

Prevalence of Preterm Birth as an Outcome of Covid-19 Infections during Pregnancy

Prevalência de nascimentos prematuros como desfechos de infecções pela Covid-19 na gestação

Prevalencia de nacimientos prematuros producto de la infección por Covid-19 durante el embarazo

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ABSTRACT

Objective: to estimate the prevalence of preterm birth in pregnant women infected with Covid-19, compare prematurity rates between infected and non-infected, and elucidate factors associated with prematurity. **Methods:** a retrospective cohort study was conducted using online survey data collected from April to December 2022, involving women who were pregnant during the pandemic, had internet access, were over 18 years old, and completed the initial online survey. The research protocol was approved by the Ethics Committee. **Results:** the initial survey was completed by 304 pregnant/postpartum women, and the follow-up survey by 82 (27%), comprising the final sample. The preterm birth rate in the initial survey was 7.2% (n=14), and in the follow-up survey, it was 8.5% (n=7). Covid-19 infection was not associated with prematurity. Prematurity was associated with low birth weight, the need for neonatal intensive care unit admission, and postnatal hospitalizations. **Conclusion:** Covid-19 infection did not influence an increase in preterm births.

Descriptors: Pregnancy; Postpartum Period; COVID-19; Premature Birth.

RESUMO

Objetivo: estimar a prevalência de nascimento prematuro em gestantes infectadas pela Covid-19, comparar índices de prematuridade entre infectadas e não infectadas e elucidar fatores associados à prematuridade. **Métodos:** coorte retrospectiva, com coleta de dados por inquérito *online*, de abril a dezembro de 2022, com mulheres que estiveram gestantes durante a pandemia, com acesso à internet, idade superior a 18 anos e que preencheram o primeiro inquérito online. Protocolo de pesquisa aprovado pelo Comitê de Ética. **Resultados:** primeiro inquérito respondido por 304 gestantes/puérperas, e o segundo por 82 (27%), compondo a amostra final. O índice de prematuridade no primeiro inquérito foi de 7,2% (n=14), já no segundo, 8,5% (n=7). A infecção pela Covid-19 não foi associada à prematuridade. A prematuridade associou-se a baixo peso, à necessidade de internação em centros de terapia intensiva neonatal e internações após o nascimento. **Conclusão:** a infecção pela Covid-19 não influenciou no aumento de nascimentos prematuros.

Descritores: Gravidez; Período Pós-Parto; COVID-19; Nascimento Prematuro.

RESUMEN

Objetivo: estimar la prevalencia de partos prematuros en gestantes infectadas por Covid-19, comparar las tasas de prematuridad entre gestantes infectadas y no infectadas y determinar los factores asociados a la prematuridad. **Métodos:** estudio de cohorte retrospectivo, con recolección de datos mediante encuesta *online*, de abril a diciembre de 2022, con mujeres que estuvieron embarazadas durante la pandemia, con acceso a internet, mayores de 18 años y que completaron la primera encuesta *online*. El protocolo de investigación fue aprobado por el Comité de Ética. **Resultados:** la primera encuesta fue respondida por 304 gestantes/puérperas, y la segunda por 82 (27%), que conformaron la muestra final. La tasa de prematuridad en la primera encuesta fue del 7,2% (n=14), en la segunda, del 8,5% (n=7). La infección por Covid-19 no se asoció con la prematuridad. La prematuridad se asoció con bajo peso, necesidad de internación en centros de cuidados intensivos neonatales e internaciones después del nacimiento. **Conclusión:** La infección por Covid-19 no influyó en el aumento de nacimientos prematuros.

Descriptores: Embarazo; Período Posparto; COVID-19; Nacimiento Prematuro.

INTRODUCTION

Worldwide, more than 760 million cases of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection, the causative agent of Coronavirus Disease 2019 (Covid-19), have been reported. Nearly seven million deaths have occurred from the disease¹, which was declared a pandemic by the World Health Organization (WHO) in 2020 and persisted as a public health emergency until mid-May 2023.

In this context, pregnant and postpartum women have shown a profile of higher vulnerability to infection due to the physiological changes of pregnancy. Immunological alterations lead to an increased predisposition to infections, while increased blood flow tends to result in more severe forms of infections, notably Covid-19²⁻⁴.

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These factors have led to their consideration among the priority risk groups for Covid-19 testing and care in Brazil and worldwide^{2,3}.

International literature has indicated that pregnancies complicated by Covid-19 infection more frequently exhibit the following outcomes: increased rates of cesarean sections due to maternal respiratory decompensation and/or fetal hypoxemia⁵⁻¹³; a significant increase in preterm births⁵⁻¹³; and the occurrence of severe cases accompanied by maternal pneumonia⁵⁻¹³, which consequently may have motivated the aforementioned outcomes (cesarean section and prematurity).

Prematurity is a complex and multifactorial problem, which can result from factors related to maternal age (extremes - adolescence or age greater than 35 years old); pregnancy-related factors such as short intervals between pregnancies (less than two years), multiple pregnancies, elective cesarean section, induction of labor, chronic or gestational diseases, infections, socioeconomic and nutritional conditions; and fetal factors such as genetic diseases¹⁴.

Globally, prematurity is the leading cause of infant mortality in children under five years of age¹⁵, with rates reaching 60% when associated with low-birth-weight¹⁴, potentially leading to long-term consequences for the child. Understanding its prevalence, associated factors, including its relationship with Covid-19, is relevant and can contribute to improvements in healthcare. Therefore, this study is justified because prematurity is an unfavorable outcome, and many studies indicate an increase in this rate during any infection, as well as in cases of Covid-19.

The objective of this study was to estimate the prevalence of preterm birth in pregnant women infected with Covid-19, compare prematurity rates between infected and non-infected pregnant women, and elucidate associated factors.

METHOD

This is a retrospective cohort study that followed the recommendations of the "Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE) and the "Revised Standards for Quality Improvement Reporting Excellence" (SQUIRE 2.0)¹⁶.

The data were obtained through an online survey, using a data collection form developed by the researchers themselves. The form was submitted for evaluation by three experts in the field, adhering to all ethical criteria.

All three experts were specialists in Obstetric and Neonatal Nursing, with one working in a tertiary care hospital, one in a birthing center, and one in academia. Two hold master's degrees, and one holds a doctorate. Additionally, one works in the state of São Paulo, one in Brasília, and one in Bahia, ensuring and expanding the scope of expertise. The selection of experts was based on their expertise in the field, their location of practice, and the diversity of practice settings. After evaluation, the form underwent adjustments in wording, achieving 100% agreement.

The virtual social media environment of an extension project served as the setting for this study. In mid-July 2020, a group of collaborating researchers conducted studies on the topic of Covid-19 during pregnancy, childbirth, and the postpartum period. They also translated and disseminated knowledge through social media platforms created for this purpose via the extension project "@nascere.covid" / "Nascer e Covid" on Instagram® and Facebook®.

In total, more than 200 posts were made on Instagram®, which had over three thousand followers at the peak of the pandemic. As of August 2023, it maintained 2630 followers, while on Facebook®, it retained 225 followers. The profile attracted followers from various population segments, including pregnant/postpartum women, family members of pregnant/postpartum women, undergraduate students in healthcare fields, healthcare professionals, and the general community.

For the sample size calculation, a cesarean section prevalence of 60.0% (average percentage of operative deliveries during the Covid-19 pandemic) was considered based on review studies^{11,12}, with a precision of 5% and a confidence interval of 95%, for a finite population of 1985 women (total number of followers on social media at the time of study design), resulting in a sample of 312 participants for the first survey. The cesarean section rate was chosen as the outcome variable as it showed a significant increase among infected pregnant women, according to the literature.

The study invitation was posted on these social media platforms, with a link to the Informed Consent Form (ICF). Upon consenting to participate in the study, women were directed to a questionnaire collecting sociodemographic data. Subsequently, if the respondent indicated she was postpartum, she was directed to a specific questionnaire to provide information on clinical and obstetric data, as well as details about Covid-19 occurrence and birth and infant information.

The study included women who had the experience of being pregnant during the pandemic, had internet access, were over 18 years old, and completed the online form. Forms that did not have complete information on the variables of interest were excluded from the analysis.

In the first survey, data were collected between August 2021 and January 2022, while in the second survey, which collected data on the newborn, information was gathered from April to December 2022. Participants were invited to participate in the follow-up via the email provided during the first survey, with new contact information indicated in the consent form. Three attempts were made to contact participants via email during the second data collection period.

The dependent variable was prematurity, and the independent variables included sociodemographic, clinical, and obstetric variables, including Covid-19 infection during pregnancy.

To identify associations between variables, they were dichotomized, and Fisher's exact test was applied, considering significant those with a p-value <0.005. To verify the actual association, Robust Poisson Regression was used, with variables having a p-value <0.20 in the bivariate analysis inserted into the model.

The project associated with this study was approved by the Research Ethics Committee of the institution involved. The "Guidelines for Research in Virtual Environments" determined by CONEP in 2021 were followed, as well as Resolution No. 466/2012 of the National Health Council. This study refers to a specific objective of the mentioned project, titled "Nascer e Covid-19 Survey".

RESULTS

The first questionnaire was completed by 304 pregnant or postpartum women. However, 82 postpartum women (27%) responded to the second survey, as shown in the flowchart presented in Figure 1.

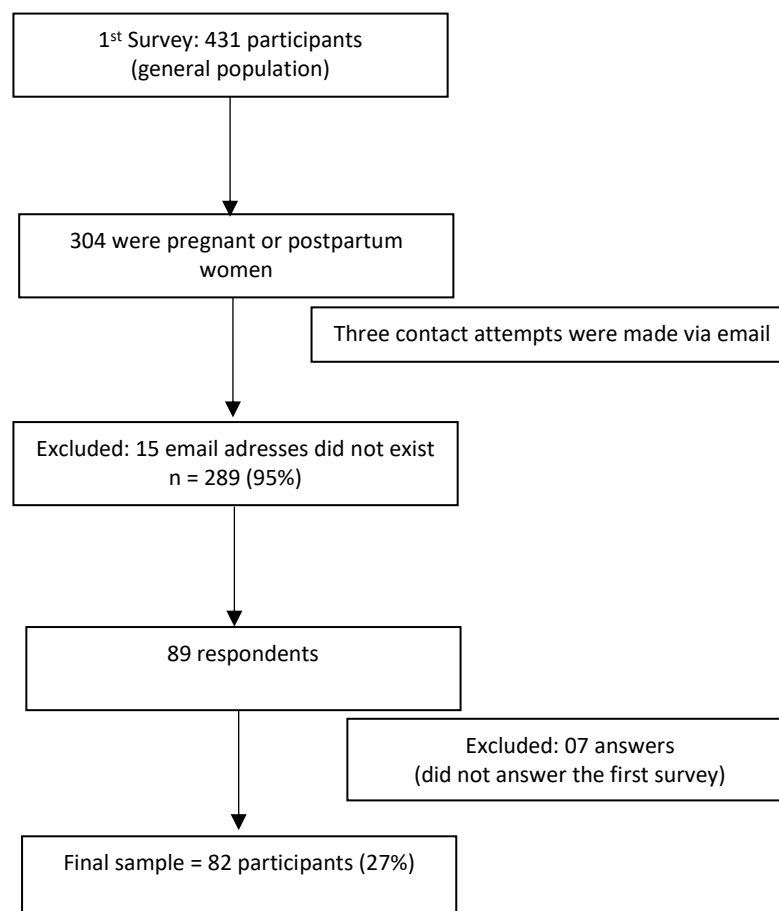


Figure 1: Flowchart of the cohort study on Covid-19 during pregnancy and its impact on neonatal health. Brazil, 2022.

Regarding the respondents' origin, the state of São Paulo - 24 (29.3%), Minas Gerais - 22 (26.8%), and Rio Grande do Sul - 06 (7.3%) were the most cited. Table 1 shows the differences between the samples in the two surveys.

Table 1: Characterization of the sample, according to data collected in the first survey in 2021 (n=304) and responses to the second survey in 2022 (n=82), Brazil, 2022.

Variable	2021 (n=304)		2022 (n=82)	
	n	f(%)	n	f(%)
Age	$\mu=34.8(\pm 5.4)$		$\mu=34.2(\pm 5.2)$	
White	210	69.1	59	72.0
Non-white	94	30.9	23	28.0
Lives with partner	257	84.3	69	84.1
Does not live with partner	47	15.7	13	15.9
Schooling level beyond Higher Education	123	40.5	67	81.7
Schooling level below Higher Education	181	59.5	15	18.3
Paid occupation	243	79.9	67	81.7
Not engaged in paid occupation	61	20.1	15	18.3
Private health insurance	235	77.3	69	85.2
Public health system appointments	69	22.7	12	14.8
Uses public health services	153	77.3	43	52.4
Does not use public health services	51	22.7	39	47.6
First-time pregnant	150	49.3	40	48.8
Multigravida	154	50.7	42	51.2
Chronic diseases	57	18.8	16	19.5
Denies pathologies	247	81.2	66	80.5
Diseases during pregnancy	48	15.8	14	17.1
No diseases	256	84.2	68	82.9
Had Covid-19	78	25.7	63	76.8
Did not have Covid-19	226	74.3	19	23.2
Covid-19 during pregnancy/postpartum	56	71.8	29	46.0
Other occasions	22	28.2	33	54.0
Hospitalization due to Covid-19	04	5.1	02	3.2
No hospitalization	74	94.9	61	96.8
ICU admission	01	25	02	100
In other units	03	75	-	-
Sequelae of the infection	03	3.8	24	39.3
No sequelae	75	96.2	37	60.6
Immunization	187	61.5	81	98.8
Not immunized	117	38.5	01	1.2
Complete vaccination schedule	120	64.2	67	81.7
Incomplete	67	35.8	14	18.3
Vaginal delivery	75	38.6	39	47.6
Cesarean section	119	61.7	43	52.4
Term neonate	180	92.8	75	91.5
Preterm neonate	14	7.2	07	8.5
Early contact with the newborn	187	96.4	75	91.5
No early contact	07	3.6	07	8.5
Early breastfeeding	124	63.9	55	67.1
Delayed initiation	70	36.1	27	32.9
Labor/Birth companion	181	93.3	78	95.1
No companion	13	6.7	04	8.5
Low birth weight	10	10.2	10	12.2
Appropriate weight	184	89.8	72	87.8
NICU admission	14	7.2	05	6.1
Rooming-in	180	92.8	77	93.9
Child had Covid-19	-	-	38	46.3
Child did not have Covid-19	194	100.0	44	53.7

Notes: μ - mean; NICU - Neonatal Intensive Care Unit.

It was observed that there were higher schooling levels, increased use of private health insurance, and a significant increase in Covid-19 cases. However, there was a reduction in cases during pregnancy. Additionally, there was an increase in admissions to intensive care units (ICUs), post-Covid-19 sequelae, and completion of the immunization schedule. There was also a slight increase in preterm births and neonates with low birth weight.

Moreover, it is noteworthy that no cases of Covid-19 were identified in children during the neonatal period. However, in this second period, 46.3% of the children had the infection.

It is worth noting that the increase in Covid-19 cases between the different data collection periods was significant ($p < 0.001$).

The age of the children ranged from two to 31 months, with a mean of 16.0 ± 6.4 months. Fifty-nine (72%) were breastfeeding, with 14 (17.1%) exclusively breastfed, five (6.1%) receiving mixed feeding, and 47 (57.3%) already introduced to solid foods. When questioned, 26 (31.7%) postpartum women reported weaning, with an average weaning age of 10.8 ± 6.6 months. Among them, four children (15.4%) were weaned early, with three (75%) being weaned before one month of age.

Among the women, 48 (58.5%) experienced complications while breastfeeding, with nipple-areolar lesions being the most commonly cited (21 - 25.6%). Ten (12.2%) reported insufficient milk supply and resorted to supplementation, while six (7.3%) reported breast engorgement, and another six (7.3%) reported mastitis.

Regarding Covid-19 in children, four (10.5%) experienced complications due to Covid-19: two had febrile seizures during the infection, one had to be weaned due to hospitalization in a critical care unit, and another developed pneumonia.

Among the children, 19 (23.2%) had or have health problems, including: jaundice (05 - 26.3%); urinary tract infection (03 - 15.7%); pneumonia (04 - 21.0%), with one mention of recurrent pneumonia; bronchiolitis (03 - 15.8%); cow's milk protein allergy (02 - 10.5%); asthma, neuro-motor development delay; motor delay; esophageal atresia; bronchitis; intestinal disease under investigation; and recurrent upper respiratory tract infections, with one mention each (5.3%). Additionally, there was one case of viral meningitis.

Regarding the need for hospitalizations, 12 (14.6%) required hospitalization. Among the reasons for hospitalization reported were: need for phototherapy (05 - 41.7%); treatment of pneumonia (02 - 16.7%); prematurity (02 - 16.7%); bronchiolitis, correction of atresia, gastrointestinal alteration, low birth weight, and sepsis were each cited as reasons for one hospitalization (8.3%).

The preterm birth rate obtained in the first survey was 7.2% ($n=14$), while in the second survey, it was 8.5% ($n=7$). Tables 2 and 3 sought to list the factors associated with preterm birth.

Table 2: Association between sociodemographic variables and neonatal variables with preterm births. Brazil, 2022.

Variable	Preterm Birth		RP	CI (95%)	p-value
	Yes n (%)	No n (%)			
Covid-19 Infection					
Yes	5 (8.1)	24 (38.7)	2.845	(0.597 - 13.566)	0.237
No	2 (3.2)	31 (50.0)			
Age					
18-35 years old	1 (1.2)	35 (42.6)	0.213	(0.027 - 1.690)	0.129
>35 years old	6 (7.3)	40 (48.8)			
Skin color					
White	6 (7.3)	53 (64.6)	2.339	(0.298 - 18.378)	0.667
Non-white	1 (1.2)	22 (26.8)			
Partner					
Lives with partner	5 (6.1)	64 (78.0)	0.471	(0.102 - 2.173)	0.306
Does not live with partner	2 (2.4)	11 (13.5)			
Schooling					
Complete High School or lower	3 (3.6)	63 (76.8)	0.299	(0.074 - 1.196)	0.111
Higher than Complete Higher Education	4 (4.9)	12 (14.6)			
Paid activity					
Engaged in paid occupation	5 (6.1)	62 (75.6)	0.560	(0.120 - 2.614)	0.606
Not engaged in paid occupation	2 (2.4)	13 (15.9)			

Table 3: Association between sociodemographic variables, clinical conditions, obstetric variables, and neonatal variables with preterm births. Brazil, 2022.

Variable	Preterm Birth		RP	CI (95%)	p-value
	Yes n (%)	No n (%)			
Has health insurance			0.348	(0.071 - 1.693)	0.215
Yes	4 (4.9)	65(79.3)			
No	2 (2.5)	10 (12.2)			
User of public health system			2.267	(0.466-11.025)	0.436
Yes	5 (6.1)	38 (46.3)			
No	2 (2.4)	37 (45.1)			
Chronic diseases			0.688	(0.089 - 5.316)	1.000
Yes	1 (1.2)	15(18.3)			
No	6 (7.3)	60 (73.2)			
Obesity			1.103	(1.026 - 1.186)	1.000
Yes	-	7 (8.5)			
No	7 (8.5)	68 (83.0)			
Number of pregnancies			0.788	(0.188 - 3.300)	1.000
First-time pregnant	3 (3.7)	37(45.1)			
Multigravida	4 (4.9)	38(46.3)			
Illness during pregnancy			0.810	(0.106 - 6.209)	1.000
Yes	1 (1.2)	13(15.8)			
No	6 (7.3)	62(75.6)			
Gestational diabetes			1.500	(0.206 - 10.940)	0.536
Yes	1 (1.2)	7 (8.5)			
No	6 (7.3)	66 (80.0)			
Delivery			0.041	(0.091 - 2.144)	0.436
Vaginal	2 (2.4)	37(45.1)			
Cesarean section	5 (6.1)	38(46.3)			
Low birth weight			2.465	(1.153 - 5.269)	<0.001
Yes	6 (7.3)	4 (4.9)			
No	1 (1.2)	71 (86.6)			
ICU admission			20.533	(6.229 -67.681)	<0.001
Yes	4 (4.9)	1 (1.2)			
No	3 (3.7)	74 (92.5)			
Covid infection			0.463	(0.095- 2.252)	0.442
Yes	2 (2.4)	36 (43.9)			
No	5 (6.1)	39 (47.6)			
Health issue			1.284	(0.271 - 6.092)	0.668
Yes	2 (2.4)	17 (20.7)			
No	5 (6.1)	56 (68.3)			
Postnatal hospitalization			7.667	(1.957 - 30.041)	0.008
Yes	4 (4.9)	8 (9.8)			
No	3 (3.7)	66 (80.5)			

No sociodemographic, clinical, and obstetric variables showed statistically significant differences. Associations of neonatal variables with prematurity were explored, revealing low birth weight ($p<0.001$), neonatal ICU admission ($p<0.001$), and a higher occurrence of postnatal hospitalizations ($p=0.008$).

No associations were found between neonatal variables and maternal Covid-19 infection, as the variables: low birth weight ($p=0.493$), ICU admission ($p=1.000$), neonatal Covid-19 infection ($p=0.068$), having health problems ($p=0.538$), and postnatal hospitalizations ($p=1.000$) presented p-values >0.05 , indicating that no statistically significant association was identified.

Table 4 presents the regression model between sociodemographic, clinical, and obstetric variables and preterm birth. Variables with a p-value below 0.20 in the bivariate analysis (maternal age above 35 years old and maternal education) were included in the model.

Table 4: Poisson regression model between preterm birth and maternal and neonatal variables. Brazil, 2022.

Sociodemographic/Clinical variables	PR	CI(95%)	p-value
Maternal			
Maternal age above 35 years old	0.417	-0.024 - 0.139	0.167
Maternal schooling level	0.769	-0.075 - 0.026	0.327
Covid-19 during pregnancy	0.443	-0.165 - 0.009	0.080
Neonatal			
Low birth weight	1.147	-0.003 - 0.446	0.056
ICU admission	1.564	-0.638 - -0.025	0.034
Covid-19 infection	0.275	-0.104 - 0.004	0.071
Postnatal hospitalization	0.437	-0.092 - 0.079	0.880

The “Covid-19 infection during pregnancy” variable was included because it was of interest to investigate the association. Preterm birth was not explained by sociodemographic variables such as advanced maternal age and education, as well as by Covid-19 infection.

Furthermore, an attempt was made to identify the association between preterm birth and the occurrence of complications in child health using the Robust Poisson Regression model. As a result, it was found that preterm birth explained only neonatal ICU admission ($p=0.034$).

DISCUSSION

The cohort results are similar to the meta-analysis in which no association between Covid-19 and prematurity was found¹⁷. Contradictorily, studies have pointed out an association between premature births and the infection^{18,19}.

However, the prematurity rates reported in both collections (7.2% and 8.5% of the births, respectively) were lower than the rates identified in other studies, which ranged from 23 to 52.3%^{20,21}. Prematurity in cases of Covid-19 infection in previous studies has been attributed to maternal pneumonia, which compromises placental blood flow¹³.

However, it is worth emphasizing that prematurity is a significant cause of neonatal morbidity and mortality, and all factors associated with this occurrence should be investigated for prevention²².

It is noteworthy that in the sample, there were no cases of neonatal death related to prematurity, nor due to Covid-19 infection.

As study limitations we include the possibility of biases: recall bias, as the data were based on participants' answers; and prevalence bias, as deceased pregnant/postpartum women due to the disease were not included in the case series.

Another limitation is the study data collection period, which was after the introduction of Covid-19 immunization for pregnant women, which might have also influenced the results.

The participants' profile stands out, as they were mostly women with Internet access, high schooling levels, formal employment, white-skinned, living in the Southeast region, and users of private healthcare (health insurance). Therefore, this profile may not reflect the reality of other Brazilian women. This fact might be justified by the online data collection method used in the study, which limits universal participation.

Additionally, the fact that it was an online survey did not allow for the classification of case severity. Another point worth discussing is that the study was conducted in a population with high purchasing power, access to adequate nutrition, medications, differentiated healthcare services, and information, which may have contributed to better outcomes regarding infection and pregnancy itself.

Study limitations

It is worth noting the small sample size, despite multiple attempts to contact participants. However, due to the remote data collection format, it was not possible to access a larger number of participants from the previous survey.

Despite these limitations, online data collection, necessitated by sanitary conditions, allowed for the presentation of the disease profile in a national sample. Presenting a cohort design, which was an innovation for the current circumstances, enabled this study. Thus, this study emerges as a potential basis for further research with

alternative designs aimed at elucidating factors that may compromise pregnancy outcomes, particularly focusing on prematurity.

CONCLUSION

An increase in Covid-19 cases was observed in the cohort; however, the infection was not associated with prematurity. Furthermore, an exponential increase in childhood infection cases was identified; nevertheless, it did not explain their health alterations. Prematurity was associated with low birth weight, the need for neonatal ICU admission, and postnatal hospitalizations.

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Conceptualization, L.M.S., J.A.S., M.W. and M.T.R.; Methodology, M.W. and M.T.R.; Validation, M.W. and M.T.R.; Formal Analysis, M.W., D.C., L.M.M.F. and M.T.R.; Investigation, L.M.S., J.A.S. and M.T.R.; Resources, M.T.R. Data Curation, .M.T.R.; Manuscript Writing, L.M.S., J.A.S., M.W., D.C., L.M.M.F. and M.T.R.; Writing – Review and Editing, L.M.S., J.A.S., M.W., D.C., L.M.M.F. and M.T.R.; Visualization, L.M.S., J.A.S., M.W., D.C., L.M.M.F. and M.T.R.; Supervision, M.T.R.; Project Administration, M.T.R. All authors read and agreed with the published version of the manuscript.