Impact of clinical severity on maternal and perinatal outcome across trimesters in Covid19 pregnancies: a prospective Cohort Study

ABSTRACT

Aims: To analyze the impact of clinical severity on maternal and perinatal outcomes across trimesters in coronavirus disease 2019 (COVID-19) pregnancies. **Study design**: This was a prospective open cohort study of pregnant women with COVID-19 during the prenatal, delivery, postpartum periods from September 2020 to March 2022. **Methodo:** For data analysis, 132 pregnant women who had no pre-existing comorbidities or pregnancy-related complications at the beginning of the cohort were selected. Data related to COVID-19, demographic, clinical, obstetric, laboratory, ultrasound and birth outcomes were collected. **Results:**A total of 132 pregnant women with COVID-19 were followed up for 2237 women-week. Among them, 19.7% experienced maternal complications such as premature rupture of membranes (19.7%), premature delivery (10.6%), postpartum hemorrhage (8.3%), and preeclampsia (6.8%), or fetal/neonatal complications, including small for gestational age (9.1%), need for neonatal intensive care unit (9.1%), and acute fetal distress (6.1%). Having moderate/severe COVID-19 on prenatal care admission (hazard ratio (HR):3.75) and 95% confidence interval (CI95%):1.63; 8.61 or contracting the infection during the second (HR: 6.35; CI95%: 2.35; 17.17) or third trimester (HR:14.35; CI95%:4.85; 42.41) of pregnancy were significantly associated with these maternal complications. Similarly, having moderate/severe COVID-19 on prenatal care admission (HR:3.90; CI95%:1.48; 10.24) or contracting the infection during the second (HR:6.84; CI95%:2.05; 22.84) or third trimester (HR:22.4; CI95%:6.57; 76.33) of pregnancy were also associated with fetal/neonatal complications. **Conclusion:** Pregnant women with COVID-19 have a higher risk of maternal or fetal/neonatal complications if they present with a moderate/severe COVID-19 on prenatal care admission or if the infection occurs in the second or third trimester of pregnancy.

Keywords: pregnancy; COVID-19; pregnancy complications; newborn complications; cohort study.

1. INTRODUCTION

From 2020 to 2021, during the period of high coronavirus disease 2019 (COVID-19) morbidity and mortality, studies involving both pregnant and non-pregnant women, whether infected with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) concluded

that pregnant women with COVID-19 had a higher risk of significant complications in addition to increased risks of adverse outcomes for fetuses and neonates [1,2]. Between 2020 and 2022, cohort and cross-sectional studies conducted in the United States and Brazil corroborated these findings, further indicating that the occurrence of severe infections, gestational diabetes mellitus (GDM), gestational hypertension, and preeclampsia were important outcomes in pregnant individuals with COVID-19 [3,4,5].

A systematic review of 28 clinical practice guidelines for the management of SARS-CoV-2 infection during pregnancy identified points of agreement among them, indicating that pregnancy represents an independent risk factor for severe SARS-CoV-2 infection and that infected pregnant women are at a higher risk of adverse outcomes than non-pregnant infected women [6]. Studies investigating the relationship between the severity of COVID-19 and obstetric/neonatal outcomes found a higher likelihood of maternal and neonatal complications in pregnant women with COVID-19, including premature rupture of membranes (PROM), preterm birth, small-for-gestational-age (SGA) newborns, neonatal intensive care unit (NICU) admissions, and postpartum hemorrhage (PPH), regardless of disease severity [7,8] or whether infection occurred in the first, second, or third trimester of pregnancy [8].

Investigating the adverse events related to COVID-19 during pregnancy could provide relevant information for the development of outpatient and inpatient care protocols for pregnant and postpartum women, fetuses, and newborns. Therefore, we aimed to analyze the impact of clinical severity on maternal and perinatal outcomes across trimesters in Covid-19 pregnancies, who were monitored at a prenatal care unit in the Central Region of Brazil.

2. MATERIAL AND METHODS

This was a prospective open cohort study of pregnant women with COVID-19 followed up during the prenatal, delivery, acute postpartum, and subacute postpartum periods from September 2020 to March 2022 to analyze their maternal, fetal, and neonatal outcomes. Pregnant women with confirmed SARS-CoV-2 infection were selected by reverse transcription quantitative polymerase chain reaction. The study was conducted at the high-risk prenatal outpatient clinic of Júlio Müller University Hospital, Cuiabá, which serves as a referral center for pregnant women with COVID-19 from the entire state of Mato Grosso, with a population of 3.04 million [9].

According to the Brazilian Obstetric Observatory, 636 cases of COVID-19 were reported in pregnant and postpartum women in the state of Mato Grosso between 2020 and 2021 [3]. For this study, a convenience sample of 189 pregnant women of any gestational age was selected and sequentially treated at the aforementioned referral service both as outpatients and during hospitalization. Among these, 33 with pre-existing comorbidities or a confirmed diagnosis of prevalent obstetric complications and 24 who couldn´t participate in the study due to various reasons such as refusal, lack of a legal guardian, or loss to follow-up after the first prenatal visit, were excluded. The remaining 132 who had no pre-existing comorbidities or pregnancy-related complications at the beginning of the cohort were included in the data analysis to ensure that the analyzed outcomes had occurred during the cohort period.

Considering a significance level of 5%, an expected minimum difference of 35% in the non-exposed group, and a proportion of maternal or fetal complications of 50% in the exposed group (given the lack of prior information regarding the proportion of such complications during the COVID-19 period), the statistical power of the studied sample was calculated to be 80%. Only six patients received COVID-19 immunization before contracting the disease.

Data were collected from the medical records during prenatal appointments or in-person visits to the obstetric ward if a pregnant woman was hospitalized. Demographic, clinical, obstetric, laboratory examination, and obstetric ultrasound data were collected during the entire follow-up period. Birth and fetal and neonatal outcome data were collected from the mothers' medical records. Sample characteristics included: age, skin color, marital status, origin, level of education, and family income. Nutritional status was defined by the body mass index [10]. Clinical data included the time of COVID-19-compatible symptoms, severity of COVID-19 at hospital admission, need for ventilator support, and/or intensive therapy on prenatal care admission [11]. Obstetric data included the gestational age (trimester) at the time of COVID-19 diagnosis, delivery type, and maternal and/or fetal/neonatal complications that occurred during the cohort period. Maternal complications were defined as the occurrence of one or more of the following events during pregnancy: PROM; preterm labor (PTL); PPH; preeclampsia; HELLP syndrome; and GDM. Fetal and neonatal complications were defined by the recording of one or more of the following events during the peri- and neonatal period: need for NICU or neonatal ventilatory support (NVS), SGA according to the Fenton growth curve [12], acute fetal distress (AFD) by obstetric ultrasound with Doppler, and an APGAR score of 6 or less at 1 and 5 min after birth. The severity of the clinical stage of COVID-19 on prenatal care admission followed the World Health Organization (WHO) guidelines. Prematurity was defined according to the WHO classification as birth occurring before 37 weeks of gestation [13].

The incidence densities of maternal or fetal/neonatal complications during the cohort period were calculated, and related factors were analyzed by determining the relative risk (RR) and their respective 95% confidence intervals (CI95%) in a comparative (univariate) analysis of non-exposure to such factors. Survival analysis was conducted to estimate the probability of pregnancy not progressing to maternal or fetal/neonatal complications during the cohort period following the baseline assessment. Censoring was performed if the pregnant woman reached the end of the cohort without presenting pregnancy complications, or if she reached

term with fetal/neonatal complications. The incidence density of maternal or fetal/neonatal complications was calculated by considering the contribution time of each pregnant woman in the cohort. The accumulated risk of remaining free from such complications was analyzed using the Kaplan-Meier empirical estimator. The association of covariates with the occurrence of complications over time was analyzed using Cox regression models to determine the hazard ratio for the studied outcomes. For factors that showed statistically significant associations, at a p-value of less 0.20 in the univariate analysis, an adjusted model was constructed using a hierarchical (forward) entry of these variables. To assess confounding factors, the model was controlled for age and obesity. Only variables that remained associated in the adjusted model ($p< 0.05$) were considered to be associated with maternal or fetal/neonatal complications. A significance level of 5% was considered for all analyses. All statistical analyses were performed using Stata software version 12.0 (StatatCorp, Texas, USA).

3. RESULTS AND DISCUSSION

The mean (standard deviation - SD) age of the pregnant women was 27.9 (6.3) years. Predominantly, pregnant women were residents of Cuiabá (82.6%), of a mixed race (65.9%), and had a married or stable union status (56.8%). Approximately half had a high school level of education (55.3%) and an average family income of 1-2 minimum wages (57.6%). Regarding body mass index, 25% and 28% of the pregnant women were diagnosed as being overweight and obese, respectively. Regarding parity, 72% of the pregnant women were multiparous and 28% were primiparous (Table 1).

Table 1. Sociodemographic. clinical and evolutionary characteristics of 132 post-COVID-19 pregnant women followed up during prenatal care at a university hospital in the Central Region of Brazil, 2020-2022.

Characteristics		**n**	**%**
Age maternal (years)	*14 – 18*	8	6.1

	19 – 25	39	29.5
	26 – 35	67	50.8
	36 - 44	18	13.6
Skin color	*White*	21	15.9
	Black	24	18.2
	Brown	87	65.9
Marital Status	*Married/Stable union*	75	56.8
	Single	54	40.9
	Divorced	3	2.3
Area of residence	*Cuiaba metropolitan area*[a]	109	82.6
	Upstate[b]	23	17.4
Schooling	*Incomplete primary education*	8	6.1
	Complete fundamental education	7	5.3
	Incomplete higt school	23	17.4
	Compelte higt school	73	55.3
	University education	21	13.9
Family income	*Up to 1 minimum wage*	24	18.2
	1 - 2 minimum wages	76	57.6
	3 – 5 minimum wages	32	24.2
Body mass index (BMI)	*Low Weight*	12	9.1
	Adequate Weight	50	37.9
	Overweight	33	25.0
	Obesity	37	28.0
Parity	*Primiparous*	37	28.0
	2 – 4	85	64.5
	5 – 7	10	7.5
Clinical classification of COVID-19	*Mild*	117	88.6
	Moderate	6	4.6
	Severe	9	6.8
Need for hospitalization due to COVID-19	*No*	117	88.6
	Yes	15	11.4
Ventilatory support	*No*	118	89.4
	Yes	14	10.6
Mechanical ventilation	*No*	127	96.2
	Yes	5	3.8

Gestational trimester of SARS-CoV-2 infection	*First trimester*	28	21.2
	Second trimester	67	50.8
	Third trimester	37	28.0
Mode of delivery	*Vaginal delivery*	58	43.9
	Cesarean section	74	56.1

[a]*Cuiabá metropolitan area: belong to the city of Cuiabá and Várzea Grande*
[b]*Interior of the state: all other cities belonging to the state of Mato Grosso.*

The mean (SD) duration of COVID-19 symptoms was 4.7 (2.1) days, and the severity on prenatal care admission was mild for the majority (88.6%) of them in all trimesters of pregnancy. Fifteen (11.4%) pregnant women required hospitalization because of moderate or severe COVID-19, 14 (93.3%) of whom required ventilatory support. Among those who underwent ventilatory support, five required mechanical ventilation. Of the pregnant women studied, 21.2% were in their first, 50.8% in their second, and 28.0% in their third trimester. Cesarean section or vaginal delivery occurred in 56.1% and 43.9% of the cases, respectively (Table 1).

The main maternal complications were: PROM (19.7%), PTL (10.6%), PPH (8.3%), preeclampsia (6.8%), GDM (3.0%), HELLP syndrome (1.5%), and deep venous thrombosis (0.8%), which mostly occurred in the third trimester of pregnancy. Fetal and neonatal complications included: SGA (9.1%), need for NICU (9.1%), AFD (6.0%), a 1 min APGAR score of 6 or less (8.3%), and a 5 min APGAR score of 6 or less (3.0%) (Table 2).

Table 2. Maternal, fetal and neonatal complications according to gestational trimester of SARS-CoV-2 infection in a university hospital in Central Brazil, 2020-2022.

Maternal outcomes n=132	**Gestational trimester** n (%)			**Total (%)**
	First	**Second**	**Third**	
PPROM	4 (15.4)	18 (69.2)	4 (15.4)	26 (19.70)
Preterm delivery	1 (7.1)	9 (64.3)	4 (28.6)	14 (10.60)
Postpartum hemorrhage – PPH	2 (18.2)	6 (54.5)	3 (27.3)	11 (8.33)
Preeclampsia - PE	1 (11.1)	6 (66.7)	2 (22.2)	9 (6.81)
Gestational diabetes mellitus - GDM	-	3 (75.0)	1 (25.0)	4 (3.03)

HELLP syndrome	-	2 (100.0)	-	2
Thrombosis	-	1 (100.0)	-	1
Fetal/neonatal outcomes n=132				
Neonatal intensive care unit - NICU	2 (16.7)	7 (58.3)	3 (25.0)	12 (9.09)
Small for gestational - SGA	2 (7.1)	5 (7.5)	5 (12.5)	12 (9.09)
Acute fetal distress - AFD	1 (12.5)	4 (50.0)	3 (37.5)	8 (6.06)
Score APGAR ≤ 6 at 1 min	1 (9.1)	8 (72.7)	2 (18.2)	11 (8.33)
Score APGAR ≤ 6 at 5 min	-	2 (50.0)	2 (50.0)	4 (3.03)

PPROM, Preterm premature rupture of membranes; HELLP syndrome: hemolysis, elevated liver enzymes, low platelet count

The incidence densities of maternal and fetal/neonatal complications during the cohort period were 2.1 per 100 women-week and 1.5 per 100 women-week, respectively. The most common maternal complications were PROM (1.2 per100 women-week) and PTL (0.6 per100 women-week). The most frequent fetal/neonatal complications were the need for NICU, SGA, and being born with a 1 min APGAR score of 6 or less, all with equal incidence densities of 0.5 per 100 women-week (Table 3).

Table 3. Incidence density of maternal and fetal/neonatal outcomes in the study population.

	Incidence density /100 pregnant women/week	
Maternal outcomes	**Rate**	**95% confidence interval**
PPROM	1.2	0.8; 1.7
Preterm delivery	0.6	0.3; 1.0
Post partum hemorrhage	0.5	0.2; 0.9
Preeclampsia	0.4	0.2; 0.8
Gestational diabetes mellitus	0.2	0.1; 0.5
HELLP syndrome	0.1	0.0; 0.3
Deep vein thrombosis	0.04	0.0; 0.2
Total maternal complications	2.1	1.5; 2.7
Fetal/neonatal outcomes		
Need for NICU	0.5	0.3; 0.9
Small for gestational age	0.5	0.3; 0.9
Acute fetal distress	0.4	0.2; 0.7
APGAR Score ≤ 6 at 1 min	0.5	0.2; 0.9
APGAR Score ≤ 6 at 5 min	0.2	0.05; 0.5
Total fetal/neonatal complications	1.5	1.0; 2.1

PPROM, Preterm premature rupture of membranes; HELLP: hemolysis, elevated liver enzymes, low platelet count. 95% IC: 95%confidence interval; NICU, neonatal intensive care unit.

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140 The univariate analysis of the probable risk factors associated with maternal or fetal/neonatal
141 complications is shown in Table 4. Significant associations with maternal complications were
142 the occurrence of COVID-19 in the second (RR:2.97; CI95%:1.27; 8.03) or third (RR:4.11;
143 CI95%:1.41; 12.72) trimesters of pregnancy and moderate/severe COVID-19 on prenatal
144 care admission (RR:2.99; CI95%:1.21; 6.51). Similarly, for fetal/neonatal complications,
145 associated factors were the occurrence of COVID-19 in the third trimester of pregnancy
146 (RR:5.75; CI95%:1.79; 21.45) and moderate/severe COVID-19 on prenatal care admission
147 (RR:3.16; CI95%:1.07; 7.81).

Table 4. Crude and adjusted analysis of factors associated with the incidence of maternal or fetal/neonatal complications among the study population.

Analyzed factors			**Crude analysis**	
Maternal complications (n=132)	**Incidence density** /100 pregnant women/week		**RR[a] (95%CI)[b]**	**p-value**
Gestational trimester of SARS-CoV-2 infection	*First*	0.86	1.00	-
	Second	2.54	2.97 (1.27; 8.03)	0.005
	Third	3.53	4.11 (1.41; 12.72)	0.005
Maternal age (years)	*18 - 35*	2.02	1.00	-
	<18 or >35	2.20	1.08 (0.46; 2.29)	0.801
Skin color	*White*	1.75	1.00	-
	Black	1.95	1.11 (0.48; 3.02)	0.830
	Brown	2.74	1.57 (0.45; 4.76)	0.363
Obesity	*No*	1.93	1.00	-
	Yes	2.18	1.13 (0.61; 2,11)	0.683
Clinical classification of COVID-19	*Mild*	1.82	1.00	-
	Moderate/ Severe	5.44	2.99 (1.21; 6.51)	0.012
Fetal/neonatal complications (n=132)				
Gestational trimester of SARS-CoV-2 infection	*First*	0.61	1.00	-
	Second	1.58	2.58 (0.92; 8.89)	0.051
	Third	3.53	5.75 (1.79; 21.45)	0.001

Maternal age (years)	*18 – 35*	1.42	1.00	-
	<18 or >35	1.70	1.20 (0.44; 2.84)	0.648
Maternal skin color	*White*	1.18	1.00	-
	Black	2.00	0.59 (0.24; 1.58)	0.234
	Brown	1.99	1.00 (0.33; 3.05)	0.994
Maternal obesity	*No*	1.32	1.00	-
	Yes	1.64	1.24 (0.59; 2.65)	0.540
Severity clinical stage of COVID-19	*mild*	1.29	1.00	-
	Moderate/ Severe	4.08	3.16 (1.07; 7.81)	0.024

[a]RR, Relative risk; [b]95% CI, 95% confidence interval; p-value: > 0.05.

In univariate analysis of the time spent until the occurrence of maternal or fetal/neonatal complications, COVID-19 during pregnancy increased the proportional risk of maternal complications, with a hazard ratio (HR) (CI95%) of 6.91 (2.65; 18.01) when the infection occurred in the second trimester and 13.02 (4.72; 35.96) when the infection occurred in the third trimester of pregnancy, compared with the first trimester. Another factor associated with maternal complications in this survival analysis was the clinical classification of moderate/severe COVID-19 on prenatal care admission, with a HR (CI95%) of 4.94 (2.21; 11.04), compared with mild COVID-19. A significant association was also observed for fetal/neonatal outcomes, with a HR (CI95%) of 7.52 (2.37; 24.11) and 20.44 (6.51; 64.15) when COVID-19 occurred in the second and third pregnancy trimesters, respectively, compared with the first trimester. Similarly, moderate/severe COVID-19 on prenatal care admission reduced the time to fetal/neonatal complications (HR:5.05; CI95%: 1.96; 13.01) compared with the mild COVID-19. Age, skin color, and obesity were not associated with maternal or fetal or neonatal complications in the survival analysis (Table 5).

Table 5. Crude and adjusted analysis of factors associated with survival time free of maternal and fetal and neonatal complications among the study population.

Analyzed factors		**Crude analysis**			**Adjusted analysis**		
Maternal complication n=132		Hazard ratio[a]	$CI_{95\%}$[b]	p	Hazard ratio	$CI_{95\%}$	p
Gestational trimester	*First*	1.00		-	1.00		

of SARS-CoV-2 infection	*Second*	6.91	2.65; 18.01	< 0.001	6.35	2.35; 17.17	<0.001
	Third	13.02	4.72; 35.96	< 0.001	14.35	4.85; 42.41	<0.001
Maternal age (years)	*18 – 35*	1.00		-	1.00		-
	<18 or >35	1.31	0.62; 2.76	0.474	0.87	0.40; 1.89	0.724
Skin color	*White*			-			
	Black	0.72	0.28; 1.85	0.489			
	Brown	0.79	0.39; 1.60	0.519			
Obesity	*No*	1.00		-	0.80	0.43; 1.51	0.496
	Yes	1.30	0.72; 2.32	0.383			
Severity clinical stage of COVID-19	*Mild*	1.00		-	1.00		-
	Moderate/Severe	4.94	2.21; 11.04	< 0.001	3.75	1.63; 8.61	0.002
Fetal/neonatal complications (n=132)							
Gestational trimester of SARS-CoV-2 infection	*First*	1.00		-	1.00		-
	Second	7.56	2.37; 24.11	0.001	6.84	2.05; 22.84	0.002
	Third	20.44	6.51; 64.15	0.001	22.40	6.57; 76.33	<0.001
Maternal age (years)	*18 – 35*	1.00		-	1.00		-
	<18 or >35	1.38	0.59; 3.22	0.453	1.01	0.42; 2.46	0.974
Maternal skin color	*White*	1.00		-			
	Black	1. 09	0.41; 2.92	0.856			
	Brown	0.65	0.28; 1.51	0.315			
Maternal obesity	*No*	1.00		-	1.00		-
	Yes	1.38	0.69; 2.75	0.359	0.81	0.38; 1.71	0.579
Severity clinical stage of COVID-19	*Mild*	1.00		-	1.00		-
	Moderate/Severe	5.05	1.96; 13.01	0.001	3.90	1.48; 10.24	0.006

[a]**Hazard ratio**: Hazard is the probability that a participant who did not have the event until a certain moment will have it at that moment; [b]**95%CI**: 95% confidence interval; ; HELLP: hemolysis, elevated liver enzymes, low platelet count; p-value: > 0.05; Variables with p<0.20 in the analysis were included in the adjusted analysis: premature rupture of membranes, pre eclampsia, HELLP syndrome, severity of COVID-19, and trimester of occurrence of COVID-19.

163 The accumulated survival probability without maternal or fetal/neonatal complications
164 progressively decreased during the follow-up period and stabilized after the 30th week
165 (Figure 1A, B). Adjusted association analysis for age at risk and obesity confirmed
166 moderate/severe COVID-19 on prenatal care admission (HR:3.75; CI95%:1.63; 8.61) and
167 infection in the second and third trimesters of pregnancy as associated factors with maternal
168 and fetal/neonatal complications in the studied cohort (Table 5).

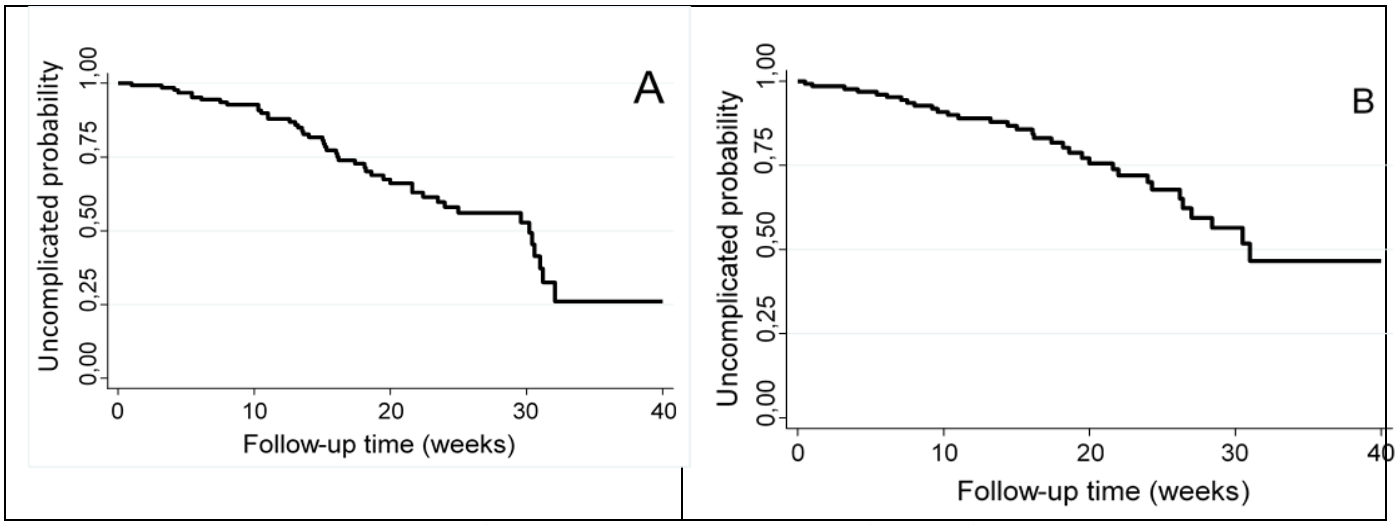

Figure 1 - Survival curves without maternal (A) or fetal/neonatal (B) complications during the follow-up of pregnant women who contracted COVID-19 followed up in a prenatal care center in Central Brazil**.**

169

170 This study demonstrated that COVID-19 during pregnancy increases the risk of maternal
171 and fetal/neonatal complications. The occurrence of infection in the second or third trimester
172 of pregnancy and a clinical classification of moderate/severe COVID-19 on prenatal care
173 admission were the main risk factors for such complications. The main maternal
174 complications found were PROM, PTL, PPH, and PE. The main fetal and neonatal
175 complications found were the need for NICU, SGA, and AFD.

176 Similarly, in Israel, Fallach et al. (2022) observed that pregnant women infected with SARS-
177 CoV-2 in the third trimester had a higher risk of maternal complications, primarily PTL, than
178 uninfected pregnant women [14]. In another study, the risk of all adverse events in pregnant
179 women with COVID-19 was low during the first trimester and increased with gestational age
180 [15]. Among pregnant Japanese women, it was observed that there was an increased risk of
181 progression to moderate/severe COVID-19 when the infection occurred in the second or
182 third trimester of pregnancy compared with non-pregnant women [16]. In contrast, an
183 American study found an increased risk of PROM before labor, PTL, fetal growth restriction,
184 and PPH in prenatal SARS-CoV-2 infections regardless of the trimester of pregnancy [8].

Major maternal complications observed in this study were PROM, PTL, PPH, and PE. The incidence of preeclampsia (6.8%) was not higher than that expected for pregnant women, which is between 3% and 8% according to the International Society for the Study of Hypertension in Pregnancy [17]. However, if we consider the exclusion of known risk factors for PE in the study population, it can be inferred that the complication rate was higher than that expected for all pregnant women with preexisting comorbidities [17].

Known risk factors for eclampsia, such as age, obesity, and skin color, were not associated with maternal complications in this study. It is likely that COVID-19 itself is associated with moderate to severe hypertensive disorders that occur during pregnancy, such as PE and HELLP syndromes. In a French cohort study, Simon et al. (2022) showed that the risk of PTL was twice as high in pregnant women with COVID-19 after adjusting for factors associated with prematurity. In the same study, the occurrence of preeclampsia and GDM was also associated with COVID-19 when comparing pregnant women with or without the SARS-CoV2 infection [18]. A study conducted in the UK suggested that SARS-CoV-2 infection may be associated with preterm birth and severe hypertensive manifestations, such as eclampsia [19]. Similarly, in Mexico, a logistic regression analysis of pregnant women infected with SARS-CoV-2 found that the risk of PE was 2.2 times higher in infected pregnant women than in noninfected pregnant women [20]. A systematic review that evaluated the quality of various clinical practice guidelines for the management of SARS-CoV-2 infection during pregnancy also identified a higher risk of severe preeclampsia, TPP, and neonatal SGA in infected pregnant women [6]. In Brazil, controversial results regarding adverse maternal, fetal, and neonatal outcomes of COVID-19 during pregnancy have been published [21]. Guida et al. (2022) reported that pregnant women with COVID-19 were not more prone to PE or HELLP syndromes; however, they also found that obesity increased the risk of PE in pregnant women with COVID-19 [21].

The most frequently observed fetal/neonatal complications in this study were the need for NICU admission, SGA birth, and AFD. In similar studies on pregnant women without COVID-19, the incidence of fetal/neonatal complications was much lower (1.8%) than that reported here, as was the incidence of the need for a NICU (5.2%). However, the incidence rates of SGA and AFD were similar [22]. In the United Arab Emirates, Dileep et al. (2022) investigated the relationship between the severity classification of COVID-19 and obstetric/neonatal outcomes in pregnant women. They included only pregnant women without comorbidities in their sample to avoid bias during the evaluation. They found that pregnant women with severe COVID-19 had a higher probability of presenting with adverse maternal and neonatal outcomes, defined as preterm birth, SGA, neonatal infection, and/or the need for NICU admission. Moreover, the study also showed a high incidence of preterm births, the need for NICU admission, and SGA, regardless of the severity of COVID-19 [7]. In contrast to our results, Piekos et al. (2022), in a retrospective cohort study assessing the impact of maternal SARS-CoV-2 infection on birth outcomes, showed that COVID-19 occurring in the first and second trimesters was a risk factor for preterm birth and stillbirth, regardless of infection severity. There was also an increased risk of neonatal SGA, suggesting that preterm birth is induced by a mechanism that may affect fetal growth [23].

In this study, maternal and fetal/neonatal complications were associated with the severity of COVID-19 on prenatal care admission. It is known that increased fetal and neonatal adverse outcomes are related to the severity of COVID-19 during pregnancy, with a higher incidence of oligohydramnios, preterm birth, and need for NICU [15,24, 28]. However, other studies have identified that the association between COVID-19 during pregnancy and adverse maternal or fetal/neonatal outcomes occurs independent of the severity of COVID-19 [3,25].Despite recently published studies disagreeing with obstetric and neonatal complications, our study was carried out in the first and second waves of COVID-19, only with normal-risk pregnant women [27].

Although there is no standardized definition of placental infection by SARS-CoV-2 and no specific placental alteration due to COVID-19, important studies have reported histopathological abnormalities in the placenta consistent with inflammation and tissue hypoperfusion, which may be associated with complications, such as PE, fetal growth restriction, and stillbirth [6,26]. Other studies investigating the impact of COVID-19 on the placenta have demonstrated that infection results in rapid placental dysfunction, trophoblastic necrosis, and massive placental hemorrhage, leading to intrauterine death. Furthermore, the acceleration of fetal growth in the third trimester of pregnancy requires greater placental function, which explains the higher frequency of harmful effects on the fetus when COVID-19 affects pregnant women during this gestational period [29,30].

This study had several limitations. First, as this was a single-center study with a small sample size, it may not be representative for the entire population of pregnant women. Second, the varying distances between the municipalities in the state of Mato Grosso and the hospital where the study was conducted may have led to delays in pregnant women accessing the referral service and consequently impacted the unfavorable progression of the infection. While these limitations may compromise the causal interpretation of the study's findings, the observed strength of the association and the exclusion of pregnant women with known risk factors for maternal and fetal/neonatal complications at the beginning of the cohort produced sufficiently consistent results to allow for a causal inference of the identified risk factors.

4. CONCLUSION

In conclusion, our findings suggest that pregnant women with COVID-19 are at a higher risk of maternal or fetal/neonatal complications when the disease is diagnosed as moderate or severe or when SARS-CoV-2 infection occurs during the second or third trimesters. This information can be useful in guiding healthcare professionals in prenatal, perinatal, and

neonatal care for the implementation of clinical measures to reduce the incidence of such complications in pregnant women. The development of preventive clinical protocols to be applied during prenatal care or hospitalization of pregnant women with COVID-19 could assist in their proper management, especially those with the risk factors identified in this study.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

AUTHORS' CONTRIBUTIONS

Kubiszeski EH, Galera MF, Carmo MAMV contributed to the conception and design of the study. Kubiszeski EH, Galera MF, Carmo MAMV, Carmo AV and Fontes CJ performed data analysis and interpretation. Kubiszeski EH, Fontes CJ and Galera MF contributed to the preliminary writing of the manuscript. Kubiszeski EH, Fontes CJ, Galera MF, Carmo MAMV, Carmo AV, Rosa AANC, Carvalho AMB and Santos NS participated in the relevant critical review of the manuscript's intellectual content. All authors approved the final version of the manuscript and are responsible for all aspects of the work, including ensuring its accuracy and integrity.

ETHICAL APPROVAL

This study was approved by the Ethics and Research Committee of the Júlio Müller University Hospital/Federal University of Mato Grosso (approval number: 4.622.295).

Consent

All participants were informed about the study's objectives and procedures only commenced after pregnant women, or their legal guardians if they were underage, provided informed consent.

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