

CASE REPORT

A case of severe COVID-19 pneumonia in pregnancy managed with tofacitinib and review of literature

Jayanta Kumar Biswas, Rajat Chauhan

Corresponding author: Dr Jayanta Kumar Biswas, Department of Obstetrics & Gynaecology, Military Hospital, Pathankot, Punjab, India; Email : jayantabiswas1977@gmail.com

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ABSTRACT

The incidence of coronavirus disease (COVID-19) is increasing each day worldwide and the clinico-pharmacological dynamics of it is also changing with time. Pregnant women do also get infected though mostly mild to moderate in nature. To date, there is no specific drug against the severe acute respiratory syndrome coronavirus disease-2 (SARS-CoV-2), more so its drug management in pregnancy in view of adverse maternal and fetal effects. There are different treatment modalities described in literature. Here, we present a case of severe COVID-19 pneumonia in second trimester pregnancy managed successfully with “off label” use of tofacitinib along with steroid pulse therapy in preventing her from going to invasive mechanical ventilation and probable catastrophe due to hyperinflammatory syndrome characterised by surge of cytokines.

Keywords: COVID-19, cytokine storm, pneumonia, teratogenicity, tofacitinib.

World Health Organization (WHO) had officially declared the COVID-19 outbreak as pandemic on 11 March 2020. It has caused 17,58,47,347 cases and 38,07,276 deaths by 15 June 2021¹. Physiological and mechanical changes in pregnancy are making pregnant women more susceptible to infections, particularly when cardiorespiratory system is affected with possibility of rapid progression to respiratory failure.

Altered immunity and elevated levels of interleukins and cytokines are associated with extensive lung damage followed by increased mortality in COVID-19 patients²⁻⁴. To date, there is no specific pharmacological agent identified against SARS-CoV-2. The usual approach is to treat symptoms limited by different conditions. Tofacitinib, a non-specific Janus kinase- signal transducers and activators of transcription (JAK-STAT) inhibitors, is potent immunomodulator approved as second line therapy for many auto-immune diseases⁵.

In this case report, we aimed to assess clinical improvement following administration of tofacitinib along

with steroids in a rapidly deteriorating pregnant patient in her second trimester with severe COVID-19 pneumonia keeping teratogenic effects in mind.

Case

A 28 years old patient with gravida 3 para 1 living 1 abortion 1 and Rh non iso-immunized status admitted at 26 weeks gestation with breathlessness (SpO₂ - 76 % in room air) without recordable fever with history of fever and cough three days back. On admission, she was maintaining her blood pressure and her fetal heart rate was 156 beats per minutes (BPM). Her base line investigations including reverse transcriptase - polymerase chain reaction (RT-PCR) for SARS-CoV-2 were requested and started with injectable 3rd generation cephalosporin, steroid nebulisation and oxygen supplementation (5 L/min) on concentrator. However, on deterioration, high flow oxygen (15 L/min) through non-rebreathing mask (NRBM) was started to achieve her SpO₂ level above 92%. She was started with dexamethasone for antenatal steroid induction.

On third day early morning, on occurrence of severe

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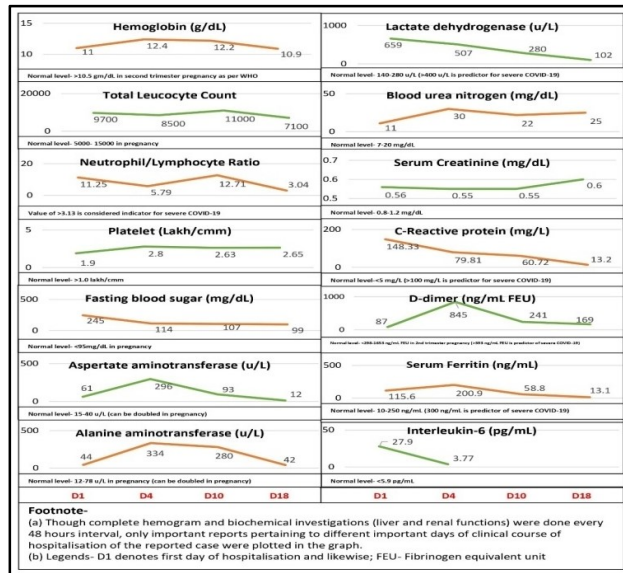


Figure 1: Date wise investigations during the course of hospitalisation.

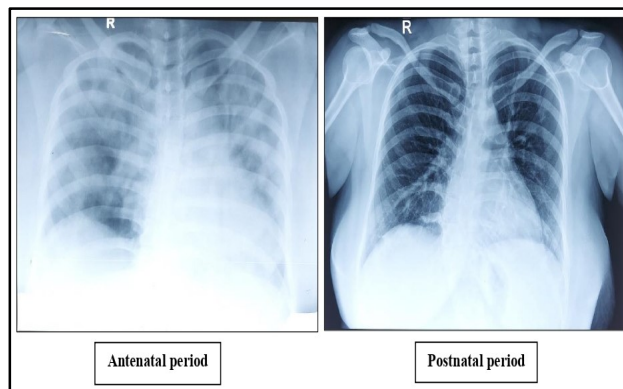


Figure 2: Comparative chest radiograph showing bilateral widespread consolidation/ opacities with severe ARDS (during antenatal period) and fine fibrotic changes (during postnatal period).

degree of hypoxic episode (SpO_2 - 54%) even with NRBM, she was immediately shifted to COVID-19 intensive care unit (ICU) and started on non-invasive ventilation (NIV) with pressure support of 15 cm of H_2O , positive end expiratory pressure (PEEP) of 8cm of H_2O and fraction of inspired oxygen (FiO_2) of 65% with intermittent NRBM. Injectable remdesivir 200mg followed by 100mg daily for next 4 days and thromboprophylaxis with low molecular weight heparin (LMWH) 40mg twice daily and oral aspirin 75mg daily were also started with concern of rising D-dimer,

C-reactive protein (CRP), serum ferritin, lactate dehydrogenase (LDH) (figure 1). Her chest X-ray was done at this stage with abdominal lead shield, showed bilateral wide spread extensive consolidation / opacities suggesting acute respiratory distress syndrome (ARDS) (figure 2). Arterial blood gas analysis (ABG) also showed arterial partial pressure of oxygen (PaO_2)/ FiO_2 ratio <100mm of Hg, indicating severe ARDS with 'cytokine storm'. In view of above findings, methyl prednisolone pulse therapy of 250mg daily for 3 days started in place of dexamethasone. On 24 hours of methyl prednisolone pulse therapy, she was requiring NIV with FiO_2 70% to maintain SpO_2 level upto 85% and her liver enzymes levels were also elevated. After counselling of patient and relatives, immunomodulation with oral tofacitinib 10 mg twice daily was added for five days with ongoing pulse therapy to halt the 'cytokine storm'. Antimicrobial agent upgraded to injectable piperacillin - tazobactam 4.5 gm six hourly and teicoplanin 400 mg daily. Oral ursodeoxycholic acid (UDCA) and L-arginine sachet were also started.

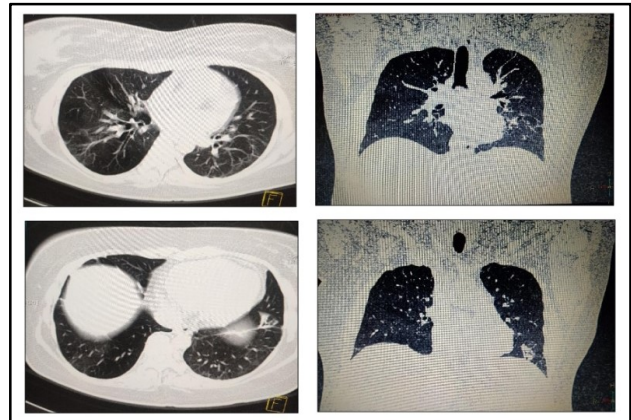


Figure 3: Multi planner high resolution CT scan of chest showing fine fibrotic changes with 'air trapping' in both lungs (postnatal period).

With this treatment, she was showing no further deterioration though prognosis was guarded in view of high flow oxygen requirement. From tenth day onwards, she started improving in terms of improving $\text{PaO}_2/\text{FiO}_2$ ratio, decreased FiO_2 on NIV and blood parameters as well. She was gradually weaned out from NIV to NRBM (15 L/min) and then via Hudson mask. Next week she was shifted to nasal prongs oxygen support. She was shifted out of COVID 19 ICU when maintaining SpO_2 level >92% with oxygen concentrator at 2-3 L/ min. She was also gradually weaned

off steroid and antimicrobials and started with novel antifibrotic agent oral pirfenidone 200mg daily for four weeks.

Throughout her hospital stay, dietary supplementation was done and frequent change of positioning was performed as per COVID awake repositioning/ proning protocol (CARP). She was psychologically counselled and explained regarding postcovid precautions with management plan. Her ophthalmological evaluation was normal and fetal heart rate was maintained between 150- 160 BPM. Her Obstetric ultrasonography was without any congenital malformation, mild degree fetal growth retardation and normal doppler study. No further chest radiograph or computed tomography (CT scan) was performed to limit teratogenic radiation exposure.

On twentieth day of admission, she was discharged with oxygen support of 1-2 L/min on concentrator and thromboprophylaxis. After three weeks of discharge (at 34th week of gestation), she was able to maintain SpO₂ level 90-92% in room air for about two hours at stretch in sitting position but her fetomaternal evaluation revealed asymmetric fetal growth restriction along with polyhydramnios and advised strict follow-up. At 36 completed weeks of gestation, fetus was in transverse lie with loops of umbilical cord occupying lower uterine pole and her dyspnoea level had also increased. In view of these findings, she was delivered by elective cesarean section under low dose spinal anaesthesia and maintaining higher PaO₂ levels by O₂ supplementation through NRBM at 15L/min; delivering an alive and healthy new born baby. Post-operative period was uneventful including blood investigations and was discharged with thromboprophylaxis and O₂ support of 1-2 L/min on concentrator. Chest X-ray and CT scan were done in post-operative period for assessment of her lung status, showing features of thin fibrotic bands with air trapping in both lungs (figure 2, 3).

Discussion

Since the onset of global pandemic of COVID-19, clinicians and medical researchers worldwide are trying to evolve measures for early recovery of patients and also to ensure every opportunity to rescue severe cases and reduce mortality.

During hypoxaemia, aberrant autoimmune inflammatory response is key mechanism for COVID-19 pneumonia and for rapid deterioration as per Lucas et al⁶. McGonagle et al not only confirm a direct relationship between COVID-19 disease severity and rising cytokine levels, but also supports

clinical approach of early intervention for achieving good outcome⁷. Oxygen saturation level, degree of inflammation (CRP, ferritin, LDH) and hypercoagulability (D-dimer) are well established markers of severity and also noted in the case reported⁸.

As no specific anti SARS-CoV-2 therapeutic agents are available, symptomatic treatment and pregnancy specific management of complications such as ARDS comprises the current standard of care. The monitored emergency use of unregistered interventions (MEURI) framework from WHO should guide the ethical use of non-licensed drugs in pregnancy during the pandemic. Interventions aimed at modulating the inflammatory immune response by reducing toxic cytokines levels is key in improving COVID-19 pneumonia outcomes; usage of dexamethasone in hospitalized patients got well established momentum after publication of recovery study⁹. The kinase inhibitors are proposed as treatment for COVID-19 as they can prevent biochemical changes involved in immune activation and inflammation in response to proinflammatory cytokines and interleukin (IL-6)¹⁰. Baricitinib, a JAK-STAT inhibitor got emergency use authorization (EUA) by food and drug administration (FDA) on 19 November 2020, when used in combination with remdesivir for hospitalized adults and children above 2 years age with COVID-19 requiring supplemental oxygen¹¹. However, there was paucity of data on usage of JAK-STAT inhibitors in pregnancy. Being small molecule drug, it can cross placenta and fetal risk cannot be ruled out¹².

Tofacitinib is prototypical JAK-STAT inhibitor and is FDA approved for treatment of rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis and ulcerative colitis as it decreases IL-6 level¹³. Like dexamethasone, tofacitinib possesses a broad anti-inflammatory effect, though target different inflammatory pathway, contrary to monoclonal antibodies¹⁴. Study by Hayek ME et al showed that adding tofacitinib based anti-inflammatory therapy into treatment regimen with dexamethasone have potential benefit in improving COVID-19 pneumonia and patient survival¹⁵. Data on pregnancy outcomes on tofacitinib used in pregnancy for other usual conditions are similar to that among the general pregnant population without any statistically significant fetal teratogenicity¹⁶⁻¹⁸.

Conclusion

Pregnant women represent a uniquely vulnerable group to any infectious disease outbreak due to altered physiology and there has been significant rise in the incidence of severe

COVID-19 disease in pregnancy as well. As there was no specific pharmacotherapy evolves till date, different modalities of anti-inflammatory therapy are being used to stem the florid immune response associated with it. Need to safeguard unborn fetus adds to the ongoing challenge. Survival benefit with use of tofacitinib is found in the reported case.

It is concluded that, a treatment protocol including anticoagulation therapy, antiviral and anti-inflammatory therapy with tofacitinib along with steroid pulse therapy offers model in management of severe COVID-19 pneumonia and averting mortality when used within 48-72 hours of 'cytokine storm' even in pregnant women.

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Jayanta Kumar Biswas¹, Rajat Chauhan²

¹ MS (Obstetrics & Gynaecology), Armed Forces Medical Services, Military Hospital, Pathankot, Punjab, India; ² MD (Anaesthesiology & Critical care), Armed Forces Medical Services, Military Hospital, Pathankot, Punjab, India.