Review Article

iMedPub Journals
www.imedpub.com

Critical Care Obstetrics and Gynecology
ISSN 2471-9803

2020
Vol.6 No.3:1

DOI: 10.36648/2471-9803.6.3.1

SARS-CoV-2 During Pregnancy and Associated Cytokine-Storm

Uysal Çetin Gülçin*

Clinic of Obstetrics and Gynecology, Tınaztepe Hospital, Izmir, Turkey

***Corresponding author:** Uysal Çetin Gülçin, Clinic of Obstetrics and Gynecology, Tınaztepe Hospital, Izmir, Turkey, Tel: 05447244524; E-mail: gcetinuysal@gmail.com

Received date: April 23, 2020; **Accepted date:** April 30, 2020; **Published date:** May 12, 2020

Citation: Gülçin UC (2020) SARS-CoV-2 During Pregnancy and Associated Cytokine-Storm. Crit Care Obst Gyne Vol.6 No.3:1.

Abstract

Coronavirus disease 2019 (SARS-CoV-2) is an emerging pandemic disease. Coronaviruses cause illness spectrums changing from the common cold to serious respiratory illness and death. Available data about coronavirus disease 2019 during pregnancy are limited because of the limited studies. However, no vertical transmission maternal to fetal is proven in recent studies. Pregnancy complicated with Coronavirus can cause spontaneous abortion, miscarriages, preterm deliveries, intrauterine growth restriction, and fetal demise. Pregnancy complicated with Coronavirus can be due to severe acute respiratory syndrome, disseminated intravascular coagulopathy, renal failure, secondary bacterial pneumonia, and sepsis. And also maternal infection during pregnancy contribute elevated cytokines leading to cytokine-storm. Cytokine-storm-related Coronavirus 19 infection at pregnancy can deteriorate fetal development. Fetal neuronal dysfunction, atypical behavioural phenotypes, autism, and attention-deficits are related to viral infections at the time of pregnancy.

Keywords: Coronavirus 2019 (SARS-CoV-2); Pregnancy; Viral infection; Cytokine-storm

Introduction

Immunologic changes are established protection and tolerance for the allogeneic fetüs in pregnancy. The maternal immune system installs the ability for protection against microbial infections by well-tuned systemically and locally immune adaptations. Maternal immunological changes providing the adaptation of fetal growth and developments. At the time of the gestational stages, different adaptive mechanisms occur. Different adaptive mechanisms occur for every different gestational stage. The embryo implantation and placentation is a pro-inflammatory state in the first trimester. To maintain the fetal growth in the second trimester is an anti-inflammatory state. And the second pro-inflammatory phase is the third trimester for parturition [1]. The maternal immune system is well organized for foreign pathogens like viruses. The immune system in pregnancy is named "immune clock" in some studies [2]. Maternal endogenous STAT5ab signaling increase across multiple T cell subsets in pregnancy. Maternal immune cells, respond potently to infectious and lead to cytokine-storm. Some adaptive immune responses during pregnancy such as decreased numbers of T and B cells [2]. But although well organized maternal immune changes the high level of estrogen and progesterone, and restricted lung expansion capacity cause pregnant women sensitive to respiratory tract infections.

SARS-CoV-2 During Pregnancy and Associated Cytokine-Storm

Maternal infections can also affect fetal and placental development. The risk of viral pneumonia is higher among pregnant women compared with the general population. SARS is a disease novel coronavirus. SARS infection leads to atypical pneumonia, progresses to severe failure. Spontaneous abortion, premature birth, and intrauterine growth restriction are the results of SARS infection during pregnancy. These complications are because of the hypoxemia and circulatory insufficiency in both the mother and fetus as a result of SARS infection. Increased amounts of proinflammatory cytokines in serum (eg. IL1B, IL6, IL12, IFNγ, IP10, and MCP1) are associated with pulmonary inflammation and extensive lung damage in SARS patients [3].

MERS-CoV infection was also reported to induce increased concentrations of proinflammatory cytokines (IFNγ, TNFα, IL15, and IL17 [4]. SARS cases fatality rate of 25% for pregnant women . There is no proof about the vertical transmission of SARS infection from the mother to the child [3].

And also COVID-19 infection is associated with increased plasma concentrations interleukins (IL2), IL-7, IL-10, granulocyte-colony stimulating factor, interferon-γ-inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1 alpha, and Tumor Necrosis Factor-α (TNF-α). Elevated plasma concentrations of interleukins at pregnancy cause cytokine-storm [5].

Pulmonary inflammation and extensive lung damage in SARS are associated with increased amounts of proinflammatory cytokines in serum (eg. IL1B, IL6, IL12, IFNγ, IP10, and MCP1). Cytokine storm in SARS-CoV-2 can be explained by Antibody-Dependent Enhancement (ADE). Previous exposure by one or more prior coronavirus exposures, and due to antigenic

epitope heterogeneity, are experiencing the effects of ADE that can explain the severe cases. Continuous inflammation, lymphopenia, and cytokine storm are responsible for severe cases and deaths [6].

The pregnant women in their first and third trimester are at the pro-inflammatory state. The cytokine-storm induced by SARS CoV-2 may induce a more severe inflammatory state in these women. The occurrence of maternal inflammation as a result of viral infection during pregnancy can affect several aspects of fetal brain development. And deteriorated neuronal functions and atypical behavioural changes. These pathologies can be recognized later in postnatal life [1]. The level of the maternal inflammatory response and the levels of inflammatory cytokines, such as interleukin IL-1, IL-6, IL-8, and TNF-α are very high, which can affect the development of the fetal brain and circulatory system, and may increase the risk of schizophrenia, autism, and mental disorders. Although the virus does not reach the fetus [7].

Approximately half of the pregnant women who are infected without showing infectious symptoms give birth prematurely, which may be related to past placental infections or acute and chronic chorioamnionitis [8]. The maternal inflammatory process leads to increased immune activation and IL-17a levels, which induces an autism spectrum-like phenotype [9].

Systemic cytokines, including TNF-α, IFN-γ, and IL-10 in women with malaria increasing showed a correlation in pregnancy complications [10]. Elevated levels of TNF-α as a systemic cytokine is related to the toxic effect on early embryo development [11]. COVID-19 infection associated fever can cause increased attention-deficit/hyperactivity disorders [12].

Hyperactive interferon signaling is a potential driver of brain pathology and abnormal brain development after congenital infections and genetic diseases. IFNγ is primarily produced by T and NK cells and induces some overlapping effectors with type I IFNs [13]. In addition to over structural malformations, Maternal Immune Activation (MIA) during pregnancy is associated with an increased risk of psychiatric diseases including schizophrenia and autism spectrum disorder [14].

One retrospective study estimates that maternal exposure to influenza virus can account for as many as 20% of cases of schizophrenia [15]. Abnormal behaviour analogous to schizophrenia and autism, including the inability to inhibit the startle response, has been recapitulated in animals by the injection of influenza virus, poly (I:C), LPS, or recombinant IL-6 [14]. The poly(I:C)-induced autism-like phenotype leads to specific defects in the dysgranular zone of the somatosensory cortex and is mediated by IL-17 [16]. IL-17 produced by maternal T helper-17 (Th17) cells presumably crosses the placenta to trigger IL-17R in the fetal neurons, resulting in cortical and behavioural abnormalities [17].

Perinatal inflammation is also recognized as an important risk factor for brain injury and development disorders including cerebral palsy, white matter injury, and autism. Elevated cytokines IL-6 and IL-1β in the amniotic fluid, as well as placental inflammation, are predictors of brain injury in premature infants [18].

A healthy pregnancy requires appropriate immune responses. Cytokines and IFNs can alter cellular function, migration, cell-cell communication, proliferation, and gene expression. İnappropriate expressed cytokines aginst the viral infections, can act as teratogens for fetüs. And can also disturb placental development. The effects of the cytokines at the time inflammation at pregnancy can cause birth defects [17].

SARS-CoV-2 is responsible for severe acute respiratory syndrome COVID-19 can cause mild upper respiratory tract infection. Respiratory tract infections symptoms are fever, cough, and typical changes in radiographic studies. Infection spectrum changes to non-life threatening pneumonia to life-threatening pneumonia [19].

All age groups, including newborns to the elders sensitive for COVID-19 disease. The effects of COVID-19 on pregnant women have not been well studied [20]. The currently published studies, existing data did not support the mother-to-child transmission [21,22]. The prevalence of morbidity and mortality of pregnant women with COVID-19 is still unknown [21-23].

Conclusion

Individualized approaches and treatments should be given to pregnant according to the severity of the disease and the advancement of the trimester of the pregnancy. Especially pregnant women in the first and second trimester with COVID-19 need more attention because of elevated inflammation cytokines. Vertical transmission of COVID-19 from the mothers to the baby is not supported by any study. But the maternal infection and inflammation as a response to the viral infection could deteriorate developing fetüs.

Early detection and intervention of COVID-19 may reduce potential obstetrical complications. Complications such as pregnancy loss, intrauterine growth restriction, and preterm delivery. Anti-viral therapy for COVID-19, such as lopinavir and ritonavir, may be beneficial for improving pregnancy outcomes. Anti-viral therapy for COVID-19 should be estimated by maternal and fetal health. Even after the viral infection is controlled, the intrauterine development of the fetüs should be closely monitored. Since they had anti-viral drug therapy and radiation exposure from CT examinations, postnatal controls are necessary.

Because of characteristic immune responses during pregnancy and potential risks from the cytokine-storm by COVID-19 infection, pregnant women with COVID-19 may face severe morbidity and even mortality. Although there is no proof for intrauterine vertical transmission, the maternal infection and inflammation occurred in response to COVID-19 could affect the developing fetus and even postnatal life. With the continuing pandemic of COVID-19, more efforts should be made to protect both mothers and fetuses. Further studies are warranted to investigate the pregnant women with COVID-19 in the first and second trimester and follow-up the pregnancy outcomes and postnatal development of the fetus.

References

1. Mor G, Aldo P, Alvero AB (2017) The unique immunological and microbial aspects of pregnancy. Nat Rev Immunol 17: 469.
2. Aghaeepour N, Ganio EA, Mcilwain D, Tsai AS, Tingle M, et al. (2017) An immune clock of human pregnancy. Sci Immunol 2.
3. Wong SF, Chow KM, Leung TN, Ng WF, Ng TK, et al. (2004) Pregnancy and perinatal outcomes of women with severe acute respiratory syndrome. Am J Obstet Gynecol 191: 292-297.
4. Mahallawi WH, Khabour OF, Zhang Q, Makhdoum HM, Suliman BA (2018) MERS-CoV infection in humans is associated with a pro-inflammatory Th1 and Th17 cytokine profile. Cytokine 104: 8-13.
5. Huang C, Wang Y, Li X, Ren L, Zhao J, et al. (2020) Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 395: 497-506.
6. Tetro JA (2020) Is COVID-19 receiving ADE from Mother coronaviruses? Microbes Infect 22: 72-73.
7. Shi L, Tu N, Patterson PH (2005) Maternal influenza infection is likely to alter fetal brain development indirectly: the virus is not detected in the fetus. Int J Dev Neurosci 23: 299-305.
8. Wang Z, Wang SS, Wang GL, Wu TL, Lv YL, et al. (2014) A pregnant mouse model for the vertical transmission of Brucella melitensis. Vet J 200: 116-121.
9. Choi GB, Yim YS, Wong H, Kim S, Kim H, et al. (2016) The maternal interleukin-17a pathway in mice promotes autism-like phenotypes in offspring. Science 351: 933-939.
10. Fried M, Kurtis JD, Swihart B, Pond-Tor S, Barry A, et al. (2017) Systemic inflammatory response to malaria during pregnancy is associated with pregnancy loss and preterm delivery. Clin Infect Dis 65: 1729-1735.
11. Yockey LJ, Iwasaki A (2018) Interferons and proinflammatory cytokines in pregnancy and fetal development. Immunity 49: 397-412.
12. Werenberg Dreier J, Nybo Andersen AM, Hvolby A, Garne E, Kragh Andersen P, et al. (2016) Fever and infections in pregnancy and risk of attention deficit/hyperactivity disorder in the offspring. J Child Psychol Psychiatry 57: 540-548.
13. Wang J, Pham-mitchell N, Schindler C, Campbell IL (2003) Dysregulated Sonic hedgehog signaling and medulloblastoma consequent to IFN-α stimulated STAT2-independent production of IFN- γ in the brain. J Clin Invest 112: 535-543.
14. Brown AS, Begg MD, Gravenstein S, Schaefer CA, Wyatt RJ, et al. (2004) Serologic evidence of prenatal influenza in the etiology of schizophrenia. Arch Gen Psychiatry 61: 774-780.
15. Patterson PH (2009) Immune involvement in schizophrenia and autism: etiology, pathology and animal models. Behav Brain Res 204: 313-321.
16. Choi GB, Yim YS, Wong H, Kim S, Kim H, et al. (2016) The maternal interleukin-17a pathway in mice promotes autism like phenotypes in offspring. Science 351: 933-940.
17. Yockey LJ, Iwasaki (2018) A Interferons and proinflammatory cytokines in pregnancy and fetal development. Immunity 49: 397-412.
18. Heymann DL, Shindo N (2020) COVID-19: what is next for public health? Lancet 395: 542-545.
19. Boyle AK, Rinaldi SF, Norman JE, Stock SJ (2017) Preterm birth: inflammation, fetal injury and treatment strategies. J Reprod Immunol 119: 62-66.
20. Favre G, Pomar L, Musso D, Baud D (2020) 2019-nCoV epidemic: what about pregnancies? Lancet 395: e40.
21. Zhu H, Wang L, Fang C, Peng S, Zhang L, et al. (2020) Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia. Transl Pediatr 9: 51.
22. Chen H, Guo J, Wang C, Luo F, Yu X, et al. (2020) Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. Lancet 395: 809-815.
23. National Health Commission of the People's Republicof China (2020) The Latest Situation of Novel Coronavirus Pneumonia as of February.