Recognition and Treatment of Severe COVID-19 in Pregnancy:

Lessons from a Cohort of 69 Infected Women and an Evidence-Based Guideline

Running Title: 'Managing Severe COVID-19 in Pregnancy'

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Abstract:

Objectives: To determine clinical and laboratory features of pregnant woman with COVID-19 who require respiratory support. To recommend a management strategy that optimises maternal and fetal outcomes.

Design: An observational cohort study of 7000 maternities between 1st March and 1st July 2020.

Setting: Five maternity centres across a maternal medicine network in north-central London, UK

Population: 69 pregnant women with confirmed acute SARS-COV2

Methods: Review of electronic healthcare records

Main Outcome Measures: Clinical and laboratory features, maternal and fetal outcomes.

Results: Respiratory support was needed by 15/69 . This cohort was more likely to present with dyspnoea (10/15 vs 10/54, $p<0.001$), a lower lymphocyte count (0.9±0.1 vs 1.4±0.1 x 10^9 cells/L; $p<0.01$) and hypokalaemia (3.8±0.1 vs 4.0±0.1 mmol/l, $p<0.05$). Radiological evidence of lung consolidation did not identify women in need of respiratory support. Women on respiratory support underwent childbirth at an earlier gestation than those who did not (36^{+4} vs 39^{+5} weeks, $p<0.001$), and required emergency c-section (6/15 vs 8/54, $p<0.05$). Childbirth did not improve respiratory function in those with severe disease, with 3 women remaining on invasive ventilation despite childbirth.

Conclusions: Routine clinical data can identify pregnant women at risk of severe COVID-19. Pregnant women should be offered the same treatment as non-pregnant patients but iatrogenic childbirth should not be the default for women with severe disease. We propose a management pathway for pregnant women with severe COVID-19.

Tweetable Abstract: Diagnosing & managing Severe COVID-19 in Pregnancy: risk factors from routine clinical information and a practical evidence-based guideline.

Keywords: COVID-19, pneumonia, pregnancy

Introduction

At the start of the SARS-CoV2 pandemic, there was international concern that pregnant women would be at high risk of severe disease. This was borne of experience from the 2002-2003 SARS epidemic where maternal mortality was 30% and mechanical ventilation was required by 40% of infected pregnant women (1). Furthermore, during the 2009 H1N1 influenza outbreak, 5% of all deaths were in pregnant women, a disproportionately high number (2,3). The high maternal mortality rate from airborne viral infections may be explained by gestational changes to the maternal immune and respiratory systems (1,4).

Large surveillance reports from the US and UK suggest that while many pregnant women with COVID-19 have good outcomes, pregnant women with COVID-19 are at increased risk of hospital admission, intensive care admission, invasive ventilation and death, compared to a matched non-pregnant population (5–7). Therefore it is essential for clinicians to be able to:

(i) Identify pregnant women at risk of becoming critically ill.

(ii) Optimise management for best maternal and fetal outcomes.

To address these challenges in the setting of pregnancy physiology, and mindful of fetal development, we identified 4 key questions that need to be answered:

1. What clinical features and biomarkers best identify a pregnant woman at risk of severe COVID-19?
2. What is the optimal type of respiratory support for maternal and fetal outcomes?
3. What therapeutic options accelerate maternal recovery without fetal harm?
4. Does iatrogenic premature child birth accelerate maternal recovery?

This analysis presents data on 69 pregnant women with confirmed COVID-19 from 5 hospitals across a central London maternal medicine network, at the peak of the initial COVID-19 pandemic. We identify the characteristics of the women who required respiratory support and describe their medical and obstetric management. We propose a pathway of escalating care for pregnant women requiring respiratory support.

Methods

This observational cohort study included all pregnant women with confirmed acute SARS-CoV-2 infection attending any one of 5 maternity hospitals (Barnet, North Middlesex, Royal Free Hospital, University College London and the Whittington) within the North Central London maternity network between 1st March 2020 and 1st July 2020. Approximately 21,000 maternities per annum are cared for across this network. Patients were not actively involved in the research.

SARS-CoV-2 infection was confirmed through RT-PCR for SARS-CoV2 nucleic acid from nasopharyngeal samples. Sample collection and laboratory processing followed World Health Organisation Guidance (8). At the start of the pandemic, SARS-CoV2 testing was restricted to those women with symptoms suggestive of COVID-19. From the last week of April 2020, increased testing capacity allowed screening of women attending for obstetric care, regardless of symptoms.

Clinical and demographic data were collected from electronic health care records on a standardised form (Appendix S1), and recorded anonymously on an electronic database.

Respiratory support was defined as a requirement for facemask or nasal oxygen, noninvasive or invasive ventilation, or extracorporeal membrane oxygenation.

Data analysis was conducted using GraphPad PRISM 8 and QuickCalc. Mean, median and ranges were documented depending on distribution of continuous data. Comparisons between women requiring respiratory support and those who did not were assessed using Student's t-tests, Mann-Whitney U tests and χ^2 tests, as appropriate.

No funding was awarded to carry out this research. All authors were midwives or doctors who contributed to the collection, analysis and interpretation of the data.

Results

During the four-month observational period, an estimated 7000 women received antenatal care in the North Central London maternity network. Acute SARS-CoV2 infection was confirmed in 69 women (69/7000 (1%)) (Figure 1).

Demographics, Clinical Features and Biomarkers in pregnant women with COVID-19

Fifteen (22%) women required some level of respiratory support. Important differences between those who did and did not require respiratory support are summarised in Table 1. There were no significant differences in age, pre-pregnancy body-mass index, ethnicity or underlying medical comorbidities between those who received respiratory support and those who did not (Tables 1 and 2). All pregnancies were singleton except one twin pregnancy in the group that did not require respiratory support. The majority of women were diagnosed with SARS-CoV2 in the third trimester of pregnancy, including all women who required respiratory support (15/15), and 89% (48/54) who did not. There was no significant difference in the median gestation at presentation between the 2 groups (median (range): 35^{+2} (27^{+1} – 38^{+6}) vs 35^{+6} (7^{+0} – 41^{+4}) weeks). Pregnant women requiring respiratory support were more likely to present with dyspnoea, cough and fever (all $p<0.05$) (Table 1).

Women who required respiratory support had significantly lower lymphocyte counts compared with those who did not ($p<0.01$), but total white cell, neutrophil and platelet counts were similar between groups (Table 3). C-reactive protein (CRP) levels were elevated (> 7mg/L) at presentation in 63/69 (91%) of women but there was no significant difference between those requiring respiratory support or not.

Women who required respiratory support had lower potassium levels (p<0.05); hypokalaemia (K^+ <3.5mmol/L) was present in 2/15 (13%) of women who required respiratory support and 2/54 (4%) of women who did not. Renal function and liver transaminases were within normal ranges and did not differ between groups (Table 3).

Chest radiographs were performed in 32/69 (46%) women. Pulmonary consolidation was evident in the majority of women with COVID-19, whether they required respiratory support (13/15 (87%)) or not (10/17 (59%)) (Table 3).

Management of COVID-19 during pregnancy

Timing of Child Birth (Table 5)

Thirty-three (48%) of the 69 women underwent childbirth while acutely infected with SARS-CoV2. Childbirth was preterm in 26% of women requiring respiratory support compared with 7% who did not (p<0.05). Gestation at delivery was significantly earlier in women receiving respiratory support (p<0.05). More women on respiratory support underwent iatrogenic childbirth (p<0.05), including emergency c-section (p=0.06). Birthweight centile did not differ significantly between groups.

Respiratory Support

Of the 15 women who required respiratory support, 10 (66%) received oxygen through nasal cannulae or face mask, 2 (13%) required continuous positive airways pressure (CPAP), and 3 (20%) were intubated and ventilated. All three ventilated women underwent caesarean section once intubated. Two of these cases are described fully elsewhere (9). In one, mechanical ventilation was required for 4 days after childbirth while another was transferred for Extra Corporeal Membrane Oxygenation (ECMO) after delivery. The third woman required mechanical ventilation for more than 4 weeks as her post-partum period was complicated by multiple pulmonary emboli and muscle weakness (Table 4).

Two women were enrolled in the RECOVERY trial, but outside the trial setting no women received medication to specifically target SARS-CoV19. Twenty-six (38%) women received antibiotics, including ceftriaxone, amoxicillin and co-amoxiclav, more so in those requiring respiratory support (p<0.05) (Table 4).

Outcomes

There was one maternal death (1.4%) unrelated to SARS-CoV2. This woman had mild symptoms suggestive of COVID-19 before childbirth but suffered cardiac arrest during labour, thought to be

due to an amniotic fluid embolus. SARS-CoV2 was confirmed on a post-mortem swab. This case has been included in the UKOSS report on COVID-19 in pregnancy (5). The remaining women have all been discharged home. Total length of hospital stay was not significantly longer in the the group who required respiratory support (Table 4).

Discussion

Main Findings

From 1st March to 1st July 2020, during the first surge of the COVID-19 pandemic, 1% of pregnant women across 5 maternity hospitals in north-central London were confirmed to have acute COVID-19 infection. At the time of study, this incidence was higher than that estimated in the total population of the region (10).

Most pregnant women with confirmed COVID-19 were in the 3rd trimester. This includes those detected during screening for routine obstetric care, which occurs more frequently in late pregnancy. However gestational immune-modulation, the proinflammatory state of the 3rd trimester, and altered respiratory physiology predispose pregnant women to viral pneumonia, which may also explain why all pregnant women requiring respiratory support presented in the 3rd trimester (11–14).

Dyspnoea at presentation was the most discriminatory symptom in identifying pregnant women with severe COVID-19 disease. Although shortness of breath is a common symptom in normal pregnancy, especially in the 3rd trimester, it is not associated with tachypnoea or reduced oxygen saturations (15). The normal ranges for these parameters are unchanged during pregnancy. One hospital in our network now offers oxygen saturation monitors to pregnant women symptomatic of COVID-19 to identify O_2 saturations <94%. Pregnant women should be offered increased respiratory support at the same thresholds of oxygen saturations and respiratory rate as outside pregnancy (16). Furthermore, requirement for respiratory support should not be based on radiographic changes. Consolidation on a chest x-ray was seen in both mild and severe COVID-19 (Figure 2).

Women with severe COVID-19 presented with lymphopenia, which is an indicator of poor prognosis in COVID-19 disease outside of pregnancy (17,18). As lymphocyte counts are elevated in healthy pregnancy compared to non-pregnant adults, even low-normal values in pregnancy should raise suspicion of severe infection (19). Pregnant women with severe COVID-19 also presented with mild hypokalaemia, but we found no cases of severe hypokalaemia (<3.0 mmol/l). Hypokalaemia may reflect increased activity of the renin-angiogensin-aldosterone system (RAAS), which is already more

active during healthy normotensive pregnancy (20). SARS CoV-2 binds the angiotensin-converting enzyme-2 (ACE-2) receptor (21), reducing its activity and resulting. In unchecked activity of RAAS (22) with increased potassium excretion.

Women requiring respiratory support were more likely to have iatrogenic childbirth by emergency caesarean section. Pregnancy increases maternal oxygen demand so iatrogenic childbirth should reduce this rapidly in women with a severe acute lung injury. However, we found that childbirth did not lead to an acute improvement in maternal respiratory function in those women requiring mechanical ventilation.

Strengths and Limitations

Observations were made on 69 pregnant women with COVID-19 from 5 hospitals, providing evidence of biomarkers that aid recognition of pregnant women with COVID-19 at risk of needing respiratory support. Our observations also question the merit of an emergency caesarean section to improve maternal outcomes in those requiring respiratory support. Our conclusions are limited by the relatively small number of pregnant women with severe COVID-19. We were unable to report on therapies made available to treat COVID-19 after the first wave of the SARS-CoV2 pandemic.

Interpretation

In the United States, the Centre for Disease Control collected data on 23,434 pregnant women who were symptomatic of COVID-19 and found that they were 2-3 times more likely to require respiratory support, be admitted to an intensive care unit or die compared with age-matched non-pregnant women (6). The absolute risk of these severe adverse outcomes was however low. For women aged 35-44 years there were 4.2 v 2.3 deaths/1000 cases in pregnant compared with non-pregnant women, respectively (6). Our study identifes early risk factors for severe COVID-19 from routinely-collected clinical and laboratory data that could reduce maternal and perinatal morbidity and mortality.

Respiratory Support in Severe COVID-19 in Pregnancy:

For the majority of pregnant women with severe COVID-19, oxygen saturations can be maintained with oxygen via nasal cannulae or face mask (23,24). If this is insufficient, either high flow nasal oxygen, continuous positive airway pressure (CPAP) or intubation and invasive ventilation may be necessary (23,25–28), with healthcare workers taking appropriate aerosol-generating procedure precautions. Non-invasive ventilation is safe in pregnancy and no adaptations are required for its

use. With intubation and invasive ventilation, there is a higher risk of failed intubation in pregnancy. Ventilator settings must also reflect both pregnancy-specific requirements (such as relative hypocapnia), and settings to optimise ventilation ARDS (29–33). To avoid aortocaval compression by the gravid uterus, ventilation in the prone or semi-prone position can be considered (31,34–36). The method of respiratory support in a pregnant woman with severe COVID-19 must be decided on a case-by-case basis, reflecting the expertise and equipment available.

We illustrate one potential pathway for respiratory support of pregnant women with COVID-19 successfully used by our maternal medicine network (Figure 3).

Timing of Child Birth

Women with severe COVID-19 are offered pre-term childbirth in the belief it will improve maternal outcomes (37). However, pregnant women requiring mechanical ventilation for pneumonia do not necessarily benefit from iatrogenic childbirth, as judged by oxygen requirements, ventilator settings or maternal outcome (30,38). A national review of maternal deaths from COVID-19 in the UK showed that each woman deteriorated despite caesarean section (39). Furthermore, medium-sized operations such as caesarean section generate their own inflammatory response (40), and this may exacerbate the effects of a COVID-19-induced cytokine storm. Preterm delivery puts the neonate at risk of adverse outcomes, even if maternal steroids have been administered to facilitate fetal lung maturation (41,42). In our opinion, caesarean section for maternal benefit, particularly if preterm, should not therefore be a default intervention for women with severe COVID-19.

Therapeutic Treatment of COVID-19 during pregnancy

Since we collected our cohort, the RECOVERY Trial demonstrated that dexamethasone (6 mg daily for 10 days, or until hospital discharge if sooner) improves 28 day all-cause mortality in adults with COVID-19 requiring oxygen therapy (43,44). Pregnant women were excluded from this element of the RECOVERY trial, as dexamethasone crosses the placenta, and there are concerns that antenatal exposure to dexamethasonse can impede childhood neurodevelopment (41,45,46). Other systemic steroids that do not cross the placenta have been recommended for use in pregnant women with COVID-19, though evidence for their efficacy is less robust (43,44,47–49). Therefore we recommend pregnant women with COVID-19 who require oxygen therapy should receive systemic steroids and ideally be offered the same dexamethasone regime (6mg daily for up to 10 days) as non-pregnant patients to improve maternal outcomes. Whether childbirth at less than 34 weeks' gestation should be expedited in order to give the mother with ongoing respiratory distress more than 24mg

dexamethasone, the usual dose given for fetal lung maturation, should be discussed with a multidisciplinary team including neonatologists, adult intensivists and obstetricians.

Some guidelines recommend using remdesivir, a viral RNA polymerase inhibitor, to shorten recovery time in adults with COVID-19 (50–52). However, it does not reduce the need for ventilation, ICU admission, or length of stay (51–53). Furthermore pregnant women were excluded from these trials and evidence for remdesivir's safety, particularly in early pregnancy, is lacking. Therefore we do not recommend the use of remdesivir in pregnant women with COVID-19.

Conclusions

In this cohort, we have shown:

1. Pregnant women with COVID-19 at risk of severe disease typically present with persistent dyspnoea around 6 days or later after the onset of symptoms, with lymphopenia and relative hypokalaemia. Consolidation on a chest x-ray does not indicate whether respiratory support will be required.

2. We could not identify the optimal respiratory support for best maternal and fetal outcomes, but suggest oxygen delivery should escalate from nasal cannulae/face mask to CPAP ± high flow nasal oxygen, then intubation and ventilation. Ventilation in the prone position is appropriate with expert obstetric-midwifery and intensive care.

3. Though our cohort preceeded the outcomes of the RECOVERY and remdesivir studies (43,51–53), we suggest that the fluorinated steroid, dexamethasone should be given to women requiring oxygen therapy to reduce mortality. Further research is needed to determine if non-fluorinated steroids such as prednisolone, which are largely metabolised by the placenta, may also improve outcomes for pregnant women with COVID-19. We do not support the use of remdesivir in pregnancy.

4. For women with severe disease, iatrogenic birth at the time of maternal infection does not itself accelerate maternal recovery and may compromise neonatal outcomes.

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Nil

Disclosure of Interests:
The authors declare no conflicts of interest pertinent to this work

Contributionto Authorship:

RS was involved in the design of the study, collecting and analysing the data and writing the manuscript

CM, HH, LH, CS, SB, IK, SKM, AA, AW, A K-M were involved in collecting the data

DW, MW, MS and EN were involved in the design of the study and writing the manuscript

Ethical Approval: the study was approved and recorded with the audit committee, in agreement with the Joint Reseach Office which categorised this as a clinical audit rather than clinical research as defined by UK Policy Framework for Health and Social Care Research.

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