Journal of Advanced Research in Medical Science & Technology
Volume 8, Issue 1 - 2021, Pg. No. 3-6
Peer Reviewed & Open Access Journal

Editorial

Severity of Maternal Illness in Pregnancy during COVID-19 Pandemic

Tusar K Giri

Department of Anesthesiology, Washington University School of Medicine, St. Louis, MO 63110.

I N F O

E-mail Id:
tusargiri@wustl.edu
Orcid Id:
https://orcid.org/0000-0003-1682-2300
How to cite this article:
Giri TK. Severity of Maternal Illness in Pregnancy during COVID-19 Pandemic. *J Adv Res Med Sci Tech* 2021; 8(1): 3-6.

The current Coronavirus Disease (COVID-19) caused by the SARS-Cov-2 virus, has caused a global pandemic with over 77.5 million confirmed cases and more than 1.7 million deaths as of late December 2020.[1] An overarching question is whether pregnant women are susceptible to COVID-19 infection and increased severity of disease. Physiological and hormonal changes during pregnancy have a significant impact on the immune system, respiratory system, cardiovascular function, and coagulation. These may have positive or negative effects on COVID-19 disease progression. Pregnancy provides a complex challenge for the maternal immune system as it needs to protect the mother against infections while creating immune tolerance of the semi-allogeneic fetus.[2-4] During the previous coronavirus infections {Severe Acute Respiratory Syndrome (SARS) and Middle Eastern Respiratory Syndrome (MERS)}, pregnant women were found at greater risk of complications and endured severe disease status. In these epidemics, MERS and SARS infections caused a mortality pooled proportion in pregnant women ranging from 25% to 30%.[5,6] Though systemic immunological changes and placental-fetal immune interaction are robustly investigated in this context,[7-10] little is known about the changes in the respiratory immune system despite epidemiological evidence for increased susceptibility and severity of respiratory viral infections in pregnant women.[11-14] For example, during the 2009 H1N1 pandemic, approximately 5% of all deaths were pregnant women despite accounting for only 1% of all infections.[15] Few studies have raised concerns that pregnant women may be more susceptible to COVID-19 pandemic,[16] but early reports from China and US suggest that a majority of pregnant women are asymptomatic carriers and not at increased risk for severe disease.[17-20]

The data relevant to the COVID-19 pandemic has been rapidly evolving and the true maternal mortality rate is yet to be determined, particularly in the higher risk pregnant population, and will only be evident over time. In a recent review by Wastnedge et al, include studies from widespread global cohort (data collected from January to September 2020) encompassing 12,260 pregnant women (mostly 3rd trimester) with confirmed SARS-CoV-2 infection had mostly mild to moderate symptoms and minority of women required critical care admission.[21] The majority of studies (from USA, UK, EU; high-income countries) reassured the earlier observation and the risk of COVID-19 in pregnancy similar to the general population. However, total maternal

death reported was 146, the vast majority of these (124) are from 2 Brazilian studies (middle-income country). Authors raised concern that only 22.6% of the women who died were admitted to the ICU and only 64% of these women were ventilated, raising the possibility that much of the excess mortality is due to inability to access critical care support. More recent data are suggesting that pregnant women with symptoms, have a higher risk of ICU admission.[22,23] In this cohort authors report that a vast majority are asymptomatic, and if they become symptomatic, they do develop severe disease just like any other respiratory viral infection. Another report from Mexico (considered as low-income country), data (between 1st and 32nd week of 2020) accessed from the Mexican Ministry of Health also reported higher mortality among pregnant women during the COVID-19 pandemic.[24] In this report they found the proportion of SARS-CoV-2 positive maternal deaths from respiratory causes went up by 32% higher in 2020 compared to previous years death. It is plausible that other low- and middle-income countries have experienced a disproportionate burden of maternal mortality related to COVID-19. Renewed focus on improving the structural competency of health care systems in other under-resourced countries is urgently needed to mitigate the adverse effects of COVID-19 on maternal health.

The possibility of immune protection against SARS-Cov-2 via pregnancy-specific biological mechanisms remains unexplored. Considering that a majority of vaccine trials exclude pregnant subjects, it is critically important to determine whether pregnancy confers increased risk or resistance to SARS-Cov-2 infection. Recently, our lab took interest to investigate the pregnancy-induced changes in the cellular components essential for viral entry and related immune modulation, using a pregnant rat model. Nasal turbinate (epithelium) is a portal for initial infection and possible reservoirs for dissemination and transmission, within and between individual. Viral entry- associated genes are co-expressed in nasal epithelial cells w/ genes involved in innate immunity, highlighting the cells potential role in initial viral infection/ spread/ clearance. The angiotensin converting enzyme-2 (ACE-2) receptor has been identified as the gateway to infection for the SARS-CoV-2 coronavirus. The androgen-sensitive transmembrane protease serine 2 (TMPRSS2), a serine protease that primes the spike protein of the SARS-Cov-2 virus. The binding of the SARS-CoV-2 spike (S) protein to ACE-2 receptors initiates the fusion of the viral membrane to the host cell membrane and TMPRSS2 facilitates the passage of the viral RNA which then hijacks the host mechanisms of protein synthesis for replication.[25] Intrigued by a recent report, demonstrated that estradiol-mediated down-regulation of ACE2 in the airway epithelium,[26] we posit that the elevated estradiol during late pregnancy will downregulate the expression of SARS-CoV-2 cell entry factors and the high asymptomatic carrier rate in pregnancy is secondary to immune changes that limit the cytokine response. The figure below represents the outcomes of our study.

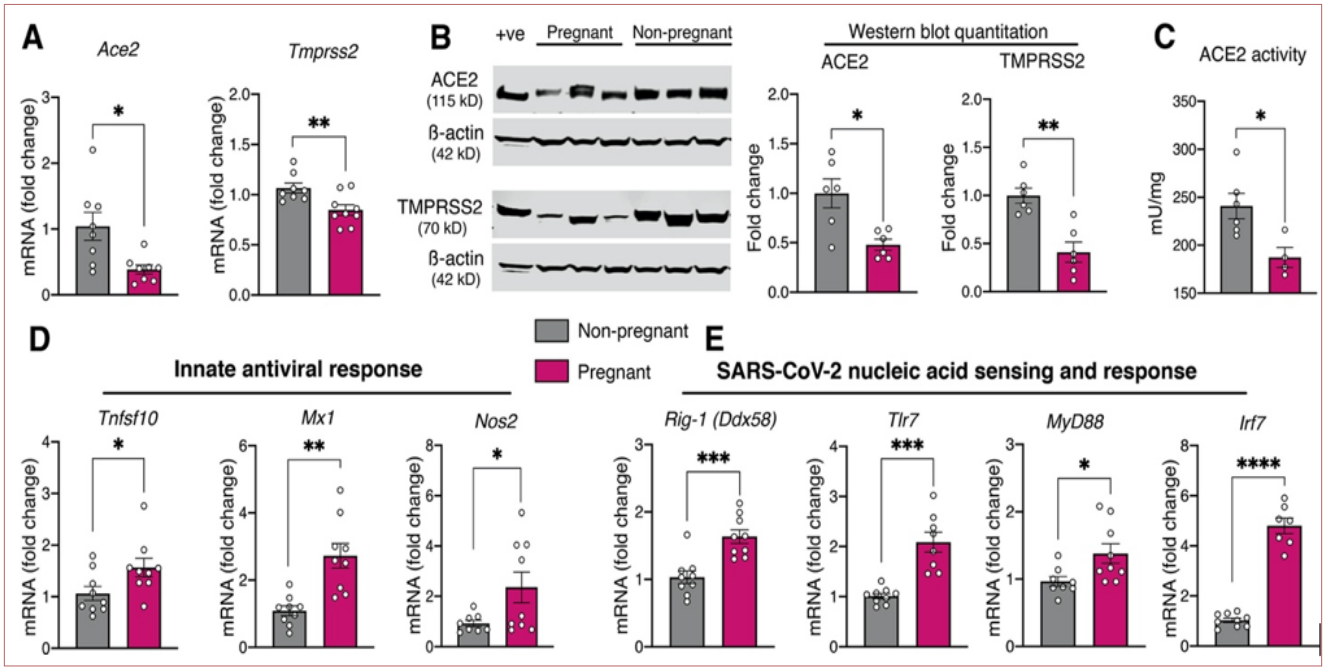

Figure 1.Assessment of viral cell entry factors and innate immune response genes in the nasal epithelium during pregnancy

A, Scatter plots showing markedly decreased expression of ACE2 and TMPRSS2 in the nasal epithelium during pregnancy. B, Representative immunoblots showing markedly reduced ACE2 and TMPRSS2 protein expression along with quantification as scatter plots. Rat small intestinal lysate was used as positive control and β-actin as the loading control. C, Scatter plot demonstrating a marked reduction in enzymatic ACE2 activity in the nasal epithelium of pregnant rats. D, Scatter plots showing substantial up-regulation of innate immune genes highly coexpressed with ACE2 (TNFSF10, MX1, NOS2). E, Scatter plots showing up-regulation of genes involved with SARS-CoV-2 detection (RIG-1, TLR7, MYD88, IRF7) in pregnant nasal epithelial samples suggesting the possibility of heightened innate immune surveillance at baseline. Expression levels of genes of interest were assayed in duplicate along with 2 endogenous housekeeping control genes (EEF2 and ACTB). All TaqMan primers were acquired from Thermo Fisher Scientific, and thermal cycling was performed in 7500 Fast Real-Time PCR System (Applied Biosystems: Makro Giannis Phil, Foster City, CA). Relative mRNA expression, normalized to the geometric mean of EEF2 and ACTB, was calculated using the 2-ΔΔCT method. Data outliers were eliminated using robust regression and outlier analysis with Q set to 10% and normality of residuals was assessed with D'Agostino-Pearson omnibus test. Normally and nonnormally distributed data were analyzed with Welch's t test and Mann-Whitney U test, respectively, with P≤.05 accorded statistical significance. Data were analyzed with Prism 8 for macOS (version 8.2.1; GraphPad Software Inc, San Diego, CA) and presented as mean±SEM; aP≤.05; bP≤.01; cP≤.001; and dP≤.0001 (n=9 each for all experiments except western blot where n=6 per group).

ACE2, angiotensin-converting enzyme 2; mRNA, messenger RNA; MYD88, myeloid differentiation primary response 88; NOS2, nitric oxide synthase 2; RIG-1, retinoic acid-inducible gene I; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SEM, standard error of mean; TLR7, toll-like receptor 7; TMPRSS2, transmembrane protease serine 2; TNFSF10, tumor necrosis factor ligand superfamily member 10.

Acknowledgement

Reprinted with permission from 2020 Elsevier Inc (License Number: 4971201358113, License date: Dec 17, 2020). American Journal of Obstetrics & Gynecology, Publication stage: In Press Corrected Proof, expected publication date; Jan 2021. Published online: October 8, 2020. Arvind Palanisamy, MD, FRCA and Tusar Giri, MD,PhD. Reduced severe acute respiratory syndrome coronavirus 2 entry factors and enhanced innate immune gene expression in the nasal epithelium of pregnant rats.

Preliminary preclinical data from our lab suggest that pregnancy is associated with a decrease in the expression of ACE2 receptors in the nasal epithelium and an increase in the expression of genes mediating antiviral activity. We hypothesize that pregnant women are relatively spared from COVID-19 because of decreased viral tropism as a result of pregnancy-induced changes in the cellular receptor mechanisms essential for viral entry. We also posit that the high asymptomatic carrier rate in pregnancy is secondary to immune changes that limit the cytokine response. These findings set the stage for comprehensive characterization of respiratory mucosal immunology in pregnant women to better understand host-pathogen interaction in this unique demographic subset.

Conflicts of Interest: None

References

1. World Health Organization WHO coronavirus disease (COVID-19) dashboard. 2020. Available at: https://covid19-who-int.beckerproxy.wustl.edu/
2. Mor G, Aldo P, Alvero AB. The unique immunological and microbial aspects of pregnancy. *Nat Rev Immunol* 2017; 17(8): 469-482.
3. Mor G, Cardenas I. The immune system in pregnancy: a unique complexity. *Am J Reprod Immunol* 2010; 63(6): 425-433.
4. Moffett-King A. Natural killer cells and pregnancy. *Nat Rev Immunol* 2002; 2(9): 656-663.
5. Di Mascio D, 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* 2020; MFM 2: 100107.
6. Wong SF, Chow KM, Leung TN et al. Pregnancy and perinatal outcomes of women with severe acute respiratory syndrome. *Am J Obstet Gynecol* 2004; 191: 292-297.
7. Aluvihare VR, Kallikourdis M, Betz AG. Regulatory T cells mediate maternal tolerance to the fetus. *Nat Immunol* 2004; 5(3): 266-271.
8. Erlebacher A. Mechanisms of T cell tolerance towards the allogeneic fetus. *Nat Rev Immunol* 2013; 13(1): 23-33.
9. Erlebacher A. Immunology of the maternal-fetal interface. *Annu Rev Immunol* 2013; 31: 387-411.
10. Mold JE, Michaelsson J, Burt TD et al. Maternal alloantigens promote the development of tolerogenic fetal regulatory T cells in utero. *Science* 2008; 322(5907): 1562-65.
11. Creanga AA, Kamimoto L, Newsome K et al. Seasonal and 2009 pandemic influenza A (H1N1) virus infection during pregnancy: a population-based study of hospitalized cases. *Am J Obstet Gynecol* 2011; 204(6 Suppl 1): S38-45.

12. Jamieson DJ, Honein MA, Rasmussen SA et al. H1N1 2009 influenza virus infection during pregnancy in the USA. *Lancet* 2009; 374(9688): 451-458.
13. Louie JK, Acosta M, Jamieson DJ et al. California Pandemic Working G. Severe 2009 H1N1 influenza in pregnant and postpartum women in California. *N Engl J Med* 2010; 362(1): 27-35.
14. Louie JK, Salibay CJ, Kang M et al. Pregnancy and severe influenza infection in the 2013-2014 influenza season. *Obstet Gynecol* 2015; 125(1): 184-192.
15. Siston AM, Rasmussen SA, Honein MA et al. Pandemic 2009 influenza A (H1N1) virus illness among pregnant women in the United States. *JAMA* 2010; 303(15): 1517-25.
16. Liu H, Wang LL, Zhao SJ et al. Why are pregnant women susceptible to COVID-19? *An immunological viewpoint. J Reprod Immunol* 2020; 139: 103122.
17. Chen L, Li Q, Zheng D et al. Clinical Characteristics of Pregnant Women with Covid-19 in Wuhan, China. N *Engl J Med* 2020.
18. Qiao J. What are the risks of COVID-19 infection in pregnant women? *Lancet* 2020; 395(10226): 760-2.
19. Schwartz DA. An Analysis of 38 Pregnant Women with COVID-19, Their Newborn Infants, and Maternal-Fetal Transmission of SARS-CoV-2: Maternal Coronavirus Infections and Pregnancy Outcomes. *Arch Pathol Lab Med* 2020.
20. Sutton D, Fuchs K, D'Alton M, Goffman D. Universal Screening for SARS-CoV-2 in Women Admitted for Delivery. *N Engl J Med* 2020.
21. Elizabeth AN, Wastnedge RM, Reynolds SR et al. Pregnancy and COVID-19. *Physiol Rev* 2021; 101: 303-18.
22. Badr DA, Mattern J, Carlin A et al. Are clinical outcomes worse for pregnant women >/= 20 weeks' gestation infected with COVID-19? A multicenter case-control study with propensity score matching. *Am J Obstet Gynecol* 2020.
23. Ellington S, Strid P, Tong VT et al. Characteristics of Women of Reproductive Age with Laboratory-Confirmed SARS-CoV-2 Infection by Pregnancy Status - United States, January 22-June 7, 2020. *MMWR Morb Mortal Wkly Rep* 2020; 69: 769-775.
24. Lumbreras-Marquez MI, Campos-Zamora M, Seifert SM et al. Excess Maternal Deaths Associated With Coronavirus Disease 2019 (COVID-19) in Mexico. *Obstet Gynecol* 2020; 136: 1114-6.
25. Verdecchia P, Cavallini C, Spanevello A, Angeli F. The pivotal link between ACE2 deficiency and SARS-CoV-2 infection. *Eur J Intern Med* 2020; 76: 14-20.
26. Stelzig KE, Canepa-Escaro F, Schiliro M et al. Estrogen regulates the expression of SARS-CoV-2 receptor ACE2 in differentiated airway epithelial cells. *Am J Physiol Lung Cell Mol Physiol* 2020; 318(6): L1280-1.