



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

See Online for appendix



Published Online

March 3, 2020

[https://doi.org/10.1016/S1473-3099\(20\)30157-2](https://doi.org/10.1016/S1473-3099(20)30157-2)

heart; their presence has previously been demonstrated on atrial and ventricular tissue, but not on cardiac valves.² However, the surface of the valves is constituted by endocardium, which histologically is a type of epithelium.³ Systemic infections, such as endocarditis, lead to the release of proinflammatory cytokines, which in turn cause upregulation of μ -opioid receptors in cardiac endothelium—for example, on cardiac valves—and these receptors are then available to bind hydromorphone.⁴

As shown in an animal model of inflammation, hydromorphone is able to disrupt endothelial tight junctions via Toll-like receptor 2 and promote bacterial translocation.⁵ Bacteria—*S aureus* in particular—are then capable of colonising the cardiac valves and disrupting their structure. The tricuspid valve is the most commonly affected valve in injection-drug users because it is the first valve encountered by the inoculated staphylococcus when it enters the right side of the heart via the injected vein and the superior or inferior vena cava.⁶

Two of three essential factors for infective endocarditis are therefore realised: the presence of a favourable anatomical substrate and bacteraemia.⁶ The third factor relates to differences in immune systems. Immune system defences in injection-drug users are frequently lower than those of the general population, and are more likely to allow bacterial proliferation. Therefore, these factors come together to create an ideal environment for the development of infective endocarditis.

I declare no competing interests.

Pier P Bassareo
piercard@inwind.it

University College of Dublin, Mater Misericordiae University Hospital, Dublin D07 R2WY, Ireland; and Our Lady's Children's Hospital, Dublin, Ireland

1 Silverman M, Slater J, Jandoc R, Koivu S, Garg AX, Weir MA. Hydromorphone and the risk of infective endocarditis among people who inject drugs: a population-based, retrospective cohort study. *Lancet Infect Dis* 2020; **20**: 487–97.

- 2 Bell SP, Sack MN, Patel A, Opie LH, Yellon DM. Delta opioid receptor stimulation mimics ischemic preconditioning in human heart muscle. *J Am Coll Cardiol* 2000; **36**: 2296–302.
- 3 Misfeld M, Sievers HH. Heart valve macro- and microstructure. *Philos Trans R Soc Lond B Biol Sci* 2007; **362**: 1421–36.
- 4 Cadet P, Bilfinger TV, Fimiani C, Peter D, Stefano GB. Human vascular and cardiac endothelia express mu opiate receptor transcripts. *Endothelium* 2000; **7**: 185–91.
- 5 Khatri R, Sharma U, Roy S. Hydromorphone exposure exacerbates inflammatory bowel disease in a mouse model. *J Am Coll Surg* 2015; **221** (suppl 1): S30.
- 6 Calcaterra G, Crisafulli A, Guccione P, Di Salvo G, Bassareo PP. Infective endocarditis triangle. Is it the time to revisit infective endocarditis susceptibility and indications for its antibiotic prophylaxis? *Eur J Prev Cardiol* 2019; **26**: 1771–74.

Guidelines for pregnant women with suspected SARS-CoV-2 infection

Coronaviruses responsible for severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) can cause severe adverse pregnancy outcomes, such as miscarriage, premature delivery, intrauterine growth restriction, and maternal death.^{1,2} Vertical transmission of the virus responsible for 2019 novel coronavirus disease (COVID-19), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has not yet been detected, whereas perinatal transmission has been suspected in one case.³

Consequences of infection with SARS-CoV-2 for pregnancies are uncertain, with no evidence so far of severe outcomes for mothers and infants; however, the possibility should be considered.⁴ The recent experience with Zika virus suggests that when a new pathogen emerges, the health-care community should be prepared for the worst-case scenario.⁵ Therefore, recommendations for management of pregnant women at risk of SARS-CoV-2 infection are urgently needed. To this end, we propose a detailed management

algorithm for health-care providers (appendix).

In the algorithm, we suggest that any pregnant woman who has travelled in a country affected by SARS-CoV-2 within the previous 14 days or who has had close contact with a patient with confirmed SARS-CoV-2 infection should be tested with a SARS-CoV-2 nucleic acid amplification test,⁶ even if asymptomatic. Pregnant women with laboratory-confirmed SARS-CoV-2 infection who are asymptomatic should be self-monitored at home for clinical features of COVID-19 for at least 14 days. These patients and those recovering from mild illness should be monitored with bimonthly fetal growth ultrasounds and Doppler assessments because of the potential risk for intrauterine growth restriction. Pregnant women with COVID-19 pneumonia should be managed by a multidisciplinary team at a tertiary care centre. When quick Sepsis-related Organ Failure Assessment criteria are met, the patient should be transferred to an intensive care unit.

For pregnant women with confirmed infection, the choice of delivery timing should be individualised depending on the week of gestation and maternal, fetal, and delivery conditions. Whenever possible, vaginal delivery via induction of labour, with eventual instrumental delivery to avoid maternal exhaustion, should be favoured to avoid unnecessary surgical complications in an already sick patient. Septic shock, acute organ failure, or fetal distress should prompt emergency cesarean delivery (or termination if legal before fetal viability).

Newborns of mothers positive for SARS-CoV-2 should be isolated for at least 14 days or until viral shedding clears, during which time direct breastfeeding is not recommended.

These recommendations should be adapted to local health-care

facilities, as well as in response to any further updates on SARS-CoV-2 and COVID-19.

We declare no competing interests.

Guillaume Favre, Léo Pomar, Xiaolong Qi, Karin Nielsen-Saines, Didier Musso, *David Baud
david.baud@chuv.ch

Materno-fetal and Obstetrics Research Unit, Department Woman-Mother-Child, Lausanne University Hospital, 1011 Lausanne, Switzerland (GF, LP, DB); CHES Center, The First Hospital of Lanzhou University, Lanzhou, China (XQ); Division of Pediatric Infectious Diseases, David Geffen School of Medicine, University of California, Los Angeles, CA, USA (KN-S); Aix Marseille Université, IRD, AP-HM, SSA, VITROME, IHU—Méditerranée infection, Marseille, France (DM); and Laboratoire Eurofins Labazur Guyane, French Guiana, France (DM)

- 1 Alfaraj SH, Al-Tawfiq JA, Memish ZA. Middle East respiratory syndrome coronavirus (MERS-CoV) infection during pregnancy: report of two cases & review of the literature. *J Microbiol Immunol Infect* 2019; **52**: 501–03.
- 2 Wong SF, Chow KM, Leung TN, et al. Pregnancy and perinatal outcomes of women with severe acute respiratory syndrome. *Am J Obstet Gynecol* 2004; **191**: 292–97.
- 3 Chen H, Guo Juanjuan, Wang C, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. *Lancet* 2020; published online Feb 12. [https://doi.org/10.1016/S0140-6736\(20\)30360-3](https://doi.org/10.1016/S0140-6736(20)30360-3).
- 4 Favre G, Pomar L, Musso D, Baud D. 2019-nCoV epidemic: what about pregnancies? *Lancet* 2020; **395**: e40.
- 5 Musso D, Ko AI, Baud D. Zika virus infection—after the pandemic. *N Engl J Med* 2019; **381**: 1444–57.
- 6 WHO. Laboratory testing for 2019 novel coronavirus (2019-nCoV) in suspected human cases. Interim guidance. Geneva: World Health Organization, 2020.

COVID-19 in pregnant women

With interest, we read the recommendation on the management of pregnant women with suspected severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by Guillaume Favre and colleagues.¹ Some of the recommendations made in the flowsheet of their Correspondence have long-term consequences (eg, termination of pregnancy, no breastfeeding)

of an unforeseeable extent, are harmful when applied to the general population (eg, early cord clamping in extremely preterm infants, no breastfeeding, separation of the mother from the newborn), are not proven to reduce the risk of transmission in other viral illnesses (eg, early cleaning of the newborn), and are contradictory to the current recommendations by the US Centers for Disease Control and Prevention (CDC) for the management of coronavirus disease 2019 (COVID-19; eg, testing of asymptomatic people, no breastfeeding).

In case reports and in the largest case series on COVID-19 in children published so far,² three neonates and 230 children with confirmed COVID-19 diagnosis are reported. There were no deaths, most patients had mild disease (including all three neonates), and severe illness was limited to patients with underlying illness.

Extrapolation from other studies of human coronavirus infections³ gives conflicting data with no harm reported in infants born to mothers with SARS-CoV and severe adverse courses in women infected with Middle East respiratory syndrome coronavirus. Current data suggest that vertical transmission of SARS-CoV-2 is at least uncommon,^{4,5} and the clinical course of infants born to infected mothers varies in the two publications. Serious illness was reported by Zhu and colleagues,⁵ however, all of these neonates tested negative, so the cause of their illness remains unclear.

On the basis of these data, we feel that clear recommendations, as proposed in the appendix of the Correspondence by Favre and colleagues, cannot and should not be made, although we realise that during the worrisome actual situation such recommendations are very sought after. However, making recommendations that can affect a large number of people requires a

sound foundation. In the absence of such a foundation, the medical and academic community should explain to the best of their knowledge what they know and what the knowledge gaps are, rather than trying to fill these gaps with unsound speculation.

We admit that the choice on which side to err is not an easy one if we simply do not know the risks associated with COVID-19 in pregnant women and neonates. Therefore, as long as national authority guidelines or evidence-based recommendations do not yet exist, clinical practitioners need to screen the literature and review their actions on a daily basis. We appeal to national and international disease control authorities such as CDC and WHO to improve and update their guidelines for specific patient groups, so that everyone can rely on the best data available.

We declare no competing interests.

***Manuel B Schmid, Jehudith Fontijn, Nicole Ochsenbein-Kölbl, Christoph Berger, Dirk Bassler**
manuel.schmid@usz.ch

University Hospital Zurich, Neonatal Department, 8091 Zurich, Switzerland (MBS, JF, DB); University Hospital Zurich, Department of Obstetrics, Zurich, Switzerland (NO-K); and University Children's Hospital Zurich, Division of Infectious Diseases and Hospital Epidemiology, Zurich, Switzerland (CB)

- 1 Favre G, Pomar L, Qi X, Nielsen-Saines K, Musso D, Baud D. Guidelines for pregnant women with suspected SARS-CoV-2 infection. *Lancet Infect Dis* 2020; published online March 3. [https://doi.org/10.1016/S1473-3099\(20\)30157-2](https://doi.org/10.1016/S1473-3099(20)30157-2).
- 2 Lu Q, Shi Y. Coronavirus disease (COVID-19) and neonate: what neonatologist need to know. *J Med Virol* 2020; published online March 1. DOI:10.1002/jmv.25740.
- 3 Schwartz DA, Graham AL. Potential maternal and infant outcomes from (Wuhan) coronavirus 2019-ncov infecting pregnant women: lessons from SARS, MERS, and other human coronavirus infections. *Viruses* 2020; **12**: e194.
- 4 Chen H, Guo J, Wang C, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. *Lancet* 2020. [https://doi.org/10.1016/S0140-6736\(20\)30360-3](https://doi.org/10.1016/S0140-6736(20)30360-3).
- 5 Zhu H, Wang L, Fang C, et al. Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia. *Transl Pediatr* 2020; **9**: 51–60.

For more on the **guidelines** see <https://www.cdc.gov/coronavirus/2019-ncov/hcp/inpatient-obstetric-healthcare-guidance.html> and <https://www.unicef.org/stories/novel-coronavirus-outbreak-what-parents-should-know>



Published Online
March 17, 2020
[https://doi.org/10.1016/S1473-3099\(20\)30175-4](https://doi.org/10.1016/S1473-3099(20)30175-4)