

# BOLETIM RAMB COVID-19

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## **Immunological aspects of coronavirus disease during pregnancy: an integrative review**

*Camila Radelley Azevedo Costa da Silva  
Lisiane Vital de Oliveira  
Lorena Peixoto Lopes  
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Isabela Karine Rodrigues Agra*

*Em um momento em que há uma emergência mundial de saúde pública, é fundamental que o conhecimento científico gerado durante a pandemia chegue rapidamente à classe médica classe médica.*

*Dentro desta dinâmica a Revista da Associação Médica Brasileira (Ramb) está adotando uma série de medidas a fim de acelerar o processo editorial para publicação de artigos sobre a Covid-19. A partir de hoje (14/04/2020), a AMB publicará o Boletim Ramb Covid-19, que antecipará os artigos científicos selecionados pelos editores da Ramb sobre o tema.*

*“Os artigos foram escritos por especialistas e selecionados dentro dos critérios da Ramb para esclarecer temas fisiopatológicos, assim como oferecer orientações de prevenção e tratamento da doença. Dessa forma, esperamos colaborar com os médicos para o melhor atendimento aos seus pacientes, com a disponibilidade mais ágil desses artigos, antes de sua publicação na Ramb”, comenta Carlos Serrano Jr., editor-chefe da Ramb.*

*Para o diretor científico da AMB, Antonio Carlos Palandri Chagas, “neste momento ímpar vivido no mundo por conta da pandemia de Covid-19, a AMB cumpre seu papel de estar levando à comunidade científica brasileira os recentes artigos sobre os mecanismos fisiopatológicos e aspectos clínicos relevantes dessa situação que assola a saúde pública”.*



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# Immunological aspects of coronavirus disease during pregnancy: an integrative review

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## SUMMARY

**OBJECTIVE:** To review the immunological aspects of the 2019 coronavirus disease (COVID-19) in pregnancy, based on the scientific evidence currently available.

**METHODS:** An integrative review was performed by two independent researchers, based on the literature available in the MEDLINE (via PubMed) and LILACS databases, using the descriptors “pregnancy” and “COVID-19”. This search included articles published up until 14th April 2020 published in English, Spanish or Portuguese. After reading the articles available in their entirety, those related specifically to the immunological aspects of the disease in pregnancy were selected. We initially found a total of 62 articles; 52 were accessed in full-text, and 5 were finally selected.

**RESULTS:** Pregnant women are more affected by respiratory diseases possibly because of physiological, immune, and anatomical changes. Some studies highlight the important shift to a T-helper lymphocyte type 2 (Th2) immune response in pregnancy, as a potential contributor to the severity in cases of COVID-19. Additionally, the cytokine storm present in severe cases leads to an increased inflammatory state, which may deteriorate the clinical prognosis in this population. Therefore, pregnant women may represent a vulnerable group to COVID-19 infection, primarily due to the immune imbalance in the maternal-fetal interface.

**CONCLUSION:** Maternal immune response probably plays an important role in the pathophysiology of this infection, although some details remain unsolved. Although further studies are needed to deeply investigate the immunological aspects of the disease in pregnancy, our findings may provide insights into the possible immune mechanisms involved in the pathophysiology of COVID-19 in pregnancy.

**KEYWORDS:** Pregnancy. Immunity. COVID-19. Coronavirus infections. Pandemics.

## RESUMO

**OBJETIVOS:** Revisar o conhecimento atual sobre os aspectos imunológicos da infecção por coronavírus 2019 (COVID-19) na gravidez, com base nas evidências científicas recentes.

**MÉTODOS:** Uma revisão integrativa foi realizada por dois pesquisadores independentes, com base na literatura disponível nas bases de dados MEDLINE (via PubMed) e LILACS, utilizando os descritores “gravidez” e “COVID-19”. Esta pesquisa incluiu artigos publicados até 14 de abril de 2020, publicados em inglês, espanhol ou português. Após a leitura integral dos artigos, foram selecionados aqueles relacionados especificamente aos aspectos imunológicos da doença na gravidez. Encontramos inicialmente um total de 62 artigos; 52 foram acessados em texto completo e 5 artigos foram finalmente selecionados.

**RESULTADOS:** As gestantes são sabidamente mais afetadas por doenças respiratórias, devido a alterações imunológicas e anatômicas fisiológicas. Alguns estudos destacam a importante mudança para uma resposta imune linfocitária T do tipo 2 (Th2) na gravidez, como potencial contribuinte para a gravidade nos casos de COVID-19. Além disso, a tempestade de citocinas apresentada em casos graves da doença leva a um aumento do estado inflamatório, que pode deteriorar o prognóstico clínico nessa população. Portanto, as mulheres grávidas podem representar um grupo vulnerável à infecção por COVID-19, principalmente devido ao desequilíbrio imunológico na interface fetal materna.

**CONCLUSÃO:** A resposta imune materna provavelmente desempenha um papel importante na fisiopatologia dessa infecção, apesar de alguns detalhes permanecerem sem solução. Embora sejam necessários mais estudos para investigar profundamente os aspectos imunológicos da doença na gravidez, nossos achados podem fornecer informações sobre possíveis mecanismos imunológicos envolvidos na fisiopatologia do COVID-19 na gravidez.

**PALAVRAS-CHAVES:** Gravidez. Imunidade. COVID-19. Infecções por coronavírus. Pandemias.

## INTRODUCTION

In December 2019, a new type of coronavirus was identified as the cause of a pneumonia outbreak of unknown etiology in Wuhan, China<sup>1</sup>. The World Health Organization (WHO) has officially named the disease 2019 coronavirus disease (COVID-19) and the virus-related disorder “severe acute respiratory syndrome coronavirus 2” (SARS-CoV-2)<sup>2,3</sup>. Despite the efforts taken to control the pathogen, COVID-19 was considered a pandemic by the WHO on 11<sup>th</sup> March 2020.

This new RNA coronavirus, which can be rapidly transmitted via airborne and interpersonal contact, can cause mild upper respiratory tract infection with fever, cough, and lower respiratory tract infection that can evolve to severe cases and life-threatening pneumonia with acute respiratory distress syndrome<sup>4</sup>. Despite having some similarities with other coronaviruses, SARS-CoV-2 is more contagious than other pathogens and currently, there is no effective target treatment for this virus<sup>5</sup>.

Up until 14<sup>th</sup> April 2020, Brazil had reported 25,262 confirmed cases and 1,532 deaths from COVID-19, which corresponds to a lethality rate of 6,1%<sup>6</sup>. Most of the cases were concentrated in the Southeast region, followed by the Northeast and South regions. Among the Federated Units, São Paulo presented the largest number of confirmed cases of the disease<sup>6</sup>. The Brazilian epidemiological bulletin did not provide information specifically regarding the number of cases involving pregnant women; instead, it considered the inclusion of pregnant and post-partum women in high-risk groups<sup>7</sup>.

The published data on COVID-19 during pregnancy are still limited, but it is well known that it represents a

group of interest and a high-risk population during infectious respiratory disease outbreaks<sup>8</sup>. This may be due to physiological and mechanical modifications, such as increased oxygen consumption, edema of the respiratory mucosa, the elevation of the diaphragm, and altered pulmonary volumes<sup>9,10</sup>. These changes contribute to reduced total lung capacity at term and inability to clear pulmonary secretions effectively<sup>11</sup>. Besides that, these physiological modifications of the maternal organism may contribute to delay the COVID-19 diagnostics in pregnancy, since classic symptoms can be mistaken by gestational complaints.

Additionally to these mechanical alterations, immunological adaptations are necessary to ensure maternal tolerance to the fetus – such as the down-regulation of lymphocyte proliferation and activation –, contributing to transform pregnant women into a more vulnerable group<sup>12</sup>. External stimulation, especially virus infection, may cause serious disorders in this complex immune balance at the maternal-fetal interface and can be related to the unique aspects of

SARS-CoV-2 infection in this specific group.

Therefore, in this review, we focused on the immunological aspects of COVID-19 during pregnancy and the great challenge that this infection represents to the immune system.

## 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. The descriptors – and their combination in Portuguese and English – used were “pregnancy” and “COVID-19”, crossed using the Boolean operator “AND”. This search was not restricted to any year of publication and included articles published up until 14<sup>th</sup> April 2020.

The inclusion criteria defined was to first select articles published in English, Spanish, or Portuguese. Initially, articles that were not available on the internet databases in its entirety or were written in languages other than those mentioned above were excluded. Then, after reading

the full extent of the articles, those that did not address specifically to the immunological aspects of COVID-19 infection in pregnancy were also excluded. For that, two independent researchers executed the search strategy in the scientific databases, and if there were disagreements regarding the final inclusion, a third 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 62 articles; 52 were accessed in full-text and, according to the inclusion and exclusion criteria adopted, 5 papers were finally selected. Figure 1 summarizes study selection.

## RESULTS

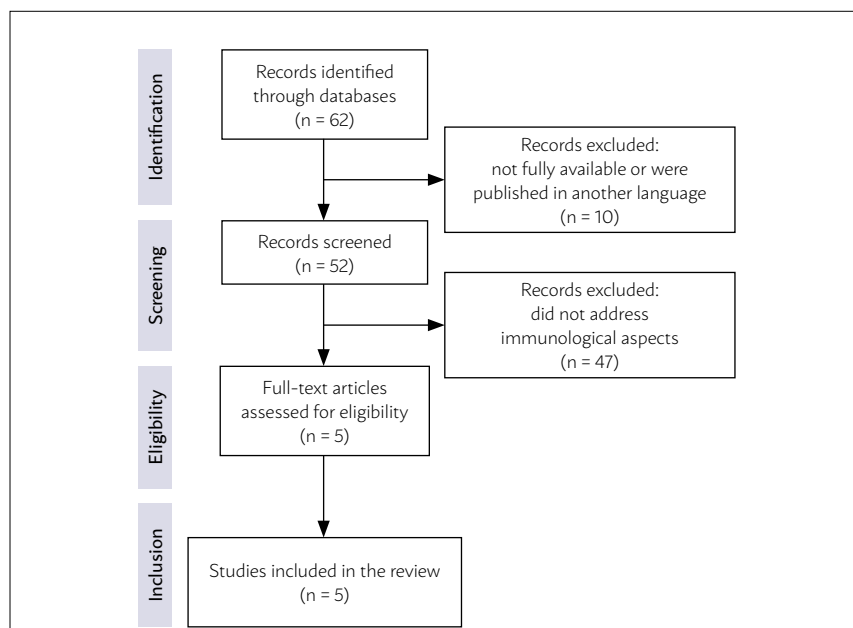
The articles selected are shown in Table 1, which summarizes their information, methodologies, and main results.

## DISCUSSION

Pregnancy is a unique immunological state, in which intricate processes take place physiologically in the maternal-fetal interface. When this fragile balance is disturbed by infections, this system can collapse. There is little evidence regarding the immune adaptation to SARS-CoV-2 infection in pregnancy, which highlights the importance of this review. There is still no robust publication, based on currently available scientific evidence, related to the specific immune aspects of COVID-19 in pregnant women. Therefore, we selected all studies relating to immunity, COVID-19, and pregnancy, in spite of the study design. All publications that were included correspond to narrative reviews, lacking details and methodological information about the selection of data.

Chen et al.<sup>13</sup> and Dashraath et al.<sup>8</sup> mentioned that pregnant women

**FIGURE 1.** PRISMA 2009 FLOWCHART FOR INCLUSION OF ARTICLES ON THE IMMUNOLOGICAL ASPECTS OF COVID-19 IN PREGNANCY.



**TABLE 1. PUBLICATIONS INCLUDED IN THIS INTEGRATIVE REVIEW**

Author, Year	Study Design	Main Results
Dashraath et al. <sup>8</sup> 2020	Narrative Review	Pregnant women are known to be more affected by respiratory illness, which is associated with increased morbidity and mortality rates. In pregnancy, the physiological shift to a Th2 dominant environment contributes to overall infections by increasing maternal susceptibility to intracellular pathogens like viruses. Patients with SARS showed preferential activation of lymphocyte T-helper type 1 (pro-inflammatory) response. Authors postulated that transition to a lymphocyte T-helper type 2 environment in pregnancy, favoring the expression of anti-inflammatory cytokines, may result in milder cases of COVID-19 in pregnancy.
Chen et al. <sup>13</sup> 2020	Narrative Review	Pregnant women are more susceptible to the virus due to immune and anatomic alteration. Alterations in cellular immunity, such as down-regulation of lymphocyte proliferation and activation, are primarily aimed at adopting maternal immune tolerance to the fetus. Despite the limited sample sizes of the studies analyzed, the authors suggest a higher fatality rate in the pregnant population.
Liu et al. <sup>14</sup> 2020	Narrative Review	Pregnant women represent a uniquely vulnerable group in any infectious disease outbreak due to their altered physiology, compromised mechanical and immunological functions. The COVID-19 infection is associated with a cytokine-storm, which leads to an important increase of inflammatory mediators at the maternal-fetal interface. As a result, pregnant women may face severe morbidity and mortality.
Jiao <sup>15</sup> 2020	Narrative Review	Update on the issues that may be faced by different groups of pregnant populations: late, middle, and early pregnancy, as the maternal immune response varies during the different stages of pregnancy. In early pregnancy, the immune system is very sensitive and unstable, favoring more severe infections and serious immune fetal and maternal disorders. The author recommended first and second-trimester follow-ups to anticipate those risks.
Ashokka et al. <sup>16</sup> 2020	Narrative Review	Given the limited knowledge about this novel coronavirus, which has both similarities and differences to SARS-CoV-1 and MERS-CoV, the authors provided a general guide based upon currently available evidence. They also postulated that cytokine-storm, leading to an increase in levels of inflammatory mediators, is associated with disease severity and admission in ICU.

COVID-19: 2019 coronavirus disease; ICU: Intensive Care Unit; SARS: Severe Acute Respiratory Syndrome.

are known to be disproportionately affected by respiratory illness and cases involving this population are more associated with increased morbidity and mortality. As pregnancy progresses, its physiological adaptations – such as elevation of the diaphragm, compression of the thoracic cage, and altered pulmonary volumes – lead to shortness of breath, inability to clear pulmonary secretions effectively, and greater risk of severe infections in this group<sup>8,13</sup>.

Additionally, Liu et al.<sup>14</sup> reported that, throughout pregnancy, the maternal immune system faces great challenges to establish and maintain tolerance to the allogeneic fetus, preserving the ability for protection against microbial agents. A successful pregnancy relies on the ability to maintain this balance. For that, it is well known that the female pregnant body has the skill to shift from a pro-inflammatory to an anti-inflammatory state depending on the pregnancy needs<sup>17</sup>.

Therefore, Jiao<sup>15</sup> postulated that, at different stages of pregnancy, the hormone level and immune status

are distinct. In early pregnancy, for example, the author suggested that the immune balance is still unstable, which can result in serious immune system disorder and internal environment imbalance in case of a viral infection, leading to abortion or abnormal fetal growth, similar to that described in other respiratory infections<sup>18</sup>. As the pregnancy progresses, the mother is constantly adjusting this immune balance, with theoretically less severity, according to this author<sup>15</sup>.

Concerning this immunological adjustment, in healthy pregnancies, there is a physiological shift to a pattern of cytokines produced by T-helper lymphocyte type 2 (Th2), characterized by anti-inflammatory substances, such as interleukin (IL) 4, IL-10, IL-13 and transforming growth factor-beta (TGF-beta)<sup>19</sup>. Dashraath et al.<sup>8</sup> reported that this shift to a Th2-dominant environment may contribute to overall infection morbidity by increasing maternal susceptibility to intracellular pathogens like viruses.

In COVID-19 infection, recent literature indicates that in severe cases

there is a cytokine-storm, which is characterized by increased concentrations of important plasma mediators, such as IL-2, IL-7, IL-10, granulocyte-colony stimulating factor, interferon-alfa-inducible protein 10, and tumor necrosis factor alpha, most of them related to an inflammatory response<sup>14,20</sup>. Liu et al.<sup>14</sup> declared that, based on the knowledge that the first and third trimesters of pregnancy constitute pro-inflammatory states, cytokine-storm induced by SARS-CoV-2 may induce a more severe inflammatory state in these women. Ashokka et al.<sup>16</sup> also found that cytokine-storms are known to be associated with disease severity and admissions at Intensive Care Units (ICU).

In contrast, Dashraath et al.<sup>8</sup> postulated that the physiological transition to a Th2 anti-inflammatory environment during pregnancy and other unidentified immune adaptations may serve as the predominant immune response to SARS-CoV-2, resulting in a lesser severe presentation of COVID-19 in this group. These findings are in consonance with the scarce current literature that affirms

that, despite being placed in high-risk groups mainly due to precautionary measures, cases of COVID-19 among pregnant women may not present greater severity and worse clinical outcomes than the general population<sup>21</sup>.

Overall, due to the lack of appropriate data about the effects of COVID-19 on the immune response during pregnancy, some aspects remain unsolved until proper evidence-based articles with a large number of cases are published.

## CONCLUSION

The global attention related to the continuing of the COVID-19 pandemic and dissemination of this disease in the vulnerable population makes it

even more important to discuss the peculiarities of this infection in pregnant women. The maternal immune response probably plays an important role in the pathophysiology of this infection, although some details remain unsolved.

Further studies are warranted to investigate the immunological aspects of COVID-19 in pregnancy. However, our findings may provide insights into possible immune mechanisms involved in the pathophysiology of COVID-19 in pregnancy.

## AUTHORS' CONTRIBUTIONS

Camila R. A. C. da Silva: Data management/analysis, manuscript writing; Lisiane V. de Oliveira: Data management/analysis, manuscript writing;

Lorena P. Lopes: Project development, data management/analysis, manuscript writing; Wancler A. G. Santos: Data management/analysis, manuscript editing; Isabela K. R. Agra: Project development, data management/analysis, manuscript editing.■

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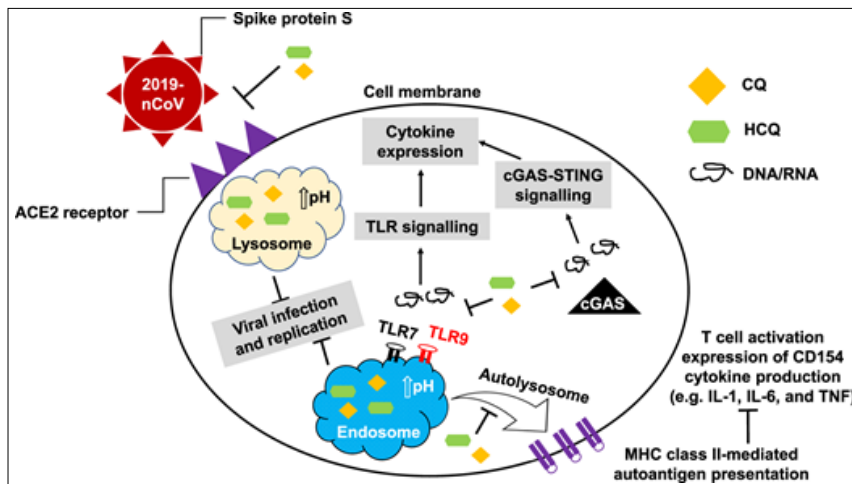
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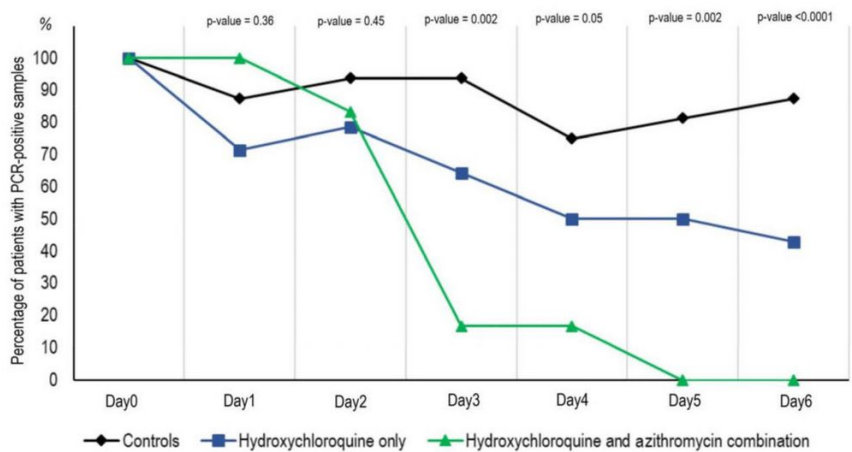
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FIGURE 1.



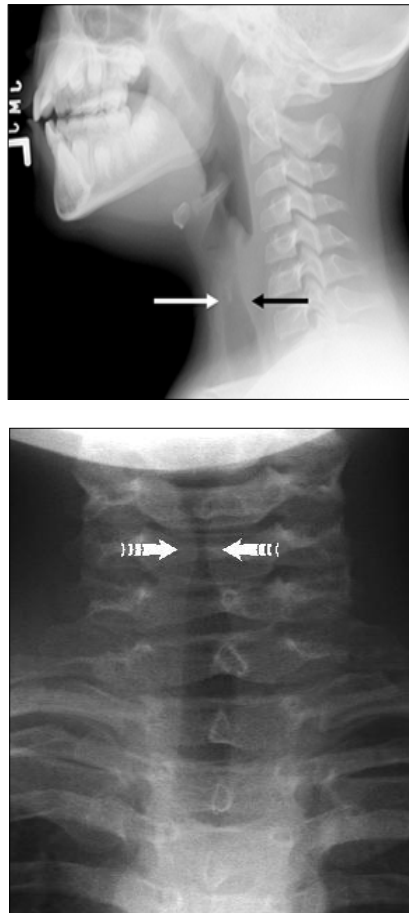
Antiviral mechanisms of CQ and HCQ. Both chemicals may interfere in the glycosylation of ACE2 and reduce the efficiency of binding between ACE2 in host cells and spike protein (S) on the surface of the coronavirus. They can also increase the pH of endosomes and lysosomes, thus preventing the process of binding of the virus with host cells and its subsequent replication. When HCQ enters APCs, it prevents antigen processing and the presentation of autoantigen mediated by class II MHC in T cells. The subsequent activation of T cells and the expression of CD154 and other cytokines are suppressed. In addition, HCQ interrupts the interaction of DNA / RNA with TLRs and the nucleic acid sensor cGAS and, therefore, the transcription of proinflammatory genes cannot be stimulated. As a result, the administration of CQ or HCQ not only blocks the invasion and replication of coronaviruses but also mitigates the risk of a cytokine storm.

**CHART 1. COMPARISON OF VIRAL CLEARANCE WITH A PLACEBO, HYDROXYCHLOROQUINE, AND AZITHROMYCIN23**





**FIGURE 2. CERVICAL RADIOGRAPHS THAT ARE SUGGESTIVE OF VIRAL CROUP. IMAGE BY JOHN MCBRIDE, MD.**



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