

Premature birth and COVID-19: an integrative review

Nascimento prematuro e COVID-19: uma revisão integrativa

DOI:10.34119/bjhrv4n4-043

Recebimento dos originais: 25/06/2021

Aceitação para publicação: 11/07/2021

Marina Presmich Pontual

Acadêmica de Medicina

Instituição: Universidade Federal de Alagoas, UFAL

Endereço: Av. Lourival Melo Mota, S/N, Tabuleiro do Martins – Faculdade de Medicina, Maceió – AL, Brazil

E-mail: marinapresmich@gmail.com

Camila Radelley Azevedo Costa da Silva

Acadêmica de Medicina

Instituição: Universidade Federal de Alagoas, UFAL

Endereço: Av. Lourival Melo Mota, S/N, Tabuleiro do Martins – Faculdade de Medicina, Maceió – AL, Brazil.

E-mail: camilaradelley@gmail.com

Lisiane Vital de Oliveira

Acadêmica de Medicina

Instituição: Centro Universitário CESMAC

Endereço: Rua Cônego Machado, 984 – Faculdade de Medicina – Farol, Maceió – AL, Brazil

E-mail: vitallisiane@gmail.com

Lorena Peixoto Lopes

Mestra em Modelagem Computacional de Conhecimento pela UFAL

Instituição: Centro Universitário CESMAC e Universidade Federal de Alagoas, UFAL

Endereço: Av. Lourival Melo Mota, S/N, Tabuleiro do Martins – Faculdade de Medicina, Maceió – AL, Brazil

E-mail: lorenapeixotolopes@gmail.com

Isabela Karine Rodrigues Agra

Doutora em Ciências pela Faculdade de Medicina da USP

Instituição: Centro Universitário CESMAC e Universidade Federal de Alagoas, UFAL

Endereço: Av. Lourival Melo Mota, S/N, Tabuleiro do Martins – Faculdade de Medicina, Maceió – AL, Brazil

E-mail: agraisabela@gmail.com

ABSTRACT

OBJECTIVE: To review the current scientific evidence of premature birth related to coronavirus disease 2019 (Covid-19). **METHODS:** An integrative review was carried out by three independent researchers, based on the literature available in the MEDLINE (via PubMed) and LILACS databases, using the descriptors "coronavirus infections" and

"premature birth". This research included case reports or case series published until 26th February 2021, in English or Portuguese. After reading the articles in their entirety, those specifically related to premature birth in pregnant women positive for Covid-19 were selected. Initially, a total of 21 articles were found, 19 were analyzed in full-text and 13 were finally selected for this study. **RESULTS:** The rate of prematurity was not reflected at the expense of spontaneous premature birth, since these were relatively low, with a cesarean section percentage higher than 80%. Most reports describe the termination of pregnancy by cesarean section due to maternal-fetal hemodynamic instability. It is known that Covid-19 can cause serious maternal or perinatal outcomes; however, it is suggested that the indication of the delivery route be individualized and the importance of quality prenatal care is emphasized. **CONCLUSION:** Covid-19 prematurity seems to be elevated by the increased number of preterm births due to cesarean sections possibly to improve maternal and neonatal clinical status. However, more studies are needed to prove the hypothesis of spontaneous premature labor caused directly by SARS-CoV-2.

keywords: Coronavirus infections, COVID-19, Premature Birth, Pregnancy.

RESUMO

OBJETIVOS: Revisar as evidências científicas atuais relacionadas ao parto prematuro e a infecção pelo novo coronavírus 2019 (COVID-19). **MÉTODOS:** Uma revisão integrativa foi realizada por três pesquisadores independentes, com base na literatura disponível nas bases de dados MEDLINE (via PubMed) e LILACS, utilizando os descritores "infecções por coronavírus" e "parto prematuro". Esta pesquisa incluiu relatos de caso ou séries de casos publicados até 26 de fevereiro de 2021, em inglês ou português. Após a leitura integral dos artigos, foram selecionados aqueles relacionados especificamente ao parto prematuro em gestantes comprovadamente infectadas para Covid-19. Inicialmente foram encontrados um total de 21 artigos, 19 foram analisados na íntegra e 13 foram finalmente selecionados para o estudo. **RESULTADOS:** A taxa de prematuridade não se refletiu às custas de parto prematuro espontâneo, pois estes foram relativamente baixos, com percentual de cesárea superior a 80%. A maioria dos relatos descrevem a interrupção da gestação por via cesárea devido à instabilidade hemodinâmica materno-fetal. Sabe-se que o Covid-19 pode causar graves desfechos maternos ou perinatais, no entanto sugere-se que a indicação da via de parto seja individualizada e ressalta-se a importância de um pré-natal de qualidade. **CONCLUSÃO:** A prematuridade pelo Covid-19 parece ser elevada pelo aumento do número de partos prematuros por cesarianas possivelmente para melhora do estado clínico materno e neonatal. No entanto mais estudos são necessários para comprovar a hipótese de trabalho de parto prematuro espontâneo causado diretamente pelo SARS-CoV-2.

Palavras-Chave: Infecções por coronavírus, COVID-19, Parto Prematuro, Gravidez.

1 INTRODUCTION

Since its first identification in December 2019 in China, coronavirus disease 2019 (Covid-19) caused by severe acute respiratory syndrome coronavirus (SARS-CoV-2) has created great concerns and numerous challenges¹. For more than one year now, organizations and health professionals are learning in real time the high spread and

lethality caused by this virus that overloads both private and public systems². Considerations about diagnostic testing and treatment still exist and there is discussion about mass testing for specific lockdown of infected cases³.

Studies on the effects of Covid-19 on pregnancy are expanding, mainly due to the advent of new scientific data and some comprehension of the mechanisms of the disease. However, robust knowledge regarding the effects of Covid-19 on pregnant women and their fetus are still scarce. Despite that, studies suggest that this particular group is more vulnerable and considered at risk for the disease^{4,5}.

The impact of Covid-19 on pregnant women draws attention in relation to morbidity, mortality and perinatal outcomes. Despite the limited data, studies report that pregnant women infected by the virus are at increased risk of some adverse obstetric outcomes, compared to non-pregnant women⁶. Based on small case series, coronavirus infection was associated with higher rates of premature birth, preeclampsia, spontaneous abortion, cesarean delivery and perinatal death⁸.

Concerning specific to premature birth, some studies detected increased numbers among infected pregnant women⁸, however these data is limited, due to the small number of cases analyzed. Therefore, the objective of this study was to perform an integrative review of available published literature on pregnancies affected by Covid-19 in order to evaluate the potential effects of the disease on prematurity rates.

2 METHODS

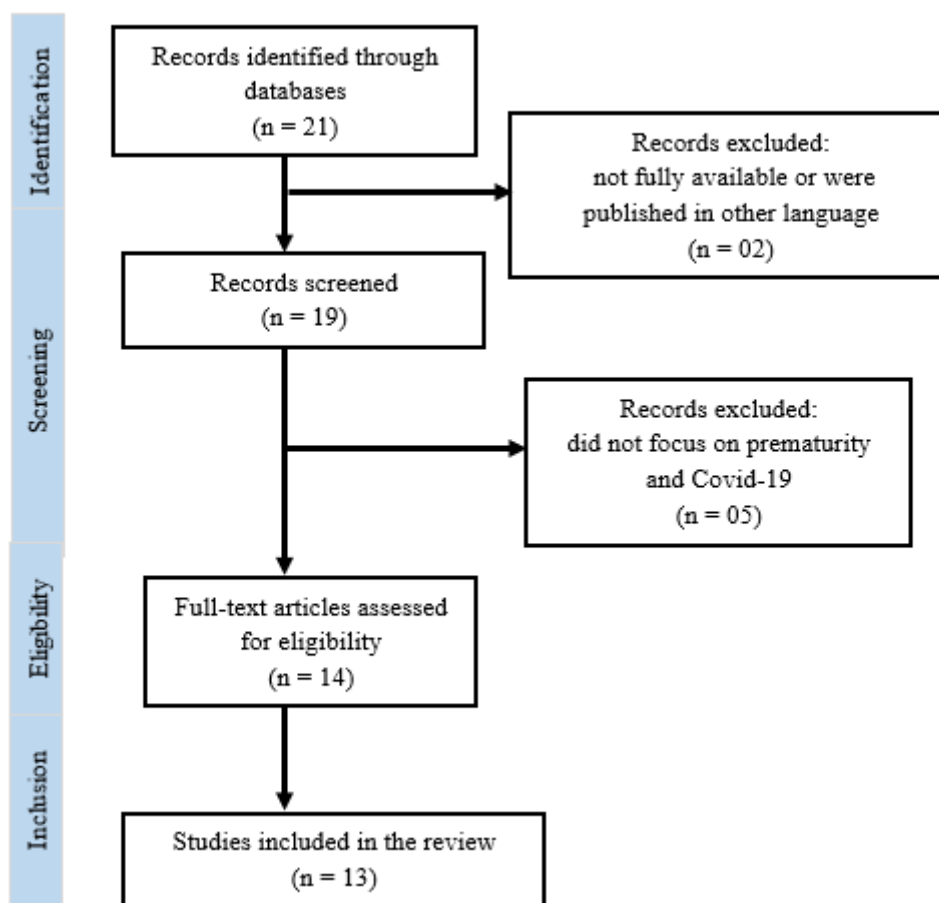
This integrative literature review was conducted in the Medical Literature Analysis and Retrieval System on-line (Medline, through access to the PubMed) and in the Latin America and Caribbean Health Sciences Literature (Lilacs) databases. To define the search terms, the Health Sciences Descriptors (DeCs) and Medical Subject Headings (MeSH) were consulted, with the following descriptors - and their combinations in English - used: coronavirus infections and premature birth, crossed with the Boolean operator “AND”. This search was included articles published up until 28th February 2021.

The inclusion criteria defined to first select articles were case series and case reports published in English or Portuguese – review articles, short communications, dissertations and management guidelines were not included. After reading the fully extent of the articles, those studies that did not address specifically to the prematurity and Covid-19 were also excluded. For that, three independent researchers performed the search

strategy in the scientific databases and, if there were disagreements regarding the final inclusion, a fourth senior researcher was consulted.

This review was performed according to a standard protocol for systematic reviews, which was based on the methodological manuals of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). We initially found a total of 21 articles; 19 were carefully screened, according to the inclusion and exclusion criteria adopted, 13 papers were finally selected. **Figure 1** summarizes studies' selection, according to identification, tracking, eligibility and justification for exclusion.

Figura 1. PRISMA 2009 flow diagram for article's inclusion on prematurity delivery at Covid-19.



3 RESULTS AND DISCUSSION

The articles selected are shown in **Table 1**, that summarizes their main information and findings regarding premature birth and Covid-19.

It is undeniable that SARS-CoV-2 has become a major challenge for health professionals, in special obstetricians and neonatologists, since it represents a multifaceted unknown form of coronavirus, with perinatal consequences still under analysis⁹.

The clinical course of the disease is generally mild and asymptomatic in pregnant women, similar to those of non-pregnant women¹⁰⁻¹². However, according to the latest report from the Center for Disease Control and Prevention¹³, pregnant women may have a greater need for mechanical ventilation (MV), extracorporeal membrane oxygenation, and intensive care unit (ICU) admission. Douglass et al.¹⁴, consider that pre-existing conditions, such as diabetes and obesity, increase the susceptibility to develop severe forms of Covid-19 in pregnancy.

In addition to that, studies also describe a direct association between preterm birth and this viral infection. According to Cruz et al.¹⁵, the infection by the new coronavirus is not an indication for pregnancy termination and the assistance provided should be individualized. Only if maternal clinical conditions are severe, leading to fetal distress, intrauterine fetal death or maternal death, pregnancy should be terminated premature. However, since the beginning of the SARS-CoV-2 pandemic, most pregnant women suspected or confirmed for Covid-19 have undergone cesarean section even without clinical indications⁹.

In our analysis, six pregnant women went into spontaneous premature labor^{12,14,16-19,22}, two had premature rupture of membranes^{18,19} and one had a placenta abruption²⁰. Three evolved to spontaneous vaginal delivery^{13,17,18} and, among them, only one received intrapartum oxytocin¹⁸. The others (13/16) delivered preterm by Cesarean section; indication of delivery was not reported in all cases; some related that termination was due to maternal-fetal hemodynamic instability²¹⁻²⁵.

One of the pregnancies was a diamniotic and dichorionic twin, which went into uncontrollable premature labor, with fetal death of both fetuses. Histological examinations of the placenta revealed chronic intervillitis and extensive fibrin deposition with ischemic necrosis of the surrounding villi, such findings support the possibility of vertical transmission by SARS-CoV-2 and spontaneous abortion due to infection cannot be ruled out¹².

It can be seen that the increase in the preterm birth rate was not reflected by the spontaneous preterm birth rates, as these were relatively low, with percentual of preterm cesarean section of more the 80% in our analysis. Blauvelt et al.²¹ already advised that the risks and benefits of early delivery should be analyzed, prioritizing maternal stability over the acute fetal state and that spontaneous vaginal delivery should be encouraged.

No maternal death was reported in our analysis, and only one woman had symptoms worsening after delivery²²; the others improved significantly postpartum. The incidence of preterm birth and unfavorable outcomes during pregnancy were related to gestational age (specially before 34 weeks), and should therefore be identified as early as possible so that proper care can be taken to ensure maternal-fetal vitality.

Concerning to neonatal mortality, according to Allotey et al²⁶, rates are low in women confirmed or suspected for Covid-19, despite of an increased risk of neonatal ICU admission. A total of eleven newborns remained healthy after delivery^{6,16,17,19,20,22,24,25}, and of these, there were triplets with a positive nasopharyngeal swab for SARS-CoV-2¹⁶.

Three newborns presented with respiratory distress after birth^{18,21,23}, and only one of them tested positive for Covid-19 by RT-PCR from a nasopharyngeal swab¹⁸. SARS-CoV-2 serology studies of one baby showed immunoglobulin G positive. The newborn was intubated 4 minutes after birth, the Apgar 1 and 5 minute were 4 and 7. On chest radiograph ground glass opacities were appreciated. SARS-CoV-2 nasopharyngeal RT-PCR were sent at birth, 24 hours, 48 hours, and 7 days after birth which were all negative. The infant was extubated within 24 hours after birth the remained in the for routine care for prematurity¹⁴.

These severe cases of neonatal morbidity seem to be related to severe maternal clinical status. Additionally, Hütter et al²⁷ and Zhu et al.²⁸ declared that both hypoxemia and respiratory failure in the severe affected pregnant woman may cause placental hypoxia and induce fetal distress, premature labor, respiratory distress, thrombocytopenia, liver dysfunction, and fetal or postnatal death.

Although Covid-19 has a pathogenic potential to cause serious adverse maternal or perinatal outcomes it is pointed out that intrauterine fetal distress and preterm delivery may not always be directly related to SARS-CoV-2 infection²⁸. The quality and efficiency of prenatal care is a fundamental step to avoid poor outcomes and this process may be compromised in the current context of the pandemic, primary due to increased absenteeism to prenatal appointments and continuous lack of good health professionals.

Table 1. Publications included in this integrative review.

Author	Date of publication	Number of pregnant women (n)	Number of neonates (n)	Gestational age	Birth weight	Type of delivery		Spontaneous labor	
						Cesarean	Normal	Yes	No
Blauvelt CA et al. ²⁰	29 Apr 2020	01	01	28s 6d	1.880g	01			01
Cooke WR et al. ²⁴	14 May 2020	02	02	28s 5d 29s	1.530g 1.400g	02			02
Sisman J et al. ¹⁷	23 Jun 2020	01	01	34s	3.280g		01	01	
Pulinx B et al. ¹¹	24 Jun 2020	01	02**	24s	*		01	01	
Easterlin MC et al. ²²	05 Jul 2020	01	01	25s 5d	810 g	01			01
Reis HLB et al. ²³	13 Jul 2020	02	02	31s 28s 6d	2.380g 1.255g	02			02
Zheng T et al. ²¹	17 Jul 2020	01	01	36s 3d	2.520g	01			01
Wang X et al. ⁵	28 Jul 2020	01	01	30s	1.830g	01			01
Lugli L et al. ¹⁹	25 Aug 2020	01	01	32s	1.614g	01			01
Alwardi TH et al. ¹⁵	13 Sep 2020	01	03	32s 5d	1.910g 1.390g 1.630g	01		01	

Douglass KM et al. ¹³	10 Oct 2020	02	02	31s 6d 27s 7d	1.465g 1.000g	02		01	01
Narang K et al. ¹⁶	22 Dec 2020	01	01	33s 5d	2.500g		01	01	
Giavoli C et al. ¹⁸	15 Jan 2021	01	01	36s	*	01		01	
Total		16	19	-	-	13	03	06	10

*The article does not report the birth weight/ ** stillborn.

4 CONCLUSION

In conclusion, Covid-19 seems to raise the rates of premature births mainly due to increased number of Cesarean sections, possibly performed to improve the maternal clinical status and ensure neonatal vitality. The hypothesis of spontaneous premature labor caused directly by SARS-CoV-2 cannot be ruled out yet, mainly due to the small number of cases reported in the literature up until now.

Further studies on prematurity associated with maternal SARS-CoV-2 infection are still needed to obtain reliable conclusions on this subject. However, it is well known that it is necessary to improve prenatal care to ensure better maternal and neonatal outcomes.

REFERENCES

1. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020; 395:497–506.
2. Silva G, Silva S, Costa M, et al. SARS-CoV, MERS-CoV and SARS-CoV-2 infections in pregnancy and fetal development. *Journal of Gynecology Obstetrics and Human Reproduction*. 2020; 49:101846.
3. Pascoal DB, Carvalho ACS, Mata LELFS, et al. Acute Respiratory Syndrome: an exacerbated immune response to COVID19. *Braz. J. Hea. Rev.*, 2020; 3(2):2978-2994
4. Qiao, J. What are the risks of COVID-19 infection in pregnant women? *Lancet*. 2020, 395: 760–762.
5. Albuquerque LP, Monte AVL, Araújo RMS. Implications of COVID-19 for pregnant patients. *Revista Eletrônica Acervo Saúde / Electronic Journal Collection Health*. 2020; 12: e4632.
6. Wang X, Zhou Z, Zhang J, et al. A Case of 2019 Novel Coronavirus in a Pregnant Woman With Preterm Delivery, *Clinical Infectious Diseases*. 2020; 71:844–846.
7. Mascio DD, Khalil A, Saccone G, et al. Outcome of coronavirus spectrum infections (SARS, MERS, COVID-19) during pregnancy: a systematic review and meta-analysis. *Am J Obstet Gynecol MFM*. 2020; 2: 100107.
8. Mullins E, Evans D, Viner RM, O'Brien P, Morris E. Coronavirus in pregnancy and delivery: rapid review. *Ultrasound Obstet Gynecol*. 2020;55(5):586-592.
9. Bellos I, Pandita A, Panza R. Maternal and perinatal outcomes in pregnant women infected by SARS-CoV-2: A meta-analysis. *Eur J Obstet Gynecol Reprod Biol*. 2021; 256:194-204.
10. Papapanou, M, Papaioannou, M, Petta, A, et al. Maternal and Neonatal Characteristics and Outcomes of COVID-19 in Pregnancy: An Overview of Systematic Reviews. *Int. J. Environ. Res. Public Health*. 2021; 18: 596.
11. Dubey P, Reddy SY, Manuel S. et al. Maternal and neonatal characteristics and outcomes among COVID-19 infected women: Na updated systematic review and meta-analysis. *Eur. J. Obstet. Gynecol. Reprod. Biol*. 2020; 252: 490-501.
12. Pulinx B, Kieffer D, Michiels I, et al. Vertical transmission of SARS-CoV-2 infection and preterm birth. *Eur J Clin Microbiol Infect Dis*. 2020; 39: 2441-2445.
13. Centers for Disease Control and Prevention. Data on COVID-19 during Pregnancy: Severity of Maternal Illness. 2021. <https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/special-populations/pregnancy-data-on-covid-19.html>

14. Douglass KM, Strobel KM, Richley M, et al. Maternal-Neonatal Dyad Outcomes of Maternal COVID-19 Requiring Extracorporeal Membrane Support: A Case Series. *Am J Perinatol.* 2021; 38:82-87.
- 15.
16. Cruz AC, Sousa MA, FREITAS BHBM, et al. Assistência ao recém-nascido prematuro e família no contexto da COVID-19. *Rev Soc Bras Enferm Ped.* 2020; 20: 49-59.
17. Alwardi TH, Ramdas V, Al Yahmadi M, et al. Is Vertical Transmission of SARS-CoV-2 Infection Possible in Preterm Triplet Pregnancy? A Case Series. *Pediatr Infect Dis J.* 2020; 39:e456-e458.
18. Narang K, Szymanski LM, Kane SV, Rose CH. Acute Pancreatitis in a Pregnant Patient With Coronavirus Disease. 2019 (COVID-19). *Obstet Gynecol.* 2021; 137:431-433.
19. Sisman J, Jaleel MA, Moreno W, et al. Intrauterine Transmission of SARS-COV-2 Infection in a Preterm Infant. *Pediatr Infect Dis J.* 2020; 39: e265-e267.
20. Giavoli C, Iurlaro E, Morelli V, et al. Case Report: Late-Onset Congenital Adrenal Hyperplasia and Acute Covid-19 Infection in a Pregnant Woman: Multidisciplinary Management. *Front Endocrinol (Lausanne).* 2021; 11: 602535.
21. Lugli L, Bedetti L, Lucaccioni L, et al. An Uninfected Preterm Newborn Inadvertently Fed SARS-CoV-2-Positive Breast Milk. *Pediatrics.* 2020; 146: e2020004960.
22. Blauvelt CA, Chiu C, Donovan AL, et al. Acute Respiratory Distress Syndrome in a Preterm Pregnant Patient With Coronavirus Disease 2019 (COVID-19). *Obstet Gynecol.* 2020; 136:46-51.
23. Zheng T, Guo J, He W, Wang H, Yu H, Ye H. Coronavirus disease 2019 (COVID-19) in pregnancy: 2 case reports on maternal and neonatal outcomes in Yichang city, Hubei Province, China. *Medicine (Baltimore).* 2020; 99: e21334.
24. Easterlin MC, De Beritto T, Yeh AM, et al. Extremely Preterm Infant Born to a Mother With Severe COVID-19 Pneumonia. *J Investig Med High Impact Case Rep.* 2020; 8:1-5.
25. Reis HLBD, Boldrini NAT, Caldas JVJ, Paz APCD, Ferrugini CLP, Miranda AE. Severe coronavirus infection in pregnancy: challenging cases report. *Rev Inst Med Trop Sao Paulo.* 2020; 62: e49.
26. Cooke WR, Billett A, Gleeson S, et al. SARS-CoV-2 infection in very preterm pregnancy: Experiences from two cases. *Eur J Obstet Gynecol Reprod Biol.* 2020; 250: 259-260.
27. Allotey J, Stallings E, Bonet, M, et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: Living systematic review and meta-analysis. *BMJ.* 2020; 370: m3320.

28. Hütter D, Kingdom J, Jaeggi E. Causes and Mechanisms of Intrauterine Hypoxia and Your Impact on the Fetal Cardiovascular System: A Review. *Int. J. Pediatr.* 2010; 1-9.

29. Zhu H, Wang L, Fang C, et al. Clinical analysis of 10 neonates born to mothers with 2019-nCov pneumonia. *Transl Pediatr.* 2020; 9: 51-60.