

Do the clinical outcomes of Covid-19 differ in pregnancy?

Covid-19'da gebeliğin klinik sonuçları farklı mıdır?

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Abstract

In this brief review, we aimed to assess Covid-19 infection from a different aspect and emphasize the advantages of patients during pregnancy. Therefore, the course of Covid-19 infection and chronic diseases during pregnancy were evaluated. The disease seems to have a positive effect on fetomaternal circulation during pregnancy. Our hypothesis on this matter is that the regulation of the host immune system which occurs due to pregnancy may reduce the cytokine storm and multiple organ failure-related mortality in Covid-19 infected pregnant women.

Keywords: Corona virus disease, Covid-19, Pregnancy, Maternal-fetal conflict

Öz

Bu kısa derlemede gebelikte Covid-19 enfeksiyonuna farklı yönden bakmak ve hastaların hamilelik sırasında avantajlarını vurgulamak istedik. Bu amaçla, hamilelikte Covid-19 enfeksiyonunun seyri ve hamilelik sırasındaki kronik hastalıklar değerlendirildi. Covid-19 enfeksiyonunun çoğu gebe hastada fetomaternal dolaşım üzerine olumlu etkisi mevcut gibi görünmektedir. Bu konudaki hipotezimiz, gebelikte konakçının immün sisteminde gelişen düzenlemenin, Covid-19 ile enfekte gebelerde sitokin fırtınası ve çoklu organ yetmezliğini azaltıcı yönde bir etki yarattığı yönündedir.

Anahtar kelimeler: Korona virüs hastalığı, Covid-19, Gebelik, Maternal-fetal çıkar

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Introduction

Corona virus disease-2019 (Covid-2019) pandemic started in the Chinese city of Wuhan within the last days of 2019 with a prominent level of person-to-person transmission rate. Mortality rate was reported as 2.67% [1]. Clinical results of a small group of pregnant women who tested positive for Covid-19 in RT-PCR were published in a preliminary study. In this series, computed thorax tomography revealed ground glass appearance in many of positive pregnant cases. Fever was seen in 13 of 15 cases with pneumonia and 2 patients were asymptomatic. Following the delivery of Covid-19 positive pregnant women, ground glass appearance disappeared in thorax CT. Clinical statuses improved in 4 cases who were still pregnant without any antiviral therapy. It was found that pregnancy and delivery did not exacerbate the disease or affect CT findings negatively [2].

Pregnancy is a state of partial immune suppression which makes pregnant women more vulnerable to viral infections, and in case of seasonal flu, mortality and morbidity may be higher. Physiological adaptations in pregnancy, such as edematous mucous membranes, elevated diaphragm, decreased lung capacity and tachypnea may render pregnant women more vulnerable to respiratory infections [3]. Therefore, the Covid-19 pandemic may have potential grave consequences for pregnant women. Previous data and knowledge of H1N1 and SARS pneumonias showed us that pregnant patients needed more advanced respiratory support and medical care in the intensive care unit. In SARS, mortality rates reached 25%. However, pregnant women with Covid-19 pneumonia and normal adult patients show clinically similar findings. Cough and fever are the most common clinical findings of the disease and lymphopenia is marked [4].

Various drugs including hydroxychloroquine, antivirals (Remdesivir, Oseltamivir, Ritonavir plus Lopinavir), cytokine antagonists and azithromycin were tried for the treatment of Covid-19 pneumonia in addition to respiratory support. No uniform treatment was suggested for Covid-19-related clinical problems. Recently it is discussed that human umbilical cord stem cells (Human Umbilical Mesenchymal Stem Cell; hUMSC) may play a role in the treatment [5].

Immune response to the virus can cause exaggerated inflammatory response and cytokine storm in the pathogenesis of the Covid-19 disease. This cytokine storm can cause edema, ARDS, cardiac injury, secondary bacterial infections, multiple organ failure and death.

Can avoiding or preventing this excess immune response be a way to reduce mortality from Covid-19 infection? The fetomaternal circulation and immune modulation during pregnancy may play roles in the different clinical courses between other viral pneumonias and pneumonia of Covid-19. Cytokine levels are regulated by two different mechanisms in pregnancy:

1) Pregnancy is a major source of mesenchymal stem cells, which have lower immunogenic properties and pluripotent differentiation potentials [6]. hUMSC are widely used in various branches of medicine such as ophthalmology due to their anti-inflammatory and immunomodulatory properties [7].

2) Higher blood progesterone levels affect cytokine levels during pregnancy.

As a steroid hormone, progesterone has a critical role in the implantation and maintenance of early pregnancy. Control of the immune response to the semi-allogeneic embryo is the cornerstone of the early development of the embryo. The role of cytokine network starts with ovulation. Local inflammatory response begins with secretion of prostaglandin, IL-6 and IL-8 during ovulation [8]. Progesterone modulates the immune system by inducing NF-kB expression which affects a number of proinflammatory factors (IL-1 beta, IL-2, TNF-alpha, INF-gamma), anti-inflammatory factors (IL-4, IL-10, TGF-beta) and IL-6 (both proinflammatory and anti-inflammatory). NF-kB is the key step in the activation of signaling pathways of cytokines [8,9]. To prevent the rejection of the allogeneic embryo, inflammatory reactions should be suppressed. In the implantation and early development process, progesterone shifts the Th1-Th2 balance to Th2 dominance. This physiologic shift helps the ongoing pregnancy by decreasing Th1-secreted IFN- γ TNF- α . IL-4 and IL-6 secretion increase, and IL-10 secretion remains unchanged [10]. Progesterone has an immunosuppressive or immunostimulatory effect on macrophages depending on the microenvironment in the pregnancy [11]. It also exerts an immunosuppressive effect on the human umbilical cord fetal T lymphocytes (Both CD4 and CD8 T lymphocytes) [12]. The use of umbilical cord stem cells in Covid-19 treatment was tried and reported by Atluri et al. [5].

Another important observation is that older mothers have improved clinical outcomes in chronic and inflammatory diseases during pregnancy. Placenta is a wonderful source of fetal stem cells which retain low immunogenicity along with immunomodulatory and anti-inflammatory activities [13]. The fetal stem cells are of great interest in regenerative medicine due to their easy collection and reliability. Although elevated levels of chimerism occurs rarely, microchimerism could be seen in the organism with a placenta. Invasion depth of placenta is the critical source of both substrate and fetomaternal cellular exchange between two different organisms.

Fetal microchimerism was documented in humans. There are many studies about fetal microchimerism: One well-known example is fetal cells which induce wound healing in the murine model. In this model, fetal cells accumulated in the maternal wound participated in maternal angiogenesis. Also, in humans, fetal cells which express markers of cytokeratin and collagen were detected in healed cesarean section scars. This finding suggests that fetal cells actively participate in maternal wound healing [13].

Inflammation mediators and cytokines such as IL-6, IL-1beta, TNF-alpha secretion increases from the aged cells. Permanent and low-grade inflammation accelerates the aging process and causes many diseases. The production and levels of these cytokines are high in cardiovascular and autoimmune diseases such as rheumatoid arthritis and multiple sclerosis [14,15].

Previous animal studies revealed that amniotic fluid cells accelerated wound healing and decreased adhesion formation [16]. The regenerative potential of pregnancy was also observed in other previous studies [17].

Conclusion

In the light of this literature data, we concur that fetal microchimerism may protect the mother from a more severe process of Coronavirus infection, which causes extensive inflammatory reaction and cytokine storm. Less severe clinical progression of Covid-19 infection in the pregnant women might be related to the progesterone effect on T lymphocyte function and immunomodulatory feature of fetal umbilical cord stem cells by microchimerism. Observations and results from small series comprise limited number of Covid-19 positive pregnant women. Maternal adaptation during pregnancy could limit extensive inflammatory reaction. Our hypothesis on this matter is that the regulation of the host immune system which occurs due to pregnancy may reduce the cytokine storm and multiple organ failure-related mortality in Covid-19 infected pregnant women.

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