BJOG An International Journal of Obstetrics and Gynaecology

DOI: 10.1111/1471-0528.16270
www.bjog.org

Commentary

How should we treat pregnant women infected with SARS-CoV-2?

V Faure-Bardon,[a,b] LJ Salomon,[a,b] M Leruez-Ville,[b,c] Y Ville[a,b]

[a] EA 73-28, Paris Descartes University, Sorbonne Paris Cité, Paris, France [b] Maternity, AP-HP, Hospital Necker-E.M., Paris, France [c] Virology Laboratory, AP-HP, Hospital Necker-E.M., Paris, France
Correspondence: V Faure-Bardon, EA 73-28, Paris Descartes University, Sorbonne Paris Cité, Paris 75005, France.
Email: valentine.faure@aphp.fr

Accepted 20 April 2020. Published Online 14 May 2020.

Please cite this paper as: Faure-Bardon V, Salomon LJ, Leruez-Ville M, Ville Y. How should we treat pregnant women infected with SARS-CoV-2? BJOG 2020;127:1050–1052.

The health crisis caused by the novel SARS-CoV-2 (formally called 2019-nCoV)-related pandemic requires urgent action, including a necessary therapeutic response. Pregnant women are just as exposed as the general population and should not be excluded because of their status, from discussions on effective and well tolerated candidate treatments. While in countries that have opted for national containment, daily non-emergency medical and surgical activities are suspended, obstetric services continue to operate relentlessly and are experiencing a surge in 'at-risk' pregnancies. Some countries have now recommended routine screening of all pregnant women[1,2] but the low availability and performance of the current tests limit their use.

Management of an infected pregnant women is essentially conditioned by maternal symptomatology. Women with little or no symptoms do not require routine treatment or in-patient care and simply need to be monitored for up to 15 days for evidence of respiratory deterioration. In the absence of validated specific treatment, the primary approach to therapy is mainly symptomatic and delivery is considered in the event of critical respiratory distress in order to maximise oxygenation and lung capacity.[3–5] However, it has been reported that women with respiratory signs may be given antiviral treatment to improve their clinical condition.[3,5]

To date, there is no proven effective strategy, although many teams are working tirelessly to identify an effective treatment. Molecular formulations are leading in this race:

1 Remdesivir is a novel nucleotide analogue prodrug which incorporates into nascent viral RNA chains and results in pre-mature termination. Its effectiveness has been already demonstrated against other coronaviruses such as SARS-CoV and MERS-CoV[6] and it has proven to be highly effective against in vitro SARS-CoV-2 infection.[7] Compassionate use in humans has also been reported[8] and phase 3 studies are currently underway.[9–12]
2 (Hydroxy)chloroquine is well known due to its effectiveness in the treatment of inflammatory diseases and against malaria. Recent studies have shown antiviral effects of chloroquine and in vitro studies concluded that it was highly effective in the control of SARS-CoV-2.[7,13] Elevation of endosomal pH and interference with terminal glycosylation of the cellular receptor, angiotensin-converting enzyme 2, block virus infection. (Hydroxy) chloroquine has been used in SARS-CoV-2-infected humans with highly controversial results[14,15] but several phase 3 studies are underway to analyse its efficacy both as a cure for patients at each stage of the disease and as a preventive measure.[16–19]
3 Lopinavir, a viral protease inhibitor, with its pharmacological booster ritonavir (LPV/R) is commonly used in HIV-positive patients. It has already been used for SARS-Cov-2. Some countries, including China and India, have approved its use in symptomatic infected patients, although the first randomised, controlled, open-label trial showed no benefit of LPV/R over standard care in patients with severe SARS-CoV-2 disease.[20] Further results are expected from new undergoing phase 3 clinical trials.[21,22]
4 Ribavirin is a guanosine analogue that interferes with the replication of RNA and DNA viruses. It has been used for years in the treatment of chronic hepatitis C. Based on its direct anti-viral activity against SARS-CoV-2 in vitro and some evidence for its potential efficacy during the prior SARS-Cov and MERS-Cov outbreaks, it has been suggested as a potential candidate for the treatment of SARS-CoV-2 disease.[23] SARS-CoV-2-infected

patients treated with Ribavirin have been reported in studies from China[5,24] but its exact benefit remains to be demonstrated in well-designed randomised studies.[25]

To date, all four drugs are being independently tested in randomised controlled trials, mostly national, to investigate their efficacy and safety in the management of SARS-CoV-2 disease. Several European countries have also set up, as a result of joint efforts since mid-March, a randomised, multicentre, open-label phase 3 trial to evaluate and compare the efficacy and toxicity of the first three treatments mentioned above.[26]

What about treating pregnant patients?

Few data are available for remdesivir. Only one study reports its use in six pregnant women in a randomised trial during Ebola epidemics. The authors reported no adverse effect.[27]

The historical use of (hydroxy)chloroquine in antimalarial treatment, but also in connective tissue diseases, has resulted in a well-documented safety and tolerance profile in pregnant women.[28] Animal studies undertaken during the Zika virus epidemic, have also suggested that chloroquine may also reduce the risk of viral transplacental transmission to the fetus.[29] The optimal dosage to be used in pregnant women will have to be specified, but it appears that there is no pharmacokinetic difference between chloroquine and its major metabolite between pregnant and non-pregnant women,[30] meaning standard, non-pregnant doses could be unaltered.

With respect to the use of protease inhibitors during pregnancy, such as lopinavir, some teams have reported an increased risk of preterm delivery. However, a specific analysis of more than 4000 pregnant women found a similar incidence and rate of adverse pregnancy outcomes compared with controls at all three trimesters of pregnancy, including preterm birth, low birthweight and birth defects.[31]

Significant teratogenic effects have been demonstrated in all animal species exposed to ribavirin and it is therefore currently contraindicated in pregnant women and in their male sexual partners, although the ribavirin pregnancy registry did not provide evidence of teratogenicity in humans.[32]

The use of antiviral therapy in infected pregnant patients should follow the same indication as in the general population, but some obstetric specificities should be emphasised.

- The main goal should be to slow down (and at best stop) the clinical progression of the disease: to remain asymptomatic or, in symptomatic patients, to avoid progression to acute respiratory distress syndrome. In the latter the obstetrician will often be called on to perform an emergency delivery and thus induce prematurity in the infant. At present expert consensus provides guidance for obstetricians, but the management between 25 and 32 weeks' remains challenging in the absence of effective antiviral treatment.[2]
- The second objective should be to decrease viral load and duration of contagiousness in infected pregnant women. The majority do well, but the infection can disrupt their 'obstetrical calendar'. Some procedures need to be performed at a specific gestational age, such as screening using first-trimester serum markers, ultrasound examinations or chorionic villus sampling (CVS). The same applies to access to termination of pregnancy. All such procedures may be delayed to limit the risk of contagion, to reduce the burden on the health care team or, in the particular case of CVS/amniocentesis, to limit the theoretical risk of fetal transmission.
- The third aim should be to introduce preventive treatment in case of maternal contact with an infected person, similar to what is done for seasonal influenza and oseltamivir.[33]

The use of immunotherapy such as tocilizumab, plasma of recovered coronavirus patient and interferons is not discussed in this commentary, as they are currently under study only for critically ill SARS-COV-2 patients. No place for these treatments in a patient who is still pregnant should be considered for the time being because, if the pregnant woman presents a very severe form, birth will be considered as a priority.

The results of the Phase 3 therapeutic studies should be available soon. It is unfortunate that infected pregnant women are not included in any appropriate research protocols. Consequently, during this period of the pandemic, there should be mutual exchange of experience between maternity hospitals in different countries to ensure the best possible management of infected pregnant women.

Disclosure of interests

VF-B and LJS have nothing to disclose. ML-V reports non-financial support from Biomérieux, other from Biomérieux, non-financial support from Abbott, non-financial support from Siemens, outside the submitted work. YV reports non-financial support from Ferring SAS, non-financial support from Siemens health Care, non-financial support from GE medical, outside the submitted work.

Contribution to authorship

YV, LJS and VFB designed the commentary. YV, LJS and VFB wrote the paper. ML-V provided virological expertise.

Funding

No funding source was necessary for this work. ■

References

1 Sutton D, Fuchs K, D'Alton M, Goffman D. Universal screening for SARS-CoV-2 in women admitted for delivery. *N Engl J Med* 2020. https://doi.org/10.1056/NEJMc2009316

2 Peyronnet V, Sibiude J, Deruelle P, Huissoud C, Lescure X, Lucet J-C, et al. Infection par le SARS-CoV-2 chez les femmes enceintes. État des connaissances et proposition de prise en charge. CNGOF. *Gynécol Obstét Fertil Sénol* 2020;48:436–43. https://doi.org/10.1016/j.gofs.2020.03.014

3 Chen H, Guo J, Wang C, Luo F, Yu X, Zhang W, 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;395:809–15.

4 Qi H, Luo X, Zheng Y, Zhang H, Li J, Zou L, et al. Safe delivery for COVID-19 infected pregnancies. *BJOG* 2020. https://doi.org/10.1111/1471-0528.16231

5 Yu N, Li W, Kang Q, Xiong Z, Wang S, Lin X, et al. Clinical features and obstetric and neonatal outcomes of pregnant patients with COVID-19 in Wuhan, China: a retrospective, single-centre, descriptive study. *Lancet Infect Dis* 2020. https://doi.org/10.1016/S1473-3099(20)30176-6

6 Sheahan TP, Sims AC, Graham RL, Menachery VD, Gralinski LE, Case JB, et al. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. *Sci Transl Med* 2017;9:eaal3653.

7 Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res* 2020;30:269–71.

8 Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H, et al. First case of 2019 novel coronavirus in the United States. *N Engl J Med.* 2020;382:929–36. https://doi.org/10.1056/NEJMoa2001191

9 Adaptive COVID-19 treatment trial (ACTT) – Full Text View – ClinicalTrials.gov [https://clinicaltrials.gov/ct2/show/NCT04280705]. Accessed 18 April 2020.

10 Study to evaluate the safety and antiviral activity of Remdesivir (GS-5734™) in participants with severe coronavirus disease (COVID-19) – Full Text View – ClinicalTrials.gov [https://clinicaltrials.gov/ct2/show/NCT04292899]. Accessed 18 April 2020.

11 Study to evaluate the safety and antiviral activity of Remdesivir (GS-5734™) in participants with moderate coronavirus disease (COVID-19) compared to standard of care treatment – Full Text View – ClinicalTrials.gov [https://clinicaltrials.gov/ct2/show/NCT04292730]. Accessed 18 April 2020.

12 The efficacy of different anti-viral drugs in COVID 19 infected patients – Full Text View – ClinicalTrials.gov [https://clinicaltrials.gov/ct2/show/NCT04321616]. Accessed 18 April 2020.

13 Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). *Clin Infect Dis* 2020. https://doi.org/10.1093/cid/ciaa237

14 Colson P, Rolain J-M, Raoult D. Chloroquine for the 2019 novel coronavirus SARS-CoV-2. *Int J Antimicrob Agents* 2020;55:105923.

15 Jun C, Danping L, Li L, Ping L, Qingnian X, Lu X, et al. A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19). *J Zhejiang Univ Med Sci* 2020;49.

16 Hydroxychloroquine, hydroxychloroquine, azithromycin in the treatment of SARS CoV-2 infection – Full Text View – ClinicalTrials.gov [https://clinicaltrials.gov/ct2/show/NCT04341727]. Accessed 18 April 2020.

17 Safety and efficacy of hydroxychloroquine as COVID-19 prophylaxis for at-risk population (SHARP): a cluster randomized controlled trial – Full Text View – ClinicalTrials.gov [https://clinicaltrials.gov/ct2/show/NCT04342156]. Accessed 18 April 2020.

18 Will hydroxychloroquine impede or prevent COVID-19 – Full Text View – ClinicalTrials.gov [https://clinicaltrials.gov/ct2/show/NCT04341441]. Accessed 18 April 2020.

19 Hydroxychloroquine versus placebo in COVID-19 patients at risk for severe disease – Full Text View – ClinicalTrials.gov [https://clinicaltrials.gov/ct2/show/NCT04325893]. Accessed 18 April 2020.

20 Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A trial of Lopinavir–Ritonavir in adults hospitalized with severe Covid-19. *N Engl J Med* 2020. https://doi.org/10.1056/NEJMoa2001282

21 Austrian coronavirus adaptive clinical trial – Full Text View – ClinicalTrials.gov [https://clinicaltrials.gov/ct2/show/NCT04351724]. Accessed 18 April 2020.

22 COVID-19 ring-based prevention trial with Lopinavir/Ritonavir – Full Text View – ClinicalTrials.gov [https://clinicaltrials.gov/ct2/show/NCT04321174]. Accessed 18 April 2020.

23 Khalili JS, Zhu H, Mak A, Yan Y, Zhu Y. Novel coronavirus treatment with ribavirin: groundwork for evaluation concerning COVID-19. *J Med Virol* 2020. https://doi.org/10.1002/jmv.25798

24 Wu J, Li W, Shi X, Chen Z, Jiang B, Liu J, et al. Early antiviral treatment contributes to alleviate the severity and improve the prognosis of patients with novel coronavirus disease (COVID-19). *J Intern Med* 2020. https://doi.org/10.1111/joim.13063

25 Lopinavir/Ritonavir, ribavirin and IFN-beta combination for nCoV treatment – Full Text View – ClinicalTrials.gov [https://clinicaltrials.gov/ct2/show/NCT04276688]. Accessed 18 April 2020.

26 Trial of treatments for COVID-19 in hospitalized adults – Full Text View – ClinicalTrials.gov [https://clinicaltrials.gov/ct2/show/NCT04315948]. Accessed 1 April 2020.

27 Mulangu S, Dodd LE, Davey RT, Tshiani Mbaya O, Proschan M, Mukadi D, et al. A randomized, controlled trial of ebola virus disease therapeutics. *N Engl J Med* 2019;381:2293–303.

28 Levy RA, Vilela VS, Cataldo MJ, Ramos RC, Duarte JL, Tura BR, et al. Hydroxychloroquine (HCQ) in lupus pregnancy: double-blind and placebo-controlled study. *Lupus* 2001;10:401–4.

29 Zhang S, Yi C, Li C, Zhang F, Peng J, Wang Q, et al. Chloroquine inhibits endosomal viral RNA release and autophagy-dependent viral replication and effectively prevents maternal to fetal transmission of Zika virus. *Antiviral Res* 2019;169:104547.

30 Lee SJ, McGready R, Fernandez C, Stepniewska K, Paw MK, Viladpai-nguen SJ, et al. Chloroquine pharmacokinetics in pregnant and nonpregnant women with vivax malaria. *Eur J Clin Pharmacol* 2008;64:987–92.

31 Tookey PA, Thorne C, van Wyk J, Norton M. Maternal and foetal outcomes among 4118 women with HIV infection treated with Lopinavir/Ritonavir during pregnancy: analysis of population-based surveillance data from the national study of HIV in pregnancy and childhood in the United Kingdom and Ireland. *BMC Infect Dis* 2015;16:1–11.

32 Sinclair SM, Jones JK, Miller RK, Greene MF, Kwo PY, Maddrey WC. The ribavirin pregnancy registry: an interim analysis of potential teratogenicity at the mid-point of enrollment. *Drug Saf* 2017;40:1205–18.

33 ACOG Committee Opinion No. 753: assessment and treatment of pregnant women with suspected or confirmed influenza. *Obstet Gynecol* 2018;132:1077–9.