DR. BETH LEONG PINELES (Orcid ID : 0000-0002-0450-2943)

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The Relationship Between Delivery and the PaO2/FiO2 ratio in COVID-19: A Cohort Study

Beth L. Pineles, MD, PhD; Angela Stephens, MD; Leena M. Narendran, MBBS; Ms. Alyssa Tigner, BS; Christopher Leidlein, MD; Claudia Pedroza, PhD, Hector Mendez-Figueroa, MD; Baha M. Sibai, MD

Author Affiliations:
Department of Obstetrics, Gynecology & Reproductive Sciences, McGovern Medical School at The University of Texas Health Science Center at Houston, Texas (Pineles, Stephens, Narendran, Mendez-Figueroa, Sibai); McGovern Medical School at The University of Texas Health Science Center at Houston, Texas (Tigner); Physicians at Sugar Creek / Memorial Family Medicine Residency Program, Memorial Hermann Medical Group (Leidlein); Department of Pediatrics, McGovern Medical School at The University of Texas Health Science Center at Houston, Texas (Pedroza).

Corresponding Author:
Baha M. Sibai, MD
Division of Maternal-Fetal Medicine
Department of Obstetrics, Gynecology and Reproductive Sciences
McGovern Medical School at The University of Texas Health Science Center at Houston
6431 Fannin St., MSB 3.260
Houston, TX 77030
Phone: (713) 500-6425; Fax: (713) 500-0799
Email: Baha.M.Sibai@uth.tmc.edu

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Abstract

Objective: To study the effect of delivery on the pO_2/FiO_2 ratio (P/F ratio) in patients with COVID-19-related acute respiratory distress syndrome (ARDS) and to compare characteristics between delivered and undelivered pregnant patients with COVID-19.

Design: Retrospective cohort.

Setting: Four hospitals in Houston, Texas

Population: Pregnant patients admitted to the hospital for COVID-19

Methods: Among patients with ARDS who were delivered during their hospitalization for COVID-19, linear mixed models were used to investigate time trends before and after delivery of the P/F ratio. Patient characteristics were compared between patients delivered during their hospitalization for COVID-19 and those discharged undelivered.

Main Outcome Measures: The P/F ratio, age, gestational age, length of stay, and severity of illness,

Results: Between May 4, 2020 and July 26, 2020, 61 pregnant patients were admitted for COVID-19. Baseline characteristics were similar between the study groups. Delivery occurred in 21 (34%) of patients during their hospitalization for COIVD-19. Delivered patients had more severe disease and were admitted at a later gestational age than patients not delivered. Ten of these 21 patients (48%) were delivered preterm, and of these, six were delivered due to complications of COVID-19 and four were delivered for obstetric indications. In patients with ARDS who were delivered (n=17), the P/F ratio had a negative slope that improved after delivery.

Conclusions: COVID-19-related ARDS in pregnancy requires multidisciplinary care and individualized decision-making, but delivery slows the deterioration of the P/F ratio in these patients.

Keywords: COVID-19, SARS-CoV-2, coronavirus, critical care, ARDS, respiratory distress, pregnancy, delivery

Tweetable Abstract: Delivery improves the P/F ratio in COVID-19-related ARDS, though individualized delivery management is needed.

Introduction

Pregnant people with Coronavirus Disease 2019 (COVID-19) are more likely to be hospitalized and admitted to the intensive care unit (ICU) compared to their nonpregnant counterparts, though rates of mechanical ventilation are similar.[1,2] Decisions regarding necessity and timing of delivery are a unique consideration of pregnant women with COVID-19 infection. In several case series of pregnant patients with COVID-19, 39%-54% percent of patients were delivered during the initial hospitalization, and 24-57% percent were delivered preterm.[3-5]

One of the major causes of morbidity and mortality in COVID-19 is acute respiratory distress syndrome (ARDS).[6] The case mortality for ARDS in pregnancy is between 9-14%.[7] Pregnant patients with COVID-19-related ARDS are likely to be delivered for maternal indications.[8] However, whether delivery improves maternal survival and reduces morbidity in ARDS is unknown.

Small case series show improvement in some, but not all, respiratory parameters with delivery in ARDS during pregnancy and no clear recommendation for delivery criteria has emerged.[9-12] The pO_2/FiO_2 ratio (P/F ratio) is a ratio of the arterial partial pressure of oxygen to the fraction of inspired oxygen, thus lower values represent worse gas exchange. It is both part of the definition of ARDS (P/F ratio <300) and defines the severity of ARDS. The P/F ratio is slightly lower in pregnant people than in non-pregnant people and has been used in this population.[13] A recent study examined respiratory parameters in ten pregnant patients with ARDS (n=6), pulmonary edema (n=3), septic shock (n=1), or neurological disease (n=1) delivered while on mechanical ventilatory support and found that oxygenation index and PEEP had significant improvements from antepartum to 12-15 hours post-delivery.[14] Though the mean P/F ratio did not change, in both patients with P/F ratios <100, the oxygenation index improved by greater than 40%. However, changes in the P/F ratio around the time of delivery have not been examined in COVID-19-related ARDS. The objective of this study is to examine whether delivery affects time to recovery in pregnant patients with COVID-19 and COVID-19-related ARDS. Our hypothesis is that delivery improves time to recovery in this population.

Methods

This was a retrospective cohort study of all hospitalized pregnant patients with laboratory-confirmed SARS-CoV-2 infection and COVID-19 admitted to one of four large metropolitan hospitals staffed by one university

physician group between May 4, 2020 and July 26, 2020. Patients with asymptomatic SARS-CoV-2 infection were not included. The primary exposure was delivery during hospitalization for COVID-19. Criteria for admission and delivery were at the discretion of the attending physician. Patients were divided into four groups based on the severity of COVID-19: mild, moderate, severe, or critical.[15] Mild COVID-19 was defined as symptomatic patients (fever, cough, fatigue, anorexia, shortness of breath, myalgias) without evidence of viral pneumonia or hypoxia. Moderate COVID-19 was defined as clinical signs of pneumonia (fever, cough, dyspnea, fast breathing) but no signs of severe pneumonia, including oxygen saturation (SpO2) ≥ 90% on room air. Severe COVID-19 was defined as clinical signs of pneumonia plus one of the following: respiratory rate > 30 breaths/min; severe respiratory distress; or SpO2 < 90% on room air. Critical COVID-19 was defined as ARDS (P/F ratio ≤ 300 mmHg), sepsis, or septic shock.[15] When blood gases were unavailable, SpO2 was converted to pO2 using an oxyhemoglobin dissociation curve. Among delivered people with ARDS, the lowest P/F ratio was computed for each day and for the 12 hours before and after delivery. Respiratory specimens were collected by nasopharyngeal swab and SARS-CoV-2 infection confirmed by reverse-transcription-polymerase chain reaction (RT-PCR).

Demographic and clinical characteristics were compared between the group of patients delivered during their hospitalization for COVID-19 and those discharged undelivered using chi-squared, Fisher exact and Wilcoxon tests as appropriate. Primary outcomes were length of stay and P/F ratios. Length of stay was compared between delivered and undelivered patients. Among patients with ARDS who were delivered during their hospitalization for COVID-19, linear mixed models were used to investigate time trends of the P/F ratio before and after delivery. For each hospital day, the lowest P/F ratio was used. The model included gestational age at delivery, a time variable (day), an indicator variable for before and after delivery, and their interaction as covariates. Random intercepts and slopes were included in the model to adjust for within patient correlation. An equal number of observations (days) was selected before and after delivery because most patients had more observations after delivery than before and all but one was discharged home on room air. These models allow us to estimate the change (slope) in the outcome before delivery and after and evaluate whether these slopes are different.

Approval was obtained from the University of Texas Health Science Center at Houston Committee for the Protection of Human Subjects. The STROBE guidelines for reporting observational studies in Epidemiology were followed in this manuscript.[16]

Results

During the study period, 386 women with COVID 19 infection were treated at our 4 hospitals, of whom 61 (15.8%) met criteria for inclusion in our study. Twenty-one (34.4%) patients were delivered during their hospitalization for COVID-19. Delivered patients had more severe disease and were admitted at a later gestational age than patients not delivered (Table 1). Length of stay was significantly longer for patients delivered during their hospitalization (12 days, interquartile range 8-39) compared to those not delivered (6 days, interquartile range 2-9, p=0.029). Ten patients (48%) were delivered preterm, and of these, six were delivered due to complications of COVID-19 and four were delivered for obstetric indications (Table 2).

Among the delivered patients, 17 had adequate data for inclusion in the P/F ratio analysis (Figure 1). The slope of the P/F ratio before delivery is negative (-28.7; 95% CI -44.8 to -12.6) indicating a decrease in the P/F ratio across time. The slope after delivery was also negative but less steep (-1.02; 95% CI -18.9 to 16.8) indicating less of a decrease in the P/F ratio across time after delivery.

Two maternal deaths occurred. The first was in a 39-year-old patient at 27 weeks who self-extubated and delivered via perimortem cesarean without return of spontaneous circulation due to inability to re-intubate. Her medical history was complicated by obesity and type 2 diabetes (Table 2). A second 18-year-old patient with obesity died nine months after preterm delivery for maternal respiratory failure on hospital day 8. She was had multi-organ failure and was never discharged home between her antepartum admission and death.

Discussion

Main Findings. Delivery for pregnant patients with COVID-19-related ARDS improved the trajectory of the P/F ratio.

Strengths and Limitations. The strengths of this study include its relatively large number of very ill patients delivered and the detailed information available about each patient. In the P/F ratio analysis, the mixed-models approach allowed us to isolate the effect of delivery from that of time by comparing the slope of the P/F ratio before delivery to after delivery. The weaknesses of the study include the overall small number of patients, which may have led to the inability to detect differences in baseline characteristics between groups. Additionally, our results do not apply to patients with COVID-19 without ARDS. Additionally, as this is an observational study, causation cannot be inferred.

Interpretation. This study is consistent with prior evidence that suggests improvement of respiratory parameters after delivery in pregnant patients with ARDS.[14] However, much clinical controversy surrounds the topic, and there is no clear recommendation on whether delivery improves the clinical course of pregnant patients with ARDS.[10,11] Multiple studies have described the clinical course of pregnant patients with COVID-19 and critical COVID-19, but this is the first to examine the effect of delivery in pregnant patients with COVID-19-related ARDS. Given the physiological changes of pregnancy that include decreases in total lung capacity, expiratory reserve volume, residual volume, and functional residual capacity, delivery may improve patients' respiratory status.[17] Length of stay was longer in delivered patients than those discharged undelivered, which is likely due to the greater severity of COVID-19 in delivered patients. Obstetric complications were rare and did not contribute significantly to length of stay.

These data provide information for clinicians caring for pregnant patients with COVID-19-related ARDS and demonstrate a small improvement in the P/F ratio. This finding is not generalizable to most pregnant patients with COVID-19 because most do not have ARDS and thus are at a substantially lower risk of morbidity and mortality. Importantly, the deliveries in this analysis occurred at a median of 38 weeks (interquartile range 34-39; range 27-40). Consistent with other case series, 48% were delivered preterm. Gestational age is a critical factor in the decision to deliver, and in our analysis, patients not delivered were at significantly lower gestational age. Importantly, a higher P/F ratio allows weaning of respiratory support which may have implications for long-term health and reduction of lung injury.[18] This paper provides data on the response of the P/F ratio to delivery to assist multidisciplinary teams with the decision to deliver, which is complex and must be individualized.

Further studies are needed to strengthen the body of evidence surrounding delivery considerations in patients with COVID-19. This study was limited to pregnant patients with ARDS, but patients with critical COVID-19 due to other organ system failures may also benefit from delivery and research is needed in this population. Larger studies that can examine mortality and long-term lung injury are sorely needed.

Conclusions. COVID-19-related ARDS in pregnancy requires multidisciplinary care and individualized decision-making, but delivery slows the deterioration of the P/F ratio in these patients.

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Disclosure of Interests: The authors report no conflict of interest.

Contribution to Authorship: BP, AS and SB conceived and designed the analysis; LN, AT, and CL collected the data, BP and CP analyzed the data, BP wrote the manuscript, and all authors contributed substantially to the revision of the manuscript for important intellectual content and approved the final version to be published.

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Table and Figure Legends

Table 1. Comparison of patient characteristics by delivery status

Table 2: Details of patients delivered during hospitalization for COVID-19

Figure 1. Change in pO_2/FiO_2 (P/F) ratio before and after delivery among patients with COVID-19-related acute respiratory distress syndrome (ARDS) (n=17). One patient delivered with ARDS is not included due to perimortem delivery without postpartum data.

Table 1. Comparison of patient characteristics by delivery status

	Not delivered (n=40)	**Delivered (n=21)**	**P value**
Maternal age	29 (26-32)	28 (24-35)	0.982
Race/ethnicity			
Hispanic	22 (55%)	13 (62%)	0.158
Non-Hispanic Black	9 (23%)	1 (5%)	
Non-Hispanic White	5 (13%)	3 (14%)	
Non-Hispanic Asian	0	2 (10%)	
Other or unknown	4 (10%)	2 (10%)	
Nulliparous	7 (18%)	6 (29%)	0.316
Twin pregnancy	0	2 (10%)	0.115
Insurance			
Government-assisted	26 (65%)	2 (10%)	0.555
Private	8 (20%)	16 (76%)	
Self-pay/uninsured	6 (15%)	3 (14%)	
Comorbidities			
Obesity[a]	30 (75%)	18 (86%)	0.332
Hypertensive disease	6 (15%)	0	0.085
Diabetes mellitus	6 (15%)	1 (5%)	0.405
Asthma	6 (15%)	3 (14%)	0.940
Gestational age at admission	**28 (25-29)**	**37 (33-38)**	**<0.001**
Gestational age at delivery	---	38 (34-39)	---
Severity of illness			
Mild	**2 (5%)**	**0**	**0.030**
Moderate	**15 (37%)**	**3 (14%)**	
Severe	**4 (10%)**	**0**	
Critical	**19 (48%)**	**18 (86%)**	
Acute respiratory distress syndrome (ARDS)	**17 (43%)**	**18 (86%)**	**0.001**
Reason for delivery			
COVID-19	---	9 (43%)	---
Labor or scheduled cesarean	---	6 (29%)	---

Preeclampsia with severe features	---	1 (5%)	---
Acute fatty liver of pregnancy	---	1 (5%)	---
Transaminitis	---	1 (5%)	---
Cholestasis of pregnancy	---	1 (5%)	---
Oligohydramnios	---	1 (5%)	---
Perimortem	---	1 (5%)	---
Length of stay	**6 (2-9)**	**12 (8-39)**	**0.029**

Data are presented as median (interquartile range) or n (percent)

[a] Body mass index >= 30 m/kg^2

Bold indicates statistical significance between groups with $p<0.05$

Table 2: Details of patients delivered during hospitalization for COVID-19

Patient number	**Severity of COVID-19**	**Age (years)**	**Gestational age at delivery (weeks.days)**	**Hospital day at delivery**	**Reason for delivery**	**Mode of delivery**	**Respiratory support at the time of delivery**	**Comorbidities**	**Complications**	**Length of postpartum hospital stay (days)**	**Lowest P/F ratio[a]**
1[b]	Moderate	33	34.5	2	Acute fatty liver of pregnancy, monochorionic-diamniotic twins	Cesarean	None	Obesity	Postpartum endometritis, ileus	5	310
2[b]	Moderate	33	38.4	2	Cholestasis of pregnancy	Vaginal	None	Obesity, asthma, late latent syphilis	None	6	329
3[b]	Moderate	31	28.5	1	Preeclampsia with severe features	Cesarean	None	Obesity	None	5	307
4	Critical	33	37.2	3	Labor, dichoronic-diamniotic twins	Cesarean	None	Obesity	None	13	60
5	Critical	27	38.0	5	Labor	Cesarea	Nasal	None	None	2	164

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6	Critical	36	38.0	2	Labor	Vaginal	None	Obesity, lupus, bipolar disorder	Disseminated intravascular coagulopathy, postpartum hemorrhage	5	96
7	Critical	27	38.1	2	Labor, non-reassuring fetal heart rate tracing	Cesarean	None	Obesity	None	7	172
8	Critical	26	38.4	4	Labor	Vaginal	Nasal cannula	None	None	6	172
9	Critical	23	39.4	1	Labor	Vaginal	Nasal cannula	Obesity	None	2	246
10	Critical	39	39.2	1	Scheduled repeat cesarean	Cesarean	None	Obesity	None	4	216
11	Critical	32	36.2	2	Oligohydramnios	Vaginal	Nasal cannula	Obesity	None	3	181
12	Critical	23	33.3	7	Transaminitis, fetal growth restriction, oligohydramnios	Vaginal	Nasal cannula	Obesity, asthma	None	3	112
13	Critical	31	27.2	4	Respiratory failure	Cesarean	Mechanical	Obesity	Respiratory failure	39	55

							ventilation				
14	Critical	31	31.0	4	Respiratory failure	Cesarean	Nasal cannula	Obesity	Respiratory failure	6	69
15[c]	Critical	18	31.5	8	Respiratory failure	Cesarean	Mechanical ventilation	Obesity	Respiratory failure, sepsis, renal failure, liver failure, trachea-esophageal fistula	293	27
16	Critical	23	34.3	4	Respiratory failure	Cesarean	Nasal cannula	Obesity	Respiratory failure, deep vein thrombosis	3	132
17	Critical	38	35.5	2	Respiratory failure	Cesarean	Non-invasive mechanical ventilation	Obesity, severe asthma	Respiratory failure	38	37
18	Critical	23	37.0	3	Respiratory failure	Cesarean	Nasal cannula	Obesity	Respiratory failure	5	106
19	Critical	35	38.0	2	COVID-19 pneumonia	Vaginal	Non-rebreather	Obesity	Respiratory failure	11	73
20	Critical	22	40.1	2	Respiratory failure, non-reassuring fetal	Cesarean	None	None	Respiratory failure	8	78

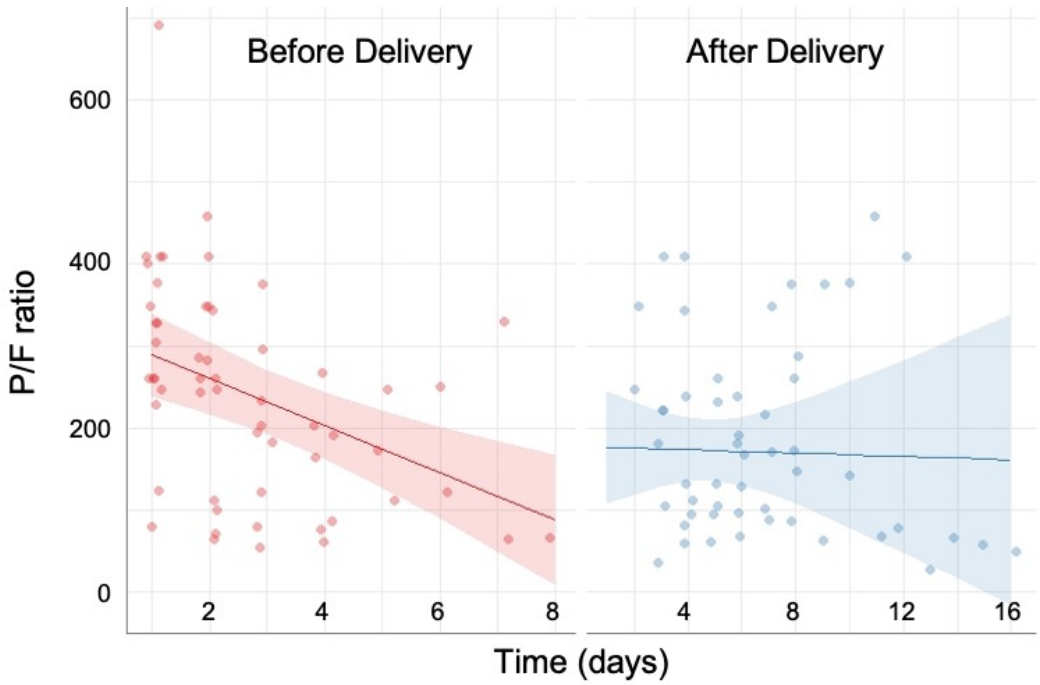
					heart rate tracing							
21[c, d]	Critical	39	27.1	3	Perimortem	Cesarean	None[c]	Obesity, diabetes	Respiratory failure with self-extubation and cardiopulmonary arrest	0	133

[a] pO_2/FiO_2 ratio

[b] Not included in P/F ratio analysis due to no adult respiratory distress syndrome

[c] No respiratory support at the time of delivery secondary to self-extubation

[d] Not included in P/F ratio analysis due to perimortem cesarean delivery with no postpartum P/F ratios



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