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Letter to the Editor

Newer modalities for treatment of severe COVID-19 infection and their use in pregnancy-boon or bane?

Sir,

We are into the second year of the COVID-19 pandemic which is caused by an RNA virus, belonging to the severe acute respiratory syndrome (SARS) family. Though the mainstay of COVID management continues to be mainly symptomatic, many new management options are coming up. Due to ethical reasons, pregnant and lactating women are never included in the clinical trials used to test drug safety and efficacy, but COVID-19 is here to stay and we should begin to analyse the effects of the various proposed drugs in its management in pregnant population.

Decidua is the modified endometrium which has special immunological characteristics. The changes in innate and acquired immune responses make pregnancy an immune-compromised state. Many viral infections have shown catastrophic outcomes in pregnancy both for the mother and fetus. The data from previous pandemics with the influenza and SARS viruses show us that mortality and morbidity is very high in pregnant women.[1] According to the interim update by FIGO released in 2020, the final effect of the virus and the drugs used in its treatment will only be available by 2030 and requires further research and deliberation.[1] Even though premature, this letter attempts to summarise what has been studied until now.

Remdesivir is a nucleoside analogue which acts on the RNA dependent RNA polymerase which enables the virus to incorporate into the host genome and replicate.[2] It has a broad spectrum of action and has proven to be useful in reducing the duration of moderate and severe COVID-19 infections.[2] It is administered through intravenous route over a period of 5-10 days and has shown to reduce the duration of hospital stay and need of ventilatory support when compared to placebo. Various side effects have been reported including nausea, vomiting, deep vein thrombosis, deranged liver enzymes, pleural effusion and sometimes hemoptysis.[2,3] Most of these side effects overlap with the pathophysiology of COVID-19 and could also be due to pregnancy and related complications. Remdesivir has not been allotted a drug class in pregnancy and the data on its teratogenicity is still lacking. Overall, the benefits with the drug outweighs the risks and it has been approved by the US-food and drug association (US-FDA) for emergent use during the pandemic.[2,3]

Tocilizumab is an immunomodulator which acts by inhibition of interleukin-6 (IL-6). IL-6 is a central cog in the intricate network of immune response generated in the body seen with infection of COVID-19 infection.[4] COVID-19 infections create a state of systemic inflammatory response which is mediated by interleukins and cytokines. This intense response is supposed to be protective to the host but in turn is a double-edged sword which breaks down the entire immune system. Tocilizumab aims to dampen this response and hence avoid the end organ damage usually seen associated with it. Tocilizumab has been used to treat other autoimmune diseases and data from those studies has not shown any significant increase in risk of malformations in the foetus.[4] Hepatitis and reactivation of dormant infections are the major side effects with this drug.[4] The incidence of reactivation of varicella and cytomegalovirus infection is seen to be on the rise in patients who have recovered from COVID-19. Tocilizumab is here to stay as a treatment modality for severe and critical COVID-19 and we have to wait and watch for its effects on pregnancy.[4]

Dexamethasone is a steroid which has been used previously also to curb the cytokine storm caused due to infectious or inflammatory or autoimmune diseases. It was not long before it got inculcated into the treatment regime for COVID-19. Methyl-prednisone has also been tried due to similar mechanism of action. Dexamethasone crosses the placenta and this may lead to chronic adrenal suppression in the fetus.[4] The neonate may have increased risk of respiratory depression and cerebral palsy may also ensue. Babies born to such mothers may have adrenal insufficiency throughout their life and may require stress dose of steroids before surgical procedures.[4] Research is still ongoing to use steroids which do not cross the placenta so that it is beneficial to both mother and foetus.[4]

Convalescent plasma, a form of passive immunotherapy extracted from COVID recovered patients was considered to be curative for COVID-19 because it contains antibodies against the infection.[4] Safety data with respect to plasma therapy is derived from previous life-threatening viral infections such as Ebola. There were no detrimental side effects documented other than blood product transfusion related reaction.[4] Plasma therapy has shown positive impact in older patients with severe COVID-19 infection by reducing viral load and slowing progression of the disease.[4,5] Though observational studies showed clear benefits, randomised control trials showed no extra benefits with plasma transfusion.[5] It was approved by the FDA as emergent treatment modality, but now is being

faded out of the treatment protocol. When given in pregnancy it always carries a risk of transmission of infection, autoimmunity and preterm birth.[4,5]

Various antibiotics and antivirals have been pushed into the healthcare system prematurely before they showed documented benefit in COVID-19 because the medical fraternity was desperate to try anything to save the life of thousands.[5] Pregnancy is a high-risk state by itself and the physiological changes of pregnancy become pathological when women acquire the COVID-19 infection. All treatment options are now oriented towards saving the life of the mother and foetus safety outlook is lacking. Data on the effect of these medicines of the foetus in short and long run will emerge slowly and offer learning and research opportunities. Up until then, our resources shall be directed towards saving maternal lives, reducing chances of sepsis and better care of the premature neonate.

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