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CLINICAL ARTICLE

Obstetrics

Mortality in pregnancy and the postpartum period in women with severe acute respiratory distress syndrome related to COVID-19 in Brazil, 2020

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Abstract

Objective: To estimate fatality rates due to severe acute respiratory distress syndrome (ARDS) related to COVID-19 in Brazilian women, comparing pregnant and postpartum women with nonpregnant women.

Methods: A cross-sectional study of 12 566 pregnant and postpartum women (obstetric group) and 90 025 nonpregnant women (nonobstetric group) aged 15–49 years reported with severe ARDS in 2020. The Brazilian ARDS Surveillance System was used to compare the outcome (death or cure) between the groups, considering age, race, or comorbidities.

Results: The mortality rate related to ARDS/COVID-19 in the obstetric group was 7.8% (377/4853) compared with 13.9% (5946/42 915) in the nonobstetric group. Comorbidity was associated with increased fatality cases for both groups, but higher in the nonobstetric group (22.8% vs 13.3%). In the obstetric group, deaths related to COVID-19 were concentrated in the third trimester or postpartum period. If comorbidity was present, deaths by COVID-19 were 4.4 times higher than ARDS due to other etiologies, and twice higher in women who self-reported as black (13.7%) than white women (6.7%). Considering ADRS etiology, deaths by COVID-19 were 3.4–6.7 times higher than any other etiology.

Conclusion: ARDS related to COVID-19 in obstetric patients was an important factor for worse clinical outcomes, with 3–6 times higher death rates than other ARDS etiologies. Pregnant and postpartum women with severe ARDS related to COVID-19 had a lower fatality rate than nonpregnant women, even with associated comorbidity.

KEYWORDS
acute respiratory distress syndrome, case fatality, coronavirus, COVID-19, maternal death, maternal mortality, mortality rate, pregnancy, SARS-CoV-2

1 | INTRODUCTION

The coronavirus disease (COVID-19) pandemic is a critical issue for global health and it has had a massive impact on all world regions. At the beginning of the pandemic, a major concern among clinicians was whether pregnant women would represent a group at risk for serious outcomes, as previously seen for acute respiratory distress syndrome (ARDS) caused by the influenza virus.[1,2]

New scientific information is continuously being collected. In July 2020, Takemoto et al.[3] reported 124 deaths of pregnant or postpartum women with ARDS caused by COVID-19 in 978 Brazilian women. The authors used information from the Brazilian Ministry of Health's ARDS national surveillance system. Up to February 2021, another three reports with the same or a smaller number of patients were published using information from that database; however, none of the studies reached a conclusion on whether pregnant or postpartum women represent a risk group for serious infection or death caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[4–6]

In a recent study, Lokken et al.[7] reported a COVID-19 case fatality rate in pregnant patients 13.6-fold higher than nonpregnant women of a similar age in Washington State, USA. However, current data indicate that pregnant and postpartum women do not appear to represent a risk group for worse outcomes due to COVID-19 and the literature shows a wide range of mortality rates for this group, ranging from 0 to 11.[7–10]

We are constantly monitoring the ARDS national surveillance system in Brazil to assess the correlation of ARDS and deaths due to COVID-19 in pregnant and postpartum women. The aim of the present study was to evaluate death rates in 2020 due to severe ARDS in pregnant and postpartum women compared with nonpregnant women in Brazil, taking etiology into consideration (i.e. diagnosis of COVID-19 or other respiratory etiologies).

2 | MATERIALS AND METHODS

A cross-sectional study was performed using data for the year 2020 from the Brazilian Acute Respiratory Distress Syndrome Surveillance System (*Sivep-Gripe*), which is the official system for recording cases and deaths due to ARDS in Brazil. The information used herein was gathered since the onset of the COVID-19 pandemic. Aggregate data are available online for public and technical consultations.[11]

A secondary databank containing information for women aged 15–49 years with severe ARDS was built from the national database, which was then divided into two groups: an obstetric group comprising pregnant women and women in the postpartum period (up to 45 days after delivery) and a nonobstetric group comprising nonpregnant women.

National surveillance rules require compulsory notification of all severe ARDS cases from all healthcare units in Brazil, public or private, according to the Brazilian Ministry of Health regulatory guidelines.[12] The notification information is entered locally into the *Sivep-Gripe* by trained healthcare professionals, who fill out a predefined form through a web platform. The informatics system and the notification rules were established in 2009, during the H1N1 pandemic. Once pregnant women were identified as a relevant H1N1 risk group, specific fields related to pregnancy and the postpartum period were incorporated into the form at that time.[13] The criteria required to define an ARDS case consists of two or more of the following symptoms: fever, chills, sore throat, headache, cough, coryza, olfactory or taste disorders AND acute respiratory condition (dyspnea, respiratory distress OR persistent chest discomfort, oppression OR oxygen saturation less than 95% in room air OR bluish coloration of the lips or face).[11]

Inclusion criteria in the present study were all severe ARDS cases in women aged 15–49 years notified between the eighth epidemiological week (starting on February 16, 2020, when the first case of COVID-19 was registered in Brazil) and the 53rd epidemiological week (January 2, 2021). We used the final classification of ARDS etiology (COVID-19 or another respiratory virus or etiological agent) exactly as defined by the Ministry of Health. The diagnosis of ARDS caused by SARS-CoV-2 was confirmed by RT-PCR or serological antibodies.

The filters applied were sex, age at diagnosis, and pregnancy period (first, second, or third trimester or postpartum period). Other analyzed variables were: race self-reported as white, black, brown, yellow (skin color), or indigenous (ethnicity), and associated comorbidities. A detailed definition of the variables and categories is available in the original surveillance recording system.[11]

All information on comorbidities recorded in the obstetric group were reviewed in detail and, in the case of more than one reported comorbidity, one was considered to be the most relevant. This main comorbidity was defined by the authors according to the following predefined order of clinical relevance: chronic respiratory disease (including asthma), cardiovascular disease, diabetes, pregestational obesity (body mass index [BMI, calculated as weight in kilograms divided by the square of height in meters] >30), and other (immune deficiency, hematologic disease, hepatopathy, genetic syndrome, chronic kidney pathology, neurology disorder, cancer, rheumatologic disease, drug addiction or trauma).

The primary outcome analyzed was the evolution of the disease, categorized as cure or death. We also conducted an exploratory analysis calculating an estimated specific mortality rate due to ARDS related to COVID-19 in the obstetric group. The ratio between the number of these deaths obtained in the *Sivep-Gripe* database and the female population aged 15–49 years according to the Brazilian official projections for 2020 was determined.[14] We also estimated a maternal mortality rate as a ratio between the number of deaths due to ARDS related to COVID-19 in the obstetric group and the number of liveborn infants in the year 2019, obtained from the Brazilian Information System on Live Births (SINASC), considering only births from women aged 15–49 years.[15] The results were reported for the whole country and by the 26 Brazilian states and the Federal District (Brazilian capital).

Statistical analysis was done using StatsDirect statistical software, version 3.2.8 2019 (StatsDirect). Groups were compared using

χ^2 test, Fisher exact test, t test, or Mann–Whitney test, and the odds ratio (OR) was calculated with 95% confidence interval (95% CI) as appropriate, with $P < 0.01$ for significance. The detailed study database is available in the Mendeley Data repository (http://dx.doi.org/10.17632/sthf63389g.1).

Evaluation of a public and open databank with anonymous information does not require previous ethical approvals according to Brazilian regulatory requirements.[16]

3 | RESULTS

Severe ARDS was reported in a total of 102 591 women aged 15–49 years: 12 566 (12.2%) in the obstetric group and 90 025 (87.8%) in the nonobstetric group. Figure 1 presents a flowchart of filtered data on severe ARDS related to COVID-19 or other etiologies, and the frequency of clinical outcome (cure or death) for each group. COVID-19 was confirmed in 45.0% ($n = 5660$) of women in the obstetric group and information on the outcome was available for 4853 women, among which there were 377 (7.8%) deaths. In the nonobstetric group, 55.4% of women ($n = 49\ 904$) were confirmed with ARDS related to COVID-19, and information on the clinical outcome was available for 42 915 women, among which there were 5946 (13.9%) deaths. When analyzing cases of severe ARDS due to other etiologies, 148 (2.4%) deaths in the obstetric group and 2694 (7.5%) deaths in the nonobstetric group were registered.
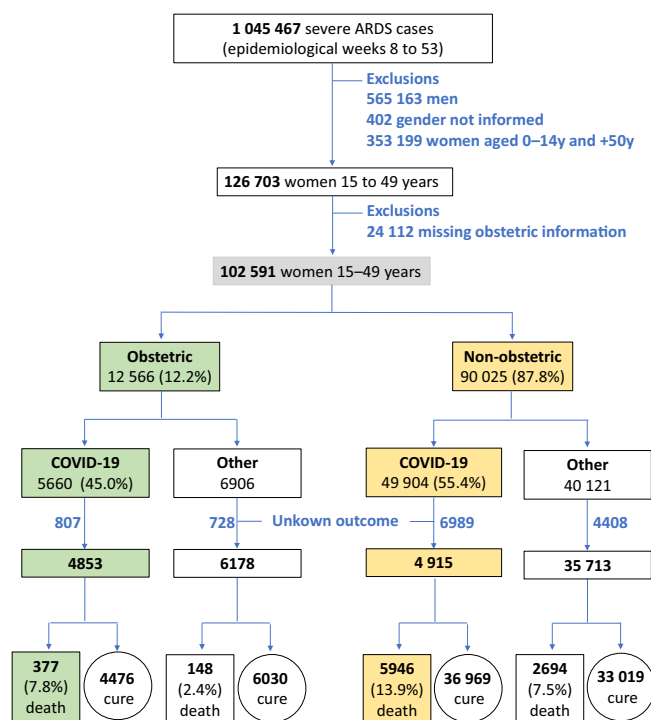

FIGURE 1 Severe acute respiratory distress syndrome (ARDS) case selection flowchart and frequency of clinical outcome (cure or death) in the study groups based on the Brazilian ARDS Surveillance System (SIVEP-GRIPE)

Table 1 shows the distribution of clinical and epidemiological variables in the obstetric group with COVID-19 according to the clinical outcome categorized as death or cure. The average age of the women who died was significantly higher than the women who were cured (31.3 vs 29.1 years, $P < 0.001$). Clinical outcome distribution by pregnancy trimester and postpartum period was also significantly different ($P < 0.001$), wherein deaths were most common in the third trimester (34.8%) and the postpartum period (38.7%). There was a significantly different distribution of death among women by race ($P < 0.001$): brown women comprised 52.5% ($n = 198$) of deaths and 45.7% ($n = 2047$) of cured cases, and black women comprised 9.3% ($n = 35$) of deaths and 4.9% ($n = 221$) of cured cases (ratio = 1.90). Comparatively, both black (13.7%, 35/256) and brown (8.8%, 198/2245) women had a higher frequency of death (9.3%, 233/2501) compared with white women (6.7%, 94/1395) and indigenous women (3.1%, 2/66) ($P < 0.001$). Pregnant women had a lower risk of death than postpartum women (OR 0.34; 95% CI, 27–0.43, $P < 0.001$), as did self-reported white women in relation to black/brown women (OR 0.70, 95% CI 0.54–0.91, $P = 0.005$). Self-reported black women had a higher risk of death in relation to brown women (OR 1.64, 95% CI 1.08–2.43, $P = 0.017$).

Comorbidity in the obstetric group was reported for 50.4% (190/377) of women who died related to COVID-19 and 27.7% (1239/4476) of cured women ($P < 0.001$). There was no statistically significant difference in the distribution of clinical outcome considering whether or not the comorbidities were pre-existing conditions or the type of comorbidity.

Table 2 provides a detailed analysis of the proportion of deaths by etiology and presence of comorbidity for the obstetric and nonobstetric groups. All findings were statistically significant ($P < 0.001$), with the exception of the "COVID-19 ARDS" group without comorbidity and the "Other ARDS" group with comorbidity. The obstetric group had a lower proportion of deaths related to COVID-19 than the nonobstetric group (7.8% vs 13.9%; OR 0.52; 95% CI, 0.47–0.58) and this difference was more evident in women with comorbidity (13.3% for the obstetric group vs 22.8% for nonobstetric group; OR 0.52; 95% CI, 0.44–0.61). If no comorbidity was reported, this inference is still valid, although the proportions are more similar between the groups (5.5% for the obstetric group vs 6.6% for the nonobstetric group). When the etiology of severe ARDS was considered in the obstetric group, death rate related to COVID-19 was 7.8% compared with 2.4% for other etiologies (OR 3.43; 95% CI, 2.83–4.17). Notably, in the cases without comorbidity, the outcome of death related to COVID-19 had an increased OR of 6.76 (95% CI, 6.41–7.52). In a similar analysis for the nonobstetric group, death related to COVID-19 remained twice more frequent as death related to other etiologies (OR 1.97; 95% CI, 1.88–2.07) and this association became more evident in women with comorbidity (OR 6.94; 95% CI, 6.41–7.52).

For the Brazilian female population aged 15–49 years in 2020, the estimated specific COVID-19 mortality rate for pregnancy and the postpartum period was 0.66 per 100 000 women. Considering the number of live births in 2019 in Brazil, the estimated maternal mortality related to COVID-19 in 2020 was 13.60 per 100 000 live

TABLE 1 Clinical outcome and risk of maternal death in obstetric patients with severe acute respiratory distress syndrome (ARDS) related to COVID-19 in Brazil, 2020

Characteristics	Death (n = 377), No. (%)	Cure (n = 4476), No. (%)	P value
Age, years median (IQR)	32 (27–36)	29 (24–34)	<0.001[a]
Age, years mean ± SD	31.3 ± 6.9	29.1 ± 7.1	<0.001[b]
Pregnancy/puerperal cycle			
First trimester	14 (3.7)	350 (7.8)	<0.001
Second trimester	74 (19.6)	827 (18.5)	
Third trimester	131 (34.8)	2295 (51.3)	
Postpartum	146 (38.7)	792 (17.7)	
Unknown	12 (3.2)	212 (4.7)	
Self-reported race (skin color/ethnicity)			
White	94 (24.9)	1301 (29.1)	<0.001
Black	35 (9.3)	221 (4.9)	
Brown	198 (52.5)	2047 (45.7)	
Yellow	5 (1.3)	37 (0.8)	
Indigenous	2 (0.5)	64 (1.4)	
Not available	43 (11.4)	806 (18.1)	
Comorbidity			
No	187 (49.6)	3237 (72.3)	<0.001
Yes (any)	190 (50.4)	1239 (27.7)	
Comorbidity onset (n = 190)			
Before pregnancy	158 (83.2)	979 (79.0)	0.381
Gestational	27 (14.2)	211 (17.1)	
Both	5 (2.6)	49 (3.9)	
Comorbidity type (n = 190)			
Respiratory (asthma)	18 (15) (9.5)	189 (152) (15.3)	0.276
Cardiovascular disease	67 (35.3)	396 (30.6)	
Diabetes	36 (19.0)	235 (19.0)	
Obesity	18 (9.5)	106 (8.6)	
Other or undefined	51 (26.8)	313 (26.5)	
Number of comorbidities (n = 190)[c]			
1	138 (72.6)	1097 (88.5)	<0.001
2 or more	52 (27.4)	142 (11.5)	

[a]Mann–Whitney test.

[b]t test.

[c]Undefined number of comorbidities was considered as 1.

births. Figure 2 shows the distribution of the 377 obstetric deaths related to COVID-19 by state. The specific mortality rate (Figure 2a) and the estimated maternal mortality rate (Figure 2b) are represented by color scale. Both mortality rates decrease progressively from north to south and from the interior regions to the country's coast.

4 | DISCUSSION

COVID-19 was associated with worse clinical outcomes for pregnant and postpartum women in Brazil, even in the absence of other known risk factors. Women in the obstetric group with ARDS related to COVID-19 had a frequency of death 3.4 times higher than women with ARDS due to other etiologies. It is possible that the number of serious cases caused by other etiologies has decreased due to the greater transmissibility and prevalence of SARS-CoV-2 infection in the population.[17] When considering comorbidities, such differences were accentuated, wherein obstetric women with ARDS related to COVID-19 had a frequency of death 4.4 times higher in the presence of comorbidities and 6.7 times higher in the absence of comorbidities compared with ARDS due to other etiologies.

In the Brazilian 2009 H1N1 pandemic, mortality rate was higher than 50% in infected pregnant women.[1] However, a COVID-19

TABLE 2 Acute respiratory distress syndrome (ARDS) outcomes according to ARDS etiology (COVID-19 or other), pregnancy, and comorbidity

Group	Comorbidity Yes			No			All cases		
	Death No. (%)	Cure No. (%)	OR (95% CI)	Death No. (%)	Cure No. (%)	OR (95% CI)	Death No. (%)	Cure No. (%)	OR (95% CI)
COVID-19 ARDS									
Obstetric	190 (13.3)	1239 (86.7)		187 (5.5)	3237 (94.5)		377 (7.8)	4476 (92.2)	
Nonobstetric	4376 (22.8)	14 804 (77.2)	0.52 (0.44–0.61)[a]	1570 (6.6)	22 165 (93.4)	0.81 (0.69–0.95)	5946 (13.9)	36 969 (86.1)	0.52 (0.47–0.58)[a]
Other ARDS									
Obstetric	128 (3.4)	3691 (96.6)		20 (0.8)	2339 (99.2)		148 (2.4)	6030 (97.6)	
Nonobstetric	773 (4.1)	18 132 (95.9)	0.81 (0.67–0.98)	1921 (11.4)	14 887 (88.6)	0.07 (0.04–0.10)[a]	2694 (7.5)	33 019 (92.5)	0.30 (0.25–0.36)[a]
Obstetric									
COVID-19 ARDS	190 (13.3)	1239 (86.7)		187 (5.5)	3237 (94.5)		377 (7.8)	4476 (92.2)	
Other ARDS	128 (3.4)	3691 (96.6)	4.42 (3.50–5.58)[a]	20 (0.8)	2339 (99.2)	6.76 (4.25–10.75)[a]	148 (2.4)	6030 (97.6)	3.43 (2.83–4.17)[a]
Nonobstetric									
COVID-19 ARDS	4376 (22.8)	14 804 (77.2)	6.94 (6.41–7.52)	1570 (6.6)	22 165 (93.4)		5946 (13.9)	36 969 (86.1)	1.97 (1.88–2.07)[a]
Other ARDS	773 (4.1)	18 132 (95.9)		1921 (11.4)	14 887 (88.6)	0.55 (0.51–0.59)[a]	2694 (7.5)	33 019 (92.5)	

[a]Statistically significant results ($P < 0.001$; χ^2 test).
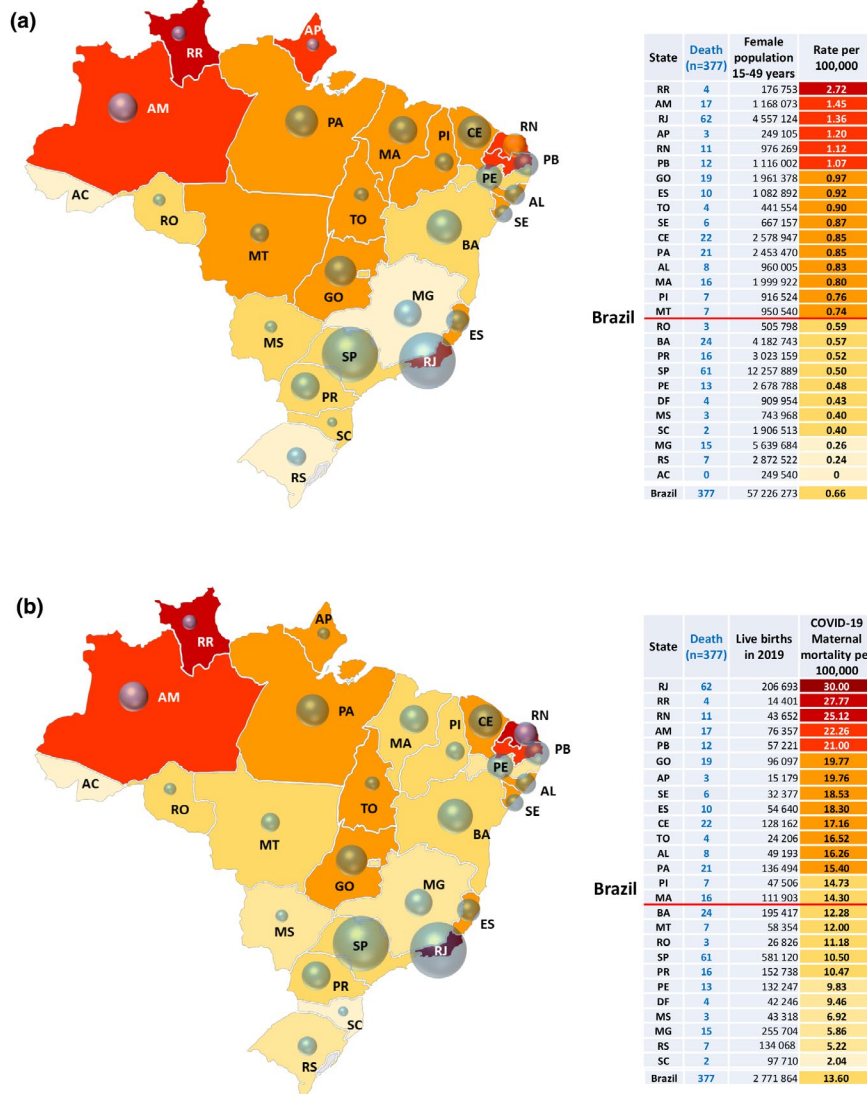
FIGURE 2 Representation of the number of deaths (proportional circles) and the estimated mortality rate (color scale) related to COVID-19 in pregnancy and the postpartum period in 2020, by Brazilian state. (a) COVID-19 specific mortality rate (exploratory). (b) Estimate of maternal mortality considering the number of live births in 2019

diagnosis in severe ARDS appears to have lower case fatality outcomes. In our study, severe ARDS related to COVID-19 in obstetric women had a 7.8% fatality rate, which was lower than in nonpregnant women aged 15–49 years (13.9%). The association with comorbidity worsened the fatality rate in both groups, more evidently in the nonobstetric group (22.8% vs 13.3% for the obstetric group). Considering the women without comorbidity, this fatality association persists, although with a more similar proportion between the groups (6.6% for the nonobstetric group vs 5.5% for the obstetric group). Moreover, comorbidities in the obstetric group were related to 50% of the deaths, but there was no difference concerning the onset of comorbidity before or during the pregnancy, or even to the types of comorbidities considered. Of course, the presence of more than one comorbidity was related to a worse prognosis.

The study by Lokken et al.[7] of 240 pregnant women reported 24 (10%) cases requiring hospitalization and three fatal outcomes (12.5%); it concluded that pregnant patients had a 13.6-fold higher case fatality rate than nonpregnant women. Although the present study had contrasting results with a lower fatality rate among women from the obstetric group (7.8%), only women who were pregnant or in the postpartum period with severe ARDS related to COVID-19 were considered, which represents a more restricted group with a worse prognosis; furthermore, we analyzed a more expressive number of cases with 377 deaths.

In another Brazilian study published in July 2020, preliminary results showed 124 deaths among 978 pregnant women with severe disease related to COVID-19 (12.7% fatality).[3,5] Such information also came from the *Sivep-Gripe* databank; however, comparatively, our study computed considerably more data from an extended period, thus attributing relatively higher relevance to the evidence presented herein. Accordingly, the Pan-American Health Organization (PAHO) report on COVID-19 disease, published on February 9, 2021,

showed that in Brazil there were 299 deaths among 5381 pregnant women who tested positive, with lethality of 5.37%.[18] This more realistic scenario with a lower fatality rate in the obstetric group may be due to improvement in assistance for pregnant women during 2020.

Furthermore, when comparing obstetric and nonobstetric groups, a critical difference in age distribution was found despite both groups having been subject to the same age range inclusion criterion. The nonobstetric group was older (median 39 years vs 29 years for the obstetric group), which may be related to a greater association of comorbidity and worse prognosis in this group. Due to the urgency in providing information, such an age difference is already expected, and the results should be interpreted with caution. Lokken et al.[7] reported similar information for 240 pregnant women with COVID-19, showing a mean age for hospitalization of 32 years compared with 28 years for those who were not hospitalized.

Considering only women in the obstetric group, the age distribution had a smaller difference regarding the clinical outcome, with a mean or median age of 31–32 years for deaths and 29 years for cured cases. Moreover, death outcomes predominated in the third trimester and postpartum period. The obstetric resolution of a severe case in the third trimester may shift many deaths to the puerperal period, as has been noted during our clinical practice. Consistently, Lokken et al.[7] also reported a higher number of COVID-19 cases diagnosed in the third trimester of pregnancy.

Looking at our findings regarding race and ethnicity in the obstetric group, we found that the proportion of deaths was higher in black women, followed by brown, white, and indigenous women. Black women had the worst mortality rate (13.6%), which was twice as high as white women (6.7%). The pandemic pattern of COVID-19 highlights the deficiencies in obstetric care and social inequities in access to health care.[2]

Brazil is a medium-income country of continental proportions and marked socioeconomic differences throughout its territory, reflected in discrepant scenarios in access to health care. Indeed, the distribution of number of deaths per state was not uniform and this is probably related to disparities in population exposure to the virus and the infrastructure available to assist severe cases. We found that, overall, the northern states and, in isolation, the state of Rio de Janeiro in the Southeast region, exhibited the worst COVID-19 mortality and estimated maternal mortality rates. Located in the north region, Manaus—the Amazonas State capital—developed a severe health crisis at the beginning of the pandemic and, more recently, its health system collapsed during the 2021 COVID-19 second wave. Another critical situation happened in the southeast, Brazil's richest region, where the State of Rio de Janeiro experienced 62 maternal deaths in 2020.

As knowledge of COVID-19 advances and vaccination spreads modestly worldwide, there is still a great debate about whether pregnant women are at greater risk for worse outcomes due to COVID-19. In general, pregnant women were more vulnerable during the pandemic. They were advised to stay at home and subsequently were prevented from continuing prenatal care owing to the closure of healthcare units. Most importantly, pregnant women have not participated in studies with vaccines.[19–21] As reported in the present study, severe cases and deaths among pregnant women occurred mainly in certain social strata and patients with comorbidities. We demonstrated that severe ARDS related to COVID-19 cannot be neglected in pregnant and postpartum women, with increasing fatality rates in the presence of comorbidity. In May 2021, the Brazilian Ministry of Health included pregnant and puerperal women with comorbidities in the priority groups for vaccination.[22]

The strengths of the present study include the high number of registries analyzed, with qualified information and nationwide coverage. The high number of complete forms entered in the system and the detailed standardization of the recorded data facilitated its coding and analysis of subgroups. The same nationwide surveillance database was used as a source for another recent research published with 250 000 hospital admissions due to COVID-19 in Brazil,[23] supporting the quality of the data analyzed herein. A limitation is the retrospective nature of the analyzed data and possible underreporting of cases or biased information, especially in the first months of the pandemic when there were some difficulties in carrying out diagnostic tests and establishing important disease definitions.

In conclusion, COVID-19 was an important factor for worse clinical outcomes in Brazilian pregnant and postpartum women with a 3.4-times higher death rate than other ARDS etiologies. In 2020, severe ARDS related to COVID-19 in obstetric patients had a 7.8% fatality rate, an alarming but lower rate than in nonpregnant women (13.9%).

CONFLICTS OF INTEREST

The authors have no conflicts of interest.

AUTHOR CONTRIBUTIONS

CS, MD, and JT: study design, planning and conduct, data analysis, and manuscript writing. DV and FS: study design, data analysis, and manuscript writing. GL: data analysis and manuscript writing.

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