the higher number of affected cases. The WHO declared COVID-19 a pandemic, with over 50 countries on the 10th of March. By the 10th of March Italy was the second most affected country after China, with more than nine thousand confirmed cases and more than 460 deaths, becoming the most affected in April.

Keywords: Coronavirus SARS-2, pregnancy, outcome.

Özet: Gebelikte COVID-19: İtalyan deneyimi

Şubat 2020 sonu itibarıyla kuzey İtalya'da, kritik derecede şiddetli pnömöni olgularında önemli bir artış gerçekleşti ve bunun sonucunda yoğun bakım ünitelerinde (YBÜ) aşırı yoğunluk meydana geldi. Hızlı COVID-19 salgını nedeniyle, hastalıktan etkilenen yüksek sayıda olgunun olduğu bölgelerde katı bir karantina uygulandı. Dünya Sağlık Örgütü, 10 Mart'ta 50'den fazla ülkede COVID-19'u küresel salgın olarak ilan etti. 10 Mart itibarıyla İtalya, teyit edilmiş dokuz binden fazla olgu ve 460'ın üzerinde ölüm ile Çin'den sonra en çok etkilenen ikinci ülkeyken, Nisan ayında en çok etkilenen ülke oldu.

Anahtar sözcükler: Koronavirüs SARS-2, gebelik, sonuç.

The current coronavirus disease (COVID-19) is a new systemic inflammatory disease caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), identified for the first time in December 2019, in Wuhan, China.^[1,2] This virus quickly spread across the rest of the country and progressively outside, such to be declared as a Public Health Emergency of International Concern (PHEIC) by the Pan American Health Organization / World Health Organization (PAHO/WHO) on the 30th of January.

By the end of February 2020, the virus spread in northern Italy (mainly Lombardy, Veneto and Emilia-Romagna), leading to a significant increase of critically severe pneumonia cases in these areas, with consequent overcrowding of intensive care units (ICU). As the number of deaths rapidly increased, due to the COVID-19 fast outbreak, a strict quarantine was imposed in the areas with the higher number of affect-

ed cases, in order to minimize the chance of contagion. From the 9th of March 2020, quarantine was extended to the whole country, with inhibition of travels within and between regions, and a complete lockdown of schools, industries and productive activities with the exception of hospitals and other essential activities (food shops, pharmacies, etc.). Meanwhile, on the 10th of March the WHO declared COVID-19 a pandemic, with over 50 countries involved. Despite these preventive measures, contagion curve exponentially increased in Italy, and within few days a total lockdown was imposed. By the 10th of March Italy was the second most affected country after China, with more than 9 thousand confirmed cases and more than 460 deaths, becoming the most affected in April.^[3]

SARS-CoV-2 is transmitted predominantly via respiratory droplets, contact and fecal-oral routes.^[4] It has been reported that coronavirus cell invasion is mediat-

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ed by specific receptor-binding virus domains interacting with the angiotensin-converting enzyme 2 (ACE2) receptor. ACE2 receptor is usually expressed in upper and lower respiratory epithelium, but it may be also found in the heart, esophagus, kidney, stomach, bladder and ileum. Once invasion has occurred, viral replication leads to a mild viremia, with generally mild flu-like symptoms and diffusion of the virus (stage I). A subsequent involvement of the lung often occurs, in the stage II or pulmonary phase of the illness, with the development of a viral pneumonia, and cough, fever and progressive hypoxia as main symptoms.^[5] The viral response progressively reduces, whereas the host inflammatory response increases, leading in a minority of patients to the stage III or hyperinflammation phase, with a progression of the pneumonia to acute respiratory syndrome, and systemic hyperinflammation syndrome, involving also extra-pulmonary tissues.^[5] In this phase, septic shock, cardiac and multiorgan failure may also occur in the worst cases. The biological mechanism leading to a disease state includes direct endothelial and vascular damage with subsequent exuberant local and systemic inflammatory response mediated by cytokines and chemokines. Complement activation and angiotensin subtypes seem to be also involved, leading to hypercoagulability and microangiopathy.^[6] Even a possible underlying mechanism of antibody-dependent enhancement promoting an increase of inflammatory responses and persistent viral replication was proposed. Moreover, immune dysfunction with overactivation and reduction of T cells contribute to pathogenesis.^[4,7] Nasopharyngeal swabs detect the presence of the virus in only 80% of affected patients, whereas high resolution computed tomography seems more accurate in detecting the pulmonary involvement, showing a ground-glass opacity, commonly related to COVID-19.^[8] Moreover, lymphopenia appears to be a common finding in the earlier stages of the disease, whereas elevated inflammatory markers (C-reactive protein and pro-inflammatory cytokines, ferritin) may be found later.

Treatment of COVID-19 patients has been subject of controversies.^[9] The main therapies proposed include anti-viral drugs such as remdesivir, antibiotics such as azithromycin, immunosuppressive drugs such as tocilizumab, chloroquine/hydroxychloroquine, corticosteroids, and more recently also plasma from con-

valescent patients.^[9,10] However, their efficacy against the novel coronavirus has not been definitively proven yet and treatment should be tailored to the patient's characteristics and disease stage. In particular, LMW heparin has been quite often used for its anticoagulant as well as immunomodulatory properties.

Recent evidences demonstrate that mean incubation period is 3–5 days, ranging from 0 to 24 days, but the first symptoms usually appear within 14 days after exposure.^[11] During this incubation period, the virus usually replicates in the upper airways, with the chance of transmission also for asymptomatic.^[10,12] Therefore, Italian health authorities recommended a 14-days quarantine in case of close contact with affected people, and after the end of symptoms for ascertained or suspected COVID-19. After quarantine, a nasopharyngeal swab is recommended to ensure a negative result.

In pregnant women, COVID-19 early symptoms are similar to those described in general population, with fever and cough occurring in the majority of cases. In a systematic review for pregnant patients, authors described an incidence of 48% and 46%, respectively. Less frequent symptoms included sore throat, fatigue, myalgia, diarrhea. However, the majority of infected cases (69%) are asymptomatic.^[13] When the viral pneumonia occurs, the pregnant patient usually develops severe hyperpyrexia, cough and dyspnea, similarly to what occurs in the general population.^[13,14] Nonetheless, the proportion of asymptomatic pregnant patients infected by SARS-CoV-2 has not been definitely assessed. Although pregnant women seem more likely to develop severe illness after respiratory viruses' infection due to the pregnancy-related changes of their immune and cardiopulmonary systems,^[15] in case of COVID-19 current evidences show that the course of the disease is not so severe as we could expect, with a very low mortality rate.^[16,17] Moreover, the incidence of infection in pregnant women seems to be lower than in general population. Various explanation had been given, related to the lower mean age of pregnant women^[18] and the shift of immune response from T1 to T2.^[19–21] Data about the impact of COVID-19 on the fetus are still scarce due to the fact that most infected women included in literature were at higher gestational age and no clear evidence of placental transmission has been yet demonstrated. On the contrary, similar infections (Middle East Respiratory syn-

drome or MERS and Severe Acute Respiratory Syndrome or SARS) have shown increased fetal morbidity and mortality.^[22] Recent retrospective studies have shown higher incidence of premature birth in COVID-19 pregnant patients, even if mainly iatrogenic, as the option of an anticipated delivery is often considered when maternal conditions worsen.^[13,14,23]

Treatments proposed for COVID-19 are not contraindicated in pregnancy. However, the option of an anticipated delivery in case of disease seems the most challenging decision for the obstetrician, as mentioned. The timing of delivery should take in account both the gestational age and the actual clinical condition of the mother. In case of severe disease in advanced gestational ages, immediate delivery could improve maternal breathing and avoid the risk of hypoxia for the fetus, with low risks of prematurity complications. At earlier gestational ages the risk of prematurity is higher, and the option of delivery should be carefully considered. The mode of delivery most frequently reported is the caesarean one,^[13] even if national^[24] and international societies support vaginal delivery.^[15,25] The transmission during vaginal delivery has not been clearly demonstrated and the virus has not yet been detected in vaginal swabs. A post-partum contact may be an underlying cause of the few reported cases of neonatal infection.^[14] Moreover, breastmilk seems not to be involved in virus as the virus has not been detected in the milk. Although breastfeeding is strongly suggested, care must be taken in order to prevent direct contact with the infected mother who should wear a surgical mask during the feeding. In severe cases, breast milk pumping should be considered.^[14,15]

In northern Italy, the sudden diffusion of the virus required a quick redistribution of the health system resources. In particular, new recommendations for obstetric vigilance and management were provided at local and regional levels, aiming to keep good standards of care and safety for pregnant women.^[18] According to the most used strategy, the centralization of pregnant patients and specialized healthcare personnel was provided in tertiary centers or “hub” hospitals, whereas smaller hospitals became exclusively dedicated to COVID-19 patients. Centralization was supported by the availability of better equipment and multidisciplinary experience in tertiary centers, with greater safe-

ty for operators and patients. Although this policy was generally accepted, there have been criticisms about the centralization of cases in “hub” hospitals which were overcrowded and not prepared to the elevated number of patients. Moreover, many caregivers pointed out several pitfalls in the network of local health services and complained about the lack of clear instructions and low availability of personal protective equipment (PPE), especially during the early stages of the emergency in Italy. This has probably been one of the reasons of the very high mortality rate due to COVID-19 in Lombardy, and justifies the important debate about the policy undertaken by the regional health institutions.

Due to this reorganization, “hub” hospitals modified their clinical activity according to the new COVID-19 emergency, providing only activities which could not be postponed (oncological activities, urgent surgeries, etc.), whereas gynecological screenings, benign surgery and assisted reproductive technology were suspended. Non-urgent pregnancy visits, routine ultrasound scans and invasive testing have been postponed for patients infected by CoV-2. Workflow was reprogrammed to reduce as much as possible the risk of virus diffusion between patients and health workers, and among patients. This was accomplished through the reorganization of appointments, with a longer time allowed for each visit in order to avoid patients’ grouping in waiting rooms.

A dedicated COVID-19 triage area is recommended, based on symptoms (fever, cough, dyspnea, etc.) and other risk factors (travel, occupation, contacts and cluster), in order to perform a nasopharyngeal swab to high-risk cases, keeping separated paths and areas for COVID-19 patients. For those with suspected or diagnosed COVID-19, the definition of designated isolation areas is recommended, including dedicated waiting areas, beds, delivery room and operating theatre. Moreover, PPE was distributed and adopted if necessary, after adequate training about its use and removal.

In conclusion, the COVID-19 emergency caused an exponentially increasing number of deaths in Italy during the first weeks of coronavirus pandemic. This can be probably related to the quick spread of the virus among northern Italy population, due to the long incubation period and the high transmission rate of the novel coronavirus. Moreover, the elevated number of

infected people needing hospitalization was not expected, with the health system unable to promptly react to this emergency. This led to a quick overcrowding of the ICUs and consequently to the difficulty to treat critical patients in an optimal way. The ongoing controversies on drugs potentially useful for COVID-19 furtherly worsened the scenario and the number of deaths, finally reduced only after introducing the strict lockdown, a preventive rather than treating strategy. In pregnant women, the disease seems less severe than previous coronavirus-related syndromes, but few critical issues need to be furtherly clarified.

Conflicts of Interest: No conflicts declared.

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