Coronavirus infection, clinical evolution in pregnancy and the relationship with maternal-fetal mortality

Infecção por coronavírus, evolução clínica na gravidez e a relação com a mortalidade materno-fetal

Infección por coronavirus, evolución clínica en el embarazo y relación con la mortalidad materno-fetal

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Objective: to analyze coronavirus infection and clinical evolution during pregnancy in relation to maternal-fetal mortality in prenatal care. **Methods:** observational, descriptive, analytical quantitative, prospective study, with correlation between variables, carried out with secondary data from pregnant women admitted to a reference hospital in the interior of the state of São Paulo, Brazil. Analysis of independence and prediction between the proposed variables was used, with the Mann-Whitney U Test. **Results:** data from 113 previously hospitalized pregnant women affected by COVID-19 were considered, with emphasis on: age group 21 to 40 years, in the third trimester of pregnancy; the pregnancies were terminated by cesarean indication in most cases, hospitalization in the intensive care unit of 37.17%. Prenatal follow-up had no statistic influence on the clinical evolution of the coronavirus during pregnancy. **Conclusion:** maternal deaths occurred between 21 and 30 years old, twin pregnancy, in the third trimester and the main cause of fetal death was fetal distress in the first and second trimester.
Descriptors: Clinical evolution; Pregnancy; COVID-19; Fetal mortality; Maternal mortality.

Objetivo: analisar a infecção por coronavírus e a evolução clínica na gravidez com relação à mortalidade materna-fetal nos cuidados pré-natais. **Método**: estudo observacional, descritivo, quantitativo analítico, prospectivo, com correlação entre variáveis, realizado com dados secundários de gestantes internadas em um hospital referência no interior do estado de São Paulo. Utilizou-se análise de independência e predição entre as variáveis propostas, com o U de Mann-Whitney. **Resultados**: considerou-se os dados de 113 gestantes anteriormente internadas acometidas pela COVID-19, com destaque para: faixa etária de 21 a 40 anos, no terceiro trimestre da gravidez; as gestações foram finalizadas por indicação de cesárea em sua maioria, internação em unidade de terapia intensiva de 37,17%. Acompanhamento pré-natal estatisticamente sem influência na evolução clínica do Coronavírus na gestação. **Conclusão**: as mortes maternas aconteceram entre 21 a 30 anos, gestação gemelar, no terceiro trimestre e a causa principal de morte fetal foi sofrimento fetal no primeiro e segundo trimestre.
Descritores: Evolução clínica; Gravidez; COVID-19; Mortalidade fetal; Mortalidade materna.

Objetivo: analizar la infección por coronavirus y la evolución clínica en el embarazo en relación con la mortalidad materno-fetal en los cuidados prenatales. **Método:** estudio observacional, descriptivo, cuantitativo analítico, prospectivo, con correlación entre variables, realizado con datos secundarios de gestantes internadas en un hospital de referencia del interior del estado de São Paulo, Brasil. Se utilizó un análisis de independencia y predicción entre las variables propuestas, con la prueba U de Mann-Whitney. **Resultados:** Fueron considerados los datos de 113 gestantes previamente hospitalizadas afectadas por COVID-19, con destaque para: franja etaria de 21 a 40 años, en el tercer trimestre de gestación; gestaciones en su mayoría interrumpidas por indicación de cesárea, internación en unidad de cuidados intensivos 37,17%. Acompañamiento prenatal estadísticamente sin influencia en la evolución clínica del Coronavirus en el embarazo. **Conclusión:** las muertes maternas ocurrieron entre 21 y 30 años, embarazo gemelar, en el tercer trimestre y la principal causa de muerte fetal fue el sufrimiento fetal, en el primer y segundo trimestre.
Descriptores: Evolución clínica; Embarazo; COVID-19; Mortalidad fetal; Mortalidad materna.

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INTRODUCTION

In January 2020, the World Health Organization (WHO) declared a Public Health Emergency of International Concern (PHEIC) - the Organization's highest alert level, in accordance to the International Health Regulations - in the face of a global outbreak of a new coronavirus. In this perspective, after one month of the first case reported in Wuhan, China, four countries were already experiencing human-to-human transmission[1]. Subsequently, the causative agent was named SARS-CoV-2, responsible for leading to an infectious disease (COVID-19), with acute respiratory manifestations. Only on March 11, 2020, the status of a pandemic in Brazil was determined[2].

SARS-CoV-2 is the seventh virus of the coronavirus family known so far, with the power to infect humans and, in addition to presenting a high percentage of morbidity and mortality, it is also very infectious[3]. Thus, the expansion of the virus in Brazil occurred at an alarming rate, initially with the low adherence of the population to restrictive measures and, later, with the collapse of the health system, caused by the maximum occupation of beds in Intensive Care Units (ICUs) and infirmary wards, care failures and the shortage of hospital supplies[4]. In order to contain the spread of the virus, the population was subdivided into groups with a higher risk of death and complications caused by the disease, among which are pregnant women. The justification is the anatomical and physiological changes that occur in women in the pregnancy-puerperal cycle.

It is known that respiratory infections caused by viruses during pregnancy cause an increase in the admission of this group of women to ICUs, requiring mechanical ventilation, a condition that can lead to maternal and/or fetal death, when compared to the general population. The SARS-CoV species corroborates negative prognoses in the mother-fetus binomial, causing serious obstetric complications, such as miscarriage, premature birth (< 38 weeks of pregnancy), premature membrane rupture, intrauterine growth restriction and complications closely linked to the virus and the mother, such as Severe Acute Respiratory Syndrome[5].

In this scenario, after one year of notification of the first case in Brazil, the country has the highest curve of deaths from COVID-19 in the world. When analyzing the deaths of pregnant women in the world, approximately 70% of them are from Brazil. According to data from the Special Epidemiological Bulletin, edited by the Secretariat of Health Surveillance, made available by the Brazilian Ministry of Health, from Epidemiological Week 08 of 2020 to Week 8 of 2021, 5,525 pregnant women with COVID-19 were hospitalized for Severe Acute Respiratory Syndrome (SARS), with the highest incidence of cases in the age group among women aged 20

to 29 years. The lethality rate among pregnant women infected with SARS-CoV-2 is 5.4%, a rate 2.3 times higher than that of the general population[6].

A survey carried out by 12 public institutions identified that 23% of women who died as a result of COVID-19 did not have access to an ICU bed, and 36% of those who required intubation did not receive it. This fact shows that there are flaws in women's health care, especially for pregnant women undergoing prenatal care[7]. Therefore, each study on clinical manifestations and gestational prognoses related to SARS-CoV-2 infection is extremely important to improve health care for the mother-fetus binomial, with the aim of providing more precise guidance on risks and severity.

In the current situation, the negative impacts of SARS-CoV-2 on the health of pregnant women are evident. In view of this, it is important to check whether there are relationships between susceptibility to severe conditions associated with COVID-19 and non-adherence to prenatal care.

Studies related to coronavirus infection are initial and little is known about its action in the body of pregnant women, a fact also observed when it comes to vertical transmission, leaving gaps on the behavior of mother/fetus transmission and, consequently, the possible risks to the fetus are unknown. Thus, when taking into account that the pregnancy cycle is a unique moment in a woman's life, it is clear that the care inherent to her health should not be discontinuous, since she is vulnerable, a fact that can be amplified by the pandemic phenomenon leading to low adherence to prenatal care. Thus, care during pregnancy should be continuous and accurate, providing women with a better quality of life.

Thus, this research aims to analyze the coronavirus infection and the clinical evolution in pregnancy in relation to maternal-fetal mortality in prenatal care.

METHODS

This is an observational, cross-sectional study with a descriptive design, quantitative approach of the analytical type, with correlation between variables. Study with secondary data considering the medical records of pregnant women hospitalized at the Hospital da Criança e Maternidade de São José do Rio Preto, São Paulo and existing in the database of the Epidemiological Hospital Center.

Exclusion criteria were as follows: absence of RT-PCR date for COVID-19, women aged < 12 years and > 45 years and non-pregnant women. Clinical data were extracted from electronic medical records, through the researcher's individual registration in the system.

The following variables were extracted from the electronic medical records and from the Epidemiological Hospital Center Database: maternal age, race, work activity, gestational history, prenatal care data, gestational age, clinical manifestations, comorbidities, chronic diseases (STIs), date of hospital admission and discharge, stay in the ICU and/or infirmary ward, use of invasive or non-invasive mechanical ventilation, treatment, use of medication, type of delivery and cause of maternal and/or fetal death, if applicable.

An instrument was used to collect data directly from the electronic medical records, containing information for the characterization of the participants and clinical analysis, contemplating the study variables. The survey period was from July 2020 to July 2021.

The study was approved by the Research Ethics Committee of the Faculdade de Medicina São José do Rio Preto (FAMERP), under Approval No. 4,794,004 of June 21, 2021. Waiver of the use of the Free and Informed Consent Term - FICF - was requested for carrying out the research project, bearing in mind that secondary data obtained from material already collected and authorized were used. Descriptive statistics methods and inferential statistics methods were used, analyzing issues of probability of a population based on sample data.

For the analysis, the following were used: mean; median; mode; standard deviation; standard error; maximum value; minimum value and significance. Non-parametric Mann-Whitney hypothesis tests were performed, in which the behavior of the correlations between the analyzed variables was analyzed.

The data were replicated absolutely and relatively in this first part. In the inferential scope, the analysis of independence and prediction between the proposed variables was used. For this, the Mann-Whitney U Test was used, within the expected standards.

The independence results between the proposed variables were given by the analysis between the P values (significance). All analyzes were obtained using the SPSS Statistics Software (Version 23) linked to the functionality of the Excel tool (version 2016).

RESULTS

Initially, 1832 medical records of hospitalized pregnant women were considered, of which 113 were analyzed referring to pregnant women with positive RT-PCR for COVID-19 undergoing treatment.

The women were aged between 15 and 42 years (median 30, mean 30.67 and standard deviation 9.17), with length of hospital stay between ward and/or Intensive Care Unit between 1 and 43 days (median 5, mean 8 .34 and standard deviation 8.65).

Pregnant women were identified as white (81.42%), mixed raced (14.15%), black (4.42%), multiple pregnancies (37.7%), second pregnancy (33.63%), first pregnancy (29.20 %) and mostly in the third trimester of pregnancy (71.68%), followed by the second trimester (23.89%) and the first trimester (4.42%).

9.73% of pregnant women were asymptomatic. Among the symptomatic group (90.27%), there was an incidence of: odynophagia (92.15%), runny nose (75.49%), chills (64.70%), dyspnea (64.70%), myalgia (46.07%), persistent cough (47.05%), O_2 saturation <95% (40.19%), intermittent fever (38.23%), anosmia (36.27%), ageusia (28 .43%), headache (25.49%), relapsing fever (20.58%), adynamia (18.62%), respiratory distress (17.64%), diarrhea (12.74%), and less than 5% reported abdominal pain, fatigue and hypotension.

Other clinical manifestations were identified in 56.6%, namely: xerostomia (48.43%), subcostal retraction (37.50%), tachypnea (31.25%), hypoxia and hypoxemia (25%), nausea (18. 75%), lower abdominal pain and emesis (17.18%), secondary infections and syncope (15.62%), tachycardia (12.5%), nasal congestion (10.93%). And also, with frequency <10%, uncontrolled blood pressure, angina, low back pain and general malaise. Also in values lower than 4%, it was observed: epiphora, hypotension, vaginal bleeding, lack of glycemic control, dysuria, pollakiuria, hematuria, nuchalgia, inguinal pain and hemoptysis.

Regarding hospitalization in the Intensive Care Unit, the number of women aged between 21 and 40 years (88.5%) in the third gestational trimester (71.68%) was significant. Of the pregnant women, 6.19% were only under clinical observation (Table 1).

Regarding the use of mechanical ventilation in coronavirus infection, it is possible to observe 42 patients admitted to the ICU. Of these, 78.5% required some type of mechanical ventilation, whether invasive or not (Table 2), bearing in mind that those who required transtracheal intubation were previously undergoing orotracheal intubation (OTI) for 10 days, and all who used mechanical ventilation invasive ventilation also made use of non-invasive ventilation (NIV).

Table 1. Type of maternal hospitalization related to age, gestational period, use of mechanical ventilation and first-line treatment used. São Jose do Rio Preto, SP, Brazil. 2021.

Information	Type of hospitalization						P Value
	Total		Intensive Care Unit		Infirmary		
	No	%	No	%	No	%	
	113	100.0	42	37.17	71	62.83	
Age							
Up to 20 years	9	7.96	3	7.14	6	8.45	
21 to 30 years	54	47.79	19	45.24	35	49.30	0.626
31 to 40 years	46	40.71	19	45.24	27	38.03	
> 40 years	4	3.54	1	2.38	3	4.23	
Gestational age							
1st Trimester	5	4.42	1	2.38	4	5.63	
2nd Trimester	27	23.89	12	28.57	15	21.13	0,728
3rd Trimester	81	71.68	29	69.05	52	73.24	
If ICU admission: use of mechanical ventilation?							
No	10	8.85	9	21.43	1	1.41	
Yes	33	29.20	33	78.57	0	0.00	**0.000**
Does not apply	70	61.95	0	0.0	70	98.59	
1st line treatment							
Oxygen therapy	3	2.65	1	2.38	2	2.82	
Prone position	0	0.0	0	0.0	0	0.00	
Medication	29	25.66	0	0.0	29	40.85	0.168
Oxygen therapy, prone position, medication	17	15.04	16	38.10	1	1.41	
Oxygen therapy, medication	57	50.44	25	59.52	32	45.07	

First-line treatments were used to combat the symptoms of COVID-19 in 93.8% of pregnant women: medication (97.1%), oxygen therapy (72.4%), prone position (16%) and 74/106 of the pregnant women needed the combination of oxygen therapy and medication, yet 100% of the prone patients needed another type of therapy. It is considered that 2.2% of pregnant women were only medical observation.

Furthermore, it was identified that the 2nd line treatment was broad and used in 92.92% of patients during hospitalization. The most used was symptomatic (61.9%), mechanical and/or drug thromboprophylaxis (60%), respiratory physiotherapy (52.3%), motor physiotherapy (21.9%), kinesiotherapy (14.2%), high-flow nasal catheter (13.3%), metabolic exercise (11.4%), sitting position (5.7%), orthostatism (5.7%) and blood transfusion (4.7%), tocolysis, BIPAP (pressure positive in airways at two levels), nitrous oxide, volume replacement with Ringer-lactate and hemodialysis were used in less than 4% of the pregnant women, which means that each of them were not used by more than two pregnant women.

Table 2. Relationship between hospitalization in the Intensive Care Unit and the use of mechanical ventilation with maternal age, gestational period, length of stay and first-line treatment used. São Jose do Rio Preto, SP, Brazil. 2021.

Information	ICU hospitalization? If yes:										
	Total		Endotracheal		Transtracheal		Use of non-invasive mechanival ventilation		Does not apply		P Value
	No 113	% 100.0	No 16	% 14.16	No 5	% 4.42	No 12	% 10.62	No 80	% 70.8	
Age											
Up to 20 years	9	7.96	1	6.25	0	0.0	1	8.33	7	8.75	
21 to 30 years	54	47.79	9	56.25	1	20.0	5	41.67	39	48.75	0.879
31 to 40 years	46	40.71	5	31.25	4	80.0	6	50.0	31	38.75	
> 40 years	4	3.54	1	6.25	0	0.0	0	0.0	3	3.75	
Gestational age											
1st Trimester	5	4.42	1	6.25	0	0.0	0	0.0	4	5.0	
2nd Trimester	27	23.89	2	12.50	4	80.0	6	50.0	15	18.75	0.702
3rd Trimester	81	71.68	13	81.25	1	20.0	6	50.0	61	76.25	
Time of hospitalization											
< 3 days	34	30.09	0	0.0	0	0.0	0	0.0	34	42.50	
3 to 6 days	35	30.97	0	0.0	0	0.0	2	16.67	33	41.25	
7 to 10 days	16	14.16	0	0.0	0	0.0	4	33.33	12	15.00	
11 to 15 days	14	12.39	7	43.75	1	20.0	6	50.0	0	0.0	
16 to 20 days	5	4.42	3	18.75	1	20.0	0	0.0	1	1.25	**0.000**
21 to 24 days	1	0.88	1	6.25	0	0.0	0	0.0	0	0.0	
25 to 30 days	3	2.65	2	12.50	1	20.0	0	0.0	0	0.0	
31 to 36 days	3	2.65	3	18.75	0	0.0	0	0.0	0	0.0	
> 36 days	2	1.77	0	0.0	2	40.0	0	0.0	0	0.0	
1st line treatment											
Oxygen therapy	3	2.65	0	0.0	0	0.0	1	8.33	2	2.5	
Prone position	0	0.00	0	0.0	0	0.0	0	0.0	0	0.0	
Medication	29	25.66	0	0.0	0	0.0	0	0.0	29	36.25	
Oxygen therapy, prone position, medication	17	15.04	12	75.0	4	80.0	0	0.0	1	1.25	0.583
Oxygen therapy, medication	57	50.44	4	25.0	1	20.0	11	91.67	41	51.25	
None	7	6.19	0	0.0	0	0.0	0	0.0	7	8.75	

Among the possible outcomes of COVID-19, there is a high rate of cesarean deliveries along with a significant number of premature births. Furthermore, it is possible to observe that more than half of the parturients did not have any complications during the infection period (Table 3).

Table 3. Delivery related to maternal age, number of fetuses, chronic diseases, complications, type of delivery and gestational age. São Jose do Rio Preto, SP, Brazil. 2021.

| Information | Delivery | | | | | | P Value |
| | Total | | No | | Yes | | |
	No 113	% 100.0	No 53	% 46.9	No 60	% 53.1	
Age							
Up to 20 years	9	7.96	3	5.66	6	10.0	0.053
21 to 30 years	54	47.79	21	39.62	33	55.0	
31 to 40 years	46	40.71	26	49.06	20	33.33	
> 40 years	4	3.54	3	5.66	1	1.67	
Number of fetuses							
One	110	97.35	53	100.0	57	95.0	0.100
Multiple	3	2.65	0	0.0	3	5.0	
Chronic Illnesses							
Does not have any chronic illness	85	75.22	42	79.25	43	71.67	0.344
Mishmash	3	2.65	1	1.89	2	3.33	
Diabetes Mellitus 2	2	1.77	1	1.89	1	1.67	
Arterial Hypertension	8	7.08	3	5.66	5	8.33	
Hypothyroidism	4	3.54	2	3.77	2	3.33	
Hyperthyroidism	0	0.00	0	0.0	0	0.0	
Hepatic steatosis	1	0.88	0	0.0	1	1.67	
Syphilis	1	0.88	1	1.89	0	0.0	
HIV	1	0.88	0	0.0	1	1.67	
Antiphospholipid Antibody Syndrome	1	0.88	1	1.89	0	0.0	
DM2 and Hypothyroidism	2	1.77	1	1.89	1	1.67	
SAH and Hyperthyroidism	1	0.88	0	0.0	1	1.67	
DM2 and SAH	1	0.88	0	0.0	1	1.67	
Sah and Hypothyroidism	3	2.65	1	1.89	2	3.33	
Complication							
No complications	78	69.03	45	84.91	33	55.0	**0.000**
Maternal complications	20	17.70	7	13.21	13	21.67	
Fetal complications	12	10.62	1	1.89	11	18.33	
Maternal and fetal complications	3	2.65	0	0.0	3	5.0	
If yes, what was the type of delivery							
Cesarean section	54	47.79	0	0.0	54	90.0	**0.000**
Vaginal	6	5.31	0	0.0	6	10.0	
Does not apply	53	46.90	53	100.0	0	0.0	
Gestational age							
Pre term	40	35.40	0	0.0	40	66.67	**0.000**
Full term	19	16.81	0	0.0	19	31.67	
Post term	1	0.88	0	0.0	1	1.67	
Does not apply	53	46.90	53	100.0	0	0.0	

The most prescribed drugs were: Dexamethasone (88.3%), Methyldopa (83.4%), Enoxaparin (69.9%), Ceftriaxone (69.9%), Azithromycin (64%), Vancomycin (55.3%) and Oseltamivir (41.7%). On the other hand, it was observed that Enoxaparin, Azithromycin and Dexamethasone are part of the institution's protocol, being associated in 18% of cases.

Other medications were offered according to the individual needs of each patient, such as: Sertraline; Alprazolam; Amikacin; Polymyxin; Linezolid; Unasyn; Oseltamivir; Unfractionated heparin; Furosemide; Amlodipine; Monuril; Nifedipine; Crystalline Penicillin; Ferrous sulphate; Carbergoline; Amoxicillin; Clavulin; Prednisone; Ambroxol; Polymyxin;

Paracetamol; Potassium phosphate; Erythromycin; Meropenem; Tazocin; Rivaroxaban; Levofloxacin; Omeprazole; Methylprednisolone; Potassium chloride; Torgena; Codein; Ultogestan; Neozine; Nipride; Decadron; Dipyrone; Cefazolin; Acetylsalicylic acid; Scopolamine butylbromide associated with Dipyrone; Noripurum; Nystatin; Metronidazole; LMWH and Ivermectin. These had an incidence of less than 9% in the study group.

Still in the outcomes of COVID-19 in pregnancy, three pregnant women and four fetuses died. The mothers were aged between 21 and 30 years and were in the 3rd trimester of pregnancy. And in maternal deaths, the women had twin pregnancies (Table 4).

Table 4. Maternal mortality related to maternal age, gestational period, number of fetuses, complications, length of stay and type of maternal hospitalization and fetal death. São Jose do Rio Preto, SP, Brazil. 2021.

				Maternal death			
	Total		*No*		*Yes*		*P Value*
Information	*N*	*%*	*N*	*%*	*N*	*%*	
	113	**100.0**	**110**	**97.35**	**3**	**2.65**	
Age							
Up to 20 years	9	7.96	9	8.18	0	0.0	
21 to 30 years	54	47.79	51	46.36	3	100.0	
31 to 40 years	46	40.71	46	41.82	0	0.0	0.497
> 40 years	4	3.54	4	3.64	0	0.0	
Gestational age							
1st Trimester	5	4.42	5	4.55	0	0.0	
2nd Trimester	27	23.89	26	23.64	1	33.33	0.892
3rd Trimester	81	71.68	79	71.82	2	66.67	
Number of fetuses							
One	110	97.35	109	99.09	1	33.33	**0.000**
Multiple	3	2.65	1	0.91	2	66.67	
Complication							
No complications	78	69.03	77	70.0	1	33.33	
Maternal complications	20	17.70	18	16.36	2	66.67	0.319
Fetal complications	12	10.62	12	10.91	0	0.0	
Maternal and fetal complications	3	2.65	3	2.73	0	0.0	
Time of hospitalization							
< 3 days	34	30.09	34	30.91	0	0.0	
3 to 6 days	35	30.97	35	31.82	0	0.0	
7 to 10 days	16	14.16	16	14.55	0	0.0	
11 to 15 days	14	12.39	13	11.82	1	33.33	
16 to 20 days	5	4.42	4	3.64	1	33.33	**0.011**
21 to 24 days	1	0.88	1	0.91	0	0.0	
25 to 30 days	3	2.65	3	2.73	0	0.0	
31 to 36 days	3	2.65	2	1.82	1	33.33	
> 36 days	2	1.77	2	1.82	0	0.0	
Type of hospitalization							
Intensive Care Unit	42	37.17	39	35.45	3	100.0	**0.023**
Infirmary	71	62.83	71	64.55	0	0.0	
Fetal death							
No	109	96.46	107	97.27	2	66.67	**0.005**
Yes	4	3.54	3	2.73	1	33.33	

In 30.97% of the mother-fetus binomials there were clinical complications that affect the quality of life. And, of 35 pregnant women, 20.35% of them suffered exclusively maternal complications, such as: fungal and/or bacterial infections (21.73%), and premature labor (21.73%), respiratory failure (13.04 %), postpartum uterine atony (13.04%) and others such as: deep venous thrombosis, acute renal failure, drug-induced hepatitis, viral pneumonia, bronchitis obliterans, acute hypertensive edema, pneumothorax, HELP syndrome, pulmonary fibrosis, sepsis, premature membrane rupture, corneal ulcer and convulsive crisis were reported only once among pregnant women.

Among fetus-related complications, the following were reported: acute fetal distress in 66.66% of fetuses, decreased fetal movements and fetal bradycardia (26.66 each), totaling 15 fetuses with clinical disorders.

Fetal death is one of the possible outcomes of COVID-19. Of all cases (No=113), there were three stillbirths and one miscarriage in the 1st and 2nd gestational trimester, unlike maternal death, which occurred more often in the 3rd trimester. Among the stillbirths due to chronic fetal distress, it was observed that the pregnant women were previously admitted to the ICU and required MV (Table 5).

The relationship between prenatal care and maternal-fetal mortality, in the context of coronavirus infection, was not significant, since 99.12% (No = 112) were undergoing prenatal care, whether low or high risk, so the result did not show influence on this relationship, since 100% of maternal deaths and 75% of reported fetal deaths occurred among pregnant women undergoing care.

Through the analysis of the inferential crossing, applying the non-parametric Mann-Whitney test, it is verified that there was a statistical trend between fetal death with the gestational period, and the result of one influences the result of another in a possible variation, considering the significance of the p value (p=0.000).

Applying the non-parametric Mann-Whitney test, it is inferred that there is a tendency towards maternal death and the number of fetuses during pregnancy (p=0.000). The non-parametric Mann-Whitney test showed a trend towards maternal death and length of hospital stay at a value of p<0.005 (p=0.023). In the use of mechanical ventilation, the non-parametric Mann-Whitney test showed an association between the use of MV and length of stay (p=0.000).

Table 5. Fetal mortality related to maternal age, gestational period, complications, type of hospitalization and use of mechanical ventilation by the mother, first-line treatment used and cause of fetal death. São Jose do Rio Preto, SP, Brazil. 2021.

Information	Total		No		Yes		P Value
	No	%	No	%	No	%	
	113	100.0	109	96.46	4	3.54	
Age							
Up to 20 years	9	7.96	9	8.26	0	0.0	
21 to 30 years	54	47.79	52	47.71	2	50.0	0.319
31 to 40 years	46	40.71	44	40.37	2	50.0	
> 40 years	4	3.54	4	3.67	0	0.0	
Gestational age							
1st Trimester	5	4.42	3	2.75	2	50.0	
2nd Trimester	27	23.89	25	22.94	2	50.0	**0.000**
3rd Trimester	81	71.68	81	74.31	0	0.0	
Complication							
No complications	78	69.03	75	68.81	3	75.0	
Maternal complications	20	17.7	19	17.43	1	25.0	0.689
Fetal complications	12	10.62	12	11.01	0	0.0	
Maternal and fetal complications	3	2.65	3	2.75	0	0.0	
Type of hospitalization							
Intensive Care Unit	42	37.17	40	36.7	2	50.0	0.590
Infirmary	71	62.83	69	63.3	2	50.0	
If ICU admission: use of mechanical ventilation?							
No	20	17.70	20	18.35	0	0.0	
Yes	23	20.35	21	19.27	2	50.0	0.900
Does not apply	70	61.95	68	62.39	2	50.0	
1st line treatment							
Oxygen therapy	3	2.65	3	2.75	0	0.0	
Prone position	0	0.0	0	0.0	0	0.0	
Medication	29	25.66	29	26.61	0	0.0	0.213
Oxygen therapy. prone position. medication	17	15.04	15	13.76	2	50.0	
Oxygen therapy. medication	57	50.44	57	52.29	0	0.0	
None	7	6.19	5	4.59	2	50.0	
Cause of death							
Does not apply	109	96.46	109	100.0	0	0.0	
Chronic fetal distress	2	1.77	0	0.0	2	50.0	**0.000**
Miscarriage	1	0.88	0	0.0	1	25.0	
Maternal death	1	0.88	0	0.0	1	25.0	

DISCUSSION

In this research, 113 pregnant women were hospitalized with a positive test for SARS-COV-2, with 71.68% in the third trimester and only 4.42% in the first. This data corroborates other studies, one carried out in Denmark, in which pregnant women in the last trimester represented more than 70%[8], and another carried out in Brazil, with 45.3% in the third trimester and 6.9% in the first[9]. A fact in common with another report from the United Kingdom, in which the vast majority of women hospitalized for COVID-19 were in the third trimester, reaffirming a pattern already observed in other viruses in pregnant women[10].

The identification of the main signs and symptoms observed reveals that approximately 68.87% of pregnant women had mild to moderate symptoms, according to the clinical

classification chart of the Brazilian Ministry of Health's manual of recommendations[11], and 31.12% of them fit into the severe cases. The most reported symptoms were: odynophagia, runny nose, chills and dyspnea, present in more than 65% of pregnant women, which contrasts with international studies[1,3], in which the main symptoms are fever, cough and shortness of breath. Also, 58% had a fever during their COVID-19 infection (remitting or intermittent).

Among 113 pregnant women with COVID-19 infection evaluated, maternal hospitalization in the ICU occurred in 37.17% of women, a high number when compared to non-pregnant women, however, the result corroborates research carried out in 2020 in the USA[12]. This confirms the inclusion of pregnant women in the risk group, as there are physiological changes during the gestational period, leading to viral infections, such as Influenza, becoming more serious[13-15].

There is a need for greater attention to pregnant women with COVID-19, especially in the last gestational semester, since, according to the findings, almost 70% of admissions to the ICU were in the 3rd trimester, in accordance to a study carried out in the state of Minas Gerais, where pregnant women in the 3rd trimester were more prone to SARS, which leads to higher rates of intensive care[16].

Hospitalization in the intensive care unit aims at more complex monitoring of the most severe patients, for example, those with changes in the Value of a Modified Early Obstetric Warning System (MEOWS) or with the need of mechanical ventilation[17], as in the findings of this research, in that 33 (78.5%) pregnant women in the ICU needed MV, a high rate when compared to 25.8% of the pregnant women analyzed in the study in Minais Gerais.

In 80% of admissions of pregnant women to the ICU there was a need for MV. Of these, 100% used non-invasive ventilation before developing a more severe SARS condition. Few (10.6%) women remained stable after NIV and did not require more invasive procedures and remained under observation, with oxygen therapy and drug therapy, in addition to spending less time in hospital, between 3 and 15 days.

On the other hand, 70% (No=21) did not show improvements in oxygenation and increased respiratory effort even with NIV, thus requiring intubation and therefore a longer hospital stay, unlike the result of the study in Minas Gerais, where invasive ventilatory support was used in 29.8% of the pregnant women[16]. In addition, of the 16 patients on OTI, 13 (81.2%) were in the 3rd trimester, confirming the highest rates of oxygen therapy, prone position and drug therapy in this group[16], since the prone position is indicated for these patients, mainly after the 24th week[11].

The SARS-Cov-2 infection led to a significant increase in premature births and cesarean sections in the country. The survey evaluated 60 women who gave birth during the period of infection and found a rate of 66.67% of prematurity, considered high when compared to the rate of preterm births in 2019, which reached 12%, also high in relation to other studies ranging from 15 to 47% of premature births[14-15,18], currently the main outcome related to COVID-19[11]. This increase in cases may be related to thromboembolic events, due to the pathophysiology of SARS-Cov-2, which causes severe uterine alterations, such as placental abruption and loss of blood supply, which may explain the high rate of preterm births[19].

Regarding surgical intervention to terminate the pregnancy, a high rate of cesarean sections (90%) was found, when compared to the rate of maternal-fetal clinical complications, which totaled 45%, twice as low as the number of surgical deliveries performed, demonstrating that infected pregnant women have a higher risk for cesarean indication, which corroborates findings from other studies, in which the incidence of cesarean sections ranges from 40 to 70%, as shown in a review study[16].

When analyzing these results, it is assumed that the indication in half of the cases was made preventively, on the occasion of saving mother and fetus in case of maternal clinical deterioration, along with fetal needs, are not favorable to both, since maternal-fetal hypoxemia – acute fetal distress, maternal SARS and low oxygen saturation - were quite frequent complications, also reported by other studies, such as obstetric indications for cesarean delivery[20-21].

On the other hand, the symptomatological profile of the pregnant women did not bring a strict indication for cesarean section, of which less than 32% had severe symptoms, which should be indicated in cases of COVID-19, due to maternal and fetal decompensation, without signs of good vitality and with severe symptoms. There were no publications that corroborated the findings of the study presented here, since conducts and protocols vary between institutions and countries, even more so when it comes to diseases with pathophysiology under investigation.

In the group of pregnant women with SARS-Cov-2, a maternal mortality rate of 2.65% is observed, with 2/3 women in the third gestational period and 2/3 of these pregnancies being twins. These data confirm the fact that the mother's organism is more susceptible to severe viral infections in the 3rd trimester[22], as the final preparation of the fetus for birth takes place, a fact that increases its need for supplies, which increases the burden and alters the woman's immune system, and in twin cases all these alterations are duplicated, making the body suffer

even more alterations, mainly immunological and cardiopulmonary, aggravating SARS in this trimester[23].

Maternal mortality was 2.65% and fetal mortality was 3.53%. Despite maternal mortality rates being higher in the 3rd trimester, fetal death rates were the opposite. Of the 113 fetuses, four died from causes associated with maternal complications from COVID-19. Of these, two died due to chronic fetal distress, with a maternal history of MV, one miscarriage and another death due to maternal death.

In the profile of medication used in the treatment of pregnant women, no difference was observed from what the general population used. The most common profile of use was antibiotics, justifiable since secondary infections are very frequent in moderate and severe cases of COVID-19, confirming findings from other studies, in which the combination of immunosuppression induced by the virus and drugs probably increased susceptibility to secondary infections[24-25]. The class of corticosteroids is also frequently prescribed - even more so in association with Azithromycin and Enoxaparin, but no published data were found to confirm these results, the most used being Dexamethasone, a corticosteroid, which also has anti-inflammatory action, indicated after seven days of symptoms due to pulmonary insufficiency[26] caused by the virus in this active period of infection.

The high prescription of corticosteroids (88.6%) for the management of coronavirus infection is something to be questioned, since it can delay the reduction of the viral load of SARS-CoV-2; severe cases such as: asthma, septicemic shock and COPD should be analyzed as risk-benefit and are the only indications for its use[27]. This data is controversial, since almost 90% of the pregnant women in the study underwent drug therapy with Dexamethasone and only three had asthma[28], which possibly has to do with the fact that it is a new virus, thus the pharmacological study is just beginning and, in cases like these, risk-benefit is used.

For prophylactic anticoagulant therapy, Enoxaparin is the most used during pregnancy due to the clinical indications that women are in during this period. Almost 70% of pregnant women were indicated for prophylactic use after confirmation of COVID-19, an important conduct in the prevention of thrombotic events, favored by the difficulty of blood circulation during pregnancy and the severe behavior of Sars-CoV-2, characterized by a immune response with hyperinflammation and hypercoagulability that can progress to thrombosis or mimic pre-eclampsia[30]. A higher rate was expected, since all patients admitted to a COVID-19 ward or ICU are considered at high risk for venous thromboembolism due to the infectious condition, and prophylaxis is initiated as long as there are no contraindications for anticoagulation.

Specific antiviral therapy for COVID-19 is still being investigated and researched, no studies were found that actually prove specific drugs for COVID-19. The clinical findings of this research show that Oseltamivir therapy was used in 41.7% of cases, although there is no evidence to date about its use in the treatment of COVID-19. Directly related to the therapy of the 2019 coronavirus infection, antiviral studies are in progress and it is necessary for the scientific world to invest in the search for specific therapies for the infection in question.

Every pregnant woman should be considered at high risk for COVID-19, due to the physiological vulnerability of the immune system, leading to greater susceptibility and more severe stages of the infection. In the research, prenatal care had no statistical influence on the maternal-fetal clinical evolution, and it was seen in the results that all pregnant women and fetuses who died or who were in more severe stages of the infection were undergoing prenatal care. Even so, these prenatal services (PN) are of paramount importance in the transmission of knowledge and in clarifying "fake news", therefore, the health services that accompany the low or high risk PN must have strategies that favor the continuity of care, so that pregnant women with infection are assisted by the multidisciplinary team during the period of isolation or post-hospitalization and also clarify forms of transmission, potential problems and sequelae due to infection of COVID-19.

In turn, the nurses present at screening, prenatal care and delivery have an essential role in patient education and, during the SARS-Cov-2 pandemic, in the dynamic and complete management of gestational anxieties. Improvements are needed to deal with COVID-19, as well as the creation of specific institutional protocols, in order to standardize care and follow-up.

CONCLUSION

The results of the study show that part of the pregnant women are in a situation of physiological vulnerability related to the infection by the coronavirus due to the gestational period. With a small population and very restricted to only one care service, it is not possible to estimate the actual lethality of COVID-19 in pregnant women, as the records are flawed and cases are underreported during the research period.

With this, the limitations of the study were the COVID-19 pandemic itself, a period in which pregnant women were unaware of some symptoms of the virus and did not always seek care centers, and the high number of underreports due to performing tests outside the appropriate period, in addition to being something new for health teams, especially when making notes in the medical records and deciding what to do in the face of the virus in pregnant women. However, it is understood that it is a starting point for other studies and for the

importance of carrying out new investigations in search of the epidemiology of COVID-19 in the group of pregnant women.

The most frequent signs and symptoms were odynophagia, runny nose, chills and dyspnea. Other symptoms such as fever, respiratory distress, anosmia and ageusia occurred in less than 40% of pregnant women. Also, there was a range of clinical manifestations reported in electronic medical records, which makes the epidemiology of SARS-CoV-2 symptoms difficult.

Most pregnant women survived and those who died were between 21 and 30 years old and the highest risk was twin pregnancy, in the third trimester of pregnancy. In fetal death, the highest prevalence was in the first and second trimester and the cause of death, fetal distress, which is related to the gestational period and clinical status of the pregnant woman, which many variables need to be studied, to exclusively verify which are the causes leading to fetal death.

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CONTRIBUTIONS
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