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Can immunity during pregnancy influence SARS-CoV-2 infection? – A systematic review

Ana Luísa Areia[a,b,*], Anabela Mota-Pinto[b]

[a] Obstetrics Department, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal
[b] University of Coimbra, Faculty of Medicine, Coimbra Institute for Clinical and Biomedical Research (iCBR), Faculty of Medicine, University of Coimbra, Coimbra, Portugal

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ABSTRACT

Background: During pregnancy, the maternal immune system must create and sustain tolerance to the allogeneic fetus while maintaining the ability to protect against microbial assaults.
Objectives: Ascertain the immunological differences in immune cells of pregnant women that may influence SARS-CoV-2 infection.
Study design: Systematic review conducted in accordance with PRISMA guidelines and registered within PROSPERO CRD42020189735.

A systematic search was undertaken across ISI, PubMed, Scopus, Embase, Cochrane Library and clinical trials.gov from January 2019 up until June 2020.

Eligibility criteria included COVID-19 infection, pregnancy, and availability of immune characteristics for the pregnant women. Two authors independently screened for the suitability of inclusion.
Main outcome measures: Information was manually extracted from full-text articles and efforts were made to identify overlapping data. Variables extracted and analysed included the quantification of white blood cells (WBC), lymphocytes, and C-reactive protein (CRP).
Results: The literature search yielded 162 studies, of which 11 were considered appropriate for selection. Only four were used in this systematic review.

Our research showed that pregnant women with COVID-19 only differ from other pregnant women in their lower WBC count. The proportion of reduced lymphocyte cases is similar in both groups, as is the case of C-reactive protein levels.
Conclusions: In line with previous coronavirus infections, severe maternal morbidity and perinatal death with COVID-19 infection were more likely to be expected in pregnancy.

Our research showed that pregnant women with COVID-19 in terms of immunity only differ from other pregnant women in their lower WBC count.

1. Introduction

Pregnancy can be characterized by modulated immunity and elevated hormone levels to actively tolerate the semi-allogenic fetus (Wu et al., 2020).

There are adaptive changes in the respiratory system during pregnancy that might induce greater respiratory morbidity, such as a decrease in respiratory volumes, higher oxygen consumption, and edema of the respiratory tract mucosa (Wu et al., 2020). Moreover, immune adaptations could make pregnant women more susceptible to respiratory pathogens and severe pneumonia (Wu et al., 2020).

In the third trimester, the pregnancy immune phenotype is characterized by an increase in blood phagocytes (neutrophils and monocytes), a repression of natural killer cell peripheral number and function, a decrease in T and B cells, and an increase in dendritic cells that produce type 1 interferon (IFN), which is very important to viral response (Kraus et al., 2012). Hence, pregnancy is a period when innate immune barriers are strengthened, and the adaptive/inflammatory immunity is reduced (Kraus et al., 2012).

Viruses activate the innate immunity, leading to an increase in IFN, which in turn recruits natural killer cells and neutrophils that attempt to eliminate virus-infected cells (Littauer and Skountzou, 2018). Specifically, the release of viral RNA inside the cell activates toll-like receptors which induce pro-inflammatory cytokines (such as IFN α and β). These activate epithelial cells capable of recruiting innate cells (natural killer

* Corresponding author at: Avenida Bissaya Barreto, 101-2B, 3000-076, Coimbra, Portugal.
E-mail address: analuisareia@gmail.com (A.L. Areia).

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and neutrophils), which induce fever and mucus production in order to shed the virus (Littauer and Skountzou, 2018). Moreover, viral antigens are engulfed by dendritic cells, which migrate to lymph nodes and initiate acquired responses by resident CD4 and CD8 T cells (Littauer and Skountzou, 2018). Consequently, pregnant women are potentially more susceptible to severe viral infections due to a shift from cellular to humoral immunity, with a decrease in cellular immunity and an increase in humoral immunity during pregnancy and puerperium (Kourtis et al., 2014; Zeng et al., 2020). Indeed, published articles on influenza A virus subtype H1N1 or circulating rhinovirus strains in healthy pregnant women indicated significantly reduced IFN responses, suggesting that there is an increased vulnerability to severe viral infection outcomes during pregnancy (Littauer and Skountzou, 2018).

The current pandemic triggered by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has created a worldwide health crisis. Compared to other known coronavirus – Middle East Respiratory Syndrome (MERS) and severe acute respiratory syndrome coronavirus (SARS-CoV), SARS-CoV-2, albeit causing a lower fatality rate, is highly contagious (Prompetchara et al., 2020). The mortality of COVID-19 is low, but the main concern is acute respiratory distress syndrome, often requiring mechanical ventilation due to viral pneumonia (Di Mascio et al., 2020).

Human reaction to viral SARS-CoV infection through type 1 IFN response is suppressed during pregnancy, so that viruses rapidly replicate and induce excessive inflammatory responses (Liu et al., 2020). As SARS-CoV-2 has a 68 % gene similarity, it is logical to assume it behaves in the same way. Moreover, the discrepancy in COVID-19 severity between different geographic areas highlights the importance of antibody-dependent enhancement, shown to be responsible not only for sustained inflammation and lymphopenia, but also for a cytokine storm, which may have deleterious effects on the host (Liu et al., 2020).

Innate immune responses against SARS-CoV-2 are a critical factor for disease outcome and are dependent on type 1 IFN recognition and signalling (Liu et al., 2020; Prompetchara et al., 2020). The major viral/host relations appear to include a diminished or suppressed type 1 IFN response during initial infection, viral replication triggering excess inflammation, an influx of activated neutrophils and inflammatory monocytes/macrophages, Th1/Th17 activation and subsequent inflammatory response exacerbation, and plasma cell production of SARS-CoV-2-specific antibodies to help neutralize the virus (Prompetchara et al., 2020).

Lymphopenia and cytokine storm may have a major role in the pathogenesis of COVID19. The increase in pro-inflammatory cytokines at the beginning of the cytokine storm leads to viral sepsis and inflammatory-induced lung injury (Prompetchara et al. 2020). Moreover, some studies have shown that a neutrophil increase and a lymphocyte drop appear to be related to disease severity and even death (Prompetchara et al., 2020).

The knowledge obtained from previous human coronavirus outbreaks suggested that pregnant women and their fetuses would be particularly prone to poor outcomes. Moreover, pregnant women might be more susceptible to COVID-19, as they are generally more predisposed to respiratory infections (Liu et al., 2020).

Furthermore, based on the understanding that pregnant women during the first and the third trimesters are in a pro-inflammatory state, the cytokine storm induced by SARS-CoV-2 may induce more serious inflammatory conditions in these women. Additionally, maternal inflammation resulting from viral infection may affect several aspects of fetal brain development (Liu et al., 2020).

The real impact of COVID-19 on pregnant women has been addressed by different authors, with systematic reviews and meta-analysis achieving distinct conclusions on the course or severity of the disease.

Accordingly, the aim of this systematic review was to determine whether there are immunological differences in immune cells of pregnant women that could influence SARS-CoV-2 infection.

2. Materials and methods

This systematic review was conducted in accordance with the PRISMA guidelines. The study protocol and review were registered within the PROSPERO registry under the number CRD42020189735.

Search strategy and selection criteria

A systematic search was undertaken by ALA across ISI, PubMed, Scopus, Embase, Cochrane Library and clinical trials.gov from January 2019 until June 2020. Only articles in English, French, Spanish and Portuguese were included.

For this study, the search terms used across all databases were: (“Pregnancy”) AND (“COVID-19” OR “coronavirus” OR “SARS-CoV-2” OR “SARS2” OR “2019-nCoV”) AND (“immunity”). A detailed analysis of the search strategy may be found in S1 Appendix.

Eligibility criteria included laboratory-confirmed COVID-19 infection using quantitative real-time polymerase chain reaction or dual fluorescence polymerase chain reaction, patient pregnancy on admission and availability of immune characteristics for the pregnant women. All primary designs were considered, including case reports, case series, review articles, randomized controlled trials, and meta-analysis on immune cells in pregnant women with SARS-CoV-2 infection. Articles from the reference lists of screened studies were also considered appropriate for assessment.

ALA and AMP independently screened citations for suitability of inclusion and a set of eligible articles was created in accordance. Following the abstracts, full-text articles were read, and article inclusion in the review was based on consensus between the authors. Studies not concerning either human pregnancy or immunity were excluded.

2.1. Data analysis

Information was manually extracted from full-text articles and efforts were made to identify overlapping data. Variables extracted and analysed included the quantification of white blood cells, lymphocytes, and C-reactive protein.

Both authors read all papers and assessed the methodological quality.

2.2. Quality assessment

The overall quality judgement of case reports included in the analysis was based on the report by *Murad et al.* (Murad et al., 2018).

In the domain “selection”, a large variation was found, ranging from case reports, case series and case-control studies. However, authors generally aimed to report all known cases and the overall quality was assessed to be high. For “ascertainment”, exposure and outcome were adequately determined, and it was deemed high by both authors.

As for “causality”, case reports could not rule out alternative causes that might explain the observations, and only one study had challenge/re-challenge and follow up was short, thus being considered of low-quality. Finally, for “reporting”, case detail was generally sufficient and resulted in medium quality.

3. Results

The literature search yielded 162 studies published between January 2019 and June 2020, 160 of which remained after removal of duplicates. These 160 publications were further screened and 130 were excluded after revision of titles and abstracts following application of the predefined criteria. This left a total of 30 articles potentially suitable for inclusion in our review. After assessing the full texts, a further 19 studies were excluded due to the absence of immunity data or data duplication. Finally, 11 publications were considered appropriate for selection, of which only four were used in this systematic review because the other were review articles or meta-analyses included information already reported in other articles.

The latest and largest meta-analysis published on COVID-19 in pregnant women (Elshafeey et al., 2020; Juan et al., 2020) revealed a comparable, but not similar trend of immune alterations. Indeed, *Elshafeey* et al. included 385 patients (Elshafeey et al., 2020), of which 14 % of pregnant women had lymphopenia, 18.7 % increased Creactive

Table 1
Immune cell results from the included studies.

Study, year	COVID-19 positive	COVID-19 negative
	↓ Lymphocytes (percentage of patients)	
Elshafeey et al.*(Elshafeey et al., 2020)*	14	–
Juan et al.(Juan et al., 2020)	43.1	–
Li et al.(Li et al., 2020)	12.5	12.6
Wu et al.(Wu et al., 2020)	12.5	0
	WBC Count	
Elshafeey et al.*(Elshafeey et al., 2020)*	–	–
Juan et al.(Juan et al., 2020)	↓/Normal	–
Li et al.(Li et al., 2020)	Normal	↑
Wu et al.(Wu et al., 2020)	Normal	↑
	↑ CRP (percentage of patients)	
Elshafeey et al.*(Elshafeey et al., 2020)*	18.7	–
Juan et al.(Juan et al., 2020)	45.7	–
Li et al.(Li et al., 2020)	32.1	58.1
Wu et al.(Wu et al., 2020)	0	0

Percentage of patients with: Low (↓), High (↑), or non-available data (-).
WBC: White blood cells.

protein (CRP) and 22.3 % increased D-dimer, an indicator of coagulation and fibrinolytic systems activation. Furthermore, thrombocytopenia was only found in a minority of cases (1%) (Elshafeey et al., 2020).

The other meta-analysis (Juan et al., 2020), though referring to the same time interval, resulted in the inclusion of 324 patients and involved some studies that were not considered by the previous authors. According to the article, lymphopenia could be found in 43.1 % of the cases, elevated CRP in 45.7 % and, of note, low or normal white blood cell (WBC) count in 80.2 % of the cases (Juan et al., 2020) (Table 1).

The findings on pregnant women with COVID- 19 were directly compared to a control group (pregnant healthy women) in only two articles (Li et al., 2020; Wu et al., 2020).

The case-control study by *Li et al.* compared 16 pregnant women with COVID-19 with 2 groups of 121 healthy pregnant women (one group from 2020 and the other from 2019). In line with our inclusion criteria, we only considered confirmed cases and the 2020 control group. Their results were that both groups had similar lymphopenia (12.5 vs. 12.6 %) and elevated CRP (12.5 vs. 12.6 %) levels, but different WBC counts. In fact, pregnant women with COVID-19 showed normal WBC, whereas healthy pregnant women showed a high WBC count, with statistical significance ($p = 0.021$). Moreover, both groups had neutrophilia, which was higher in the healthy pregnancy group ($p = 0.007$) (Li et al., 2020).

The other research reported results not only from pregnant women with and without COVID-19, but also from COVID-19 patients before and after delivery (Wu et al., 2020). Although including fewer cases, the comparisons between both groups did not show differences in lymphopenia, WBC count or CRP. In contrast, laboratory tests in women with COVID-19 before and after delivery showed a large increase in WBC, a substantial decrease in lymphocytes (*vs.* no alterations in women without COVID), and a large increase in CRP levels after delivery (Wu et al., 2020) (Table 2).

Moreover, this study indicates that pregnant women seem to have milder symptoms than non-pregnant ones, which might raise the hypothesis of a swift in steroid hormone concentration during the immediate post-partum period and changes in the immune cells that trigger the onset of SARS-CoV-2 infection after delivery (Wu et al., 2020).

4. Discussion

4.1. Main findings

Pregnant women with COVID-19 had immune characteristics resembling healthy pregnancies, except for the lower-than-predicted number of white blood cells.

Table 2
Comparison of immune cells before and after delivery.

Wu et al.(Wu et al., 2020)	COVID-19 positive	COVID-19 negative
Immune cells	***Before delivery***	
Lymphocytes	↓ / Normal	Normal
WBC	Normal	↑
CRP	Normal	Normal
	After delivery	
Lymphocytes	↓↓	Normal
WBC	↓↓	↑
CRP	↑↑	↑

Slight increase (↑); High increase (↑↑).
Slight decrease (↓); High decrease (↓↓).

4.2. Comment

During pregnancy, hormones such as estrogens and progesterone have the ability to modulate immune responses in and outside the uterus (Littauer and Skountzou, 2018). Essentially, estrogens increase Th2 responses and humoral immunity (Kourtis et al., 2014). Th2 cells are important for the creation of a cytokine-tolerant environment between mother and fetus at the maternal fetal interface, preventing the activation of natural killer cells against fetal cells (Littauer and Skountzou, 2018). For this reason, hormone-mediated suppression of inflammatory cytokine production and cellular activation are critical to a successful pregnancy in the short term by protecting the placenta from inflammation, which could culminate in poor fetal outcomes. However, adequate inflammatory signals must still be elicited for an infection response. Hence, poor fetal results during pregnancy could be due to an indirect exposure to maternal inflammatory cytokines or to hormonal milieu dysregulation (Littauer and Skountzou, 2018).

As a general rule, inflammatory cytokine levels are reduced during pregnancy, whereas levels of cytokines that induce phagocytic cell recruitment and activation increase (Kourtis et al., 2014).

Our research showed that pregnant women with COVID-19 only differ from other pregnant women in their lower WBC count. The proportion of reduced lymphocyte cases is similar in both groups, as is the case of C-reactive protein levels.

Recent investigation has shown that only a minority of immune cells express angiotensin-converting enzyme 2, the putative receptor for SARS-CoV2 (Prompetchara et al., 2020). Consequently, unlike with SARS and MERS, SARS-CoV-2 patients typically show decreased WBC counts, lymphopenia, an increase in various interleukins leading to higher Th1 responses, and an increase in interleukins 4 and 10, which suppress inflammation (Huang et al., 2020).

Placental transmission of inflammatory cytokines is likely to induce hormone signalling dysregulation, which added to oxygen deprivation due to respiratory distress leads to poor neonatal outcomes. This could explain some pregnancy complications related to COVID-19 (Littauer and Skountzou, 2018; Liu et al., 2020).

Recent meta-analyses comparing the three coronavirus infections demonstrated that in pregnancy, SARS-CoV-2 is responsible for fewer admissions to intensive care units, less need for mechanical ventilation, and fewer maternal deaths than the other two coronaviruses (Di Mascio et al., 2020). On the other hand, SARS-CoV-2 has unfortunately shown higher rates of preterm birth, pre-eclampsia, C-sections and perinatal death (Di Mascio et al., 2020).

Nevertheless, immune characteristics were unexpectedly similar among pregnant women with COVID-19 and non-pregnant adults (Chen et al., 2020; Huang et al., 2020).

Therefore, one hypothesis for the better-than-expected outcome shown in *Elshafeey* et al. study (385 pregnant women) may be that human chorionic gonadotropin and progesterone have the ability to inhibit the Th1 proinflammatory pathway, decreasing the cytokine storm and resulting in COVID-19 severity being similar in pregnancy and non-pregnancy (Elshafeey et al., 2020). Moreover, pregnant women showed milder or no symptoms compared to non-pregnant women (Li et al., 2020).

4.3. Clinical implications

Many authors agree that human responses to SARS-CoV-2 are dependent on cellular immunity, mostly through type 1 IFN. Although without solid data yet, it seems that cellular immune response, with the subsequent cytokine release and antibody dependent enhancement, may cause most of the damages, mainly in the lungs (Arvin et al., 2020; Liu et al., 2020; Tetro, 2020). Consequently, it could be postulated that since pregnancy can be characterized by a decrease in cellular responses, damages would be less severe in pregnant women. However, the physiological adaptations of the human body to pregnancy, in particular anatomical and hormonal modifications, are definitely disadvantageous.

Consequently, the outcomes in pregnant vs. non-pregnant women with COVID-19 would be similar.

Weighing all the evidence, COVID-19 during pregnancy may not be as hazardous as initially thought.

However, according to the review of 108 pregnancies by *Zaigham et al*, severe maternal morbidity could not be ruled out (Zaigham and Andersson, 2020).

One of the most feared findings for both obstetricians and pregnant women would be the vertical transmission of SARS-CoV-2. However, this can be counteracted by a potential protection of the fetus from infection by a maternal antibody specific for SARS virus discovered in the umbilical cord and amniotic fluid (Jiang et al., 2004). Furthermore, due to a very low expression of angiotensin-converting enzyme 2 receptors in most cell types at the maternal-fetal interface, some authors claim that COVID-19 cannot be passed from mother to child through transplacental transmission (Paraluppi et al., 2020).

Objectively, it is imperative to thoroughly investigate the cases of infected newborns to ascertain and/or confirm the actual risk of vertical transmission.

4.4. Strengths, limitations, interpretation

The main strength of the present study is the uniqueness of the meta-analysis, since to the best of our knowledge this is the first meta-analysis showing immunological differences in immune cells from pregnant women that could influence SARS-CoV-2 infection. Moreover, several inclusion criteria were used, and a thorough literature review using PRISMA guidelines was conducted.

Nonetheless, some limitations in our meta-analysis need to be mentioned: the number of articles with complete immunity data was relatively small and some studies had missing data. Furthermore, selective reporting bias could not be ruled out.

Additionally, we only included published studies, so publication bias is also present.

5. Conclusions

In line with previous coronavirus infections, severe maternal morbidity and perinatal death with COVID-19 infection were more likely to be expected in pregnancy.

Our research showed that pregnant women with COVID-19 only differ from other pregnant women in their lower WBC count.

In sum, this systematic review highlights the probable immune advantages of pregnancy, since the SARS-CoV-2 infection seems to be less severe than expected in pregnant women.

5.1. Implications for research

As the pandemic progresses, further information will be required to ascertain and/or confirm our hypothesis. Ideally, multinational research studies comparing immune cells from pregnant women with COVID-19 *vs.* without COVID-19 should be conducted.

Author contribution

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Ana Luísa Areia and Anabela Mota-Pinto. The first draft of the manuscript was written by Ana Luísa Areia and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Ethics approval

No ethics approval was required as the analysis only involved published and anonymous data.

Declaration of Competing Interest

The authors report no declarations of interest.

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