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Two critically ill pregnant patients with SARS-CoV-2: A clinical cases report from the Republic of Cyprus

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Abstract

An interdisciplinary and individualized approach should be implemented with regard to the management of severe COVID-19 in pregnancy. The present study deals with the clinical course of 2 pregnant women who have been diagnosed with this disease and needed admission to an ICU and mechanical respiratory support in Cyprus. The data collection took place in a general ICU of the General Hospital of Nicosia. In certain regions of the world, up to 15% of pregnant women were found to have a positive result on polymerase chain reaction testing for SARS-CoV-2 upon admission for delivery. While pregnant women do not appear to be at substantially higher risk of severe manifestations from COVID-19 compared with non-pregnant adults, the disease has resulted in severe maternal morbidity and mortality in both high- and low-resource settings.

Key word: COVID-19, Critical care, Intensive care, ARDS, Pulmonology Respiratory disease, Pregnancy, Coronavirus

Introduction

Pregnant women are a vulnerable group of the population as they are more vulnerable to respiratory infections such as the flu. In addition, due to their reduced functional residual capacity, they are at increased risk of hypoxemia and the development of Acute Respiratory Difficulty Syndrome¹. The anatomical and immunological changes that occur

during pregnancy in conjunction with the disease require careful interdisciplinary strategy for the management of pregnant women with COVID-19².

The present study deals with the clinical course of 2 pregnant women who have been diagnosed with this disease and needed admission to an ICU and mechanical respiratory support in Cyprus. The data

collection took place in a general ICU of the General Hospital of Nicosia. There is currently limited research data on the clinical course of women with severe disease³. According to the Centers for Disease Control and Prevention, COVID-19 does not appear to be associated with increased mortality among pregnant women compared to the general population, although pregnant women appear to be at increased risk of ICU admission and respiratory support¹.

Case study

Case 1

This is a 30-year-old patient with a history of 20 weeks gestation who was diagnosed with covid - 19 on

8/7/21 (Table 1). On 7/18/21 she was admitted to a COVID-19 clinic with symptoms of cough and myalgia. Initially she was respiratory stable with low oxygen demand. Five days after admission, the need for respiratory support increased and treatment was started with High Flow Nasal Cannula (HFNO) with which she showed a partial response. She also presented atypical abdominal pain and epigastric pain and was evaluated by a gynecologist with an ultrasound without any particular findings. Three days after atypical abdominal pain showed further deterioration with intense shortness of breath and decreased hemoglobin saturation (SPO2). The patient was intubated and transferred to the Intensive Care Unit of the Nicosia

Table 1. Pregnant women with severe and critical COVID-19.

CHARACTERISTICS	CASE 1	CASE 2
Age (years)	30	30
GA diagnosis (weeks)	20	13
Medical comorbidities	None	hyperemesis gravidarum bronchial asthma
Pregnancy risk factors	-----	hyperemesis gravidarum
Labs on admission in icu (WBC, Plt, CRP, D-dimer, PCT)	WBC: 4.02 Plt:143 CRP:85.51 D-dimer:700.9	WBC: 7.55 Plt:252 CRP: 171.30 D-dimer: 1377
Arterial blood gas on admission (pH/ pCO2/bicarbonate)	pH 7.14 Pco2 61.9 Bicarbonate 17.3	pH 7.22 Pco2 42,5 Bicarbonate 16.5
Disposition	ICU	ICU
Treatments in ICU	*mechanical ventilation on admission, NRM,	*mechanical ventilation on admission, HFNO,
* Oxygen therapy, Antibiotics and antivirals	HFNO, mask venture 60% 15L O2 *Ceftriaxone 1000mg iv BD	NRM *Ceftriaxone 2000mg iv daily
Corticosteroids	Dexamethasone Sod. Phosphate 6mg iv daily	Dexamethasone Sod. Phosphate 6mg iv daily
Magnesium sulfate	Magnesium Sulfate 20% 2gm stat	Magnesium Sulfate 20% 2gm daily
Other treatments	Omeprazole 40 mg iv daily Human Albumin 20% 100ml IV BD Furosemide 10 mg iv BD	Omeprazole 40 mg iv daily Human Albumin 20% 50ml IV BD
LMWH	Enoxaparin 6000 units sc daily	Enoxaparin 4000 units sc BD
Outcome	6	6
*Length of stay in ICU (total days)		

WBC: white blood cell count; CRP: C-reactive protein; LMWH: low molecular weight heparin

General Hospital for further treatment. The patient was suppressed by continuous infusion of Propofol and analgesia by continuous infusion of fentanyl. Muscle relaxation was also given in continuous infusion with Rocuronium. After intubation, the patient status confirmed Severe Acute Respiratory Distress Syndrome (ARDS) and she was treated with protective mechanical ventilation. Assist Control-Volume Control mode was used with Inhaled Oxygen Mixture (FiO₂- Fraction of Inspired Oxygen) 100%, (VT-Tidal Volume) 350 ml, Breathing Frequency (RR)) 25 per minute, Positive End Expiratory Pressure (PEEP) 12 cmH₂O and PPlateau 24, [Target value below 30, Compliance initially 19. During her hospitalization in the Intensive Care Unit she gradually improved with protective mechanical ventilation and without the need for a prone position. She was extubated on 7/27/21, initially with the need for a High Flow Nose Cannula (HFNO). She improved with physiotherapy and mobilization and was discharged with Venturi mask with FiO₂ = 60% with good gas exchange. At the time of discharge the patient had a very good level of communication and was hemodynamically stable and without fever. A recent fever episode was treated by removing the central venous line and upgrading the antibiotic to piperacillin Tazobactam.

Case 2

This is a 30-year-old patient She was in her second pregnancy at 13 weeks, without a history of vaccination (Table 1). She was found positive in covid - 19 on 7/26/21, and she was admitted to the intensive care unit on 1/8/21, she was intubated due to shortness of breath and fever. Past medical history was positive for... possibly bronchial asthma. Her first pregnancy 6 years ago was delivered by caesarean section. When she was admitted to the Intensive Care Unit, she was sweating profusely, with sinus tachycardia, without hemodynamic instability During her hospitalization in the Intensive Care Unit, she

improved her breathing with protective mechanical ventilation [Assist Control-Volume Control model was used, with breathing volume = 380 ml, PEEP = 12. In the evaluation of respiratory parameters he presented p-plateau 24, compliance = 35.]and was extubated on 4/8/21. After extubation she needed initially non-re-breathing mask and High Flow Nasal Canula with which she maintained good saturation. She improved with physiotherapy. She mobilized out of bed. She was discharged with a good level of communication, hemodynamically stable, she is taking ceftriaxone empirically without fever. On admission 2 pairs of blood culture were positive for staph epi. But were considered to be without clinical significance..A gynecologist was informed who confirmed that the fetus was normal for the week of pregnancy. A chest x-ray with protection of the fetus revealed a thickening in the right upper lung field.

Discussion

In this series of clinical cases, we describe two pregnant women with severe pneumonia, ARDS and mechanical ventilation due to COVID-19. Of these, both required mechanical ventilation. A CDC study of 8,207 pregnant women with SARS-CoV-2 in the United States found that pregnant women were at greater risk of being admitted to the ICU and mechanical ventilation than non-pregnant women of childbearing potential⁴.

Physiological changes during pregnancy increase the risk of acute respiratory failure and the need for mechanical respiratory support. The chest wall shrinks by about 30% during pregnancy. The risk of respiratory failure increases further with decreasing FRC⁵. Mechanical ventilation in pregnant women poses many challenges, including an increased risk of intubation failure due to increased airway swelling, reduced FRC⁶. Because of reduced chest wall compliance caused by the gravid uterus, increased plateau airway pressures may be noted, and careful

attention to these pressures is required⁶.

Pulmonary ventilation in patients with ARDS includes Respiratory Volume 6 ml / kg of ideal body weight with a permissible range of 4-8ml per kg of ideal weight. Regarding the ventilation model, in most cases the Controlled Ventilation with Controlled Volume is chosen due to the fact that the Assist Control-Pressure Control ventilation must be closely monitored because there is a risk of increase of the respiratory volume beyond the acceptable one. Regarding the mechanical properties of the lung, the Plateau pressure must be less than 30cmH₂O and drivind pressure [PPlateu -PEEP <12-15. The SPO₂ target is 94-98% with the lowest possible FiO₂. Target PCO₂ is 30-32 to replicate normal physiology during pregnancy since pregnant women maintain a respiratory alkalosis due to respiratory stimulation by progesterone⁶.

At this stage in both cases there was no question of premature birth or miscarriage. In a series of cases of five pregnant women requiring endotracheal intubation, Hirshberg et al. (2020) reported three women who required preterm delivery due to deterioration of the mother's respiratory status and improvement after delivery. In contrast, Hantoushzadeh et al. (2020) report seven maternal deaths due to COVID-19, six of which occurred after childbirth as part of a worsening clinical condition despite childbirth. In our case, in which conservative obstetric treatment was chosen, which included two women who needed mechanical ventilation and were discharged without requiring urgent childbirth. These cases, together with two similar cases described by Hirshberg et al., (2020) suggest that the mother's clinical condition may improve without childbirth. Avoiding iatrogenic preterm births and associated morbidity and mortality is particularly important for women with a severe clinical picture of COVID-19 in older pregnancies.

Medication to prevent or treat certain conditions of

the mother and fetus is an integral part of the obstetric care routine. The use of two classes of drugs has caused controversy during the COVID-19 pandemic: (1) prenatal corticosteroids. (2) MgSO₄. Practice recommendations are summarized in Table 2.

There is strong evidence to support the use of a single cycle of prenatal corticosteroids (betamethasone or dexamethasone) in women at risk for preterm birth between 24 and 34 weeks of gestation. Prenatal corticosteroids have been shown to reduce the risk of perinatal death, respiratory distress syndrome, intra-abdominal bleeding, necrotic enterocolitis, need for respiratory support and admission to the neonatal intensive care unit (NICU), even in preterm infants⁹. More recent data suggest that the benefits of prenatal corticosteroids may be extended to infants born at 22-24 weeks¹⁰ and between 34 + 0 and 36 + 6 weeks¹¹. However, not all guidelines recommend that they be used in extreme cases of prematurity.

Corticosteroids were associated with an increased risk of mortality in a systematic review of 30 studies that examined their use as adjunctive therapy for influenza¹². However, this study included only one randomized controlled trial (RCT) and the reliability of the available data from observational studies was considered low due to the likelihood of confusion with indication. In addition, the doses used were 4-10 times higher than the standard dose given in pregnancy for fetal lung maturation¹³. In addition, a weak recommendation has been issued for the use of corticosteroids in patients with acute respiratory distress syndrome, based on indirect data¹⁴, and more recently, data from RCTs have shown that a corticosteroid regimen may be beneficial for some patients with COVID-19 pneumonia.

MgSO₄ has been shown to be effective in preventing and treating seizures in preeclampsia at any gestational age¹⁵, and for fetal neuroprotection (reducing the risk of cerebral palsy) when administered to women at immediate risk of preterm

Table 2. Recommendations for use in pregnant patients with COVID-19, drugs regularly administered during pregnancy.

MEDICATION	FDA PREGNANCY CATEGORY	RECOMMENDATIONS
Corticosteroids - Dexamethasone	C	Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
MgSO ₄	D	<ul style="list-style-type: none"> • A new Warning stating that continuous administration of magnesium sulfate injection beyond 5-7 days in pregnancy for the treatment of pre-term labor can cause low calcium levels and bone changes in the baby. • A new Teratogenic Effects section conveying the potential harm to developing babies by changing the Pregnancy Category to D from A. This section also includes the concerns described under the new Warning. • Pregnancy Category D means there is positive evidence of human fetal risk, but the potential benefits from using the drug in pregnant women may be acceptable in certain situations despite its risks. • Pregnancy Category A means that adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy, and there is no evidence of risk in later trimesters. • A new Labor and Delivery section emphasizing that continuous administration of magnesium sulfate injection to treat pre-term labor is not approved and that the safety and efficacy of use for this indication are not established²⁵.
Propofol	B	Propofol is ideal for use during procedural sedation due to the quick onset of action, easy titration, and short duration of action. Propofol does cross the placenta and induces vasodilation of isolated vessels, but has not been shown to alter fetal placental vascular resistance. Animal studies demonstrate no evidence of impaired fertility or harm to the fetus with propofol doses equivalent to those used in humans. ⁴⁸ Although human data is limited, there is no evidence that propofol is associated with fetal adverse effects ²⁴ .
Human Albumin	C	Animal reproduction studies have not been performed with Albumin (Human) 25%. It is also not known whether Albumin (Human) 25% can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Albumin (Human) 25% should be given to a pregnant woman only if clearly needed ²⁶ .
Furosemide	C	Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks ⁶ .
Ceftriaxone	B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women
omeprazole	C	Omeprazole is currently classified as a category C drug (Animal studies show risk but human studies are inadequate or lacking or no studies in humans or animals). However, since the category rating for omeprazole was established, multiple studies have been published demonstrating that omeprazole is as safe as any other PPI for pregnant women ⁴ .
piperacillin Tazobactam	B	Piperacillin/tazobactam is a bacteriolytic combined antibiotic. The least common reported adverse reactions of piperacillin/tazobactam are haematological reactions (<1%). The use of piperacillin/tazobactam during pregnancy is considered to be moderately safe (pregnancy category B) for the human embryo-foetus ²⁸ .

delivery, especially weeks of pregnancy¹⁶. Although MgSO₄ may be associated with an increased risk of maternal respiratory failure, no risk of respiratory failure has been demonstrated¹⁶. Several professional companies support the use of MgSO₄ when indicated in pregnant women with COVID-19. An individual patient should be evaluated for the risks and benefits of using MgSO₄, especially in women with hypoxia. Alternative dose regimens for neuroprotection could be considered on an individual basis, such as a single dose of 4 g MgSO₄ intravenously. According to standard practice, the dose of MgSO₄ should be adjusted in patients with acute renal impairment, which may be characteristic of COVID-19¹⁷.

Both pregnancy alone and covid-19 infection are associated with an increased risk of thrombotic complications, which is considered a cause of morbidity and mortality associated with COVID-19¹⁸. That is why in both cases they take enoxaparin sc daily or BD. The mechanism is probably multifactorial, although the interdependence between inflammation and the coagulation system, or thrombotic inflammation, appears to play an important role¹⁹. High rates of thrombotic complications have been reported in patients with severe and critical COVID-19²⁰. These events are the result of at least two mechanisms: pulmonary microvascular thrombosis (immunothrombosis) and nosocomial venous thromboembolism (VTE)²¹. As pregnancy is a pre-thrombotic condition, the potential for increased risk of thrombosis in pregnant women with COVID-19 has become a matter of concern. However, published data do not suggest that pregnant women have an increased risk of COVID-19 associated thrombotic complications.

A recent announcement by the US Food and Drug Administration (FDA) on drug safety²² suggested that long-term maternal sedation may pose a potential risk to fetal neurodevelopment, although this report does not specifically mention ICU sedation. The ACOG disputed this statement, identifying a

lack of clinical data. Case reports describe the use of propofol during mechanical ventilation without significant damage other than hypotension with an associated reduction in uterine placental perfusion. A report of propofol infusion in two pregnant women undergoing prolonged neurosurgery describes the development of acidosis, as an atypical propofol infusion syndrome²³. In general, safety data on the use of drugs by pregnant women are very poor. The vast majority of drugs currently on the market have never been studied in pregnant women in the pre-licensing trials. On the contrary, any safety data comes from the epidemiological surveillance of medicines after their release on the market. It is worth noting that even for dose titration or drug efficacy, conclusions are drawn by contact, from studies in men or non-pregnant women. Phase I studies for precautionary reasons, while the pharmaceutical companies themselves do not show much interest in this population group, both for commercial and legal reasons. Let's see what conclusions we can come to by looking at the best data so far for the above in our topic through the table above (table 2)²⁴⁻³².

Conclusions

The Intensive Care Unit of the Nicosia General Hospital in Cyprus, is the unit that receives all intubated patients with covid-19 from all over Cyprus, as well as pregnant intubated patients with covid - 19. In addition, we provide details about the obstetric treatment of the women. Our study is constrained by the small sample size, which excluded us from presenting aggregate estimates.

With regard to COVID-19, the incidence of complications for women during pregnancy appears to be equivalent to the general population. Around 85% of pregnant women will have mild symptoms, 10% will have moderate symptoms and 5% are expected to be seriously ill. Research data today indicate that pregnant women with COVID-19 have an increased

risk of miscarriage, premature birth, preeclampsia and caesarean section, especially when hospitalized for pneumonia²⁴. Newborns are at high risk of endometrial death, respiratory failure and admission to the Neonatal Intensive Care Unit²⁵.

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