

## 1 INTRODUCTION

2 COVID-19 is caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and includes a  
3 several characterization, from asymptomatic patients to respiratory failure, cardiac and cardiovascular  
4 complications, thromboembolic and inflammatory complications. Pregnancy does not appear to increase  
5 susceptibility to this infection, but physiological changes during pregnancy, such as reduced functional residual  
6 volumes, diaphragm elevation, and altered cell immunity may be at increased risk for severe disease  
7 necessitating maternal intensive care unit admission, mechanical ventilation, and in rare cases, extracorporeal  
8 membrane oxygenation<sup>1, 2</sup>. Deaths have been reported equally in pregnant as in non-pregnant women of  
9 reproductive age<sup>3</sup>. Among pregnant women, especially who develop COVID-19 pneumonia, there is an  
10 increased risk of preterm and cesarean delivery due to fever and hypoxemia<sup>4</sup>.

11 The aim of this report is to describe a case of a third trimester pregnant woman with severe acute respiratory  
12 syndrome from COVID-19, treated with convalescent plasma and undergoing urgent cesarean section with  
13 livebirth without evidence of COVID-19.

## 14 MATERNAL MANAGEMENT

15 On 24 May 2020 a 34-year-old Asian woman at 28 weeks and 4 days of gestation, presented to Villa Sofia  
16 Cervello Hospital, Palermo, with fever, dyspnea and pelvic pain, rapidly deteriorating without benefiting from  
17 paracetamol intake. Negative personal history; obstetric history revealed two livebirths with vaginal delivery  
18 and two miscarriages. At admission, a fetal ultrasound showed a live fetus with regular biometry, without  
19 evaluation of the fetal anatomy in consideration of the gestational age and the clinical condition of the patient;  
20 physical examination showed decreased breath sounds to both lungs basis. Furthermore, arterial blood gases  
21 (ABG) showed: pH 7,439; PaCO<sub>2</sub> 33, 6 mmhg; PO<sub>2</sub> 38, 9 mmhg; SO<sub>2</sub> 70% in room air. Body temperature was  
22 39, 5 °C, blood pressure 125/70 mmhg, pulse rate 124 beats for minutes, and the patient was thachypneic with a  
23 persistent severe hypoxia and a P/F (PaO<sub>2</sub>- FiO<sub>2</sub> ratio) of 64.4. The laboratory findings included a leukocyte  
24 count of 14 x 10<sup>3</sup>μl, neutrophils of 12, 15 x 10<sup>3</sup>μl, lymphocytes of 1,22 x 10<sup>3</sup>μl, C-reactive protein of 14,47  
25 mg/dl, lactate dehydrogenase (LDH) of 445 UI/ml, hypokalemia with 2.9 mEq/L, D-dimer of 474 ng/ml (normal  
26 value in pregnancy). The other exams were within limits. Molecular nasopharyngeal swab for SARS-Cov-2 was  
27 performed with a positive result. The patient was transferred to a negative-pressure isolation room where O<sub>2</sub>  
28 flow was increased from initial 5 to 15 L/min and non-invasive ventilation (NIV) was attempted without  
29 improvements in respiratory failure. So after six hours she was moved to intensive care unit (ICU) and a lung  
30 ultrasound showed thickening of the pleura and multiple irregular confluent pleural lines (B-lines) as from

interstitial pneumonia. A high-flow nasal cannula (HFNC) oxygen therapy was attempted (FiO<sub>2</sub> between 80% and 90%; flow 60 lt/min; temperature at 31°C). There was a slight improvement of oxygenation, but tachypnea persisted and the ABG worsened. Therefore, the patient was sedated and endotracheal intubation with invasive mechanical ventilation was started with improvement of clinical and blood gases findings. Venous thromboembolism prophylaxis with enoxaparin sodium (4000 units twice a day) and empiric antibiotic therapy with Clarithromycin (500 mg twice a day) and Ceftriaxone (2 gr daily) to prevent bacterial superinfection were began. Following this was substituted by Vancomycin (2 gr daily) because *Staphylococcus Aureus* was isolated by bronchoalveolar lavage (BAL) and by hemoculture. Betamethasone (12 mg daily for 2 days) was administered to accelerate fetal lung maturity. During hospitalization serial ultrasound assessments of fetal growth, amniotic fluid volume and Doppler in the umbilical artery were obtained because in patient with severe or life-threatening disease, development of fetal growth restriction is a theoretic concern and has been described with other SARS infections<sup>5</sup>. On 26 May, the patient was placed in prone position <sup>6,7</sup>, due to the persistence of respiratory failure, with the use of supports and pads beneath shoulders and hips to prevent aortocaval compression. The patient started a 12-hour daily cycle of pronation, and a progressive improvement of oxygenation was registered, allowing a FiO<sub>2</sub> decrease. The patient underwent a total of four cycles of pronation, lasting 12 hours each. The last cycle was performed on the fourth day of hospitalization, with no consistent changes in respiratory parameters; therefore, no more cycles were performed. On 27 May, after ethic committee's consent, a sack of convalescent plasma (CP) was administered with improvement of clinical and laboratory findings. The following day, a second sack of CP was administered without complications and with the increase of IgG and IgM the following days. A chest radiograph showed bilateral multiple ground-glass opacities, worse on the left lung, confirming interstitial pneumonia. Lung ultrasounds were used for daily monitoring, to reduce the pregnant patient's exposure to ionizing radiations. On 8 June, the antibiotic therapy was modified, with the addition of Meropenem (1 gr three times a day) because of a bronchial aspirate positive for *Pseudomonas aeruginosa*. The following day the patient's bronchial aspirate came back negative for SARS-CoV-2, but chest radiograph showed an increase of the bilateral opacities, contextually hypoxia and hypercapnia worsened. So on 11 June, at 31 weeks and 1 days of gestation, after a multidisciplinary consultation between obstetrics, pediatrics and anesthetists and after suspension of venous thromboembolism prophylaxis, a cesarean section under general anesthesia (patient was already intubate) was performed without complications. The next day after cesarean section a chest CT scan of the mother confirmed the bilateral ground-glass opacities and broncovascular interstice thickening, as from acute respiratory distress syndrome (ARDS). The patient was

underwent to BIPAP ventilation and on 13 June a tracheostomy was done. Then, the clinical conditions and laboratory findings improved gradually. Patient developed CMV infection with also ocular localization, which was treated with Acyclovir. Finally 18 June patient was in spontaneously breathing and lung ultrasound showed an improvement of findings, confirmed at the next chest CT. So on 26 June patient was transferred from ICU to department of pneumology. A maternal chest X-ray on 02 July showed a resolution of infiltrates of both lung fields. Patient was discharged on 6 July, after a total length stay (LOS) of 43 days, in good general conditions, afebrile, without any respiratory symptom/sign.

## NEONATAL MANAGEMENT

A preterm female infant weighing 1400gr was delivered with APGAR 3-6-7 at one, five and ten minutes. After two ventilation cycles with FiO<sub>2</sub> increasing from 21 to 30%, the infant was intubated about three minute from birth due to the lack of effective respiratory activity. She was connected to a ventilator in synchronous positive pressure ventilation (SIPPV) with the following parameters: PIP 22 cmH<sub>2</sub>O, PEEP 5.5 cmH<sub>2</sub>O, FiO<sub>2</sub> 0.30, FR 45 acts/min, SatO<sub>2</sub> 96% and FC 146 bpm. Two hours after birth, after Rx chest and pulmonary ultrasound that showed the prevalence of confluent B lines, signs of Respiratory Distress Syndrome (RDS), surfactant was administered at 200 mg/kg. The baby was extubated 24 hours after birth and was placed in nasal continuous positive airway pressure (nCPAP) in ambient air. The patient was subjected to one swab and a BAL for the detection of SARS-Cov2 at birth, at 24 hours and 48 hours of life, with negative results. She received total parenteral nutrition for 24 hours; therefore, minimal enteral feeding was undertaken. The patient was treated with dopamine at 5 mcg/kg/min for pressure support for 72 hours and with broad spectrum antibiotic therapy. A brain ultrasound was obtained and it showed: notes of immaturity, not IVH, moderate dilation of the occipital horns, resistance index of anterior cerebral artery (RI-ACA) 0.8. The echocardiography showed the presence of bidirectional Botallo Arterial Duct; a wide 3.5 mm peri-membranous interventricular defect; a large atrial foramen (3.5 mm); a right ventricular chamber with normal contractility; a slightly dilated pulmonary arterial trunk. Blood tests were normal. Five days from birth, patient was transferred to a pediatric cardiac surgery center in Taormina (Messina) for pulmonary bandaging. This surgical operation was performed at 40 days of life. The child's conditions during hospitalization were satisfactory, with good weight gain. The three serological tests performed at the Pediatric Cardiac Surgery Center showed IgM anti Sars-Cov2 negative and a decreasing of IgG values of probable maternal origin due to transplacental passage.

## DISCUSSION

Majority of pregnant women experience only mild or moderate cold/flu-like symptoms, cough, fever, headache, and smell and taste disturbance whereas shortness of breath, myalgia, sore throat and diarrhea are the less common symptoms<sup>8</sup>. Several studies revealed that pneumonia during pregnancy is associated with increased morbidity, mortality and obstetric complications with perinatal adverse outcomes compared to non-pregnant state especially due to changes in immune responses<sup>9, 10</sup>. The physiologic changes of pulmonary function during pregnancy are important to consider severity of disease and to guide ventilator FiO<sub>2</sub> parameters. Indeed, during pregnancy, maternal peripheral oxygen saturation (SpO<sub>2</sub>) should be maintained greater than 95% and maternal PaO<sub>2</sub> greater than 70 mmHg is desirable to maintain a favorable oxygen diffusion gradient from the maternal to the fetal side of the placenta<sup>11</sup>.

In the presence of ARDS of any etiology, prone positioning has proven beneficial effects on oxygenation and mortality<sup>12</sup>. Our data confirmed that pregnant women may be safely prone and this position may improve clinical and blood gasses findings to relieve both diaphragmatic compression from abdominal contents and aortocaval compression from the gravid uterus<sup>13</sup>.

The use of convalescent plasma for the treatment of acute viral illnesses is an established therapy that has previously shown benefit in the treatment of SARS, MERS, and Ebola virus patients<sup>14</sup>. Our patient's clinical conditions partially improved. Therefore, we think that it may be an efficient therapy but probably complete benefit is reached when given early in the course of severe or life-threatening disease<sup>15</sup> and changes in immune response in pregnant women may influence complete response. Anyway, our case confirms the success and safety of convalescent plasma treatment in pregnant patients, as already described by a limited number of other papers<sup>16, 17</sup>.

We showed like severe maternal respiratory disease improved by delivery. Indeed increased oxygen consumption and reduced functional residual capacity, which are normal in pregnancy, may facilitate maternal deterioration in patients with pneumonia<sup>18</sup>. So delivery should be considered as a component of the management of refractory hypoxemic respiratory failure or worsening critical illness in pregnant women. However, maternal care and delivery decisions are best individualized after multidisciplinary discussion with anesthetist, obstetrics, pediatrics to balance risk and benefit for maternal and fetal status.

We also confirmed that lung ultrasound examination is an accurate imaging method to detect pulmonary and pleural conditions useful especially to monitor those patients who require serial exams and pregnancy women because it is a radiation free exam<sup>19, 20</sup>.

119 Some studies report newborn infections and placental infections, so precautions during delivery were necessary  
120 to prevent the rare but possible vertical transmission<sup>21,22</sup>.

121 In the future perspective, other studies on larger numbers of pregnant women with COVID-19 need to be  
122 conducted to better understand the correct maternal and fetus care and the efficacy of several therapies, such as  
123 convalescent plasma.

#### 124 **DISCLOSURE OF INTEREST**

125 All authors have no conflicts of interest to declare, include relevant financial, personal, political, intellectual or  
126 religious interests.

#### 127 **CONTRIBUTION TO AUTHORSHIP**

128 C.G. and T.M.: study concept, data interpretation; M.M.: planning, carrying out and writing of the work; T.D.:  
129 writing of the work for neonatal management; C.S.: data collection, writing of the work; L.B.V., G.E.: data  
130 interpretation for obstetric management; R.B., D.M.: data interpretation for maternal management; T.F.: study  
131 design, data collection, data interpretation.

#### 132 **DETAILS OF PATIENT'S CONSENT**

133 Written informed consent was obtained from the patient for publication of this case report. A copy of the written  
134 consent is available for review by the Editor-in-Chief of this journal on request.

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