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Management and outcomes of pregnant women admitted to intensive care unit for severe pneumonia related to SARS-CoV-2 infection: the multicenter and international COVIDPREG study

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Abstract

Purpose: Management and outcomes of pregnant women with coronavirus disease 2019 (COVID-19) admitted to intensive care unit (ICU) remain to be investigated.

Methods: A retrospective multicenter study conducted in 32 ICUs in France, Belgium and Switzerland. Maternal management as well as maternal and neonatal outcomes were reported.

Results: Among the 187 pregnant women with COVID-19 (33 ± 6 years old and 28 ± 7 weeks' gestation), 76 (41%) were obese, 12 (6%) had diabetes mellitus and 66 (35%) had pregnancy-related complications. Standard oxygenation, high-flow nasal oxygen therapy (HFNO) and non-invasive ventilation (NIV) were used as the only oxygenation technique in 41 (22%), 55 (29%) and 18 (10%) patients, respectively, and 73 (39%) were intubated. Overall, 72 (39%) patients required several oxygenation techniques and 15 (8%) required venovenous extracorporeal membrane oxygenation. Corticosteroids and tocilizumab were administered in 157 (84%) and 25 (13%) patients, respectively. Awake prone positioning or prone positioning was performed in 49 (26%) patients. In multivariate analysis, risk factors for intubation were obesity (cause-specific hazard ratio (CSH) 2.00, 95% CI (1.05–3.80), $p = 0.03$), term of pregnancy (CSH 1.07, 95% CI (1.02–1.10), per + 1 week gestation, $p = 0.01$), extent of computed tomography (CT) scan abnormalities > 50% (CSH 2.69, 95% CI (1.30–5.60), $p < 0.01$) and NIV use (CSH 2.06, 95% CI (1.09–3.90), $p = 0.03$). Delivery was

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required during ICU stay in 70 (37%) patients, mainly due to maternal respiratory worsening, and improved the driving pressure and oxygenation. Maternal and fetal/neonatal mortality rates were 1% and 4%, respectively. The rate of maternal and/or neonatal complications increased with the invasiveness of maternal respiratory support.

Conclusion: In ICU, corticosteroids, tocilizumab and prone positioning were used in few pregnant women with COVID-19. Over a third of patients were intubated and delivery improved the driving pressure.

Keywords: Acute respiratory distress syndrome, COVID-19, Mechanical ventilation, Neonates, Oxygenation, Pregnancy, Prone positioning, Prognosis

Introduction

Since December 2019, SARS-CoV-2 is an emerging coronavirus responsible of a worldwide pandemic of SARS-CoV-2-related pneumonia, known as coronavirus disease (COVID-19) [1].

Pregnancy is a risk factor for severe form of SARS-CoV-2 infection [2] due to pregnancy-related changes in physiology, immunity and respiratory mechanics [3, 4]. Pregnant women > 35 years old, obese, with chronic and/or gestational hypertension, diabetes and pre-eclampsia are at risk of developing a severe form of SARS-CoV-2 pneumonia [5–8]. Furthermore, SARS-CoV-2 infection may also increase the rate of obstetric complications with more frequent premature deliveries, more cesarean sections and more frequent postpartum hemorrhage [2, 5, 7–10].

Pregnant women with COVID-19 are more likely to be admitted to intensive care unit (ICU) [11] and to require invasive mechanical ventilation or venovenous extracorporeal membrane oxygenation (VV-ECMO) [5, 6, 11–14]. Nevertheless, only few case series have specifically focused on ventilatory management and outcomes of pregnant women with COVID-19 admitted to ICU [15–18] and although French recommendations address the criteria for ICU admission, there are currently no specific recommendations for ICU management of pregnant women with COVID-19 [19, 20].

The first aim of this study was to assess the ventilatory management of pregnant women with COVID-19 admitted to ICU. The second aims were to assess obstetric management and to report on maternal and neonatal outcomes.

Methods

This retrospective multicenter and international study was conducted in 29 French ICUs, 2 Belgian ICUs and 1 Swiss ICU and was approved by the Ethics committee of the Société de Réanimation de Langue Française (CE SRLF 21–78) and by the Ethic committee of Erasme Hospital (P2020/253). Informed consent was waived but all patients or next of kin were informed about the study. The study complied with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement guidelines (Supplemental methods).

Take-home message

In this retrospective multicenter and international study, corticosteroids, tocilizumab and prone positioning were used in few pregnant women with coronavirus disease 2019 (COVID-19) admitted to the intensive care unit (ICU). Over a third of patients were intubated and had to be delivered during ICU stay mainly due to maternal respiratory worsening, which improved the driving pressure. Despite low maternal and fetal/neonatal mortality rates, the rate of maternal and/or neonatal complications increased with the invasiveness of maternal ventilatory support.

We included all consecutive pregnant women over 18 years old admitted to the different ICUs for SARS-CoV-2 pneumonia from March 2020 to December 2021 with a positive real-time reverse transcriptase-polymerase chain reaction assay for SARS-CoV-2 in nasal swabs or pulmonary samples. There were no exclusion criteria.

Ventilatory management and measurements

Ventilatory support in the different ICUs included standard oxygenation, high-flow nasal oxygen therapy (HFNO), non-invasive ventilation (NIV) or invasive mechanical ventilation, according to the severity of respiratory failure and local protocols. Indications for intubation were left at the discretion of the attending physician but was based on usual clinical and/or oxygenation parameters in critically ill patients.

Mechanically ventilated patients were sedated by propofol (1–3 mg/kg/h) or midazolam (0.1–0.2 mg/kg/h) associated with sufentanil (0.1–0.5 µg/kg/h) or remifentanil (0.05–0.25 µg/kg/h), according to local protocols. Neuromuscular blocker agents and prone positioning sessions were used according to current recommendations in non COVID-19 patients [21]. Awake prone positioning sessions were performed in patients under HFNO or NIV [22].

In patients under standard oxygenation, inspired oxygen fraction (FiO_2) was calculated as follows: $FiO_2 = (\text{oxygen flow} \times 3) + 21$ [23]. The compliance of the respiratory

system was calculated as tidal volume/(plateau pressure − total positive end-expiratory pressure). The driving pressure was calculated as plateau pressure − total positive end-expiratory pressure.

Fetal monitoring

All but one of the maternity units associated with each participating ICU (level 2A) were level-3 maternity units. In all ICUs, fetal monitoring included fetal heart rate monitoring and/or ultrasound according to the term of pregnancy. The frequency of these exams depended on local protocols and results of fetal heart rate monitoring.

Data collection and outcomes

Demographic characteristics, comorbidities of patients, clinical, biological and radiological data, therapeutics as well as clinical outcomes were collected and analyzed. Biological and radiological data were collected at ICU admission. The closest ventilatory and oxygenation parameters before and after delivery (i.e., within hours) were also collected in patients who were intubated. The severity of computed tomography (CT) scan abnormalities was assessed by the radiologist and divided into five categories according to the extent of ground-glass opacities and consolidations as a percentage of the total lung parenchyma: < 10%, 10–25%, 25–50%, 50–75 and > 75% [24].

Respiratory outcomes were the intubation rate in pregnant women with COVID-19, the proportion of patients only treated with HFNO and NIV, the proportion of patients in whom prone positioning was performed, the risk factors of intubation and the duration of invasive mechanical ventilation. Obstetric outcomes were the proportion of patients requiring delivery, the maternal ICU mortality rate and the maternal and neonatal complications rate during ICU and/or hospital stay.

Maternal complications included obstetric complications (postpartum hemorrhage and gynecologic infection) and all complications related to ICU stay. Neonatal complications included fetal or neonatal death, preterm birth (at < 32 and < 37 weeks' gestation), small for gestational age [25], organ failure or need for ICU admission. Preterm birth at < 32 weeks' gestation included both live and stillbirths at > 20 weeks' gestation but < 32 weeks' gestation [25]. Preterm birth at < 37 weeks' gestation included both live and stillbirths at > 20 weeks' gestation but < 37 weeks' gestation [25].

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range, IQR) according to normal distribution and categorical variables as numbers (percentages). Between-group comparisons were performed by Student or Mann–Whitney tests for continuous variables and by Pearson's Chi-square or Fisher exact tests for categorical variables. Within-group comparisons were performed by paired Student or Wilcoxon tests for continuous variables and by Mc Nemar or Fisher exact tests for categorical variables.

Risk factors for intubation were identified with a Cox cause-specific model, with ICU discharge alive or death in ICU without intubation as competing events and results were given as cause-specific hazard ratio (CSH) with their 95% confidence interval (CI). For this analysis, patients who were intubated before ICU admission were excluded ($n = 145$). All covariates related to ICU management (ventilatory management and treatments received during ICU stay) were assessed as time-dependent covariate. Covariates included in the Cox cause-specific model were selected a priori based on clinical relevance: term of pregnancy, obesity, extent of CT scan abnormalities, HFNO and NIV use and corticosteroids' administration.

The effects of delivery on respiratory mechanics and oxygenation in intubated patients were investigated only in the subgroup of patients with a complete dataset for all respiratory mechanics and oxygenation variables before and after delivery ($n = 27$). Analyses concerning the rate of maternal and/or neonatal complications were stratified on the invasiveness of the oxygenation technique. For this purpose, patients who received more than one of the four techniques were classified according to the most invasive technique used, assuming intubation to be more invasive than NIV, NIV to be more invasive than HFNO and HFNO to be more invasive than standard oxygenation [26].

Analyses were performed with R 3.1.1 (R foundation for Statistical Computing Vienna, Austria). Descriptive statistics were only carried out on the available data. The percentage of missing data for each variable is detailed in Table S1. Missing values for covariates included in the multivariable model were handled by multiple imputations with chained equations [27]. All tests were two-sided, and a p value < 0.05 was considered statistically significant.

Results

Study population

Among the 2480 pregnant women with COVID-19 hospitalized in the different participating centers during the study period, 187 (8%) were admitted to ICU for severe SARS-CoV-2 pneumonia. Among them, 82 (44%) were followed in the maternity unit associated with the participating ICU since the beginning of pregnancy and 105 (56%) were transferred due to the severity of

COVID-19. Patients were 33 ± 6 years old and had a gestation length of 28 ± 7 weeks: 14 (7%) patients were in the first trimester, 71 (38%) were in the second trimester, 102 (55%) were in the third trimester of pregnancy and 9 (5%) patients had twin pregnancy. Overall, 76 (41%) patients were obese, 12 (6%) had diabetes mellitus and 66 (35%) had pregnancy-related complications (Table 1). Among patients eligible for vaccination according to recommendations in France, Switzerland and Belgium during the study period, 95% were not vaccinated against SARS-CoV-2. The delay from the onset of symptoms to ICU admission was 9 ± 5 days and CT scan was performed in 142 (76%) patients. Overall, 157 (84%) patients received corticosteroids for SARS-CoV-2 infection at ICU admission, 41 (22%) patients received betamethasone for fetal lung maturation and 6 (3%) patients received methylprednisolone for unresolved ARDS. Tocilizumab was administered in 25 (13%) patients within 48 h of ICU admission, if there was increased blood inflammatory biomarkers and no respiratory improvement (Table 1).

Ventilatory management in COVID-19 pregnant women

Standard oxygenation, HFNO and NIV were used as the only oxygenation technique in 41 (22%), 55 (29%) and 18 (10%) patients, respectively, and 73 (39%) patients were intubated. Overall, 72 (29%) patients required several oxygenation techniques, 64 (34%) received neuromuscular blocker agents and 15 (8%) patients required VV-ECMO (Table 1, Fig. 1). The VV-ECMO was implanted before delivery in 4 (27%) patients and after delivery in 11 (73%) patients. Awake prone positioning or prone positioning was performed in 49 (26%) patients and before delivery in 37% of them (Table 1).

The delay from the onset of symptoms and ICU admission to intubation was 9 (6–11) days and 1 (0–2) days, respectively: 3 (4%) patients were intubated in the first trimester, 26 (36%) in the second trimester and 44 (60%) in the third trimester. The duration of mechanical ventilation was 9 (5–18) days (Table 1). Among intubated patients, 50 (68%) were treated with HNFO and 23 (32%) with NIV as first-line ventilatory support, 64 (88%) received neuromuscular blocker agents and prone positioning was performed in 41 (56%) of them with a median of 3 (1–6) sessions (Table 1).

Risk factors of intubation in COVID-19 pregnant women during ICU stay

Obesity, pregnancy-related complications, a more advanced term of pregnancy and NIV use were more frequent in patients who required to be intubated (Table 1). In multivariate analysis, obesity (CSH 2.00, 95% CI (1.05–3.80), $p = 0.03$), term of pregnancy (CSH 1.07, 95% CI (1.02–1.10), per + 1 week gestation, $p = 0.01$), extent of CT scan abnormalities > 50% (CSH 2.69, 95% CI (1.30–5.60), $p < 0.01$) and NIV use (CSH 2.06, 95% CI (1.09–3.90), $p = 0.03$) were associated with a higher risk of intubation (Fig. 2).

Obstetric management and maternal and neonatal outcomes in COVID-19 pregnant women

Delivery occurred before ICU admission in 20 (11%) patients, during ICU stay in 70 (37%) patients and after ICU discharge in 97 (52%) patients, including one patient who decided to voluntarily terminate her pregnancy after ICU discharge (Table 2, Fig. 1). Among the 70 patients who delivered during ICU stay, 47 (67%) were intubated, 6 (9%) were treated by NIV, 11 (15%) by HFNO and 6 (9%) patients received standard oxygenation. Indications for delivery during ICU stay were maternal respiratory worsening in 56 (80%) patients, fetal distress in 7 (10%) patients and spontaneous delivery in 7 (10%) patients. Except for the patients who delivered spontaneously, all deliveries required cesarean section (Table 2).

Delivery during ICU stay (64% in intubated vs. 20% in non-intubated patients, $p < 0.001$), cesarean section and preterm birth were more frequent in case of maternal intubation (Table 2). Overall, delivery significantly increased PaO_2/FiO_2 ratio by 9% ($p = 0.02$) and significantly decreased the driving pressure by 27% ($p = 0.02$). There was also a trend towards an 8% decrease in plateau pressure ($p = 0.05$) and a 26% increase in respiratory system compliance ($p = 0.07$), whereas the other ventilatory and oxygenation parameters remained unchanged (Table S2, Fig. 3). The 10 patients with decreased driving pressure tended to be more frequently obese (80 vs. 56%, $p = 0.19$), while other patient characteristics did not differ.

The maternal ICU mortality rate was 1%, 26 (14%) patients had obstetric complications and 117 (62%) had ICU-related complications. The main ICU-related complications were infection and pulmonary embolism (47% and 10% of patients, respectively) (Table 2). The fetal and neonatal mortality rate was 4% with 4 (2%) miscarriage at < 20 weeks' gestation, 3 (2%) stillbirth at > 20 weeks' gestation, 47 (25%) preterm birth at < 32 weeks, 79 (42%) preterm birth at < 37 weeks and 107 (57%) full-term birth. Overall, 59 (32%) neonates required ICU admission with an ICU length of stay of 15(4–42) days, 44 (24%) presented at least one organ failure and 9 (5%) were small for gestational age (Table 2). The rate of maternal and/or neonatal complications increased with the invasiveness of maternal ventilatory support (Table 2, Fig. S1).

Table 1 Characteristics and ICU management in pregnant women with COVID-19

	No intubation ($n=114$)	Intubation ($n=73$)	p value
Characteristics			
Age (years)	33 ± 6	34 ± 5	0.14
Body mass index (kg/m^2)	29.1 (26.4–33.5)	31.5 (27.1–34.5)	0.02
SAPS-2 score	18 (14–26)	27 (20–39)	< 0.001
SOFA score at ICU admission	2 (1–3)	4 (3–7)	< 0.001
Obesity, *n* (%)	35 (31)	41 (56)	< 0.001
Diabetes mellitus, *n* (%)	6 (5)	6 (8)	0.54
Smokers, *n* (%)	8 (7)	3 (4)	0.53
Asthma, *n* (%)	10 (9)	4 (5)	0.40
Immunosuppression, *n* (%)	2 (2)	0 (0)	0.52
CT scan, *n* (%)	84 (74)	58 (79)	0.37
Extent of CT Scan abnormalities, *n* (%)			< 0.001
< 10%	3 (4)	3 (5)	
10–25%	26 (31)	3 (5)	
25–50%	32 (38)	12 (21)	
50–75%	20 (23)	29 (50)	
> 75%	3 (4)	11 (19)	
Obstetric history			
Term of pregnancy at ICU admission (weeks' gestation)	27 ± 8	29 ± 6	0.04
Previous pregnancy, *n* (%)	53 (46)	33 (45)	0.86
Twin pregnancy, *n* (%)	5 (4)	4 (5)	0.74
Gestational hypertension, *n* (%)	3 (3)	7 (10)	0.05
Gestational diabetes, *n* (%)	23 (20)	25 (34)	0.03
Preeclampsia, *n* (%)	2 (2)	6 (8)	0.06
Oxygenation variables at ICU admission			
FiO_2 (%)	40 (30–51)	70 (50–97)	< 0.001
PaO_2 (mmHg)	81 (68–100)	85 (70–120)	0.06
PaO_2/FiO_2 ratio	198 (148–302)	147 (96–206)	< 0.001
SaO_2 (%)	96 (94–98)	97 (94–98)	0.79
$PaCO_2$ (mmHg)	30 (27–33)	31 (26–37)	0.05
pH	7.44 (7.40–7.46)	7.40 (7.31–7.44)	< 0.001
Lactate (mmol/L)	0.9 (0.7–1.4)	1.0 (0.7–1.3)	0.47
Ventilatory management			
Standard oxygenation, *n* (%)	41 (36)	0 (0)	< 0.001
HFNO, *n* (%)	70 (61)	50 (68)	0.32
NIV, *n* (%)	18 (16)	23 (32)	0.01
Intubation, *n* (%)	0 (0)	73 (100)	< 0.001
Awake prone positioning, *n* (%)	5 (4)	3 (4)	1.00
Awake prone positioning under HFNO, *n* (%)	5 (7)	3 (6)	1.00
Awake prone positioning under NIV, *n* (%)	1 (5)	0 (0)	0.47
Prone positioning, *n* (%)	0 (0)	41 (56)	< 0.001
Number of prone positioning sessions	0 (0)	3 (1–6)	NA
Neuromuscular blocker agents, *n* (%)	0 (0)	64 (88)	< 0.001
Venovenous ECMO, *n* (%)	0 (0)	15 (21)	< 0.001
Veno-arterial ECMO, *n* (%)	0 (0)	3 (4)	0.06
Tracheostomy, *n* (%)	0 (0)	6 (8)	< 0.01
Treatments during ICU stay for SARS-CoV-2 infection			
Corticosteroids, *n* (%)	100 (88)	57 (78)	0.08
Dexamethasone, *n* (%)	91 (91)	55 (96)	

Table 1 (continued)

	No intubation ($n=114$)	Intubation ($n=73$)	p value
Prednisolone, *n* (%)	3 (3)	1 (2)	
Prednisone, *n* (%)	3 (3)	0 (0)	
Hydrocortisone, *n* (%)	3 (3)	1 (2)	
Tocilizumab, *n* (%)	14 (12)	11 (15)	0.58
Delays and duration of ventilatory support			
Delay from onset of symptoms to hospital admission (days)	7 (4–9)	6 (3–7)	0.26
Delay from onset of symptoms to ICU admission (days)	9 (7–10)	8 (5–10)	0.68
Duration of HFNO (days)	3 (2–4)	2 (1–3)	0.01
Duration of NIV (days)	4 (2–5)	1 (1–3)	0.01
Duration of invasive mechanical ventilation (days)	0 (0–0)	9 (5–18)	< 0.001

Variables are summarized as mean ± standard deviation, median (interquartile range) or number (percentages)

Patients who were intubated < 24 h for fetal extraction only were considered non-intubated

CT computed tomography, *ECMO* Extracorporeal membrane oxygenation, FiO_2 inspired oxygen fraction, *HFNO* high-flow nasal oxygen therapy, *ICU* intensive care unit, *NA* non-available, *NIV* non-invasive ventilation, PaO_2 partial arterial pressure of oxygen, $PaCO_2$ partial arterial pressure of carbon dioxide, SaO_2 arterial oxygen saturation, *SAPS* simplified acute physiology score, *SOFA* sepsis-related organ failure assessment

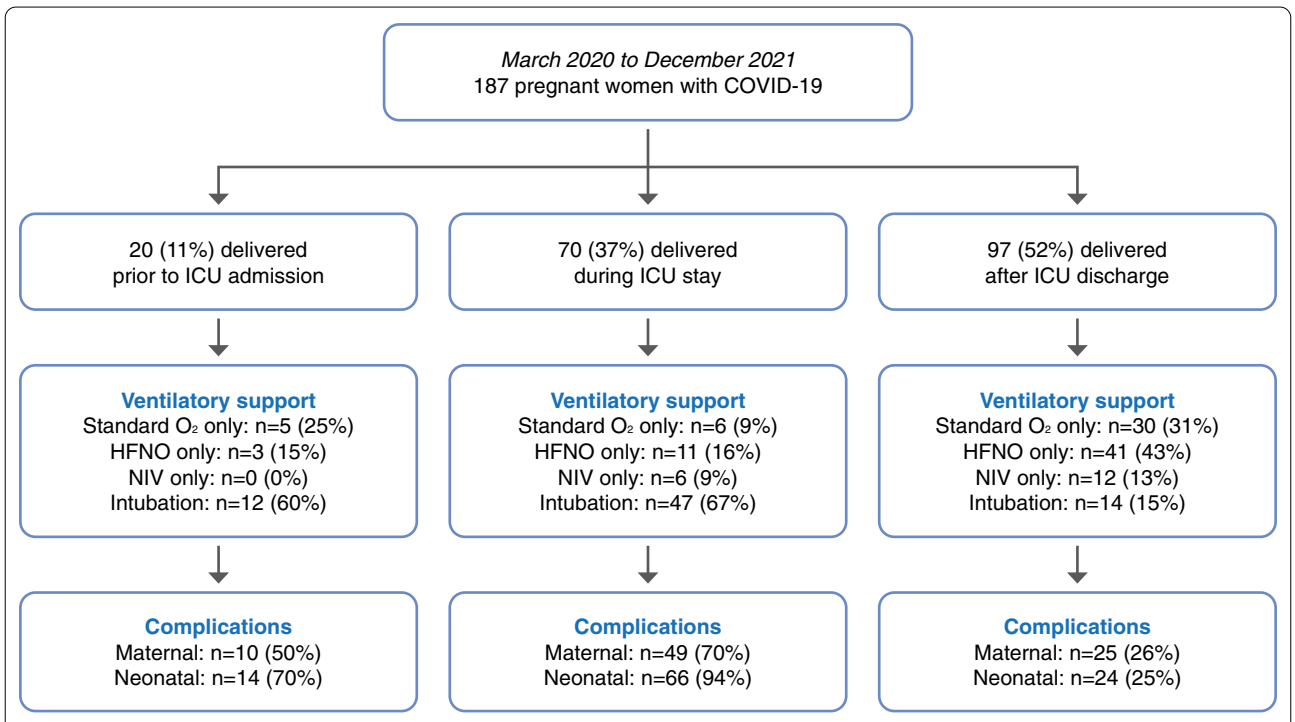

Fig. 1 Flowchart of the study summarizing ventilatory and obstetric management as well as maternal and neonatal complications in pregnant women with COVID-19 ($n=187$). Maternal complications included postpartum hemorrhage, gynecologic infection and ICU-related complications. Neonatal complications included fetal or neonatal death, preterm birth, small for gestational age, organ failure or need for ICU admission. *ICU* intensive care unit, *Standard* O_2 standard oxygenation, *HFNO* high-flow nasal oxygen, *NIV* non-invasive ventilation

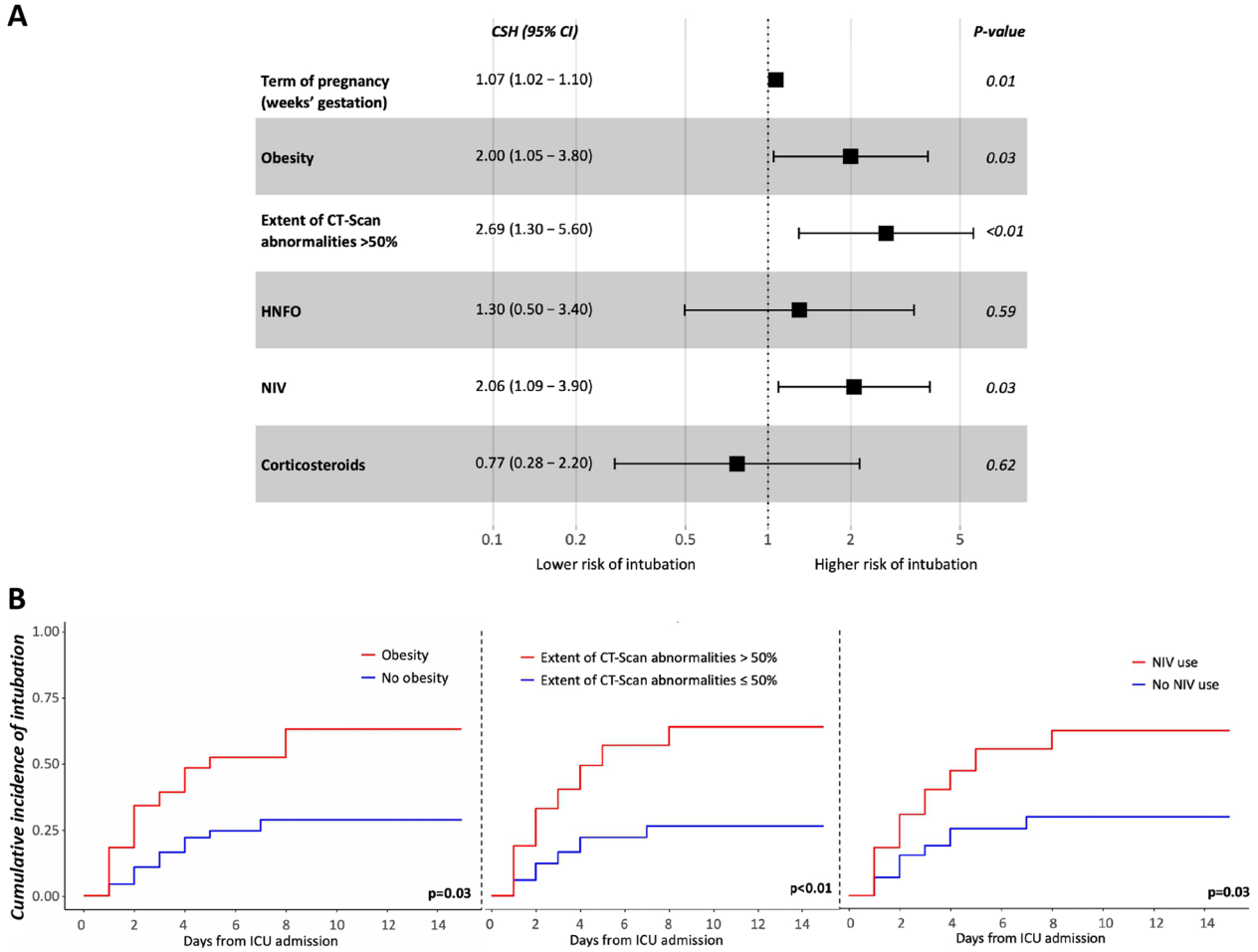

Fig. 2 **A** Risk factors for intubation during the intensive care unit stay ($n = 145$). *CI* Confidence interval, *CSH* cause-specific hazard ratio, *HFNO* high-flow nasal oxygen therapy, *NIV* non-invasive ventilation. **B** Cumulative incidence of intubation after admission in intensive care unit (ICU) according to obesity, extent of CT scan abnormalities > 50% and non-invasive ventilation (NIV) use

Discussion

To our knowledge, we report the first international and largest cohort of pregnant women admitted in ICU for a severe form of SARS-CoV-2 infection. We found that 8% of pregnant women with COVID-19 required to be admitted to ICU. Corticosteroids, tocilizumab and prone positioning were used in few pregnant women with COVID-19, over a third of patients required intubation and delivery improved the driving pressure and oxygenation. Term of pregnancy, obesity, extent of CT scan abnormalities > 50% and NIV use were associated with a higher risk of intubation. Despite low maternal and fetal/neonatal mortality rates, the rate of maternal and/or neonatal complications increased with the invasiveness of maternal ventilatory support.

Non-invasive ventilatory support was mainly preferred as first-line ventilatory support but 39% of patients required to be intubated although all of them received corticosteroids. This rate of intubation is similar to the 30% rate shown in pregnant women with pneumonia non-related to SARS-CoV-2 infection [17] but much lower than the 63% rate found in a recent small cohort of 26 critically ill pregnant women with COVID-19 [18]. This discrepancy should be considered with caution as the intubation rate depends on ICU admission criteria and the ventilatory and/or obstetric management of patients, which may differ from country to country due to potentially different local organization of care in the absence of strong international recommendations. Risk factors for intubation were term of pregnancy, obesity, extent of CT scan abnormalities > 50% and NIV use. Previous studies showed that obesity was a risk factor of intubation in pregnant women with COVID-19 [5, 8] and that NIV but not HFNO use was not associated

Table 2 Obstetric management and maternal/neonatal outcomes in pregnant women with COVID-19

	No intubation ($n=114$)	Intubation ($n=73$)	p value
Obstetric management			
Timing of delivery			
Term of delivery (weeks' gestation)	37 (34–39)	31 (28–36)	< 0.001
Delivery before ICU admission, *n* (%)	8 (7)	12 (16)	0.04
Delivery during ICU stay, *n* (%)	23 (20)	47 (64)	< 0.001
Delivery after ICU discharge, *n* (%)	83 (73)	14 (19)	< 0.001
Indications and modalities of delivery during ICU stay[a]			
Maternal respiratory worsening, *n* (%)	16 (70)	40 (85)	0.20
Fetal distress, *n* (%)	2 (9)	5 (11)	1.00
Spontaneous delivery, *n* (%)	5 (22)	2 (4)	0.03
Cesarean birth, *n* (%)	19 (83)	44 (94)	0.21
Maternal outcomes and complications			
Mortality, *n* (%)	0 (0)	2 (3)	0.15
ICU length of stay (days)	3 (2–5)	13 (8–27)	< 0.001
Hospital length of stay (days)	10 (8–16)	24 (15–40)	< 0.001
Obstetric complications			
Postpartum hemorrhage, *n* (%)	5 (4)	6 (8)	0.34
Gynecologic infection, *n* (%)	2 (2)	13 (18)	< 0.001
ICU complications			
Pulmonary embolism, *n* (%)	3 (3)	16 (22)	< 0.001
Pneumoniae, *n* (%)	20 (18)	49 (67)	< 0.001
Urinary tract infection, *n* (%)	3 (3)	9 (12)	0.01
Catheter infection, *n* (%)	2 (2)	5 (7)	0.11
Severe hemorraghe, *n* (%)	1 (1)	9 (12)	< 0.01
Neonatal outcomes and complications			
Fetal or neonatal mortality, *n* (%)	3 (3)	5 (7)	0.27
Term of delivery			
Miscarriage < 20 weeks' gestation, *n* (%)	2 (2)	2 (3)	0.65
Stillbirth > 20 week's gestation, *n* (%)	1 (1)	2 (3)	0.56
Preterm birth (< 32 weeks' gestation)[b], *n* (%)	9 (8)	38 (52)	< 0.001
Preterm birth (< 37 weeks' gestation)[c], *n* (%)	25 (22)	54 (74)	< 0.001
Full-term birth, *n* (%)	88 (77)	19 (26)	< 0.001
Birth's weight (g)	3060 (2375–3495)	1902 (1275–2968)	< 0.001
Small for gestational age, *n* (%)	1 (1)	8 (11)	< 0.01
Organ failure, *n* (%)	16 (14)	28 (38)	< 0.001
ICU admission, *n* (%)	21 (19)	38 (54)	< 0.001
ICU length of stay (days)	8 (3–17)	22 (6–44)	0.09
Hospital length of stay (days)	6 (3–14)	41 (8–65)	< 0.001

Variables are summarized as median (interquartile range) or number (percentages)

Patients who were intubated < 24 h for fetal extraction only were considered non-intubated

ICU intensive care unit

[a] Among patients who were delivered during ICU stay: $n=23$ for "no intubation" group and $n=47$ for "intubation" group

[b] Preterm birth at < 32 weeks' gestation included both live and stillbirths at > 20 weeks' gestation but < 32 weeks' gestation

[c] Preterm birth at < 37 weeks' gestation included both live and stillbirths at > 20 weeks' gestation but < 37 weeks' gestation

with a reduction in oxygenation failure in a large cohort of COVID-19 [26], probably because NIV was mainly used as a rescue therapy before intubation, as this was the case in our cohort. Awake prone positioning or prone positioning was performed in 26% of patients and before delivery in only 37% of them, although both of these postural maneuvers improve oxygenation in COVID-19 and non-COVID-19 patients [21, 22, 28], suggesting that

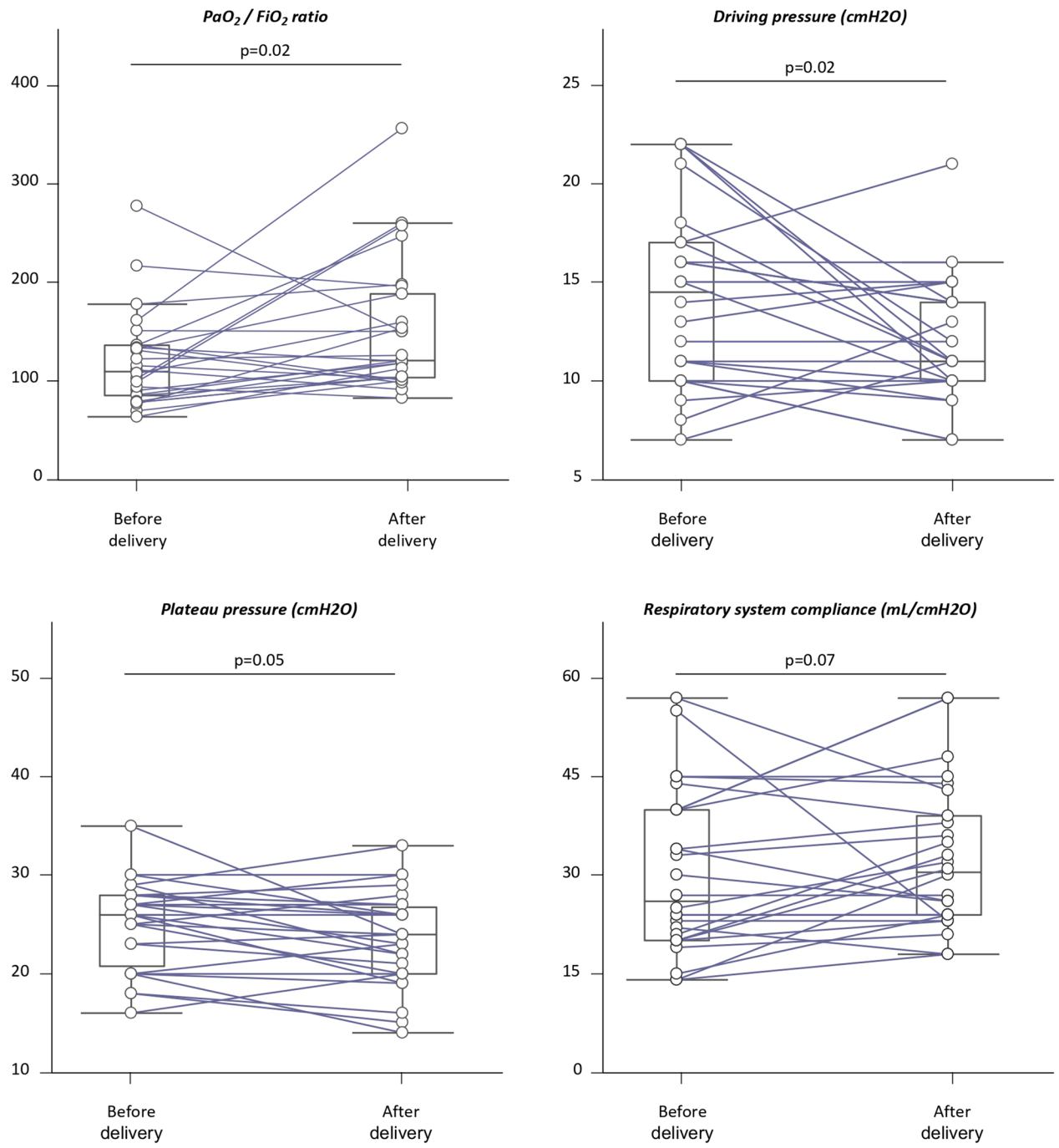

Fig. 3 Effects of delivery on respiratory mechanics and oxygenation in intubated pregnant women with COVID-19 ($n = 27$). The box shows the 25th and 75th percentiles, the line in the box the median and the whiskers the minimum and maximum values. Lines represent the individual changes. FiO_2 inspired oxygen fraction, PaO_2 partial arterial pressure of oxygen

physicians feared potential difficulties with fetal monitoring [29].

We found that 84% and 15% of pregnant women with COVID-19 received corticosteroids and tocilizumab, respectively, for SARS-CoV-2 infection, whereas the proportion of patients receiving corticosteroids and Tocilizumab varies from 12 to 100% and 0 to 100% in the existing literature [10, 18, 25]. These differences between the different studies and the low proportion we found in our cohort may be explained by the lack of strong recommendation, which may result in significant variability in

practice between countries and centers within a country regarding indications and timing of administration.

Regarding obstetric management, 37% of patients had to be delivered during their ICU stay, mainly due to maternal respiratory worsening, and cesarean section was used in 90% of cases. Delivery improved both maternal respiratory mechanics (decreased driving pressure) and oxygenation (increased PaO_2/FiO_2 ratio). To our knowledge, this is the first study to report such effects on driving pressure. However, these results should be considered with caution due to the large interindividual variability and limited sample size for these analyses, and larger studies are needed to confirm these potential beneficial effects of delivery on respiratory mechanics. We also found a 42% rate of preterm births at < 37 weeks' gestation. Preterm births resulted from spontaneous delivery in 10% of cases and from induced deliveries due to maternal respiratory worsening and/or fetal distress in 90% of cases. Our results are consistent with the existing literature, reporting a rate of delivery during ICU stay for maternal respiratory worsening ranging from 38 to 69% with a rate of cesarean section from 54 to 86% [8, 17, 18] and a rate of prematurity ranging from 27 to 48% [8, 17]. Compared to non- or less severe pregnant women with COVID-19 [5, 9, 25, 30–32], we found a higher rate of maternal and neonatal complications, which increased with the invasiveness of maternal ventilatory support. Maternal complications appeared to be due to ICU-related complications rather than obstetric complications, the most common being infections and pulmonary embolism. Rather than a direct fetal impact of SARS-CoV-2 infection, neonatal complications were most probably related to the severity of the maternal respiratory failure, leading to an increased risk of prematurity [2, 5, 7–10]. Thus, delivery during ICU stay and preterm birth were more frequent in case of maternal intubation.

Our results may suggest that all pregnant women with COVID-19 requiring ICU admission should be systematically admitted to a hospital with units capable of managing preterm neonates, given the 42% incidence of preterm births at < 37 weeks. Moreover, the respiratory management in pregnant women with a severe form of SARS-CoV-2 infection might be similar to that of other patients with COVID-19 and that non- or minimally invasive oxygenation strategies might be preferred. In the most severe patients with persistent or refractory hypoxemia delivery might be considered to improve maternal respiratory mechanics and oxygenation. However, the exact timing of delivery should always be discussed between intensivists, obstetricians and pediatricians.

We acknowledge some limitations to our study. First, standards of care have changed over the different pandemic waves and ventilatory and obstetric management of pregnant women may differ between the different participating centers. However, we used a competing risk model that took into account some of these changes to strengthen our results. Second, data on SARS-CoV-2 variants were not available at all centers and it was, therefore, not possible to assess the impact of each variant on maternal and neonatal outcomes. Third, our results are not generalizable to newly emerging SARS-CoV-2 variants and to pregnant women who have received immunomodulatory treatments and/or who have been vaccinated. It has been suggested very recently that vaccination may be associated with lower maternal respiratory severity without adverse peripartum outcomes [33–35]. Finally, we did not study the management of analgesia during labor in patients who were not intubated for delivery and further studies are needed to specifically address this issue.

Conclusions

Corticosteroids, tocilizumab and prone positioning were used in few pregnant women with COVID-19 admitted to ICU. Over a third of patients were intubated and had to be delivered during ICU stay, mainly due to maternal respiratory worsening, which improved the driving pressure. Despite low maternal and fetal/neonatal mortality rates, delivery during ICU stay and preterm birth were more frequent in case of maternal intubation and the rate of maternal and/or neonatal complications increased with the invasiveness of maternal ventilatory support.

Supplementary Information

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Author contributions
EP, FB and MJ conceived and designed the study. All the authors and members of the COVIDPREG study group collected data in each participating center. EP, FB and MJ analyzed the data. EP, FB and MJ drafted the first version of the manuscript. All the authors contributed drafting the manuscript and approved the final version of the manuscript.

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Declarations

Conflicts of interest
The authors have no conflict of interest to declare.

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