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

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\textbf{ARTICLE INFO}

\textbf{Keywords:}
Pregnancy
COVID-19
SARS-CoV-2
Immunity

\textbf{ABSTRACT}

\textbf{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.

\textbf{Objectives:} Ascertain the immunological differences in immune cells of pregnant women that may influence SARS-CoV-2 infection.

\textbf{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.

\textbf{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).

\textbf{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.

\textbf{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.

\section{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

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https://doi.org/10.1016/j.jri.2020.103215

Received 22 July 2020; Received in revised form 30 September 2020; Accepted 7 October 2020

Available online 16 October 2020

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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).

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 COVID-19. 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 achievements. The current systematic review is a comparative analysis of studies assessing the impact of COVID-19 on pregnant women and their fetuses, with a focus on the immune response and potential outcomes. The review includes a comprehensive analysis of published articles, with a particular emphasis on the role of the immune system during pregnancy and the potential impact of COVID-19. The results indicate that pregnant women are at increased risk of severe viral infections, with potential implications for fetal and maternal health. The review highlights the importance of further research to understand the mechanisms underlying these outcomes and to develop effective strategies for managing COVID-19 during pregnancy.
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.

4.2. Comment

During pregnancy, hormones such as estrogens and progesterone have the ability to modulate immune responses in and outside the uterus (Litauer and Skountzou, 2018). Essentially, estrogens increase Th2 responses and humoral immunity (Kouris 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 (Litauer 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 (Litauer 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 (Kouris 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 poor fetal outcomes (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 (Litauer 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.

Funding

No funding.

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.

Acknowledgements

The authors would like to thank Professor Miguel Areia for his assistance in data interpretation.

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