Virological and clinical features of acute respiratory failure associated with COVID-19 in pregnancy: a case–control study

Jean-Christophe Richard, Emilie Frobert, Grégory Destras, Hodane Yonis, Mehdi Mezidi, Francois Dhelft, Sophie Trouillet-Assant, Paul Bastard, Adrian Gervais, William Danjou, Frederic Aubrun, Fanny Roumieu, Jean-Marc Labaune, Laurence Josset, Antonin Bal, Bruno Simon, Jean-Laurent Casanova, Bruno Lina, Jean-Charles Picaud, Corinne Dupont, Cyril Huissoud and Laurent Bitker

Pregnancy has emerged as an important risk factor for acute respiratory failure (ARF) and intensive care unit (ICU) admission following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.[1] About 8% of pregnant women with coronavirus disease 2019 (COVID-19) require ICU admission,[2,3] with ICU mortality ranging between 0% and 15%,[4-11] but with substantial neonatal morbidity.[5,6,8,12]

Management of pregnant ICU patients with severe COVID-19 and a viable fetus relies on expert opinions,[13-16] and is based on individualised delivery planning depending on gestational age. Whether pregnant patients with COVID-19 and ARF benefit from emergency delivery remains largely conjectural at this time, although a recent study on 17 pregnant patients with COVID-19 and acute respiratory distress syndrome (ARDS) who required invasive mechanical ventilation suggested that emergency delivery slowed the deterioration of oxygenation over time.[11] Furthermore, since pregnant patients are usually excluded from clinical trials of therapeutic agents for SARS-CoV-2 infection, the benefit of antiviral administration in this population remains unknown. This issue is critical since the susceptibility of pregnant patients to severe forms of COVID-19 may be related to immunological impairment during pregnancy.[17]

We hypothesised that COVID-19-associated ARF during pregnancy is a particular phenotype of ARF, and that viral load in the respiratory tract might be higher in pregnant patients than in non-pregnant patients as a consequence of pregnancy-associated immunological alterations.

Methods

Study aims

The primary objective of the study was to identify whether viral load is higher in pregnant ICU patients with COVID-19 and ARF, independent from

ABSTRACT

Objective: Pregnancy is a risk factor for acute respiratory failure (ARF) following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. We hypothesised that SARS-CoV-2 viral load in the respiratory tract might be higher in pregnant intensive care unit (ICU) patients with ARF than in non-pregnant ICU patients with ARF as a consequence of immunological adaptation during pregnancy.

Design: Single-centre, retrospective observational case–control study.

Setting: Adult level 3 ICU in a French university hospital.

Participants: Eligible participants were adults with ARF associated with coronavirus disease 2019 (COVID-19) pneumonia.

Main outcome measure: The primary endpoint of the study was viral load in pregnant and non-pregnant patients.

Results: 251 patients were included in the study, including 17 pregnant patients. Median gestational age at ICU admission amounted to 28 + 3/7 weeks (interquartile range [IQR], 26 + 1/7 to 31 + 5/7 weeks). Twelve patients (71%) had an emergency caesarean delivery due to maternal respiratory failure. Pregnancy was independently associated with higher viral load (–4.6 ± 1.9 cycle threshold; $P < 0.05$). No clustering or over-represented mutations were noted regarding SARS-CoV-2 sequences of pregnant women. Emergency caesarean delivery was independently associated with a modest but significant improvement in arterial oxygenation, amounting to 32 ± 12 mmHg in patients needing invasive mechanical ventilation. ICU mortality was significantly lower in pregnant patients (0 *v* 35%; $P < 0.05$). Age, Simplified Acute Physiology Score (SAPS) II score, and acute respiratory distress syndrome were independent risk factors for ICU mortality, while pregnancy status and virological variables were not.

Conclusions: Viral load was substantially higher in pregnant ICU patients with COVID-19 and ARF compared with non-pregnant ICU patients with COVID-19 and ARF. Pregnancy was not independently associated with ICU mortality after adjustment for age and disease severity.

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confounding factors, than in control non-pregnant ICU patients with COVID-19 and ARF.

The secondary objectives of the study were:

- to identify whether severe forms of COVID-19 during pregnancy are related to specific mutations in the viral genome;
- to evaluate the impact of emergency caesarean delivery on arterial oxygenation in patients undergoing invasive mechanical ventilation; and
- to identify whether pregnancy is an independent risk factor for ICU mortality in patients with COVID-19 and ARF.

Study design

We undertook a single-centre, retrospective observational case–control study of patients admitted between 1 January and 15 September 2021 to an adult ICU in a French university hospital with a level 4 regional neonatal intensive care unit (NICU). The study was conducted in accordance with the amended Declaration of Helsinki, complied with the STROBE criteria,[18] and was approved by our institutional Ethics Committee (Hospices Civils de Lyon, CSE HCL – #21_640). The patients were informed of their right to oppose to the retrospective use of their data for non-interventional research, according to French regulation.

Patients

Eligible participants were adults consecutively admitted to the ICU with ARF associated with COVID-19 confirmed by a SARS-CoV-2 real-time reverse transcriptase polymerase chain reaction (RT-PCR) test in respiratory swab or a rapid antigen test, and pneumonia on chest imaging. Exclusion criteria were previous inclusion during a prior ICU stay, time between first symptoms and ICU admission > 21 days, and lack of consent to participate. Patients were classified into the pregnant group if they were pregnant at ICU admission or if they were admitted to the ICU immediately after delivery.

Study endpoints

The primary endpoint was viral load assessed by the cycle threshold value on the first semi-quantitative RT-PCR performed during the hospital stay. The secondary endpoints of the study were:

- mutations in SARS-CoV-2 genomes;
- worst arterial partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) ratio during the 24 hours before intubation, and on the calendar day after intubation in pregnant patients undergoing delivery and non-pregnant patients; and
- ICU mortality.

Statistical analysis

Statistical analyses were performed using R version 4.0.1. A two-sided $P < 0.05$ was chosen for statistical significance. We anticipated that the study would have at least an 80% power to detect an effect size of at least 0.8 on the primary judgment criteria if at least 200 controls and 15 pregnant patients were included.

Categorical variables were expressed as count (percentage) and continuous data were presented as medians (interquartile range [IQR]). Data were compared between groups with the Fisher exact test for categorical variables and the *t* test or Mann–Whitney test for continuous variables, as indicated. Multivariable analyses were performed by selection of variables, with $P < 0.2$ in univariate analysis and other variables deemed relevant, and by a backward selection algorithm. The confounding effect of sex and age was adjusted in all models. Additional information regarding the methods is provided in the Online Appendix.

Results

Population characteristics

Missing data per variables are reported in the Online Appendix, table 1. Data collection stopped with the end of the fourth wave of COVID-19 in our area. Two-hundred and fifty-one patients were included in the study, of which 17 were pregnant (Online Appendix, figure 1). Pregnant patients were significantly younger, had a lower Simplified Acute Physiology Score (SAPS) II score and higher PaO_2/FiO_2 ratio during the first 24 hours in the ICU than the non-pregnant patients (Table 1). Requirement for invasive mechanical ventilation was not statistically different between groups (59% *v* 56% in pregnant and non-pregnant patients respectively).

Biological data

Semi-quantitative RT-PCR and quantitative RT-PCR tests were highly correlated in a subset of 37 patients (Spearman correlation coefficient, –0.86; $P < 0.0001$; Online Appendix, figure 2). Distribution of SARS-CoV-2 variants were significantly different between pregnant and non-pregnant patients (Table 1). The Delta variant was more frequently identified in pregnant patients (59% *v* 22%), while the Alpha variant was more frequently identified in non-pregnant patients (33% *v* 56%). Viral load was significantly higher in pregnant patients, with a median difference amounting to 5 cycle thresholds (95% CI, 2–8). Pregnancy was independently associated with higher viral load (–4.6 ± 1.9 cycle threshold; $P < 0.05$; Table 2) after adjustment for

Table 1. Patients' characteristics

Variables	Whole population	No pregnancy	Pregnancy
Total number of patients	251	234	17
Age, years, median (IQR)	61 (52–71)	62 (54–71)	33 (32–40)*
Sex, male	164 (65%)	164 (70%)	0*
Antiviral treatment			
Casivirimab/indevimab	2 (1%)	2 (1%)	0
Convalescent plasma therapy	12 (5%)	11 (5%)	1 (6%)
SARS-CoV-2 vaccination			
One dose or non-vaccinated	243 (97%)	227 (97%)	16 (94%)
Fully vaccinated	8 (3%)	7 (3%)	1 (6%)
Immunosuppression	17 (7%)	17 (7%)	0
BMI, kg/m^2, median (IQR)	29 (26–34)	30 (26–34)	29 (27–34)
Time between first symptoms and ICU admission, days, median (IQR)	8 (6–11)	8 (6–11)	7 (6–10)
SAPS II score at ICU admission, median (IQR)	38 (28–51)	39 (29–52)	24 (21–27)*
SOFA score at ICU admission, median (IQR)	3 (2–4)	3 (2–5)	3 (2–3)
Worst PaO_2/FiO_2 ratio during the first 24 hours in ICU, mmHg, median (IQR)	82 (65–131)	80 (64–130)	118 (74–158)†
Most invasive ventilatory support during ICU stay			
Standard oxygen therapy	41 (16%)	37 (16%)	4 (23%)
High flow oxygen	69 (28%)	66 (28%)	3 (18%)
Invasive mechanical ventilation	141 (56%)	131 (56%)	10 (59%)
ARDS during ICU stay	136 (54%)	126 (54%)	10 (59%)
ARDS severity†			
Mild	1 (1%)	0	1 (10%)
Moderate	26 (19%)	22 (17%)	4 (40%)
Severe	109 (80%)	104 (83%)	5 (50%)
High flow oxygen failure	98 (62%)	89 (61%)	9 (75%)
Duration of high flow oxygen therapy, days, median (IQR)	2 (1–4)	2 (1–4)	1 (1–2)
Worst PaO_2/FiO_2 ratio during the 24 hours before intubation, mmHg, median (IQR)	53 (49–57)	52 (49–55)	57 (55–65)*
Worst PaO_2/FiO_2 ratio during the calendar day following intubation, mmHg, median (IQR)	95 (74–123)	94 (74–120)	108 (77–147)
Prone position during ICU stay‡	135 (96%)	126 (96%)	9 (90%)
Prone position sessions during ICU stay,‡ median (IQR)	10 (5–17)	11 (6–18)	3 (2–4)*
Inhaled nitric oxide‡	64 (46%)	60 (46%)	4 (40%)
ECMO during ICU stay	41 (16%)	39 (17%)	2 (12%)
Vasopressor during ICU stay	136 (54%)	127 (54%)	9 (53%)
RRT during ICU stay	62 (25%)	62 (26%)	0†
Invasive mechanical ventilation duration, days, median (IQR)	19 (10–36)	19 (10–38)	11 (6–15)
Ventilator-free days at day 60 from ICU admission, median (IQR)	42 (0–60)	39 (0–60)	54 (47–60)
ICU length of stay, days, median (IQR)	10 (4–32)	10 (4–32)	7 (4–15)
ICU mortality	82 (33%)	82 (35%)	0†
SARS CoV-2 variant†			
Alpha	79 (54%)	75 (56%)	4 (33%)
Delta	37 (25%)	30 (22%)	7 (59%)
Other variants	30 (21%)	29 (22%)	1 (8%)
Time between symptoms and RT-PCR, days, median (IQR)	11 (7–14)	11 (7–14)	9 (6–10)
Sampling site			
Upper respiratory tract	127 (67%)	115 (66%)	10 (83%)
Lower respiratory tract	62 (33%)	60 (34%)	2 (17%)
Viral load (cycle threshold), median (IQR)	27 (22–32)	27 (23–33)	22 (21–25)†

ARDS = acute respiratory distress syndrome; BMI = body mass index; ECMO = extracorporeal membrane oxygenation; FiO_2 = fraction of inspired oxygen; ICU = intensive care unit; IQR = interquartile range; PaO_2 = arterial partial pressure of oxygen; RRT = renal replacement therapy; RT-PCR = real-time reverse transcriptase polymerase chain reaction; SAPS = Simplified Acute Physiology Score; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SOFA = Sequential Organ Failure Assessment. * $P < 0.001$. † $P < 0.05$. ‡ In patients needing invasive mechanical ventilation.

confounders. Time between symptoms onset and RT-PCR, SARS-CoV-2 Delta variant, and upper respiratory tract site of sampling were also independently associated with viral load (Table 2), while age and sex were not.

The analysis of SARS-CoV-2 sequences did not identify clustering regarding the phylogeny of sequences (Online Appendix, figure 3). In addition, no significant over-represented mutation was identified in SARS-CoV-2 genomes of pregnant women. Neutralising autoantibodies against interferon (IFN)-α and IFN-ω were detected in the serum of one patient among the 13 analysed (8%).

Management and clinical course of pregnant patients and newborns

Ten pregnant patients (59%) were mechanically ventilated, among whom nine (52%) were intubated because of high flow oxygen therapy failure, and one to allow for urgent delivery in relation with ARF. Emergency caesarean delivery was performed in 12 patients (71%), exclusively for maternal respiratory failure. Patient characteristics as a function of emergency caesarean delivery status are reported in Table 3. Patients in the emergency caesarean delivery group were more severely hypoxaemic, and all patients with worst PaO_2/FiO_2 ratio below 150 mmHg during the first 24 hours in the ICU underwent emergency caesarean delivery (Figure 1, A). Overall, preterm birth was observed in 81% of the patients and was more frequent in the emergency caesarean delivery group (92% *v* 50%). Most preterm birth occurred before 32 weeks' gestational age (69%), and newborn admission to the NICU was common (65%), but no newborn fatalities were reported (Table 3).

Impact of delivery on arterial oxygenation

In pregnant patients, the PaO_2/FiO_2 ratio decreased significantly from the first 24 hours in the ICU to the 24 hours preceding emergency caesarean delivery and increased significantly after delivery except in one patient (Figure 1, A).

To take into account the confounding effect of mechanical ventilation in oxygenation improvement after delivery, pregnant patients needing invasive mechanical ventilation before delivery were compared with non-pregnant patients needing invasive mechanical ventilation for the worst PaO_2/FiO_2 ratio during the 24 hours preceding intubation and on the calendar day following intubation (and delivery in pregnant patients). A significant interaction was found between the timing of measurement and pregnancy status (Figure 1, B), with a linear interaction coefficient amounting to 32 ± 12 mmHg; that is, the increase between before and after intubation in pregnant patients was higher by 32 ± 12 mmHg compared with non-pregnant patients (Online Appendix, table 2).

Mortality risk factors

Overall ICU mortality amounted to 33% and was significantly lower in pregnant than in non-pregnant patients (0% *v* 35%; $P < 0.05$). Univariate risk factors for ICU mortality are provided in the Online Appendix, table 3. Age, SAPS II score, and ARDS were independent risk factors for ICU mortality, while pregnancy status or virological variables were not (Table 4).

Table 2. Variables associated with cycle threshold values

Variables	Univariate model coefficient ± SE	Univariate *P* value	Multivariable model coefficient ± SE	Multivariable *P* value
Intercept	-	-	23.1 ± 2.4	< 0.001
Time between symptoms onset and RT-PCR (per day)	0.6 ± 0.1	< 0.001	0.6 ± 0.1	< 0.001
Site of sampling (ref = lower respiratory tract)	0.3 ± 1.0	0.75	2.5 ± 1.0	< 0.05
Pregnancy (ref = No)	–5.5 ± 1.8	< 0.01	–4.6 ± 1.9	< 0.05
SARS-CoV-2 variant (ref = Alpha)				
Delta	–3.2 ± 1.1	< 0.01	–2.9 ± 1.0	< 0.01
Other variants	–0.5 ± 1.1	0.66	0.7 ± 1.0	ns
Immunosuppression (ref = No)	–6.0 ± 1.8	< 0.01	–3.2 ± 1.6	0.05
Age (per 10 years)	0.0 ± 0.4	0.92	–0.5 ± 0.4	ns
Sex (ref = male)	–2.5 ± 1.0	< 0.05	0.1 ± 0.9	ns

ns = not significant; ref = reference; RT-PCR = real-time reverse transcriptase polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SE = standard error.

Table 3. Maternal and fetal/neonatal characteristics as a function of emergency caesarean delivery status

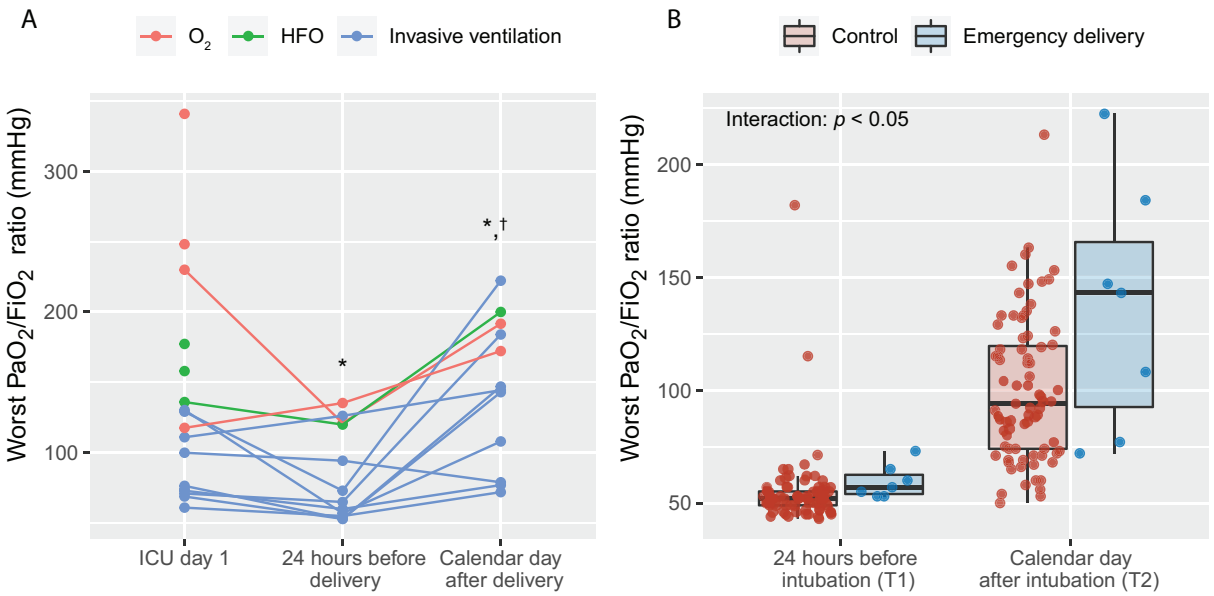
Variables	Pregnant patients	Non-emergency caesarean delivery	Emergency caesarean delivery
Total number of patients	17	5	12
Maternal age at ICU admission, median (IQR)	33 (32–40)	33 (32–35)	33 (32–40)
Maternal comorbid conditions			
None	11 (65%)	2 (40%)	9 (75%)
Obesity	3 (17%)	1 (20%)	2 (17%)
Other	3 (17%)	2 (40%)	1 (8%)
Worst PaO_2/FiO_2 ratio during first 24 hours in the ICU, mmHg, median (IQR)	118 (74–158)	177 (158–248)	106 (73–129)
Invasive mechanical ventilation	10 (59%)	1 (20%)	9 (75%)
Antenatal steroids for fetal maturation	15 (88%)	4 (80%)	11 (92%)
Time between antenatal steroids and delivery, days, median (IQR)	3 (1–5)	73 (71–80)	2 (1–3)
Time between ICU admission and delivery, days, median (IQR)	2 (1–12)	71 (59–76)	1 (1–2)
Anaesthesia modality during emergency caesarean delivery			
General anaesthesia	8 (67%)	na	8 (67%)
Spinal anaesthesia	4 (33%)	na	4 (33%)
Lowest maternal SpO_2 during emergency caesarean delivery, %, median (IQR)	88 (77–90)	na	88 (77–90)
Gestational age at ICU admission, weak + day, median (IQR)	28 + 3/7 (26 + 1/7 to 31 + 5/7)	28 + 1/7 (25 + 0/7 to 28 + 5/7)	28 + 3/7 (26 + 2/7 to 31 + 4/7)
Gestational age at delivery, weak + day, median (IQR)	30 + 3/7 (27 + 2/7 to 34 + 4/7)	37 + 3/7 (33 + 2/7 to 39 + 4/7)	29 + 3/7 (27 + 2/7 to 31 + 4/7)
Preterm birth before 37 weeks' gestational age	13 (81%)	2 (50%)	11 (92%)
Preterm birth before 32 weeks' gestational age	11 (69%)	1 (25%)	10 (83%)
Fetal death *in utero*	1 (6%)	1 (20%)	0
Apgar score 1 min after delivery, median (IQR)	6 (2–9)	9 (9–10)	5 (1–7)
Apgar score 5 min after delivery, median (IQR)	9 (6–10)	10 (10–10)	9 (6–9)
Apgar score 10 min after delivery, median (IQR)	10 (8–10)	10 (10–10)	9 (7–10)
Newborn body weight, g, median (IQR)	1560 (935–2735)	3490 (3480–3655)	1375 (865–1715)
Newborn admission to NICU	11 (65%)	0	11 (92%)
Oxygen therapy in newborns	11 (65%)	0	11 (92%)
Time between delivery and oxygen weaning in newborn, days, median (IQR)	48 (28–65)	na	48 (28–65)
Newborn hospital death	0	0	0

ARDS = acute respiratory distress syndrome; BMI = body mass index; FiO_2 = fraction of inspired oxygen; ICU = intensive care unit; IQR = interquartile range; na = not applicable; NICU = neonatal intensive care unit; PaO_2 = arterial partial pressure of oxygen; SpO_2 = oxygen saturation measured by pulse oximetry. Statistical analyses were not performed between groups owing to the small sample size.

Discussion

After adjustment for confounding factors, our study shows that the viral load in pregnant patients with ARF associated with COVID-19 was significantly and substantially higher than in non-pregnant patients with ARF associated with COVID-19. In addition, viral molecular characteristics were not significantly different between pregnant and non-pregnant patients, suggesting that host-related factors associated with pregnancy are involved in disease severity. Furthermore, emergency caesarean delivery was independently associated with a modest but significant

Figure 1. Changes of arterial partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) ratio in pregnant patients (A), and in all intubated patients before and after intubation/delivery (B). Patients in the emergency delivery group had a caesaren delivery immediately after intubation



HFO = high flow oxygen; ICU = intensive care unit; O_2 = oxygen; T1 = 24 hours before intubation; T2 = calendar day after intubation. * $P < 0.05$ *v* ICU day 1. † $P < 0.05$ *v* 24 hours before delivery.

improvement in arterial oxygenation, amounting to 32 ± 12 mmHg in patients needing invasive mechanical ventilation. Moreover, pregnancy was not an independent risk factor for ICU mortality in patients with ARF associated with COVID-19.

Virological factors associated with a severe form of COVID-19 during pregnancy

In a prospective cohort study including 127 pregnancies, viral load was shown to be higher in symptomatic pregnant patients compared with asymptomatic ones.[19] In the present study, viral load was independently and substantially higher in pregnant than in non-pregnant patients. This result is consistent with an impaired immune response to the SARS-CoV-2 during pregnancy and relates to several suspected mechanisms, including shift in CD4+ T cell population toward the Th2 phenotype, decrease in circulating natural killer and in circulating plasmacytoid dendritic cells, and alterations in the innate immune system, among others.[17] The effect size of pregnancy regarding viral load was of similar magnitude as the effect size of immunosuppression (–4.5 ± 1.9 *v* –3.1 ± 1.6; Table 2). Based on viral molecular analyses, pregnant women were not infected by viruses carrying specific mutations differing from non-pregnant patients. This suggests that the increased viral load in pregnant women with ARF associated with COVID-19 was related to the immune host-response in this population. Interestingly, the relatively low occurrence of neutralising auto-antibodies against IFN-α and IFN-ω in our study suggests that other impaired immune mechanisms are responsible for high viral load and COVID-19 severity during pregnancy.[20,21] The over-representation of the SARS-CoV-2 Delta variant in pregnant patients in our study is also in line with a recent study identifying higher rate of serious morbidity and adverse perinatal outcomes in the period following its widespread diffusion compared with the preceding period.[22] The higher viral load with the Delta variant in our study is also in line with previous reports,[23] and this effect was taken into account in our multivariable analysis.

Oxygenation improvement associated with delivery

We report a high rate of emergency caesarean delivery in line with previous studies on ICU patients,[6,10] suggesting that the management of these patients regarding emergency caesarean delivery was similar to previous studies. Improvement of respiratory parameters after delivery in pregnant patients with ARF remains controversial.

Table 4. Multivariable risk factors for intensive care unit (ICU) mortality

Variables	Odds ratio (95% CI)	*P*
Age (per one-year increment)	1.06 (1.03–1.09)	< 0.001
SAPS II subscore at ICU admission (per one-unit increment)*	1.04 (1.01–1.06)	< 0.001
ARDS during ICU stay (ref = No)	9.91 (4.46–22.01)	< 0.001
Sex (ref = male)	0.98 (0.49–1.95)	0.95

ARDS = acute respiratory distress syndrome; ref = reference; SAPS = Simplified Acute Physiology Score. The following variables were entered in the multivariable model: pregnancy status, age, sex, body mass index, SAPS II subscore without age component, Sequential Organ Failure Assessment (SOFA) score at ICU admission, worst arterial partial pressure of oxygen (Pao_2)/fraction of inspired oxygen (Fio_2) ratio during the first 24 hours in the ICU, ARDS occurrence during ICU stay, viral load, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variant, time between first symptoms and ICU admission and immunosuppression status. Model calibration assessed with the Hosmer–Lemeshow test, $P = 0.21$. Model discrimination assessed with the C-statistic, 0.84.
* Without age component.

One study performed in ten patients who needed invasive mechanical ventilation identified a significant improvement in the oxygenation index at 12–15 hours after delivery, but most patients were mildly to moderately hypoxaemic and some of the respiratory conditions leading to intubation were rapidly reversible.[24] Another case series of ten patients mechanically ventilated for ARF observed modest effects of delivery on maternal respiratory function with a 28% reduction in Fio_2 at 24 hours after delivery.[25] Finally, a recent study on 17 patients with ARF associated with COVID-19 showed that emergency caesarean delivery did not improve oxygenation but only slowed the deterioration of oxygenation over time.[11] All these studies lacked a control group, and the use of control patients with the same risk factor for ARF in our study allowed us to identify a modest but significant positive impact of emergency caesarean delivery on oxygenation, the clinical relevance of which may be questionable.

ICU mortality of pregnant patients

In our study, ICU mortality of pregnant patients was in the lower range of previous studies.[4-11] However, policy regarding ICU admission may vary among national health care systems and over time as a function of the epidemic dynamics, hence baseline risk of death at ICU admission may be highly heterogeneous among studies. Nevertheless, the rate of requirement of invasive mechanical ventilation for pregnant patients in our study was within the range of previously published studies, suggesting similar respiratory severity. Surprisingly, no virological factors were associated with ICU mortality in our study, as opposed to previous studies performed during the first COVID-19 pandemic wave (with different SARS-CoV-2 variants; population, pregnant *v* non-pregnant; and design, repetitive *v* single measurements[26,27]). Finally, pregnancy status was not independently associated with ICU mortality, suggesting that the low mortality rate of this subgroup is mostly explained by younger age according to our multivariable analysis, although our strategy regarding fetal extraction on occurrence of maternal respiratory worsening may have influenced outcome.

Strength and weaknesses

Our study had some limitations. A moderate rate of missing virological data should be acknowledged, although this has been taken into account by adequate statistical methods. The sample size of the pregnancy group was relatively small, as a consequence of both the rarity of the disease and the single-centre design, although the coexistence of the ECMO referral centre and of a level 4 NICU on site should have ensured that virtually all pregnant patients with ARF and a viable fetus in the regional area would have been referred to our centre. The control group differed substantially from the pregnancy group on important characteristics (age and sex notably), and this may have biased the results, although sex and age were adjusted for in our multivariable analysis. The impact of delivery on oxygenation could only be assessed in intubated patients, and our data do not provide any insight regarding non-intubated pregnant patients. The viral load was assessed by a semi-quantitative technique as the normalised quantitative reference technique is not performed routinely. However, both techniques were highly correlated in a subset of our samples. Finally, most of the patients were unvaccinated, and the impact of vaccination on viral load in pregnant women with ARF associated with COVID-19 remains unknown.

Nevertheless, the strengths of our study include consecutive patient enrolment over a well defined period, explicit inclusion and exclusion criteria, use of a sizable control group of non-pregnant ICU patients with COVID-19, availability of valuable semi-quantitative RT-PCR and genomic sequencing data for most of the study patients, and a consistent management algorithm of pregnant patients throughout the study period.

Clinical implications

The substantially higher viral load in pregnant patients with ARF associated with COVID-19 (of similar magnitude with that of immunosuppressed patients) would suggest a

potential benefit of early antiviral treatment, as reported recently,[28] but to date, this remains speculative. Regarding timing of delivery, our data confirm previous reports about the modest impact of delivery on maternal oxygenation,[11,25] although a slight increase in oxygenation related to delivery may be of clinical importance in mechanically ventilated patients with severe hypoxaemia as a life-saving procedure.

Conclusions

Viral load was significantly and substantially higher in pregnant patients with COVID-19 and ARF compared with non-pregnant patients. The SARS-CoV-2 Delta variant was over-represented in pregnant patients with ARF and may have intrinsically triggered a severe form of COVID-19 during pregnancy. Emergency caesarean delivery in patients needing invasive mechanical ventilation was independently associated with a modest but significant improvement in arterial oxygenation and may be viewed as a life-saving procedure in severely hypoxaemic patients.

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Competing interests

All authors declare that they do not have any potential conflict of interest in relation to this manuscript.

Author details

Jean-Christophe Richard[1,2]
Emilie Frobert[3,4,5]
Grégory Destras[3,4,5]
Hodane Yonis[1]
Mehdi Mezidi[1,4]
Francois Dhelft[1,2]
Sophie Trouillet-Assant[5,6]
Paul Bastard[7,8]
Adrian Gervais[7,8]
William Danjou[1]
Frederic Aubrun[9,10]
Fanny Roumieu[11]
Jean-Marc Labaune[12]
Laurence Josset[3,4,5]
Antonin Bal[3]
Bruno Simon[3]
Jean-Laurent Casanova[8,13,14,15]
Bruno Lina[3,4,5]
Jean-Charles Picaud[4,12]
Corinne Dupont[4,16]
Cyril Huissoud[4,17]
Laurent Bitker[1,2]

1 Service de Médecine Intensive Réanimation, Hôpital de la Croix Rousse, Hospices Civils de Lyon, Lyon, France.
2 Université de Lyon, Université Claude Bernard Lyon 1, INSA-Lyon, UJM-Saint Etienne, CNRS, Inserm, CREATIS UMR 5220, U1294, Lyon, France.
3 Laboratoire de Virologie, Institut des Agents Infectieux, Hospices Civils de Lyon, Department of Virology, Infective Agents Institute, North Hospital Network, Lyon, France.
4 Université de Lyon, Université Claude Bernard Lyon 1, Lyon, France.
5 CIRI, Centre International de Recherche en Infectiologie, Univ Lyon, Inserm, U1111, Université Claude Bernard Lyon 1, CNRS, UMR5308, ENS de Lyon, Team Virpath, Lyon, France.
6 Joint Research Unit Hospices Civils de Lyon-bioMérieux, Hospices Civils de Lyon, Lyon Sud Hospital, Pierre-Bénite, France.
7 Laboratory of Human Genetics of Infectious Diseases, Necker Branch, INSERM U1163, Necker Hospital for Sick Children, Paris, France.
8 Imagine Institute, University of Paris, Paris, France.
9 Service d'Anesthésie-Réanimation, Hôpital de la Croix Rousse, Hospices Civils de Lyon, Lyon, France.
10 Research on Healthcare Performance (RESHAPE), INSERM U1290, Lyon, France.
11 Service de gynécologie-Obstétrique, Hôpital de la Croix Rousse, Hospices Civils de Lyon, Lyon, France.
12 Service de réanimation néonatale, Hôpital de la Croix Rousse, Hospices Civils de Lyon, Lyon, France.
13 Laboratory of Human Genetics of Infectious Diseases, Necker Branch, Institut National de la Santé et de la Recherche Médicale U1163, Necker Hospital for Sick Children, Paris, France.
14 St Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, The Rockefeller University, New York, USA.
15 Howard Hughes Medical Institute, New York, USA.
16 Réseau périnatal Aurore, Lyon, France.
17 Service de gynécologie-obstétrique, Hôpital Femme Mère Enfant, Hospices Civils de Lyon, Lyon, France.

***Correspondence*:** j-christophe.richard@chu-lyon.fr

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