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Oxygen saturation in pregnant individuals with COVID-19: Time for re-appraisal?

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Condensation: Evidence to support maintaining oxygen saturation ≥95% in pregnancy is lacking; we suggest the use of a range of 92-96% in critically ill patients.

Short Title: Oxygen saturation targets in pregnant individuals.

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Abstract:

Managing pregnant individuals with acute respiratory disease secondary to Coronavirus disease 2019 has been a challenge. Most professional societies including the Society for Maternal Fetal Medicine recommend keeping oxygen saturation greater than or equal to 95% in pregnant individuals. Reaching this target has been increasingly difficult in some patients, especially with the latest wave of the virus attributed to the delta variant. In the absence of strong data, and in the setting of reassuring fetal status, we propose maintaining maternal oxygen saturation between 92-96% for admitted patients with acute respiratory failure requiring supplemental oxygen. This may prevent unnecessary invasive interventions that might not be of maternal or fetal benefit, specifically at very preterm gestational ages.

Keywords: Pregnancy, oxygen saturation, COVID-19

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Introduction & Current guidelines

During pregnancy, several professional societies recommend maintaining oxygen saturation (SpO2) at 95% or greater.[1,2,3] In response to the current Coronavirus disease 2019 (COVID-19) pandemic, the Society for Maternal Fetal Medicine (SMFM) recommends to consider targeting an oxygen saturation that is higher in pregnant individuals with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) than would be recommended for non-pregnant population (SpO2≥92%). Furthermore, they recommend consideration for inpatient monitoring of pregnant individuals with moderate or severe signs/symptoms of COVID-19 and those with SpO2 below 95% on room air with exertion. These patients should call their healthcare provider, undergo prompt evaluation, and be considered for inpatient admission, as they may require higher level of care units such as an intensive care or step-down units. [1]

Other professional societies such as the Royal College of Obstetricians and Gynaecologists (RCOG) and The International Federation of Gynecology and Obstetrics (FIGO) have advocated for a similar cutoff of maintaining an oxygen saturation ≥95%.[2,3] However, the evidence supporting this cutoff is limited. Meanwhile, the World Health Organization (WHO) suggests maintaining SpO2 ≥ 92–95% in pregnant individuals with severe respiratory infection secondary to COVID-19.[4]

What is the evidence behind using a SpO2 of ≥ 95%?

There are no published trials or clinical studies demonstrating that a SpO2 at or above 95% is necessary for pregnant individuals to maintain adequate fetal oxygenation. Expert opinions suggest initiating supplemental oxygen in pregnant individuals when SpO2 falls below 94% and this is based on known physiologic changes in pregnancy such as increase in partial

pressure of oxygen and increased oxygen demand.[5] Some of the current guidelines that suggest maintaining a SpO2 ≥ 95% [3,6,7] cite a paper published by Bhatia et. al.[8] These authors state that a partial pressure of oxygen (PaO2) of 70 mmHg is required to maintain adequate fetal oxygenation, which they also associate with a maternal SpO2 of 95%.[8] Bhatia et. al. make this conclusion based on a study by Catanzarite et al., that included twenty-eight women with acute respiratory distress syndrome (ARDS) requiring intubation during pregnancy or within one week postpartum.[9] This study is limited as it used the older definition of ARDS, included patients only if they were intubated and within 7 days of delivery, and used the birth outcome of "perinatal asphyxia" compared to historical data to suggest a causal mechanism of neonatal hypoxia.[9] Applying this data to modern guidelines ignores the more than 20 years of progress that has been made in the management of ARDS as well as confounding conditions such as the high rate of maternal multisystem organ failure. While evidence from severe acute respiratory syndrome (SARS) and COVID-19, have suggested a higher rate of fetal growth restriction in cases of severe maternal illness,[10,11,12] this is likely multifactorial rather than limited to hypoxemia. There is no compelling objective evidence that a SpO2 of 95% is required for adequate fetal oxygenation.

Mallampali et al., recommend maintaining the maternal PaO2 greater than 60–70 mmHg to avoid adverse effects on uteroplacental perfusion.[13] Whereas other experts suggest that a PaO2 above 60 mmHg (correlating with SpO2 above 90%) is a reasonable target in pregnant individuals with acute respiratory failure.[12,14] This is due to fetal hemoglobin having a higher affinity for oxygen than adult hemoglobin making the fetus more resistant to changes in maternal oxygen saturation and some degree of hypoxia.[15,16] A PaO2 of 60 mmHg was also supported as being adequate for fetal oxygen delivery based on data from pregnant individuals living at high

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altitudes.[17] While this is a chronic rather than acute exposure to hypoxia (and is accompanied by compensation such as tachypnea and relative polycythemia), the majority of pregnant individuals are young and healthy and have good reserve to tolerate even acute hypoxia.[18]

In an effort to decrease maternal morbidity and mortality, early warning models have been developed to assist in the timely recognition of acutely ill patients,[19,20,21] with some models included SpO2 as one of the parameters.[19,20] Unlike other vital signs parameters used, which were associated with increased risk of maternal morbidity, the use of SpO2 <95% was not (relative risk RR 1.3, 95% CI 0.2-7.9).[19] Shields et al. published a maternal early warning tool using different cutoffs for SpO2. They used a SpO2 less than 90% as a single severe parameter and a SpO2 less than 93% as a non-severe parameter. However, low oxygen saturation (whether <90 or <93) was a rare occurrence, seen in less than 0.1% of included patients.[20] In conclusion, the paucity of clinical data and lack of significance seen in early warning models do not provide strong evidence to support using a SpO2 ≥ 95% as a cutoff in pregnant individuals presenting with acute respiratory distress.

Challenges in maintaining a SpO2 ≥ 95%

In non-pregnant individuals with acute respiratory failure secondary to COVID-19, current guidelines recommend starting supplemental oxygen when levels drop below a SpO2 of 90% (strong recommendation, moderate quality evidence) and suggest its use when SpO2 falls below 92% (weak recommendation, low quality evidence).[22] In acutely-ill patients, high quality evidence showed that liberal oxygen therapy (median baseline SpO2 of 96%) is associated with increased mortality.[22] Moreover, practice guidelines for acutely ill patients, including COVID-19 patients with acute hypoxemic respiratory failure, do not recommend administration of

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supplemental oxygen above 96% (strong recommendation, moderate quality evidence) as it may lead to worse outcomes.[22,23,24] In pregnant individuals, Pacheco et. al. also recommend that oxygen therapy should be titrated to avoid SpO2 levels above 96%.[5] Using a minimum target of 95% for oxygen saturation in pregnancy would make it more difficult to titrate oxygen supplementation in order to avoid SpO2>96%.

When COVID-19 progresses to ARDS, there is a paucity of data to guide oxygen goals. Generally, PaO2 goals are 55-80 mmHg extrapolated from the original ARDSNet trial [25] and used more recently in the ACURASYS [26] and ROSE [27] trials. While there may be phenotypes of COVID-19 associated ARDS (CARDS) that respond to high amounts of non-invasive supplemental oxygen support, such as heated high-flow nasal cannula, many of these patients will require invasive mechanical ventilation.[28,29] Indeed, some emerging data suggest that non-invasive positive-pressure ventilation (CPAP or BIPAP) may increase mortality and fail to decrease rates of intubation in critically ill COVID-19 patients.[30] Other modern therapies for ARDS such as prone positioning have been used as alternative interventions to avoid invasive mechanical ventilation and improve oxygenation in COVID-19 patients,[31,32] although these present unique challenges in the pregnant individual.

The criteria to mechanically ventilate pregnant and non-pregnant individuals are similar. These include airway protection, hypoxia, hypercarbia, and hemodynamic instability.[15] Pregnant individuals affected by COVID-19 with the delta variant are more critically ill, requiring oxygen support more often compared with previous variants.[33,34] In pregnant individuals with acute respiratory failure secondary to COVID-19, guidelines suggest targeting maternal oxygen saturation at or above 95% as per professional societies recommendations, while non-pregnant patients often target a PaO2 of 55-80 mmHg or an SpO2>90%. In order to meet this higher goal,

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pregnant individuals may need increased non-invasive oxygen delivery, earlier intubation and mechanical ventilation, increasing fraction of inspired oxygen (FiO2), mean airway pressure, or positive end-expiratory pressure (PEEP). In addition, pregnant individuals will have cephalad displacement of the diaphragm, increased intra-abdominal pressure which prove a mechanical disadvantage in oxygenation, as well as increased oxygen consumption from the developing fetus. This increased oxygenation target is difficult to achieve, especially in patients with COVID-19' latest wave attributed to the delta variant.[33,35] Thus, pregnant patients may be more likely to be exposed to increased invasive interventions when maternal oxygenation goals of 95% are unable to be maintained on non-invasive methods of oxygen supplementation, with potential risks and without clear maternal or fetal benefit.

In its guidance for managing COVID-19 patients, SMFM suggests delivery at or after 32 weeks in settings of refractory maternal hypoxemia.[1]While a cutoff of SpO2 ≥95% seems reasonable and safe to target in the majority of clinical situations, challenges in treating pregnant individuals affected by the most recent COVID-19 wave have raised questions regarding revisiting this recommendation, especially in patients at extreme preterm gestational ages. Designing a randomized controlled trial comparing clinical outcomes with O2 saturations of 92 versus 95 % would be ideal and might be warranted. However, designing and completing such a trial in a timely fashion with the current COVID-19 wave is unrealistic. Individualized patient care based on maternal clinical status and gestational age is of utmost importance.

External fetal monitoring as a non-invasive tool

Fetal oxygenation depends on maternal oxygenation and placental perfusion. Significant disturbances to maternal oxygenation may lead to fetal hypoxia which is often reflected as a non-

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reassuring fetal status on fetal heart rate monitoring.[36] External fetal monitoring can be used as an indicator of fetal wellbeing and having a reassuring fetal heart rate is associated with adequate oxygenation and perfusion of the fetus.[37,38] Fetal heart rate monitoring can be used as an additional "vital sign" that may help manage the maternal condition and guide the decision to move towards additional invasive interventions, if needed. As long as fetal monitoring is reassuring, tolerating maternal O2 saturations between 92-96% is prudent and might prevent detrimental outcomes associated with invasive interventions that could negatively affect both mother and baby.

Furthermore, tolerating lower maternal O2 saturations may prevent unnecessary fetal interventions that could happen at time of intubation or ECMO cannulation which could be challenging depending on the maternal characteristics. In many instances of difficult intubations, maternal oxygen saturation can transiently drop as low as 60-70% and is often associated with changes in variability and decelerations on fetal monitoring.[39] Sustained non-reassuring fetal status often warrants acute interventions such as emergent cesarean delivery which carries significant additional morbidity[40,41] to the mother on top her acute respiratory failure secondary to COVID-19. More so, in cases of very preterm pregnancies, a classical cesarean delivery may be indicated which carries an increased risk of bleeding[42,43] and long-term implications for future pregnancies.[44,45]

Conclusion

A SpO2 below 95% in a pregnant individual with COVID-19 should prompt evaluation by health care provider and may require inpatient admission. For pregnant individuals on supplemental oxygen for acute respiratory failure secondary to COVID-19 infection, there is lack

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of strong evidence supporting the current recommended SpO2 equal to or greater than 95%. We suggest maintaining oxygen saturation in a range of 92-96% in critically ill individuals admitted to the hospital on oxygen supplementation.

In the setting of reassuring fetal heart rate monitoring, this could possibly prevent unnecessary invasive interventions including endotracheal intubation with mechanical ventilation and ECMO. This is especially significant when the decision to escalate towards these measures is based on the concern for maintaining fetal oxygenation rather than supporting the mother's respiratory status. In these situations, external fetal monitoring can be used as an additional non-invasive tool to monitor the fetal well-being and reserve invasive interventions for maternal respiratory status indications as long as fetus is not showing signs of distress.

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