

## Role of Co-Infection in the Immunopathology of COVID-19 in pregnancy

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### Abstract:

“Co-infection” differs from single infection mainly in the effect of co-infection on the host health which may be harmful, beneficial or absent. This effect occurs mainly due to changes in host immune response. Co-infection is used in treatment of other diseases not just infectious ones. It’s well known that co-infection may have beneficial effects that can improve overall outcome better than single agent infection especially in case of viruses. There are many immunological mechanisms to achieve that. As co-infection has a beneficial effect that we may use it in treatment, there is harmful effect that we should avoid. In this review we tried to evaluate the effect of co-infection in pregnancy with coronavirus disease-2019 (COVID-19) and how the immune system of the pregnant women will respond to co-infection.

**Keywords:** Pregnancy, co-infection, COVID-19, immunopathology

### Introduction

Coronavirus disease-2019 (COVID-19) is a new member of the CORONA virus family that firstly appeared in China in December 2019. In January 2020, the World Health Organization (WHO) declared it a pandemic and asked all countries to get ready to face this enemy. Since then and the world is in a continuous war against COVID-19. Actually, it is not the first time for the world to face this family. In 2002, SARS-CoV appeared in China and rapidly spread, causing an outbreak resulting in the death of hundreds of people with a mortality rate of 11%. In 2012, another member of the CORONA family called MERS-CoV appeared in Saudia Arabia and also spread to the whole world, killing people with a mortality rate of 37%.<sup>1</sup> Since the appearance of this novel virus, every day, we hear about new cases. Among these cases are pregnant

women. Those women need special care and attention during this era.

### What is meant by Co-Infection?

Co-infection is an infection of the host by more than one organism at the same time. The difference between single infection and co-infection is the effect of co-infection on the host health, which may be harmful, beneficial, or absent. This effect occurs mainly due to changes in the host immune response and may be drug-drug interaction. However, recently almost all infections are considered to have some sort of co-infection as we all had a normal flora in our bodies when we exposed to external infections either in acute or chronic way.<sup>2</sup>

Beneficial effect of co-infections means than one infection can be a treatment for the other infection in the same host or, one infection decrease the severity of another infection or, treatment

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of one infection leads to recovery from the other infection or, treatment of one infection decrease the susceptibility to certain other infections.<sup>3-5</sup> Harmful effects of co-infection mean one infection increase the severity of other infection or, both infections increase the severity of each other, or harmful drug-drug interactions occurs during their treatment.<sup>2</sup>

### Beneficial Effect of Co-Infections in Some Infectious Diseases

Treatment of neurosyphilis by co-infection of malaria due to the effect of cytokines related to malaria fever, which is called then malaria therapy.<sup>3</sup> Malaria therapy was also used in the treatment of mental diseases such as psychotic disorders, schizophrenia, and irritation syndrome. Additionally, malaria therapy was used in the treatment of AIDS and Lyme disease.<sup>4</sup>

Some helminths infections as nematodes decrease severe malaria due to immune modulation.<sup>4</sup> As reported, more than half of the malaria resistant children were children who are infected with *Ascaris lumbricoides*.<sup>6</sup> Antiretroviral treatment of HIV protect children from malaria due to its antimalarial effect, as children treated by Lopinavir–ritonavir–based ART as compared with NNRTI-based ART reduced the incidence of malaria by 41% and also reduction in the recurrence of malaria after treatment with artemether-lumefantrine.<sup>7</sup>

Azithromycin, which is used in the treatment of ocular trachoma, also reduce the prevalence of genital Chlamydia infection.<sup>8</sup> Also this drug decreases infectious diarrhea in children for a short time.<sup>9</sup>

Co-infections in HIV infection leads to immune activation in infected patients in which is called Immune Reconstruction Inflammatory syndrome (IRIS), chronic infection as HSV, HCV, CMV and HBV are important factors in persistent immune activation in chronic treated HIV also these infections have harmful effects.<sup>10</sup>

### Beneficial Effect of Co-Infections in Some Non-Infectious Diseases

Infection with two or more types of HPV from the same or different species protects from high-grade cervical cancer,

caused by an immune cross-protection between HPV types; it's the same mechanism by which bivalent and quadrivalent HPV vaccines leads to cross-protection against non-vaccine HPV types.<sup>11</sup>

### Harmful Effect of Co-Infections in Some Infectious Diseases

HIV infection and TB infection, which worsen and increase the progression of HIV.<sup>2</sup> Moreover, HIV and Hepatitis B and C viruses; HIV patients are more susceptible to end-stage liver disease, kidney disease, and lymphoma.<sup>2</sup> All of these examples may occur during pregnancy.

### Co-Infection Alters the Process of Invasion and Replication of Viruses of Other Species.

Viruses can manipulate post-translation modifications proteins by adding or removing modifications from these proteins. Coronaviridae family encodes a macrodomain in an abundant non-structural protein. This domain is essential for virulence and replication of viruses. Mutations of catalytic mutants of viruses as murine hepatic virus and Sindbis virus decrease the severity of diseases like hepatitis and encephalitis. SARS-CoV N1040A deprived of catalytic activity leading to an increase in levels of IFN, ISGs, and other cytokines while conserved macrodomin of SARS-CoV2 that suppress pro-inflammatory cytokines. In an experimental study on mice, we find that mice co-infected with both wild type and N1040A had better outcomes compared to mice infected by the wild virus only. This clarifies the role of innate immunity in decreasing the lethality of disease.<sup>12</sup>

The respiratory system is exposed to multiple pathogens; viruses, bacterial, and others. Viruses as influenza virus found to induce innate immunity that recognizes other pathogens as *L. pneumophila* through multiple mechanisms as Naip5/Birc1e dependent pathway. Also genes in lungs as TNF $\alpha$ , nitric oxide synthase 2, and many others are highly expressed compared to single infection, high neutrophil infiltration in lung and elevated levels of IL-1 $\beta$ , and TNF $\alpha$  in broncho-alveolar lavage fluid. The deficiency of the IFN- $\alpha/\beta$  receptor ends by more susceptibility to co-infection.<sup>13</sup>

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There are two types of immunity of human body type1 and type2 represented by Th1 and Th2. Th2 is induced by extracellular pathogen as parasites. Intracellular organisms stimulate th1 as mycobacteria, leishmania, viruses, etc. that in turn provokes the release of many pro-inflammatory cytokines as IL1, IL2, IL12, INF- $\gamma$ , and TNF- $\alpha$ . The natural infection provides more immunity than vaccines as it leads to high levels of IgA Abs.<sup>14</sup>

There is cross-immunity between mycobacteria and different types of influenza viruses that are proved by an experimental study on mice. Mice are co-infected with influenza A, and BCG showed decreasing numbers and frequency of CD8 T cells in comparison to mice infected with BCG alone. As BCG produce specific CD8 T cells in the expense of viral CD8 cell that downregulate cytokine storm. These results could be used in COVID-19.<sup>14</sup>

There is a case report of a positive HIV patient who showed fever and typical pneumonia of COVID-19 on CT scan. Also SARS-CoV-2 RNA test was negative, but plasma anti-SARS-CoV-2 antibodies are detected. A study showed that HIV infection increases level of type I IFN that may clear SAR-CoV-2 infection and leading to decrease level SARS-CoV-2 antibody titer and high level of IgM for 42 days, so infection in this patient is delayed compared to other patients with COVID-19 of the same severity of illness. The mechanism of that still unclear and need more studies.<sup>15</sup>

As SAR-CoV-2 infects the host cell by binding of its surface spike glycoprotein (S protein) to receptor ACE2 expressed in the lung, intestine, and other organs as the brain and heart. In patients with IBD showed that more expression of ACE2 receptors either inflamed or not and also release of cytokines as IFN-gamma that stimulates expression of ACE2 in addition to these IBD to upregulate of trypsin-like proteases that cleave S protein of SAR-CoV-2. All of these mechanisms make patients more susceptible to COVID infection.<sup>16</sup>

In the interaction between parasites and viruses, *T. spiralis* and *Nematospiroides* dubious moderate pathological changes of viral infections as influenza A and SARS-

CoV-2. *T. spiralis* downregulates cytokines release in the lung and inhibit the pathology of viral infection. *N. dubious* decrease viral load in the lung.<sup>17</sup>

### Can Co-Infection be used in COVID-19 Treatment?

It's well known that co-infection may have beneficial effects that can improve overall outcomes better than single-agent infection, especially in case of viruses; there are many immunological mechanisms to achieve that. As infection with one pathogen may hinder new infection with COVID-19 through competition on cell receptors. Also, it can be useful when infection occurs already if antigens in common stimulate host immunity more much or if beneficial mutation reveals antagonistic epistasis, which is more common in RNA viruses.<sup>18</sup> With that in mind, we should make more effort in using co-infection in the management of COVID-19.

### Did we use Co-Infection with Other Corona viruses?

MERS-Cov., A sixth human coronavirus, was isolated in 2012. 3C-like protease (3CL<sup>pro</sup>) analogous to picornavirus 3C protease (3C<sup>pro</sup>) is essential in the CoV replication cycle and as hence regarded as a valued drug target. Peptidomimetic inhibitors of enterovirus 3C<sup>pro</sup> (6b, 6c, and 6d) inhibited MERS-CoV 3CL<sup>pro</sup>. In MERS-CoV-infected cells, the inhibitors showed antiviral effect by downregulating viral protein production in cells, as well as reducing the release of infectious viral particles into culture supernatants.<sup>19</sup> Evidence is that recombinant viral vectors (MVA, Adenovirus, Parainfluenza virus, Measles, Rabies) vaccine that its target antigen (which is in common) is S and SolS proteins. This vaccine reached Preclinical: in vitro, efficacy stage of development.<sup>20</sup>

### Complications for Co-Infection

Relative to harmful effect of co-infection, many complications may result from co-infection in a pregnant woman with COVID-19 that may be due to complications of COVID-19 itself that is augmented by other infection, both infections can increase complications of each other or due to interactions between drugs used for the

treatment of those infections.<sup>21</sup> So, complications of COVID-19 that could be augmented by other infections due to decrease host immunity is preterm labor, which defined as delivery before 37 completed weeks of gestation. It is one of the most common obstetrical complications and the leading cause of morbidity and mortality of neonates, premature infants. If they survive, they will suffer from chronic long term health issues and sometimes severe neurological impairments.<sup>22, 23</sup>

Women with other coronavirus infections as SARS-CoV and MERS-CoV during pregnancy, other perinatal complications observed as intrauterine growth restriction, spontaneous abortion, young babies relative to gestational age, admitted to intensive care unit, kidney failure, and intravascular coagulation, sometimes other respiratory viral infections during as influenza virus may be helpful as they are associated with adverse neonatal outcomes like preterm delivery and low birth weight.<sup>24</sup> Physiological changes during pregnancy in COVID-19 patients will increase the risk and severity of pneumonia, which is associated with high perinatal mortality rate, so pneumonia in these cases will need proper supportive treatment, including hydration and oxygen to be prevented.<sup>25</sup> Hypoxic episodes during acute stages of the disease in the pregnant female will be associated with maternal placental blood flow abnormalities that will lead to changes in the placenta of the mother, so maternal hypoxia should be corrected urgently as fast as possible like pneumonia.<sup>26</sup>

Limited data available on the risk of congenital malformation associated with maternal fever but no sufficient data about COVID-19 in increases the risk of miscarriage.<sup>27</sup> Co-infection in pregnant COVID-19 mother can augment complications of other infections like hepatitis C, B, A and HIV infections that can lead to jaundice and increase risk of hepatic insufficiency, cirrhosis, and hepatocellular carcinoma and finally lead to death if untreated.<sup>28</sup> Ebola virus co-infection also leads to hemorrhagic fevers that mainly in the form of vaginal and uterine bleeding, and increases the mortality rate for pregnant women.<sup>29</sup>

### Challenges of co-Infection in COVID-19

As co-infection has a beneficial effect that we may use it in the treatment of COVID-19, there is a harmful effect that we should avoid. As co-infection involves a lot of pathogens, has a different impact on host and it is hard to expect it's work and how it works, as there are many possible challenges includes the presence of additional infection, timing, order, and natural history of each infection.<sup>30</sup>

### Co-infection between Dengue and COVID-19

Patients with fever in endemic areas such as Singapore, Thailand, and Malaysia in Southeast Asia can be infected by COVID-19 and dengue at the same time. As COVID-19 and dengue have the same clinical signs, according to a recent study of 1,099 patients, 87.9% of COVID-19 patients present with fever, 67.7% present with cough, and 13.7% present with headache. Some patients present only with fever when infected with SARS-CoV-2. In another study of 1,792 patients, 100% of dengue fever patients presented with fever, and 25.7% presented with headache.<sup>31</sup>

The problem increases as COVID-19 can lead to false-positive in screening tests that may cause a delay in diagnosis of COVID-19, and more spread of the virus.<sup>32</sup> So, we should be careful and do more investigations when we deal with patients with clinical signs common in both like fever, cough, and headache.

### Co-Infection between Seasonal Influenza and COVID-19

According to the data of the disease, other respiratory infectious diseases will enter the epidemic season with COVID-19.<sup>33</sup> Their clinical manifestations are similar to the new coronavirus pneumonia, and it is difficult to differentiate between them by clinical signs and chest imaging.<sup>34</sup> This will interfere with the prevention and control of the epidemic. So it is necessary to strengthen epidemiological investigations, optimize laboratory testing strategies, take adequate measures, increase the prevention and control of influenza epidemics, and minimize the interference with the prevention and control of new coronavirus pneumonia epidemics.<sup>35</sup>

### Conclusions

Co-infection is an infection of the host by more than one organism at the same time. This effect occurs mainly due to changes in the host immune response. Still, recently almost all infections are considered to have some sort of co-infection as we all have beneficial and harmful effects of co-infections in some infectious diseases. The beneficial effects can improve overall outcomes better than single-agent infection, especially in the case of viruses, as there are many immunological mechanisms to achieve that. Many complications may result from co-infection in a pregnant woman with COVID-19 that may be due to complications of COVID-19 itself that is augmented by other infections. Both infections can increase complications of each other or due to interactions between drugs used for the treatment of those infections. Therefore, complications of COVID-19 that could be augmented by other infections due to decreased host immunity are severe. Preterm labor is the most serious complication due to co-infection in COVID-19 pregnant women as it is the leading cause of morbidity and mortality of neonates.

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