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COVID-19 in Pregnancy presenting with Neurological Symptoms – A Dilemma for Obstetricians

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Abstract
The novel coronavirus disease (COVID-19), the global pandemic poses great challenges towards health care system. Optimal treatment to the disease has not been determined and is often guided by institutional guidelines. COVID-19 and its effect in pregnancy is yet not known, but is extrapolated from the experiences of previous pandemics and infectious diseases like SARS and MERS that since pregnancy is a high-risk state in the context of infectious diseases, pregnancy makes women more susceptible to pathogens and may lead to adverse outcomes.
The implications of COVID-19 in pregnancy still remains understudied.
Here we report our experience with a case of COVID-19 positive pregnant female presenting to our emergency department at 21^{+3} weeks of gestation with a history of fever, headache and convulsion. Through this case we would like to highlight the difficulties faced in diagnosing and treating this patient with unique challenges that COVID-19 presents with in pregnancy.

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I. Introduction

COVID -19,a pandemic, as declared by the World Health Organization(1), is spreading around the world and the cases of outbreak doesn't seem to cease.

Patients with coronavirus disease 2019 (COVID-19) typically present with fever and respiratory illnesses like cough and dyspnea(2). However, There are emergingreports of COVID-19 positive patients presenting with isolated neurological symptoms.

The novel coronavirus, Severe acute respiratory syndrome 2 (SARS-CoV-2), shares significant structural and biological similarities with SARS-CoV, and is known to be neuroinvasive particularly with brainstem involvement.

A growing body of evidences are showing that neurotropism is one of the common features of coronaviruses.

Increasing evidences show that the coronaviruses are not always only confined to the respiratory tract, but their neuroinvasive propensity helps them invade the central nervous system inducing neurological diseases(3).

Cerebrovascular complications because of the hypercoagulable state are also reported as a feature of COVID-19(4).

Neurological symptoms associated with COVID-19 infectionsso far reported are including,but not limited to, seizures, coma, encephalitis, Guillan-Barre syndrome, and cerebrovascular events including ischemic stroke, ICH, and cerebral venous sinus thromboses.

An understanding of potential neurological manifestations in COVID-19 cases is crucial to provide optimum care for patients and also to reduce the disease burden on the medical facility.

An immediate neurological care is important to minimize the mortality and morbidity of patients with convulsion and other neurological emergencies.

Here, we report a very interesting and a challenging case of a pregnant patient who presented to us in the emergency department with a history of fever and headache for 3 days. She had an episode of seizure before arriving to the ER with acute generalised edema and altered sensorium.

Case Presentation

This is 22 years old, primigravida, 21^{+3} weeksgestation by dates, unbooked, previously healthy, with no underlying medical comorbidities was bought to the ER in a confused state with a history of fever for the past 3 days, associated with headache andacutegeneralised edema. Her husband gave history of her having a generalized tonic colonic convulsion at home that lasted approximately for about 20 minutes. Convulsion was associated with loss of consciousness, frothing and up rolling of her eyes. She regained consciousness while she was in the ambulance being bought to the hospital but wasn't alert and oriented.

She does not have any history of having epilepsy or CNS disorders previously.

She has had a history of having close contact with a COVID-19 positive patient.

There was no history of any abdominal pain, nausea, vomiting, diarrhoea, dysuria, cough, dyspnoea or any vaginal blood or fluid loss.

Past surgical history is unremarkable.

No history of any allergy to food or drug.

No history of blood transfusion or admission to the hospital.

Patient is a university student.

She is a non-smoker, non-alcoholic and does not consume any form of recreational drugs.

On examination –

Patient was conscious, but in a drowsy state, not oriented. She was not responding to commands.

Vitals: Her temperature on arrival was 38.5 C, heart rate 108 beats/min,blood pressure 180/113 mmHg, respiratory rate 28/min, SPO2 - 92% at room air.

She withdrew her limbs to painful stimuli; patient's Glasgow Coma Score 12/15 and Glasgow Coma Scale was E3V4M5.

On physical examination

No pallor or yellowish discoloration seen in the eyes.

No biting of tongue or blood seen in the mouth.

Skin turgor was intact.

Chest was auscultated and bilateral crepitations were heard with reduced air entry, bilaterally.

Cardiac examination was normal with normal heart sounds.

Abdominal examination showed no scars, no striae, soft abdomen, non-tender, no palpable contractions, fundal height was 1 cm above the umbilicus.

Vaginal examination revealed no vaginal blood loss or discharges.

Lower libs showed no signs of deep venous thrombosis.

The ER physicians did anemergency OBGYN consultation for monitoring the fetus.

Patient was seen by the OB physician on duty.

Patient was transferred to negative pressure room as a case of suspected COVID-19 patient.

Blood pressure measurement was repeated in 15 minutes and was checked manually as well.It was in the range of 170 – 195mmhg systolic and 100-125 mmhg diastolic.

Patient connected to 2 large bore IV lines, received hydration, oxygen and perfalgan.

Due to repeated markedly elevated blood pressure, patient was started on Labetalol and magnesium sulphate infusion ($MgSO_4$) for the presumed superimposed pre-eclampsia.

Differential diagnoses in view of the current pandemic are COVID-19 with neurological manifestations, pre-eclampsia, eclampsia, hypertensive encephalopathy and sepsis.

Blood was extracted for CBC, Coagulation profile, LFT, RFT, Uric Acid, ESR, CRP, blood culture, Protein Creatinine Ratio andserum lactic acid. Ultrasound abdomen and pelvis, Chest Xray and MRI brain were requested.

Covid-19 RT- PCR swab test was also performed.

Obstetrics ultrasound revealed (in fig. 1)single, intrauterine, non-viable fetus of 22 weeks and 1 days of gestation withno fetal cardiac activity.An anteriorly located fundal placenta was seen. There was no retroplacental collection or evidence of abruptio seen. Cervical os was closed, cervical length at the time of examination was 4 cm.

Abdomen and Pelvis ultrasonographyrevealed bulky maternal right kidney which measures 13 x 8.0cm. There was a gross right hydronephrosis with ballooning of renal pelvis likely due to PUJ obstruction associated with severe thinning of renal parenchyma on right side. Rest of the abdominal findings remains unremarkable.

MRI brain showed multiple near symmetrical ill-defined areas of T2 / FLAIR hyperintensities involving the cortical and subcortical white matter of bilateral parieto-occipital lobes as well the pons, bilateral basal ganglia and right cerebellar hemisphere, they are likely to represent changes of posterior reversible encephalopathy syndrome (PRES) with atypical central involvement as shown in (fig. 2).

Portable chest X-ray showed bilateral opacities in lungs fields (fig. 3), which prompt us to perform further radiological investigation including the HRCT, which revealed bilateral ground glass appearance with CO-RAD 5, indicating atypical pneumonia.

Patient was then admitted to the ICU for closed monitoring and stabilisation.

Initial lab findings were as follows: Hb- 12.5g/dL, WBC- 10,000,Plat – 238, 000, Urea – 0.67 mg/dL, Creatinine – 1.3mg/dL, CRP 56, Urinary analysis showed urine protein 3+, negative leucocytes, nitrites and RBC's. Protein Creatinine ratio was 2.3.

LFT was within the normal range.

RT- PCR for the (SARS – COV2) infectionwas positive.

Blood culture revealed no growth after 48 hours.

Hence patient was managed for COVID19 with superimposedpre-eclampsia by the ICU team. Family was informed about the diagnosis and the management plan. After stabilization and recovering from COVID-19 in 2 weeks, patient was induced for termination of pregnancy. Patient was discharged home in good health condition.

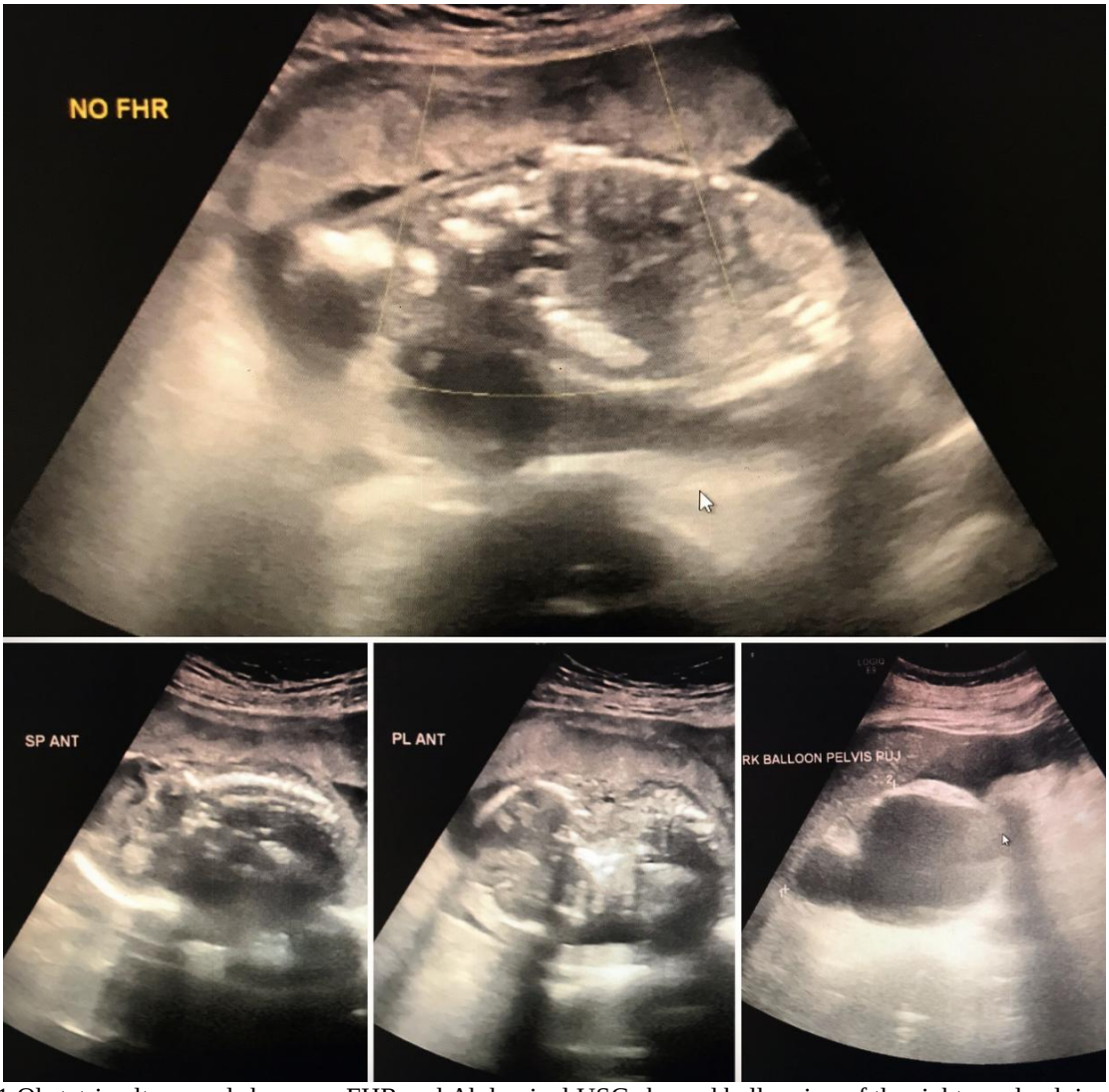

Fig.1:Obstetric ultrasound shows no FHR and Abdominal USG showed ballooning of the right renal pelvis

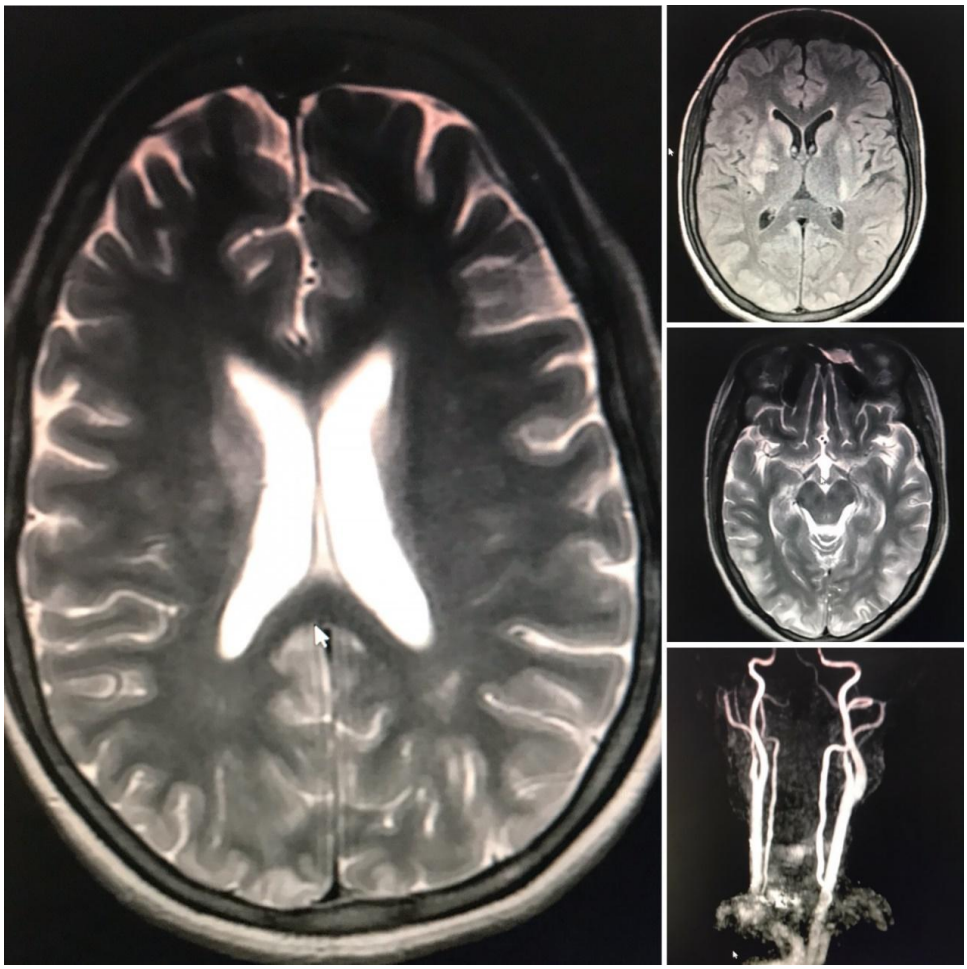

Fig.2: MRI brain shows multiple near symmetrical ill-defined areas of T2/FLAIR hyperintensities involving the cortical and subcortical white matter of bilateral parieto-occipital lobes as well the pons, bilateral basal ganglia and right cerebellar hemisphere.

MRI angiography shows no significant stenosis or thrombosis.

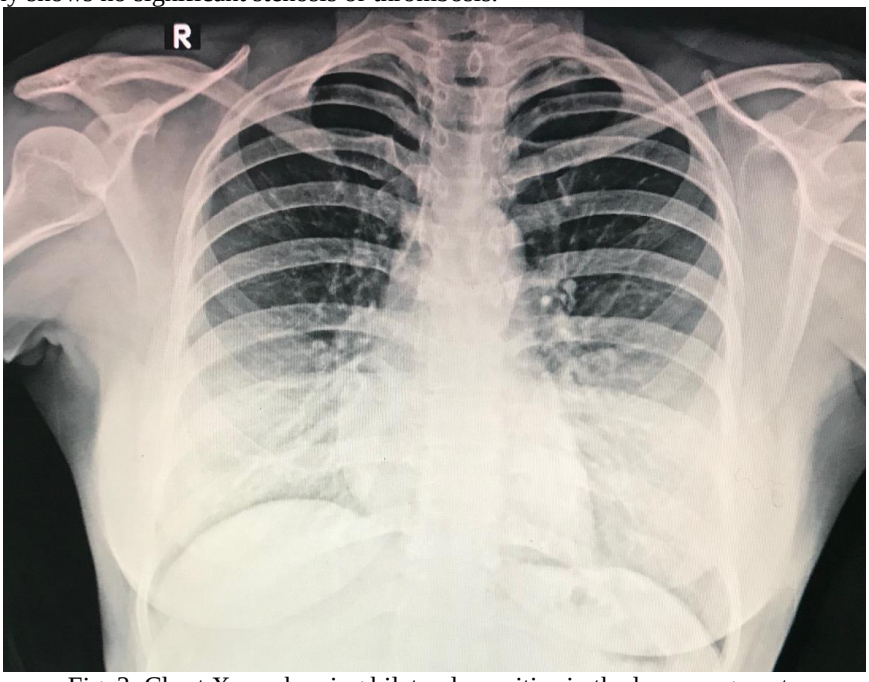

Fig. 3: Chest X-rayshowing bilateral opacities in the lower segment.

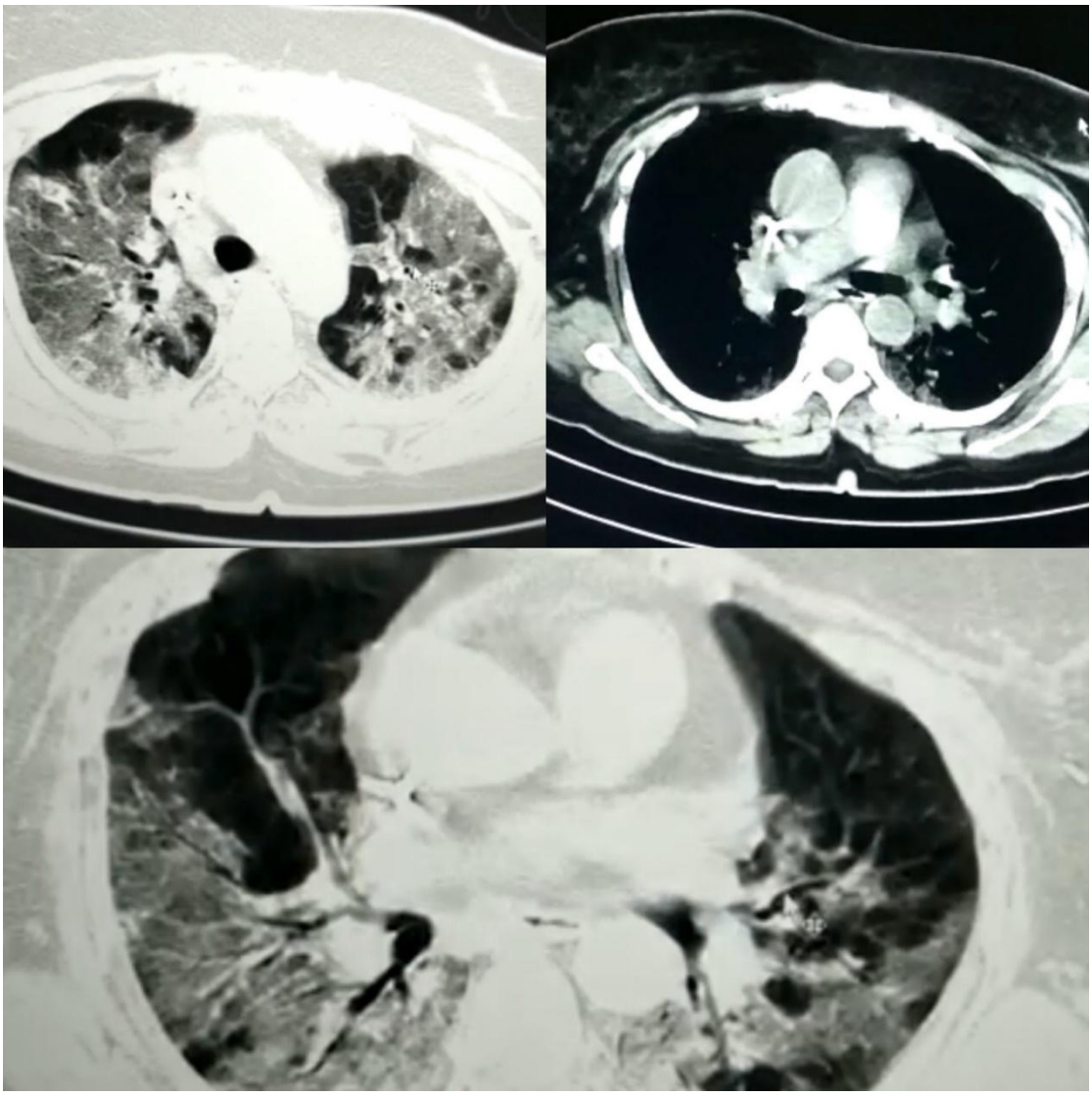

Fig. 3: High resolution - CT demonstrating bilateral ground glass appearance in the lung field.

II. Discussion

The novel COVID-19, was first reported in Wuhan, china in December 2019 (5). From the earlier epidemiological studies, it has been known that the novel causative virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a highly contagious and communicable disease with human to human transmission (6). After crossing the mark of 25 million confirmed cases and over 850,000 deaths worldwide, COVID-19 pandemic continues to burden and impose unique challenges to the health care facility(7).

As COVID-19 is an emerging infectious disease and since pregnant women are regarded as high risk state in the context of infectious conditions, the optimal treatment has not been determined and management often is based on individual institutional guidelines (8).

Pregnant women and foetuses are represented as a high-risk population during an infectious disease outbreak. Physiological, mechanical and immunological changes in pregnancy make pregnant women more susceptible to infectious pathogens in general, particularly when the cardiovascular system is affected.

Pregnancy bias of dominance of T-helper 2 cells due to physiological shift, protects the fetus, but makes the mother vulnerable to viral infections which are more contained by the cell mediated immunity by Th1 system, contributing to overall infectious morbidity by increasing susceptibility to various pathogens (9)

Thus leading to rapid progression and deterioration of a gravida's health overall causing respiratory failure and creating a hypoxic state (10).

Clinical manifestations of COVID-19 are similar to those of severe acute respiratory syndrome and Middle East respiratory syndrome.Although, data on SARS and MERS in pregnancy is sparse and mostly extrapolated from non-pregnant population. Drawing from previous experiences of infectious disease entities

involving respiratory illness, there is an anticipation that pregnancy not only puts a woman on high risks of complications but also increases risk of maternal and neonatal mortality (11-13).

In the midst of rapidly evolving outbreak, various clinical characteristics of COVID-19 infection have been documents in the literature.

Most commonly reported symptoms include fever, cough, shortness of breath, fatigue and myalgia. Less frequently, gastrointestinal symptoms like nausea, vomiting and diarrhoea are also reported (14, 15).

While neurological symptoms are common over the course of infection with SARS-COV-2, they are not very well defined. Symptoms like anosmia, hypogeusia, headache, seizure, impaired consciousness, confusion, depression and coma are also reported in a few case series (16, 17).

It is not clear as to neurological manifestations are a consequence of hypoxia or are related to neurotropic properties of SARS-COV-2 (18).

Here, in this report, we summarised the clinical features of a pregnant woman with COVID19 who presented to us in Emergency department. Thus, addressing the obstetric complexities in diagnosing and managing a pregnant patient with the disease and hence, demanding a pragmatic and an integrated frame work in managing the unique needs ofpregnant women.

In our case, the patient presented with some symptoms specific to COVID-19, such as fever, headache and altered sensorium, while she also had elevated blood pressure and a history of seizure at home.

Primigravida, in itself is a well-known risk factor for preeclampsia. Our patient being a primigravida, was at a risk of preeclampsia and her overlapping symptoms prompted us to investigate for preeclampsia.

Hypertensive disorders in pregnancy attributes to one of the leading causes of maternal morbidity and mortality worldwide (19).

Preeclampsia, particularly, is the most feared complication of pregnancy. Preeclampsia complicates about 2-8% of pregnancies worldwide (20).

There are several risk factors which attributes to increased probability of preeclampsia like nulliparity, prior history of preeclampsia, chronic hypertension, obesity, advanced maternal age, diabetes, kidney disease, assisted reproductive technology, autoimmune diseases, thrombophilia and multifetal gestations (21-23).

However, it is very important to keep in mind that most cases of preeclampsia happen in nulliparous women who are previously healthy and have no significant risk factors as in our case.

Preeclampsia is a specifically a disorder of pregnancy and is associated with a new onset of hypertension, occurring mostly after 20 weeks of gestation with proteinuria or without proteinuria in presence of other signs and symptoms of severe disease (24).

The diagnostic criteria for Pre-eclampsia is shown below in Box 1, taken from the ACOG Practice bulletin(25).

Diagnostic Criteria for Preeclampsia

Blood pressure

- Systolic blood pressure of 140 mm Hg or more or diastolic blood pressure of 90 mm Hg or more on two occasions at least 4 hours apart after 20 weeks of gestation in a woman with a previously normal blood pressure
- Systolic blood pressure of 160 mm Hg or more or diastolic blood pressure of 110 mm Hg or more. (Severe hypertension can be confirmed within a short interval (minutes) to facilitate timely antihypertensive therapy).

and

Proteinuria

- 300 mg or more per 24 hour urine collection (or this amount extrapolated from a timed collection) or
- Protein/creatinine ratio of 0.3 ~~mg/dL~~ or more or
- Dipstick reading of 2+ (used only if other quantitative methods not available)

Or in the absence of proteinuria, new-onset hypertension with the new onset of any of the following:

- Thrombocytopenia: Platelet count less than 100,~~000~~ $\times 10^9$/L
- Renal insufficiency: Serum creatinine concentrations greater than 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease
- Impaired liver function: Elevated blood concentrations of liver transaminases to twice normal concentration
- Pulmonary edema
- New-onset headache unresponsive to medication and not accounted for by alternative diagnoses or visual symptoms

Convulsive manifestations of hypertensive disorders in pregnancy is termed as Eclampsia. Pathogenesis of eclampsia is largely unknown but known to be among the severe manifestations of the disease.

Eclampsia is defined by sudden onset of tonic- clonic seizures, new in onset, without a prior history of epilepsy, transient cerebral ischemia, infarction, intracranial haemorrhage or drug use in the presence of generalised enema, hypertension and proteinuria. (26).

However, women with eclampsia present with a wide spectrum of signs and symptoms in terms of severity to absent or minimal symptoms of hypertension, proteinuria or edema(27, 28).Significant number of women do not present with the classical signs and symptoms of preeclampsia (hypertension and proteinuria) before the seizure episode (29, 30).

Nervous system manifestations in eclampsia are usually proceededby premonitory signs of cerebral irritation such as severe and persistent headache, decreased visual acuity or blurred vision, photophobia, altered mental status and/or an episode of seizure(28, 31, 32). Headaches are the most common presenting complaint and are believed to be due to elevated cerebral perfusion pressure, cerebral edema and hypertensive encephalopathy (33-35).

Most cases of eclampsia (91%) happen in the third trimester. Only remaining 7.5% of cases happen between the 20^{+0} and 27^{+6} weeks of gestation. And about 1.5% happen at or before 20^{+0} weeks of gestation (36). Women, early in pregnancy who present with seizures may be misdiagnosed as having hypertensive encephalopathy, thrombotic thrombocytopenic purpura(37), or in the view of current pandemic situation, COVID-19 with neurological symptoms (38, 39). Hence, any pregnant woman who present with convulsion in association with/ without hypertension and proteinuria during the first half of pregnancy must be considered to have eclampsia until proved otherwise (28).

In eclampsia, autoregulation mechanism that maintains cerebral circulation and perfusion is altered due to acute changes in blood pressure, as the result, the cerebral vessels becomes dilated, ischemic and increasingly permeable. The hyper perfusion and cerebral edema (mostly vasogenic) results in compression of the vessels causingdecreased cerebral blood flow(28).

Hypertensive encephalopathy is another possible differential diagnosis of eclampsia, as in this acute condition, there is an abrupt severe rise in blood pressure and subsequent increase in intracranial pressure.

Cerebral imaging finding in eclampsia is similar to that seen in patients with hypertensive encephalopathy.

The classical findings are referred to as Posterior Reversible Encephalopathy Syndrome (PRES)(40, 41). It is a constellation of a wide range of clinical neurological signs and symptoms similar to those of preeclampsia like visual deficit, headache, confusion or seizure (42).

The suspicion for PRES is also highly increased in a woman who presents in the setting of eclampsia, preeclampsia with headache, altered consciousness or visual disturbance (43).

The diagnosis of PRES, a clinic-radiological syndrome, is characterised by white matter vasogenic edema affecting the posterior occipital and parietal lobes of the brain on MRI (42, 44).

PRES is also commonly associated with infection, sepsis, autoimmune disease, chemotherapy and reaction from bone marrow/stem cell transplantation(45).

Reversible Cerebral Vasoconstriction syndrome is another condition that may be confused with preeclampsia or eclampsia.

Reversible cerebral vasoconstriction syndrome is characterised by reversible, multifocal narrowing of the cerebral arteries presenting with similar signs and symptoms of thunderclap headache, focal neurological deficits like edema, stroke or seizures (46).

Altered perfusion as in case of Eclampsia, pre-eclampsia, hypertensive encephalopathy, PRES, Reversible cerebral vasoconstriction syndrome or infectious condition like COVID-19, stands as a risk for both mother and the fetus. There is a slightly increased risk of maternal death (0.8-1.8%) in developed countries and high mortality rate of about 14% in developing countries (28).

Perinatal mortality and morbidity also remains high (5.6-11.8%) and is related to preterm delivery, prematurity, placental abruption and severe fetal growth restriction and intrauterine fetal demise (28).

III. Conclusion

With the ongoing pandemic and the greater risk of pregnant women becoming susceptible to various infections, an understanding of potential neurological manifestations in COVID-19 cases is crucial, so as to provide optimum care for patients and also to reduce the disease burden on the medical facility.

Both, pulmonary and extra-pulmonary manifestations can be seen with COVID-19 infection. Multi-organ involvement of the disease is reported and cited extensively in the literature, but only limited data is present regarding obstetric population.

It is not yet known if COVID-19 increases the severity of diseases in pregnancy,resulting in increased disease burden. Earlier reports and lesson from the previous pandemic infections suggest pregnancy makes women susceptible and the pregnant female may have a severe clinical course.

Some neurological symptoms like loss of taste and smell are more likely to be specific for COVID-19, but physicians must bear in mind that other symptomatology may also overlap with diseases specific in pregnancy. Hence, any patient in the obstetric population complaining of headache, cerebrovascular accidents and seizures must prompt investigations to rule out preeclampsia.

An immediate multidisciplinary approach is important to minimize the mortality and morbidity of pregnant patients with convulsion and other neurological emergencies.

It is also important to be vigilant about the spread of the disease in the community.

Team –based care is recommended for pregnancies to be managed in a health care facility to provide optimal care.

Hence, a pragmatic and an integrated multidisciplinary frame work is needed to provide surveillance for early detection of worsening maternal course of illness and also to prevent complications like preterm labour, preterm delivery, low birth weight foetuses, still birth and fetal demise.

Author's Information:
Author's Contribution:
Mutarba Altaf Khan – was involved in reviewing the case and do a literature search on similar cases. Also was involved in writing the manuscript after reviewing publications and data.
Jaanam Altaf Khan – The patient upon arrival was assessed, evaluated and a detailed history and physical examination was performed by Jaanam Khan. She is also the one who first initiated in drafting the manuscript.

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