

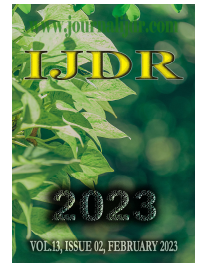


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RESEARCH ARTICLE

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## THE IMPACT OF COVID-19 ON PREMATURE DELIVERIES

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### ABSTRACT

**Objective:** To consolidate scientific evidence on the association between premature birth in pregnant women infected with COVID-19. **Method:** This was an Integrative Literature Review, with a bibliographic survey carried out in the Medical Literature Analysis and Retrieval System databases online (MEDLINE), via the Virtual Health Library Portal (VHL), Web of ScienceTM, SCOPUS and Base. **Conclusion:** It was evident that the risk of premature birth seems to increase in pregnant women infected with SARS-CoV-2. **Final considerations:** Premature birth associated with complications from COVID-19 in pregnant women is still a reality that needs to be studied in greater depth, given the new scenario imposed by the new coronavirus.

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## INTRODUCTION

It is known that COVID-19 is the result of infection with Coronavirus 2 (SARS-CoV-2) (MARTINEZ-PEREZ *et al.* 2021). It is a betacoronavirus, of the same subgenus as the severe acute respiratory syndrome virus (SARS) (GASPAR & SILVA, 2021). Symptoms of the disease range from mild to severe, including fever, cough, shortness of breath and pneumonia. In severe cases, neurological, gastrointestinal, liver and respiratory complications may occur. In pregnancy, it can compromise the immune system and, potentially, the risk of developing pneumonia, when compared to non-pregnant women (AGARWAL *et al.* 2021). Immunological and physiological changes resulting from the gestational period may explain the increased risk of complications, which include spontaneous abortion, premature delivery and intrauterine growth retardation. In addition, admission to the Intensive Care Unit, tracheotomy, need for mechanical ventilation, renal failure and disseminated intravascular coagulation (VAEZI *et al.* 2021) are highlighted. Such complications probably result more from the pathophysiology of the maternal disease than from the direct effect of the virus, which could also explain the occurrence of growth restriction and premature birth (BENTLIN *et al.* 2020). Premature birth, also called preterm birth, corresponds to the delivery that takes place before 37 weeks of gestation and after exceeding 20 weeks. It is considered an important obstetric problem, considering that complications related to prematurity are considered responsible for more than 75% of mortality and morbidity among newborns (PEIXOTO, 2014). An understanding of the clinical implications of SARS-CoV-2 infection in the viable preterm period and the risk of preterm delivery are important for clinical obstetric management decisions based on assessment of maternal risks and consequent complications related to prematurity (GULERSEN *et al.*

2020). Although there is currently no evidence of intrauterine infection in pregnant women with confirmed COVID-19 in late pregnancy, the risk of fetal and neonatal infection is among the main concerns in pregnant women (VAEZI *et al.* 2021). Thus, the objective of this study was to consolidate scientific evidence on the association between premature birth in pregnant women infected with COVID-19.

## METHODS

The methodological course of this study took place through an Integrative Literature Review, a method which summarizes the past of the empirical or theoretical literature, to provide a more comprehensive understanding of a given phenomenon, allowing the combination of several methodologies and incorporation of scientific evidence into clinical practice (SOUSA *et al.* 2017). The research was divided into six stages, namely: identification of the theme and selection of the hypothesis or research question; definition of inclusion and exclusion criteria for the study, using the databases and selection of studies based on the criteria; identification of pre-selected studies, by reading abstracts, keywords and titles of publications and organization of studies; categorization of selected studies; analysis and interpretation of results and presentation of the review and synthesis of knowledge (LEMOS & PENICHE, 2016). The research question was elaborated according to the "PEAK" strategy: Patient, Intervention, Comparison and "Outcomes" (outcome) (SANTOS *et al.* 2007). The following structure was considered: P: pregnant women; I: COVID-19; Co: Premature birth. Thus, the following question was elaborated: "In pregnant women with COVID-19, what is the relationship with premature labor?". The bibliographic survey took place in September and October 2021. The following databases were chosen: Medical Literature

Analysis and Retrieval System online (MEDLINE) via the Virtual Health Library Portal (VHL), Web of Science™, SCOPUS and Embase. The combination of descriptors was performed using the Boolean operators “AND” and “OR”, aiming to expand the number of studies. The descriptors were extracted from the Health Sciences Descriptors (DECS) in the VHL Portal and from the Medical Subject Headings (MESH) in the National Library. Chart 1 describes the strategy generated in each informational resource consulted from the combination of terms with the Boolean operators OR and AND.

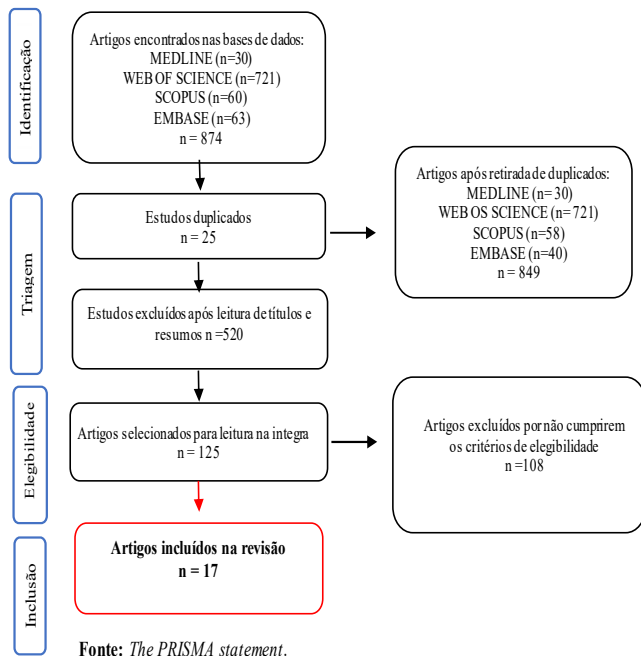


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations

Chart 1. Search expression generated in the investigated informational resources. Aracaju, Sergipe, Brazil, 2022

Data Base	Search Expression
MEDLINE	(COVID-19) AND (premature labor) AND (premature birth)
WEB OF SCIENCE	TOPIC: (COVID-19) AND TOPIC: (Premature Birth) OR TOPIC: (Obstetric Labor, Premature)
SCOPUS	(TITLE-ABS-KEY (COVID-19) AND TITLE-ABS-KEY ("obstetric AND labor, AND premature") AND TITLE-ABS-KEY ("premature AND birth" )
EMBASE	'COVID-19' AND 'premature labor' AND 'premature birth'

Source: Survey data.

The inclusion criteria established for the review were primary studies that addressed the topic in question, in Portuguese, English and Spanish and complete texts. Researches that did not address the association between premature birth and COVID-19 or duplicate articles, literature reviews, theses, dissertations, opinion articles and editorials were excluded. The selection of studies was carried out independently by two reviewers, the process of search and selection of studies followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations, as shown in Figure 1. For data extraction, an instrument constructed by the authors was chosen, considering the study identification variables: database, main author and year of publication, study title, study objective, methodological aspects (design) and main results.

## RESULTS

On 08.05.2021, Brazil registered, through the Ministry of Health (MS) vaccination panel against Covid-19, 149,469,803 doses applied, of which 6,411,157 were awaiting confirmation by state agencies and 143,028,646 doses had been applied and registered on the MS platform. Of the registered doses, 101,128,317 were related to the 1st

dose and 41,900,329 were related to the second dose. During this period, 2,457,511 doses were administered in 24 hours. As for distribution by sex, it was observed that 55.3% of the vaccines were given to women and 44.7% to men. Individuals aged between 18 and 19 years accounted for less than 1% of the percentage of doses applied, in turn, individuals aged between 20 and 59 years represented 60% of this vaccine coverage. Of the 17 selected studies, 14 were published in 2021 (82%) and 3 in 2020 (18%). Nine cohort studies predominated (52%), followed by three (17%) retrospective studies, two (11%) observational studies, one (5%) cross-sectional study and one (5%) prospective study. The majority of articles (65%) showed that the risk of preterm delivery seemed to increase in pregnant women infected with SARS-CoV-2 (GASPAR *et al.* 2021; MULLINS *et al.* 2021; ABEDZADEH-KALAHROUDI *et al.* 2021; TAGHAVI *et al.* 2021; MOR *et al.* 2021; MARTINEZ-PEREZ *et al.* 2021; MELGUIZO *et al.* 2021; ANGELIDOU *et al.* 2021; VIELMA *et al.* 2020; GULERSEN *et al.* 2020; GUO *et al.* 2021). Additionally, six studies (35%) found no association between preterm delivery and women with COVID-19 (SHAH *et al.* 2021; PASTERNAK *et al.* 2021; AGARWAL *et al.* 2021; VAEZI *et al.* 2021; HANDLEY *et al.* 2021; HANDLEY *et al.* 2021; JANEVIC *et al.* 2021).

## DISCUSSION

Pregnant women had similar clinical characteristics for COVID-19 when compared to the general population, however, they were more asymptomatic. Higher odds of cesarean delivery and premature birth among pregnant patients with COVID-19 suggested a possible association between COVID-19 infection and pregnancy complications. Interpretations of these results must be made with caution due to the heterogeneity between studies (JAFARI *et al.* 2021). In a meta-analysis, Allotey *et al.* (2020) reported a higher prevalence of preterm delivery among pregnant women with COVID-19 (15.9%) compared to uninfected women (6.1%), although the numbers included in this comparison were small and encompassed case series as well, as pre-prints that have not been peer-reviewed. Research conducted in Dallas showed that among 10 pregnant women with severe or critical illness diagnosed before 37 weeks, pregnancy loss or premature delivery (iatrogenic or spontaneous) occurred in 6 women (60%). Although the risk of delivery at less than 37, 34 and 28 weeks increased with the severity of maternal COVID-19, no placental abnormalities were associated with disease severity (ADHIKARI *et al.* 2020). The increased proportion of women admitted with complications, including premature birth, during the COVID-19 lockdown may suggest that women at high risk of complications are seeking out health facilities more frequently or that the number of complicated cases has increased due to delays and other blockade challenges (ASHISH *et al.* 2020). With the purpose of understanding the real motivations for the increase in the occurrence of premature births during the pandemic, the decrease in primiparous and hypertensive pregnant women was considered, according to indexes of health portals, when compared to the same populations in the pre-pandemic period. However, this effect should have been associated with a decrease in premature births and not with an increase, which can be explained by the reduction in the demand of this group of pregnant women for health services, causing a situation of non-previous diagnosis of comorbidities such as hypertension and diabetes pregnancy, these being relevant risk factors for the occurrence of prematurity (KHALIL *et al.* 2020). Due to physiological, immunological and cardiopulmonary changes, the pregnant woman is more susceptible to respiratory and systemic complications in viral infections. In influenza A (influenza A virus subtype H1N1) pregnant women constituted 1% of patients, but had 5% of deaths. SARS-CoV and MERS-CoV were responsible for a high number of maternal complications, such as the need for assisted ventilation, renal failure and death. In pregnant women who had SARS-CoV and MERS-CoV, there was a high number of preterm births, growth restriction, miscarriage and fetal death (OLIVEIRA *et al.* 2021). The pathophysiological mechanism by which SARS-CoV 2 induces pre-eclampsia is still unclear, but an association with the production of vasoconstriction and an inflammatory state has been suggested (MENDOZA *et al.* 2020).

AUTHOR/ YEAR	TITLE	OBJECTIVE	OUTLINE	MAIN RESULTS
Shah et al. 2021.	Preterm birth and stillbirth rates during the COVID-19 pandemic: a population-based cohort study.	To assess changes in preterm birth and stillbirth rates before and during the COVID-19 pandemic in Ontario, Canada.	Retrospective cohort study.	No changes in slope or gap between pre-pandemic and pandemic periods were found using interrupted time series analyses.
Gaspar et al. 2021.	SARS-CoV2 in Pregnancy - The First Wave.	To evaluate obstetric outcomes in pregnant women in whom SARS-CoV-2 was detected by RT-PCR of the nasopharyngeal swab, upon admission to the maternity ward.	Retrospective descriptive study.	The risk of premature birth appeared to be increased in pregnant women infected with SARS-CoV-2, occurring in approximately 20% of pregnancies.
Mullins et al. 2021.	Pregnancy and neonatal outcomes of COVID-19: reporting of common outcomes from PAN-COVID and AAP-SONPM registries.	To report the outcomes of pregnancies with SARS-CoV-2 infection, using data from the PAN-COVID study and the AAP-SONPM National Perinatal COVID-19 Registry.	Cohort study.	Premature birth affected a greater proportion of women than expected based on historical and contemporary national data.
Abdzadeh-Kalahroudi et al. 2021.	Maternal and neonatal outcomes of pregnant patients with COVID-19: A prospective cohort study.	To determine maternal and neonatal outcomes of pregnant women with COVID-19 infection.	Cohort study.	The rate of preterm labor in the exposed group was higher than in the control group.
Pasternak et al. 2021.	Preterm birth and stillbirth during the COVID-19 pandemic in Sweden: a nationwide cohort study.	To investigate associations between birth during a period when many public health interventions designed to mitigate the spread of COVID-19 were applied and the risk of preterm birth and stillbirth.	Cohort study.	No association between being born during a period when many public health interventions designed to mitigate the spread of COVID-19 were applied and risk for any of the preterm or stillbirth categories.
Taghavi et al. 2021.	Obstetric, maternal, and neonatal outcomes in COVID-19 compared to healthy pregnant women in Iran: a retrospective, case-control study.	To assess obstetric, maternal, and neonatal outcomes in COVID-19 compared to healthy pregnant women in Iran.	Retrospective case-control study.	It was found that women with COVID-19 were twice as likely to experience preterm labor.
Mor et al. 2021.	Impact of the COVID-19 pandemic on excess perinatal mortality and morbidity in Israel.	To assess the effect of the first wave of the COVID-19 pandemic on emergency obstetric care in a low-risk population and the corresponding perinatal outcomes.	Retrospective cohort study.	A significant rate of prematurity has been observed in the COVID-19 pandemic.
Agarwal et al. 2021.	Coronavirus disease 2019 in pregnancy: Maternal and perinatal outcome.	To study the clinical features and maternal, fetal, and perinatal outcomes of COVID-19 infection in pregnancy and the potential for vertical transmission of SARS-COV-2 infection.	Descriptive prospective observational study.	There was no association between the occurrence of preterm delivery and SARS-COV-2 infection.
Vaezi et al. 2021.	Characteristics, clinical and laboratory data and outcomes of pregnant women with confirmed SARS-CoV-2 infection admitted to Al-Zahra tertiary referral maternity center in Iran: a case series of 24 patients.	To assess the clinical and laboratory characteristics and outcomes of 24 pregnant COVID-19 patients and their newborns referred to Al-Zahra tertiary maternity hospital in Tabriz, Iran.	Retrospective study.	There was no increase in the risk of premature birth or miscarriage in the cases studied.
Martinez-Perez et al. 2021.	The association between SARS-CoV-2 infection and preterm delivery: a prospective study with multivariable analysis.	To determine whether exposure to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, the cause of COVID-19 disease) in pregnancy, compared with no exposure, is associated with infection-related obstetric morbidity.	Multicenter prospective study.	SARS-CoV-2 infection increased the odds of preterm delivery.
Melguizo et al. 2021.	Pregnancy outcomes and SARS-CoV-2 infection: the Spanish obstetric emergency group study.	To better understand the relationship between maternal infection and perinatal outcomes, with a focus on preterm birth and the underlying medical and interventional factors.	Prospective observational study.	Prematurity in pregnancies affected by SARS-CoV-2 resulted from a predisposition to termination of pregnancy due to maternal illness.
Angelidou et al. 2021.	Association of maternal perinatal SARS-CoV-2 infection with neonatal outcomes during the COVID-19 pandemic in Massachusetts.	To verify the percentage of neonates born to mothers with positive SARS-CoV-2 test results during hospitalization for delivery, the clinical and sociodemographic factors associated with positivity of the neonatal test result, and the clinical and virological outcomes for newborns during pregnancy, hospitalization and 30 days after discharge.	Cohort study.	The burden of exposure to SARS-CoV-2 on the newborn's health was associated with premature birth, which was motivated by the worsening of the maternal disease.
Handley et al. 2021.	Changes in preterm birth phenotypes and stillbirth at 2 Philadelphia hospitals during the SARS-CoV-2 pandemic, March-June 2020.	To determine whether the rates of preterm birth, spontaneous preterm birth, medically indicated preterm birth, and stillbirth changed during the SARS-CoV-2 pandemic.	Cohort study.	This study found no significant changes in preterm or stillbirth rates during the SARS-CoV-2 pandemic.
Vielma et al. 2020.	Premature delivery in COVID-19 patients at San Juan de Dios Hospital.	To characterize pregnant women with COVID-19 who delivered and determine the risk of premature birth in this group compared to those who did not have the disease at the Maternity Hospital of San Juan de Dios, and determine the rate of premature births.	Retrospective observational cohort study.	Among patients with COVID-19, a trend towards an increased risk of preterm delivery was observed, compared to those without the disease.
Gulersen et al. 2020.	Clinical implications of SARS-CoV-2 infection in the viable preterm period.	To determine the preterm birth rate (PBR) during hospitalization among women diagnosed with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) between 23 and 37 weeks of gestation and whether this rate differs by gestational age at diagnosis of infection.	Cross-sectional, retrospective study.	The likelihood of PBR during hospitalization with SARS-CoV-2 infection was significantly lower among women diagnosed in the early preterm period compared to late preterm.
Guo et al. 2021.	Case series of 20 pregnant women with 2019 novel coronavirus disease in Wuhan, China.	To evaluate perinatal outcomes in relation to the clinical presentation in pregnancy and the potential for vertical transmission of COVID-19.	Retrospective study.	The incidence of preterm delivery was 20%.
Janevic et al. 2021.	Racial/ethnic disparities in very preterm birth and preterm birth before and during the COVID-19 pandemic.	To assess whether racial/ethnic disparities in very preterm birth (VPBR) and preterm birth (PBR) increased during the first wave of the COVID-19 pandemic in New York City.	Cohort study.	No evidence was found for increased racial/ethnic disparities in PBR, between women who tested positive or negative for SARS-CoV-2.

Infections at the beginning of pregnancy were more associated with the development of hypertensive disorders, while, towards term, the association was not observed (MENDOZA *et al.* 2020). Placental alterations were also verified, mainly in the findings of poor fetal vascularization. Such alterations could suggest impairment of the vascular supply to the fetus, causing growth restriction and prematurity. Findings have even been reported in asymptomatic pregnant women (ALLOTEY *et al.* 2020). A possible cause for the occurrence of premature births as a result of COVID-19 could be attributed to the emergence of a more severe inflammatory reaction in the maternal organism as a result of the viral infection. This is because, especially during the third trimester of pregnancy, gestational physiological changes generate a pro-inflammatory condition to prepare the body for childbirth. However, a recent study indicated that infections associated with COVID-19 in pregnant women could increase the production of cytokines, which intensified inflammatory reactions, which resulted in previous uterine contractions, consequent rupture of the fetal membrane and premature birth. Even if this inflammatory configuration did occur, studies in the area of obstetrics have associated membrane rupture and premature birth with maternal pneumonia arising from various agents, and not exclusively from the coronavirus, and, therefore, strong evidence that the viral infection by COVID-19 was related to preterm births (MELO & ARAÚJO, 2020). In addition, the possible contamination of the fetus by the virus from the mother through the intrauterine route or during labor must be taken into account. At the time of delivery, samples of vaginal and amniotic fluid were collected from segments of the umbilical cord, fetal membrane, placenta, nasopharynx of the neonate and meconium, in order to test the presence of the coronavirus by the qRT-PCR, however, until then, there was no evidence of vertical transmission, since the rare positive samples for SARS-CoV-2 and MERS-CoV, in neonates, were exclusively by nasopharyngeal swab, which suggested postpartum transmission, by direct contact with other infected individuals (DIRIBA *et al.* 2020). During prenatal care, pregnant women received guidance from multidisciplinary teams on the development of pregnancy, allowing the delivery of a healthy newborn, without impact on maternal health, including addressing psychosocial aspects and educational and preventive activities, however, unfavorable maternal and neonatal outcomes in the presence of moderate and severe COVID-19 have been demonstrated in the literature (SILVA *et al.* 2021). Pregnant women infected with SARS-CoV-2 are more likely to be hospitalized, admitted to an intensive care unit and mechanically ventilated (BRASIL, 2020). In this follow-up, it is necessary that all precautions are taken, avoiding unnecessary exposure of the pregnant woman. Prenatal care must be guaranteed, and consultations may be spaced out. For optimization, it is recommended to include the collection of exams and ultrasounds on the day of the face-to-face consultation. The time interval between consultations should be determined taking into account the gestational age, the presence or absence of maternal or fetal diseases, comorbidities and the evolution of the pregnancy. In order to space out consultations while maintaining care, the use of teleconsultation with the appropriate record in the pregnant woman's medical record was considered (OLIVEIRA *et al.* 2021).

## CONCLUSION

Since the beginning of the National Vaccination Campaign against Covid-19, more than 145 million doses have been administered. In all, 102.8 million Brazilians have already received at least one dose of the vaccine. This equates to 64.25% of the target audience. So far, 42.7 million people have completed the vaccination schedule. This study underscores the importance of effective public health policies for investment to distribute vaccines to the entire Brazilian population equally, in order to combat the COVID-19 epidemic. In addition, there is a need to develop more studies that help build valid and reliable ways to manage this type of public health emergency, both in the short and long term. Most of the studies included in this review showed higher rates of premature births in pregnant women with COVID-19, however, it has not yet been possible to robustly define the direct implications of COVID-19 with the occurrence of premature birth. In view of the new scenario imposed by the

Coronavirus, it is observed that the relationship between the occurrence of premature birth associated with complications due to COVID-19 is still a reality that needs to be studied in greater depth. Thus, it is extremely important that pregnant women carry out prenatal care on a regular basis, with trained professionals, following all guidelines and care, reinforcing the importance of immunization against COVID-19.

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