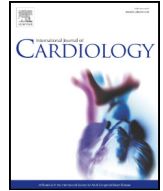




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Women's perspective on the COVID-19 pandemic: Walking into a post-peak phase

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ABSTRACT

The pandemic of *Novel Coronavirus Disease 2019* (COVID-19), caused by *severe acute respiratory syndrome coronavirus 2* (SARS-CoV-2), has provoked hundreds of thousands of deaths, resulting in catastrophe for humans.

Although some insights have been garnered in studies on women, children and young adults infected with COVID-19, these often remain fragmented in literature.

Therefore, we discussed the impact of COVID-19 pandemic on women, children and young patients, particularly those with underlying cardiovascular comorbidities or congenital heart disease. Furthermore, we gathered and distilled the existing body of literature that describes their cardiovascular complications and the recommended actions in favour of those patients toward the post-peak pandemic period.

Although many questions still require answers, this article is sought to help the practicing clinician in the understanding and management of the threatening disease in special populations.

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1. Introduction

The *Novel Coronavirus Disease 2019* (COVID-19) pandemic and its related morbidity and mortality are nowadays a main public health concern [1,2].

This article focuses on the impact of COVID-19 pandemic on women, children and young adults (Fig. 1).

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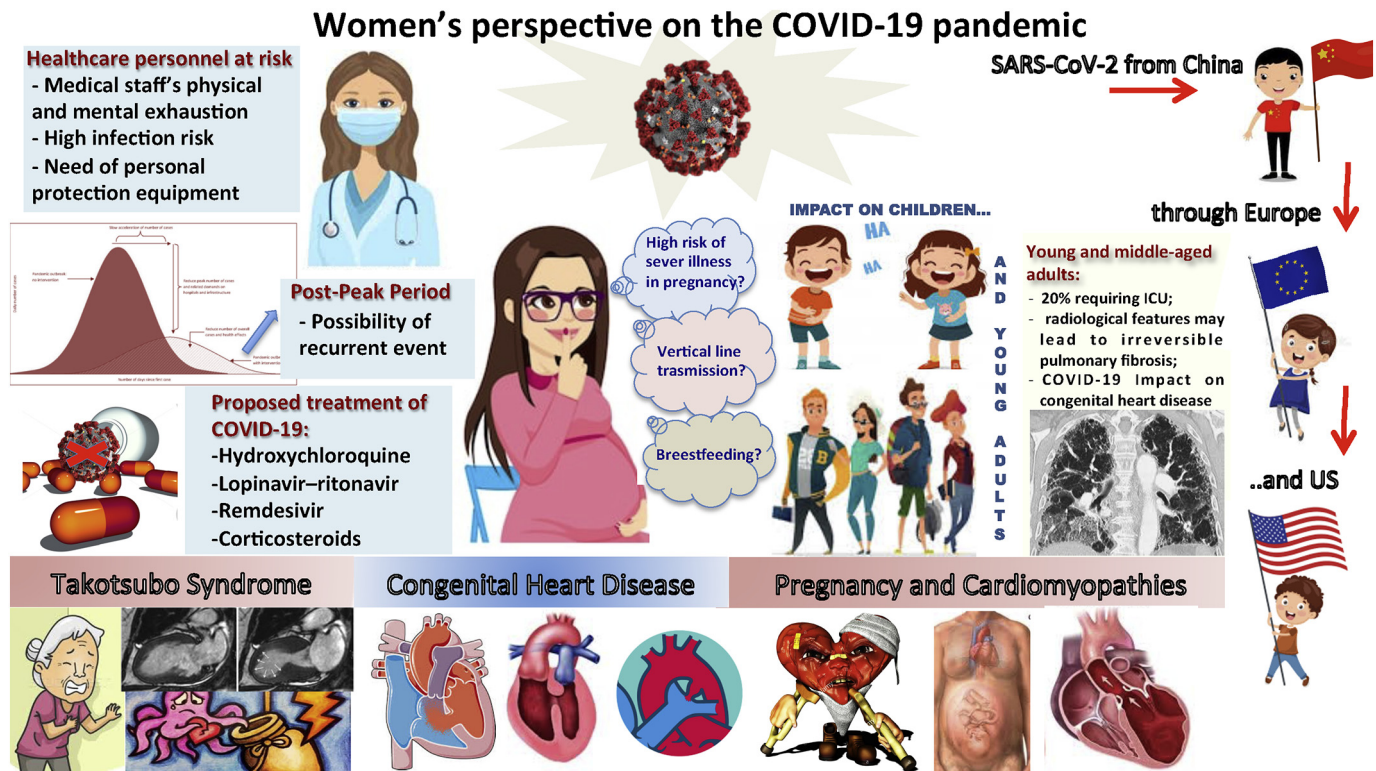


Fig. 1. Illustrates the impact of COVID-19 pandemic on a multidisciplinary perspective. CV = cardiovascular; COVID-19 = Novel Coronavirus Disease 2019.

2. The sex differences in COVID-19

By reviewing records worldwide at this point of the pandemic, even though sex ratio of COVID-19-infected individuals varies among cities [Table 1], men appear to have disproportionately higher mortality rates [2–5] [Table 1]. Adverse outcomes of COVID-19 seem to be associated with comorbidities [2] and behaviours (cardiovascular and lung diseases, smoking, alcohol abuse) that are more prevalent in men.

However, some anecdotal cases of Takotsubo syndrome caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been described in women [6–8]. Takotsubo syndrome in COVID-19 patients might well be related to stress-induced adrenergic burst secondary to fever and the inflammatory response to infection. A direct injury by SARS-CoV-2 causing microvascular vasoconstriction with consequent transient left ventricular apical dysfunction might also be an option [6–8].

Table 1
Number of cases and deaths according to gender worldwide [4–5].

Nation	Number of cases	Number of deaths	Females	Female Deaths
China	83157	3342	48.90%	36.23%
Italy	238050	33209	54.21%	41.75%
Spain	248335	20527	57.01%	43.43%
Germany	190431	8880	51.85%	44.62%
Australia	7613	102	48.59%	44.12%
Afghanistan	25987	423	27.48%	20.57%
Canada	101276	8412	56.22%	54.35%
Colombia	40719	1308	44.78%	38.76%
England	228742	37664	56.98%	42.87%
Indonesia	47896	2535	47.30%	39.40%
Peru	257447	8223	41.80%	29.16%
Pakistan	185034	3695	25.90%	28.61%
South Africa	105308	2100	57.10%	48.24%
Mexico	185122	22584	44.97%	33.91%

Data are presented as number or %.

However, women might be exposed to a completely different burden during COVID-19 pandemic. There is a growing concern over a surge in domestic violence. Also, women's sexual and reproductive health services have been temporarily disrupted on a large scale during the acceleration phase of the pandemic, in order to limit the virus contagion and to overcome the healthcare system overstressing.

At the peak of pandemic, worldwide spread of COVID-19 with rapid increase of infected cases has pushed the healthcare system to a breaking point [2]. Among the healthcare personnel many are women and, being at the front line in contact with patients, have been unwillingly in infection reservoirs [2]. Several reports described medical staff's physical and mental exhaustion, being tormented of difficult triage resolutions, the pain of losing patients and colleagues and the high risk of being infected themselves [9].

Although the so far evidence suggests that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is likely to have a lower fatality rate in women, the course of the disease during pregnancy is not fully understood. With the lack of solid data we cannot exclude that the unique 'immunological' condition caused by pregnancy may increase susceptibility to infection and to a more severe COVID-19 course [10]. Based on available information, however, women infected with SARS-CoV-2 during pregnancy generally had mild symptoms and seem to have the same risk as women who are not pregnant with good outcome for both mother and newborn [8–10]. Notwithstanding, to date reports have been investigating third trimester cases, while viral infections during pregnancy are usually more severe during the first 20 weeks [10–12].

Of note, sparse cardiomyopathy cases have been reported in pregnant women with COVID-19 infection [13]. However, in a cohort of 64 pregnant women with severe or critical COVID-19 at twelve U.S. institutions no cases of cardiomyopathy were observed [14]. Nevertheless, more research is needed to ascertain the incidence of cardiomyopathy from COVID-19 during pregnancy. Also, performing an echocardiogram in those with pneumonia or severe disease is highly encouraged.

The American Obstetrics and Gynaecology Association strongly suggests applying physical distancing for pregnant women during the COVID-19 outbreak [10,15,16].

Hospital visits should be restricted and modified according to a well-managed system [15,16] that provides pregnant women with maternal health care with minimal exposure risk. Use of telehealth across as many aspects of prenatal care should be maximized as possible. Women with suspected or diagnosed COVID-19 during pregnancy are needed to be isolated in a specific obstetric single-person room with door closed [17].

Currently, there is not enough evidence supporting viral vertical transmission and SARS-CoV-2 should not be a reason to avoid a natural delivery [17–19]. However, it is recommended to isolate from other healthy infants a newborn whose mother is infected with COVID-19. Also, facilities may be considered to temporarily separate patients who have confirmed COVID-19 from their newborns.

Studies published so far reported SARS-CoV-2 has not been detected in breast milk [17–19]. There are limited exceptions when breastfeeding is not recommended. At this point of the pandemic, the leading concern is not whether SARS-CoV-2 can be transmitted through breast milk, but rather whether an infected mother could transmit the virus through respiratory droplets while breastfeeding [17–19].

3. Epidemiology, clinical manifestation and management of children with COVID-19

Despite the initial belief that children might be exempt from COVID-19, a number of infected children have been confirmed worldwide [20].

It is estimated children represent 1–5% of all COVID-19 cases [21], but this percentage could be widely underrated because of children's milder clinical symptoms [20] and fewer diagnostic tests taken.

In most cases, viral transmission happens within the family environment [22]. Since children are largely oligosymptomatic, they may also represent a reservoir for the virus [23]. In line with World Health Organization (WHO) reports on general population [24], children incubation period ranges between 2 and 10 days [25]; all ages can be infected, but boys seem to be slightly more affected than girls [20].

In children/young adults and women, a higher expression of ACE2 has been postulated as the mechanism underlying the less severe course of the COVID-19-related lung disease. Indeed, in rat lungs a higher expression of ACE2 has been observed in younger females animals than in adult males [26].

Despite adult patients with cardiovascular co-morbidities have a worse course of the disease, and higher mortality rate, when we look at children infected by SARS-CoV-2 with concomitant congenital heart disease (CHD), they seem to have the same clinical trend and mortality of peers without CHD. It has been observed that parents may have a role in this phenomenon because of their overprotection [27], further reducing children exposure to the infection. There is also a certain trend among all cardiopathic patients to avoid medical care and hospitals in fear of being infected.

On the other side, with economical resources directed toward COVID-19 wards and services and the hospitals willingness of limiting infections, all non-urgent cases have been lost their priority and CHD clinics have been postponed, with potential negative implication on adherence to follow up and outcome of CHD patients [28].

In general, children experience mostly cough, pharyngeal erythema and fever (37.5–39 °C). Diarrhoea, vomiting, rhinorrhoea, fatigue and myalgia are other common features [21]. Severe disease, such as dyspnoea, cyanosis, oxygen desaturation <92%, and critical disease, including acute respiratory distress syndrome, shock and multi-organs failure, were reported in 5.2% and 0.6% of cases, respectively [20], with higher prevalence in children <1 year of age. Young patients usually recover in 1–2 weeks after the onset of symptoms [29]. However, sporadic cases need intensive care and/or have a fatal outcome, the latter primarily occurring in patients with underlying diseases [21]. Similarly to adult

patients, some cases of myocardial dysfunction have been described [30]. Lastly, an Italian study has recently reported ten cases of Kawasaki-like disease, raising new concerns about an association between COVID-19 and Kawasaki disease, but further studies are needed to confirm these data [31].

Laboratory abnormalities are less common than in adults; indeed, the white blood cell count is generally normal and values of C-reactive protein and procalcitonin are also often within limits [24]. Chest X-ray and thoracic CT scan are performed to confirm the diagnosis.

Treatment is largely supportive and includes bed-rest, adequate calories and fluid intake. In case of fever >38.5 °C, physical cooling or antipyretic drugs such as ibuprofen or acetaminophen should be prescribed and, in case of hypoxia, oxygen therapy should be given [32]. In children with more pronounced symptoms, Interferon alpha nebulization is the only antiviral drug clearly recommended [33]; it should be used carefully in patients younger than 2 months and it is contraindicated if creatinine clearance (CrCl) is <50 ml/min or in case of mental illness, severe heart disease, or aplastic anaemia. Lopinavir/Ritonavir (LPVr) is another choice; it can be used in patient >6 months (China) or >14 days (USA), but it is contraindicated in children with severe hepatic failure or jaundice [30]. Ribavirin is usually used as a combined drug; it can be used in children >3 years old (USA and Europe) or >6 years old (China), but it is not recommended if creatinine clearance is <50 ml/min and should be avoided in children with heart disease [33]. Finally, antibiotics, corticosteroids, mechanical ventilation, and other more invasive intervention, such as extracorporeal membrane oxygenation (ECMO) should be applied cautiously and reserved to the most severe and complicated cases [29].

All in all, even though in “phase one” the transmission of infection have been relatively contained in children, now that the “phase two” is starting parents are advised to not let their guard down, cleaning and sanitizing surfaces and common area and washing children's toys and objects. Children are urged to continue to wash frequently their hands and to keep distance from sick people.

4. Cardiovascular burden in young patients with COVID-19

Nearly 20–55% of hospitalized COVID-19 patients are young and middle aged, and up to 18.5% of them have severe course of the disease [34]. Despite their younger age, they have a similar degree of lung injury and inevitably similar long-term respiratory consequences compared to older patients [35]. As pulmonary fibrosis rates range 30–45% in COVID-19 patients, this might pose a major care burden [35].

The frequently asymptomatic course, the longer duration of viremia and the prolonged persistence in the gastrointestinal tract might increase the transmission rate from young adults [36].

It's widely known that patients with underlying cardiac disease are at higher risk to contract viral infection and to cope with adverse clinical outcome COVID-19-related [2]. So far, despite the efforts of adult congenital heart disease (ACHD) societies to investigate on ACHD patients with COVID-19 infection and to predict outcomes in ACHD population, this topic still represent a huge question mark needing further data and research exploration.

Only few cases of COVID-19 have been reported in literature among ACHD patients [37]. A 19-year old boy with tricuspid atresia and single ventricle physiology with Fontan palliation [38] presented mild respiratory symptoms, increased inflammatory markers and liver enzymes, while cardiac enzymes were within normal range. He was treated with hydroxychloroquine, diuretics, aspirin. After therapy with sildenafil, an improvement of clinical symptoms was noted [38].

Owing to a lack of consistent data, current pharmacological therapies in ACHD are derived from those used in COVID-19 adults with cardiovascular disease. Indeed, ACHD patients could be considered at high risk of complications related to COVID-19, on the basis of different underlying anatomic complex substrates [39]. Conversely,

they could take advantage from their relative younger age. Thus, it has been hypothesized a risk stratification of ACHD patients based on the different anatomic stages, determining a decreased functional reverse or a reduced immunity. However, no difference in medical treatment had been advocated for ACHD patients, but they should be followed in tertiary specialized centres with dedicated expertise [40]. In these tertiary hubs, telehealth visits and deferment of elective/diagnostic procedures should be instituted to minimize risk of COVID-19 exposure during the post-peak phase until the end of pandemic [40,41]. In some tertiary hubs, ACHD are enrolled to cardiac rehabilitation programs with telemonitoring, telesurveillance and telerehabilitation [42,43]. In this period, surgical schedule of ACHD patients must be reserved to the most urgent cases, considering lack of resources, clinical status of the patient, risk of exposure of the patients and his family members, comorbidities and complexity of the procedure [44]. ACHD patients should apply social distancing as well as other patients. However, these social measures may cause physical inactivity among young patients with CHD, which could lead to negative physical and mental consequences and lower quality of life [45].

5. Conclusion

While publication of new data is fast and we are gaining a better understanding of COVID-19, many questions still require answers. Focus should be kept on what we are missing: *pharmacological studies and vaccines*.

Declaration of Competing Interest

None.

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