

Covid-19 Maternal Mortality in Abu Dhabi and the Northern Emirates and a review of all described maternal mortalities

Ghalia Ashoor¹, Juan Acuna², Saleema Wani³, Tarek Ansari³, Sally El Deeb⁴, Jane Kelly³, and Paul Bosio³

¹Fetal Medicine Research Institute

²Khalifa University of Science Technology and Research

³Corniche Hospital

⁴Sheikh Khalifa General Hospital

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Abstract

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Covid-19 Maternal Mortality in Abu Dhabi and the Northern Emirates and a review of all described maternal mortalities

Authors: Ghalia Ashoor-Almahri (Subspecialist in Maternal and Fetal Medicine)^{1,2}, Juan Acuna (Chair of the Department of Epidemiology and Public Health)³, Saleema Wani (Consultant in Obstetrics and Gynaecology)¹, Tarek Ansari (Consultant in Anaesthesia)¹, Sally El Deeb (Consultant in Obstetrics and Gynaecology)⁴, Jane Kelly (Head of Quality)¹, Paul Bosio(Consultant in Obstetrics and Gynaecology)¹

1 Corniche Hospital, SEHA Health services, Abu Dhabi, UAE

2 Harris Birthright Research Centre, Kings College Hospital, London, UK

3 Khalifa University, Abu Dhabi, UAE

4 Sheikh Khalifa General Hospital, Umm-Al-Quwain, UAE

Running title: A review of Covid-19 related Maternal Mortality

Corresponding author: Dr Ghalia Ashoor, Harris Birthright Research Centre, Kings College Hospital, London, SE5 9RS, email: ghalia@doctors.org.uk

Abstract

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Introduction

The case fatality rate of Covid-19 in pregnancy varies based on the current published studies (UKOSS 2020, Lumbreras-Marquez et al 2020). The UK Obstetric Surveillance System (UKOSS 2020) is the largest cohort published to date of 427 pregnant women with a positive SARS-CoV 2 RT-PCR test. In that cohort, 40 women (9%) required level 3 critical care, of those 31 needed delivery due to COVID-19 and 9 were still pregnant whilst four required extracorporeal membrane oxygenation. In this study, 5 women died (3 of which were postnatal women) giving a case fatality rate of 1.2% and a SARS-CoV 2 associated maternal mortality rate of 5.6: 100,000 maternities (UKOSS). Whilst The percentage of women needing critical care is slightly higher than what has been reported from China (Phua et al 2020), the mortality rate is lower, perhaps reflecting a lower threshold for admitting pregnant women to level 3 critical care. It is important to note that 30 women (10 antenatal and 20 postnatal) were still inpatients at the time of analyses (UKOSS). Further, whether the maternal deaths recorded were related to Covid-19 is also unclear in this interim report.

The first Covid-19 case maternal mortality reported in the UK (see Table 1: case 1), was of a 29 year old woman of Pakistani origin with multiple comorbidities including obesity, type 2 diabetes mellitus (T2DM), renal tubular acidosis, asthma, and vitamin D deficiency (Ahmed et al 2020). She also had a still born baby in her first pregnancy which may also reflect her poor background health status. Booking investigations revealed HbA1c of 9.7% and a high albumin creatinine ratio, correlating with subsequent poor diabetes control on metformin and insulin and an ultrasound scan at 26 weeks showing a large for gestational age baby and polyhydramnios. She had over 20 hospital attendances with reduced fetal movements and she eventually was administered corticosteroids for fetal lung maturity. At 29 weeks' gestation she was admitted with a fever and had a normal chest x-ray, was treated with antibiotics and prophylactic low molecular weight heparin (LMWH) and discharged home. She re-attended a week later with severe breathlessness requiring 100% oxygen and diabetes ketoacidosis. She had a caesarean section the following day under GA. The baby was SARS-CoV 2 negative. She improved immediately post-delivery and was extubated on day 3 of admission(?) and continued on intermittent CPAP. However, on day 7 of admission her respiratory function deteriorated and she complained of new onset blurred vision. A CTPA revealed a right lower lobar pulmonary embolism with extensive bilateral ground-glass and patchy solid consolidation consistent with Covid-19 pneumonia and a head CT revealed basilar artery thrombosis. Both her respiratory and neurological conditions rapidly deteriorated and care was withdrawn the following day. This case highlights the thrombotic complications of Covid-19 in pregnancy (Ahmed et al 2020).

In another large cohort of 308 pregnant women with Covid-19 disease reported from Mexico as of the 17th of May, there were 7 maternal deaths (Lumbreras-Marquez et al 2020). This study reports a case fatality rate of 2.3% in pregnant women with Covid-19 disease. The demographics and clinical characteristics of those that survived was compared to those that died and this illustrated that those that suffered a maternal mortality were older, were more likely to be diabetic and obese and have other comorbidities. However, of the 7 maternal deaths only two received intensive care and only one was intubated, raising questions about the quality of maternal care provided to these women. The complications of Covid-19 in pregnancy and the exact causes of the maternal deaths were not described.

In another report from New York on 43 infected pregnant women who presented to hospital for obstetric and non-obstetric reasons, only 2 women needed ICU admission and both recovered (Breslin et al 2020). This cohort included women that were screened for the disease (33% were asymptomatic) and therefore likely reflects less severe disease at presentation. A much larger case series of 462 pregnant women from New York confirmed to be Covid-19 positive by RT-PCR between the 1st of March to the 6th of May was recently published (Blitz et al 2020). The number of women that were classified as severe or critical was 70 (15%) and 13 (2.8%) women were admitted to intensive care due to acute hypoxia. Among this group, 2 died (see Table 1: Case 2 and 3) and 11 were discharged from hospital. Therefore, the case fatality rate in this cohort was 0.4%, still much lower than the UK and Mexican data (Blitz et al 2020, Lumbreras-Marquez et al 2020, UKOSS 2020).

The maternal mortality due to Covid-19 in Iran was recently published from seven level three maternity

hospitals over a 30 day period. The total number of infected pregnant women is not reported and therefore the case fatality rate is not known in this cohort of women (Hantoushzadeh et al 2020). They had 9 pregnant women with severe Covid-19 disease (defined by a positive SARS-CoV 2 RT-PCR nucleic acid testing with dyspnea, blood oxygen saturation <93% on room air or partial pressure of arterial oxygen to fraction of inspired oxygen <300 and an available death certificate) and there were 7 mortalities among these (See Table 1: case 2-8). All Covid-19 pneumonia was treated with osteltamivir, hydroxychloroquine, lopinavir/ritonavir, and low molecular weight heparin prophylaxis. If any of the following clinical signs occurred, loss of consciousness, respiratory rate >24, blood pressure <90/60 mmHg, multilobar lung infiltration on CT or chest x-ray or hypoxemia <90%, then ribavirin was added to the treatment protocol. Steroid treatment was not recommended and all these patients were admitted before 8th of March except one case. Antibiotic administration was dependent on the attending physician's clinical judgement. The cause of death in all seven cases is described in table 1 with the timeline of deterioration and intubation. The seven women were all in the second and third trimesters of pregnancy. Two of the women had no comorbidities, one was obese, three were over the age of 35 years and one suffered from gestational diabetes in pregnancy but none of them had significant hypertension, cardiovascular disease, asthma or renal disease. The women died between 5 to 32 days from the initiation of symptoms. As for the two survivors reported with severe disease, one was still on a ventilator for 35 days at the time of reporting and the other recovered following extubation after 20 days.

We are reporting our Covid-19 related mortality cases at the largest maternity hospital in United Arab Emirates (UAE) providing tertiary referral services. Corniche Hospital has been instrumental in the care of pregnant women in the Emirate of Abu Dhabi during this pandemic. As the primary designated referral centre, minimal care was provided for Covid-19 positive pregnant women outside our facility elsewhere in the Emirate of Abu Dhabi (Abu Dhabi city, Western region and Al Ain). We also provide outreach services and consultation to hospitals in the Northern Emirates of UAE. The Covid-19 related mortalities in pregnancy occurred in May and June; two of these occurred in the Emirate of Abu Dhabi and one was a referral case from the Northern Emirates. These cases should include all the Covid-19 related mortalities in the UAE outside the emirate of Dubai.

UAE Case A:

A Filipino (see Table 1: case 11) primigravida in her late twenties at 27 weeks' gestation was referred to our Hospital from a private facility with a 1 week history of fever and a dry cough. She was otherwise fit and well with no relevant past medical history or recognized co-morbidities and a body mass index of 22. She had been tested with her partner 3 days previously and the RT-PCR results were negative. On arrival she had a borderline temperature of 37.7 degrees after taking paracetamol at home. Her oxygen saturations were 97% in room air and her cardiovascular parameters were all stable. She was admitted to an isolation room but 3 hours later her oxygen saturations dropped to 92% in room air, with a respiratory rate (RR) of 25/min, blood pressure (BP) 91/56 mmHg and a heart rate (HR) of 95 beats per minute. She was initially started on 5l/min oxygen through a nasal cannula and commenced on piperacillin-tazobactam antibiotics, anti-viral (lopinavir-ritonavir), hydroxychloroquine and prophylactic low molecular weight heparin (LMWH). Three hours later, her BP dropped to 82/47mmHg with a stable pulse rate of 99 beats per minute and oxygen saturations at 99% on the 5 L/min nasal oxygen and RR of 20 breaths/min. She was given a fluid challenge and started on a higher treatment dose of LMWH twice a day. The chest x-ray illustrated mid and lower zone pulmonary consolidation and ground glass patchy opacification consistent with COVID-19 pneumonia. A few hours later her saturations continued to drop on oxygen to 90% and therefore she was started on 15 L/min oxygen using a non-rebreathing mask whilst her BP remained stable at 99/59mmHg. She was moved to HDU for continuous monitoring where she initially remained stable until she attempted to mobilise when she desaturated again to 84%. Arterial blood gas (ABG) showed partial pressure of oxygen (PaO₂) of 66, prompting her team to switch her to 20 L/min high flow nasal cannula (HFNC). Her BP was recording borderline low and therefore she was given another fluid challenge which stabilised her readings. The oxygen delivery was increased to 30 L/min HFNC and a repeat ABG showed a PaO₂ of 67.5 and evidence of hyperventilation. Proning was discussed with her but she was unable to tolerate it as she was getting exhausted with increasing shortness of breath. She was therefore started on non-invasive ventilation (NIV) using BIPAP with a PEEP of 8 which

improved her gasses significantly to a PaO₂ of 172. Since her ABG were normal, the FiO₂ was gradually decreased from 0.95 to 0.7 over the subsequent 24 hours. Although her oxygen saturations were normal, repeat ABG showed a PaO₂ of 83 and therefore the FiO₂ (fraction of inspired oxygen) was again increased accordingly. She was stable and repeat arterial blood gasses (ABG) were normal until the morning of day 8 of admission (and day 7 of critical care) with a PaO₂ of 65 on BiPAP (bilevel positive airway pressure) and FiO₂ of 0.7%. Throughout the day the FiO₂ was gradually but repeatedly increased to increase her saturations but her PaO₂ was still 66 and she was getting increasingly physically exhausted. She was therefore intubated that same evening and a central line inserted under ultrasound guidance. The patient remained unstable with little improvement in her PaO₂ and was showing signs of haemodynamic instability when the decision to proceed with an emergency Caesarean section was made. This was performed bedside in the ICU and was surgically uneventful. Her oxygen saturation continued to drop and a bedside chest ultrasound showed a loss of the sliding sign and therefore a pneumothorax was suspected. Repeat chest x-ray confirmed a massive right-sided tension pneumothorax with right lung compression and mediastinal shift to the left in addition to severe progressive bilateral pulmonary consolidation. A chest drain was successfully inserted, and the central line was changed to a quad lumen catheter, but she continued to deteriorate despite full ventilation and inotropic support and arrested 2 times before resuscitation was stopped after 5 cycles of unsuccessful CPR (cardiopulmonary resuscitation) on the occasion of her third cardiac arrest in the early hours of the next morning.

UAE Case B:

A Nepalese woman (see Table 1: case 12) in her mid-thirties was admitted from the Emergency Department(ED) with severe ARDS on presentation. She was cyanotic on admission, with saturations of 30% and was very agitated. She was clearly pregnant and was booked for antenatal care at a private facility but no documentation on gestational age was available on presentation. Collateral history suggested she was approximately 26 weeks into her first pregnancy and had been symptomatic at home for 5 days prior to arriving in hospital. Although she had an elevated BMI of 36, she had no other reported co-morbidities. She was immediately intubated in the ED and started on antibiotics and prophylactic LMWH and transferred to the ICU. In the ICU she was also commenced on antivirals as well as hydroxychloroquine and needed norepinephrine to maintain a MAP above >65. A chest x-ray demonstrated extensive patchy airspace opacity bilaterally in keeping with Covid-19 pneumonia. A bedside ultrasound indicated a likely gestational age of 26 weeks and a decision was made for delivery following multidisciplinary discussions in order to improve maternal resuscitation measures; intramuscular betamethasone was given for fetal lung maturity. On Day 2 following admission, an uncomplicated caesarean section was done bedside in ICU and a 800g baby boy was delivered in reasonable condition, intubated and transferred to NICU. During the Caesarean section, intra-operative oxygen saturations dropped to 78% and there was a mild drop in blood pressure for which she received 500mls of albumin. She was started on hydrocortisone and meropenem postoperatively and proning administered for 16 hours per day. Repeat nasopharyngeal RT-PCR taken after the antivirals were started was negative for Covid-19 but the patient continued to demonstrate clinical and radiological signs consistent with active progressive Covid-19 infection. On Day 3 post-Caesarean Section the dose of LMWH was increased to a therapeutic dose and the following day a repeat chest x-ray showed a mild improvement of the previously noted bilateral pulmonary ground glass opacification with no evidence of pleural effusion or pneumothorax. On Day 5 she was clinically stable, afebrile and inflammatory markers had all improved; all the culture results were negative and therefore the 7 day course of antibiotics and steroids were stopped. However the next day she suddenly deteriorated rapidly over the space of one hour with a temperature of 40 degrees, tachycardia and a gradual but sustained drop in blood pressure that was unresponsive to norepinephrine. She developed deep ST depression in association with worsening hypotension which was then followed by a ventricular escape rhythm with progressive bradycardia and then asystole. The cause of death was likely overwhelming septic shock.

UAE Case C

A Filipino lady in her late thirties (see Table 1: case 13) who presented at 22 weeks and has been symptomatic

for 5 days with a fever, cough, runny nose sore throat and shortness of breath. She is para 3 and had three previous caesarean sections and her risk factors are a BMI of 39 and not receiving any antenatal care during this index pregnancy. On admission her RR was 28/min, oxygen saturation was 93%, BP 130/85 and a HR of 105 beats/min and an oxygen mask with 2 L/min was needed to maintain her oxygen saturations at 97%. She was swabbed for COVID-19 the day prior to admission and the result was positive on admission. Her chest x-ray demonstrated patchy opacification involving both lung fields. She was started on antibiotics and LMWH on the same day. She deteriorated a few hours later and required increase in oxygen flow to 7 L/min to maintain the saturations of 95% and her respiratory rate was stable at 28. The next day she developed metabolic acidosis likely secondary to diabetes with a serum bicarbonate of 11 and ketonuria, her previous history of gestational diabetes puts her at high risk of pre-existing undiagnosed diabetes mellitus for which she was treated. In addition, she also required increasing oxygen demand, and was started on HFNC and was treated with another broad spectrum antibiotic, an IL-6 inhibitor, low dose methylprednisolone and the dose of LMWH was increased to therapeutic dose. The same day further hypoxia resulted in the patient being intubated and mechanically ventilated. A bedside scan showed a singleton pregnancy with an EFW corresponding to 24 weeks of gestation and normal amniotic fluid volume. She remained stable on FiO₂ of 40% but continued to spike fevers so Tazobactam-piperacillin was changed to Merpenem. Her respiratory condition continued to improve and sedation was tapered down on day 10 of admission, however she was unresponsive and sluggish pupillary reflexes were noted. An MRI brain was performed which showed diffuse brain oedema with inferior brain herniation likely secondary to COVID-19 related encephalitis. Therefore dehydration measures were started and a CT brain a few days later was suggestive of global hypoxic injury with impending conisation. A neurological review demonstrated absent pupillary response, absent corneal reflex, no response to deep painful stimuli, spontaneous triggered responsiveness likely due to sparing of lower brain stem. A multidisciplinary team concluded that maternal outcome is poor due to irreversible neurological insult, and since the mothers cardiovascular condition is stable delivery will be delayed until a fetal ultrasound reassessment is performed at 28 weeks gestation and steroids for fetal lung maturity administered. However in the case of maternal cardiorespiratory deterioration then delivery would be expedited. She started to spike temperatures again nearly 3 weeks after admission and blood, urine and sputum cultures all grew *Candida Auris* and she was started on antifungal treatment. A repeat fetal ultrasound scan showed a normally growing fetus with an EFW of 1.15kg and since the temperature spikes continued with increasing frequency and severity a decision was made to expedite delivery to avoid fetal compromise and she had an upper segment caesarean section and cord gasses were normal. The placental histology was examined and there was no evidence of an inflammatory process and a swab from the placenta showed no growth on culture. A repeat CT brain 5 weeks after admission showed more progressive ischemic changes of the cerebellar hemispheres. Using the brain death policy issued by the UAE government, brain death determined by neurological criteria is equivalent to the death of the individual even though the heart continues to beat and spinal cord function may persist.

Discussion

The total number of pregnant women with COVID-19 disease identified in Abu Dhabi so far is 515 (unpublished data) and therefore our case fatality rate in Abu Dhabi is 0.5% lower than what has previously been published (UKOSS 2020, Lumbreras-Marquez et al 2020). All 10 mortalities described due to COVID-19 disease that have been published so far have occurred during the 2nd or 3rd trimester of pregnancy and our three cases also occurred in the second half of pregnancy (see Table 1). This is consistent with the 2009 H1N1 influenza pandemic (Siston et al 2010), where only 7% of the maternal deaths occurred in the first trimester and 27% occurred in the second and the vast majority (64%) occurred in the third trimester. The most common comorbidity in these women is the raised BMI (5 of the 13 women had a BMI > 35), being of South Asian origin (4 of the 13 cases), advanced maternal age in 3 women and T2DM in 2 women.

The cause of death in our case series varied significantly indicating the wide range of COVID-19 related pathology, the first case was due to ARDS and a superimposed pneumothorax, the second case was overwhelming sepsis and the third case was secondary to encephalitis. The maternal death occurred between 5 to 32 days from symptom onset and between 2 to 22 days from admission date (see Table 1). Overall, cause

of death was secondary to ARDS in 10 of 13 cases (77%) and a pneumothorax complicated this in 3 of the 13 cases (23%) which is therefore a likely adverse outcome of the lung disease due to COVID-19 and patients should be closely monitored for such complications. One patient suffered from both a pulmonary embolus as well as an ischemic stroke and was on LMWH from day 1 of symptoms however this patient has multiple comorbidities (see Table 1: case 1) which also highlights the thrombotic complications of COVID-19 disease in addition to the background increased risk of pregnancy and emphasises the need to start high treatment dose as soon as patient is admitted. Of course in cases where the delivery of the baby may be indicated then unfractionated heparin can be used for easier drug reversal. It is important to note that the 3rd case is still on respiratory support and patient remains hospitalised at the time of this publication. Sepsis and septic shock contributed to the cause of death in 3 cases and in our second case (see Table 1: case 12) was the main cause as she deteriorated very quickly after the cessation of antibiotics after 9 days of administration even though clinically she was stable with improving inflammatory markers.

The rate of deterioration was rapid in all three cases in UAE from the point of admission to NIV or intubation indicating that patients were likely to have delayed hospital attendance until symptoms worsened which may also indicate that overall adverse outcome of other non-COVID-19 related pregnancy complications is likely to have increased during this pandemic and this needs further investigations. The majority have started antibiotics and antivirals as well as a LMWH on date of admission. However the treatment protocol differs in different units due to evolving knowledge and experience of the disease and there is a need for a more standardised evidence based approach as more evidence becomes available. The data published from the RECOVERY trial on the significant reduction in mortality in patients that need oxygen therapy is encouraging and should be taken into account when treating COVID-19 pregnant patients however data on pregnancy specific outcomes is still awaiting (Horby et al. 2020).

Disclosure of Interest: Nil

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Ethical approval: Ethical approval was granted for this study by the Abu Dhabi Covid-19 Research IRB Committee. Consent was obtained from the next of Kin of the 3 cases of Maternal mortality for the publication of this manuscript.

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Table 1: Clinical overview of the x maternal mortality cases published to date. Days documented are relative to the initial onset of COVID-19 symptoms except when * then these are days from point of admission as days of symptom onset prior to admission is unknown

**Patient is diagnosed brain dead however life support machine not yet switched off

Abbreviations: UN (unknown), PE (pulmonary embolus), ARDS (acute respiratory distress syndrome), OSA (obstructive sleep apnea), NA (not applicable), BMI (body mass index), T2DM (type 2 diabetes mellitus)

Case	Age (years)	Ethnicity	Comorbidities	GA weeks	Fetal outcome	Day of admission	Diagnosis	Deterioration (day)	Cause of death	Therapy initiation (day)	Therapy initiation (day)	T
1 UK Ahmed et al	29	South Asian	BMI 35, T2DM, Renal tubular acidosis, Asthma, Vitamin D deficiency	31	Alive	8	Viral pneumonia	8	ARDS, PE, Basilar artery thrombosis	UN	1	
2 US Blitz et al	UN	UN	BMI 40, OSA	<24	Miscarriage	UN	Viral pneumonia	8 *	Multiple organ failure	UN	UN	U
3 US Blitz et al	UN	UN	None	37	Alive	8	Viral pneumonia	8	ARDS, Multiple organ failure, Sepsis	UN	UN	U

Case	Age (years)	Ethnicity	Comorbidities	GA weeks/Ethnicity	Fetal outcome	Day of admission	Diagnosis	Deterioration (day)	Cause of death	Therapy initiation (day)	Therapy initiation (day)	Therapy initiation (day)
4 Iran Hantoushaeh et al	25-29	Persian	None	30	Stillbirth	4	Viral pneumonia	5	ARDS	4	4	
5 Iran Hantoushaeh et al	25-29	Persian	Bmi >35	38	Alive	2	Viral pneumonia	4	ARDS	2	2	
6 Iran Hantoushaeh et al	40-44	Persian	Advanced maternal age Sub-clinical hypothyroidism	30	Alive	7	Viral pneumonia	10	ARDS	11	11	
7 Iran Hantoushaeh et al	30-34	Persian	None	24	Stillbirth	4	Viral pneumonia	7	ARDS Pneumothorax	4	4	
8 Iran Hantoushaeh et al	30-34	Persian	Gestational diabetes	36	Alive	2	Viral pneumonia	3	ARDS Pneumothorax	4	4	
9 Iran Hantoushaeh et al	35-39	Persian	Advanced maternal age	24	Twins both stillborn	3	Viral pneumonia	6	ARDS Septic shock DIC Heart failure	4	5	
10 Iran Hantoushaeh et al	45-49	Persian	Advanced maternal age BMI<20	28	Twins both alive	14	Viral pneumonia	15	ARDS	14	14	
11 UAE	28	South Asian	None	27	Alive	3	Viral pneumonia	10	ARDS Pneumothorax	3	3	
12 UAE	36	South Asian	BMI 36	26	Alive	6	ARDS, Septic shock	15	Septic Shock	6	6	
13 UAE	39	South Asian	BMI 39 T2DM	22	Alive	6	Viral pneumonia	8	Encephalitis	NA	6	