INTRODUCTION

In September 2020, the World Health Organization (WHO) warned that pregnant women have an increased risk of developing severe coronavirus disease 2019 (COVID-19), especially older, overweight women or those with preexisting medical conditions, such as hypertension and diabetes. The overall rate of a COVID-19 diagnosis in pregnant and recently pregnant women who have been tested is 10% (7%–12%). However, population data analyses on pregnant women have reported a 1.03% prevalence of COVID-19 in England and 2.2% in the USA. Most pregnant women with COVID-19 present with no symptoms or mild respiratory complaints, possibly because pregnant women are younger and healthier than non-pregnant women. However, severe COVID-19 has been associated with pregnancy, especially among women with certain neurologic complaints, such as fatigue, myalgia, and headache. The severity of COVID-19 is also associated with preeclampsia, and this obstetric complication...
is much more frequently associated with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection.7

Neurologic symptoms, such as fatigue and headache, are among the most common presenting symptoms of COVID-19.8–11 Moreover, anosmia and ageusia are the most specific neurologic manifestations for diagnosing COVID-19, although they present a low sensitivity.12 Besides being prevalent and affecting almost half the patients with COVID-19,13 neurologic complaints may be a warning sign of several neurologic complications.

Although relatively rare in previously reported coronaviruses, there have been frequent reports of both central and peripheral nervous system involvement among patients with COVID-19.14,15 Encephalopathy, Guillain–Barré syndrome (GBS), and stroke are the most common neurologic conditions reported in association with COVID-19.8,11,15 Delirium, as a presenting feature of encephalopathy, and stroke have been associated with severe COVID-19.15,16,17

During pregnancy, the innate and adaptive immune responses shift from an inflammatory phenotype to an anti-inflammatory phenotype.18 Moreover, physiological and immunomodulatory changes during pregnancy may exacerbate the presentation of COVID-19,2 and the neuroinvasive propensity of coronaviruses may be magnified by the physiologic susceptibility of pregnancy.19 However, we found no specific reviews regarding neurologic complications in pregnant women with COVID-19.

In this scoping review, we consider which neurologic complications of COVID-19 have been reported during pregnancy and postpartum and have summarized the evidence to date for complicated COVID-19 in women during the peripartum period. We have also examined the reported putative mechanisms of COVID-19-associated neurologic disease in this subgroup of patients.

2 | METHODS

A search was undertaken of PubMed/MEDLINE, Cochrane Library, LILACS, and SciELO databases for articles on COVID-19 from inception to November 25, 2021, with no language restrictions, using the terms “COVID-19,” “novel coronavirus,” “SARS-CoV-2,” or “coronavirus” and “pregnancy,” “pregnant women,” or “postpartum period” in combination with “neurological,” “nervous system,” “encephalitis,” “encephalopathy,” “seizure,” “ataxia,” “myelopaty,” “Guillain–Barré syndrome,” “myopathy,” “rhabdomyolysis,” “peripheral neuropathy,” “neuritis,” “cerebrovascular,” “stroke,” “cerebral venous sinus thrombosis,” “neuromuscular,” or “brain.”

The references of the selected studies were also reviewed for additional articles. Publications with a precise neurologic diagnosis were included, especially those with extensively investigated neurologic manifestations, and ranged from case reports to cases included in case series, with a confirmed diagnosis of COVID-19 based on either a real-time polymerase chain reaction (RT-PCR) or SARS-CoV-2 antibodies. Publications were excluded with strictly psychiatric presentations with no evidence of neurologic disease or cases with isolated neurologic symptoms or neurologic disease not directly associated with COVID-19.

From the selected case reports, we registered the following: the month of publication; the clinical presentation data (maternal and gestational age, previous gestational history and complications in the current gestation, initial respiratory or neurologic symptoms, and neurologic examination); the detection method of SARS-CoV-2, plus blood tests and radiology findings; the neurologic investigations (brain or spinal cord images, angiographic studies, cerebrospinal fluid analysis, electroencephalogram, nerve conduction study, and needle electromyography); COVID-19, obstetric and neurologic management; findings on disease progression during follow-up; COVID-19, obstetric, fetal and maternal neurologic outcomes; and diagnosis of the neurologic condition.

3 | RESULTS

A total of 80 articles were found, and 14 publications were selected, to which we added three published reports found in the references of these selected articles. Finally, we reviewed 18 case reports from the selected 17 papers (Tables 1 and 2).19–35

Nine women (50%) presented with central nervous system (CNS) involvement. There were no cases with both CNS and peripheral nervous system (PNS) involvement at the same time. The overall maternal age ranged from 19 to 40 years for the 18 women, with a median age of 32.5 (25–35) years. The gestational age ranged from 12 to 40 weeks in 16 of the reported cases, with a median age of 34 (30–36.5) weeks. Seven out of 18 women (38.9%) presented at least one previous medical condition.

Thirteen out of 17 women (76.5%) reported some respiratory symptom. All cases with reported data presented abnormalities in the blood tests (n = 15) and chest images (n = 10); these findings were associated with COVID-19 in all cases. The median maternal age, median gestational age, and previous medical condition or respiratory symptoms were similar to patients with CNS and PNS involvement. In addition, we were unable to find the COVID-19 vaccination status for any of the reported cases.

Thirteen out of 17 women (76.5%) received immunotherapies, including either corticosteroids and intravenous immunoglobulin prescribed for treating the neurologic complication or hydroxychloroquine and convalescent plasma infusion for the treatment of COVID-19. There was no difference when the CNS and PNS involvement subgroups were compared.

Eight out of 18 women presented acute respiratory distress syndrome due to COVID-19, according to the WHO classification of disease severity, and there were six cases (66.7%) with CNS involvement and two patients (22.2%) with PNS involvement (Chi-square test, p = .06). Nine out of 18 women (50%) needed to be admitted to ICU, seven cases (77.8%) with CNS involvement, and two patients (22.2%) with PNS involvement (Chi-square test, p = .018). The odds ratio for this association was 12.25 (95% confidence interval = 1.33–113.06). Eight of these nine women (88.9%) required mechanical ventilation while in ICU, and there was no difference when comparing CNS and PNS involvement.
| Case ID | First author, date of publication, number of cases | Clinical presentation | SARS-CoV-2 diagnostics | Relevant blood tests and radiology findings |
|---------|--------------------------------------------------|-----------------------|------------------------|-----------------------------------------------|
| 01      | Mahajan, 2020 Dec 1 case—India                   | • 34-year-old woman   | • RT-PCR positive      | • Low hemoglobin value                        |
|         |                                                  | • 30 weeks of gestation|                        | • Minimal pleural effusion (image method not reported) |
|         |                                                  | • G5 P1, 3 spontaneous abortions, and 1 stillbirth |                        |                                               |
|         |                                                  | • History of preeclampsia in a previous gestation |                        |                                               |
|         |                                                  | • 18 h of agitation, mental confusion, sleep disturbance, headache, violent behavior with no fever or respiratory symptoms; diagnosis of preeclampsia |                        |                                               |
|         |                                                  | • Similar episode 4 days postpartum with no psychotic phenomenon |                        |                                               |
| 02      | Shankar, 2021 Jun 1 case—India                   | • 34-year-old woman   | • RT-PCR positive      | • Elevated liver enzymes, LDH, interleukin-6, procalcitonin |
|         |                                                  | • 32 weeks of gestation|                        | • Chest radiographic study showed bilateral symmetrical peripheral opacities suggestive of COVID-19 pneumonia |
|         |                                                  | • G1 P1               |                        |                                               |
|         |                                                  | • 3 days of hypertension and headache, presenting with generalized tonic-clonic seizures |                        |                                               |
|         |                                                  | • Disoriented, confused, and irritable; hypoxemia and extreme agitation |                        |                                               |
| 03      | López-Pérez, 2020 Jul 1 case—Spain               | • 24-years-old woman  | • RT-PCR positive      | • Chest radiographic study showed findings suggesting bilateral interstitial pneumonia |
|         |                                                  | • Gestational age not reported |                        | • Increased interleukin-6, CPR, and procalcitonin values |
|         |                                                  | • Obstetric history not reported |                        |                                               |
|         |                                                  | • 3 days of fever, cough, and dyspnea |                        |                                               |
|         |                                                  | • Confusional state after extubation and 2 days later evolved with mild hemiparesis, fluctuating consciousness with increasing somnolence, motor aphasia intercalating with agitation, and respiratory worsening |                        |                                               |
|         |                                                  | • Episodes of hypertension |                        |                                               |
|         |                                                  | • Inattention, apathy, and asymmetric mobilization of the right lower limb after 5 days in the intensive care unit |                        |                                               |
| 04      | Garcia-Rodrigues, 2020 Oct 1 case—Spain          | • 35-year-old woman   | • RT-PCR positive      | • Increased LDH and D-Dimer levels, normal creatinine values |
|         |                                                  | • 40 weeks and 6 days of gestation |                        |                                               |
|         |                                                  | • Obstetric history not reported |                        |                                               |
|         |                                                  | • Hypothyroidism |                        |                                               |
|         |                                                  | • Optimal blood control, no respiratory symptoms |                        |                                               |
|         |                                                  | • Sudden generalized tonic-clonic seizures, high blood pressure after C-section, and sudden bilateral blindness |                        |                                               |
|         |                                                  | • Light and shadows vision, absence of the bilateral blink-to-threat reflex |                        |                                               |
| Neurological investigations                                                                 | Management, progression, and outcome                                                                 | Neurological diagnosis, WHO COVID–19 disease severity |
|-------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|---------------------------------|
| • Brain CT scan was normal                                                                 | • Dinoprostone gel, vaginal delivery                                                                  | • Delirium                      |
| • Brain MRI showed several areas of altered signal intensity in the left temporal lobe, occipital lobes, and basal ganglia | • Magnesium sulfate, mannitol, anti-hypertensives, 3 packed cell volume transfusion                    | • Mild COVID-19                 |
| • Control brain MRI was normal after 8 days                                                | • Restraintment; midazolam and haloperidol                                                             |                                |
| • Brain CT scan was normal                                                                 | • Gradual improvement                                                                                  |                                |
| • Brain CT angiography was normal                                                           | • Neonatal death after 31 days due to extreme prematurity                                              |                                |
| • CSF analysis showed normal cell count, protein, and glucose levels                       | • Discharged after 31 days                                                                             |                                |
| • Electroencephalogram showed marked slowed pattern with occasional triphasic waves, more prominent in the left temporal and no epileptiform activity |                                                                                                                                                      |                                |
| • Brain MRI showed extensive T2 hyperintense lesion with no restricted diffusion bilaterally, but to a greater extent in the right hemisphere, involving the parasagittal parietal and frontal areas; mild leptomeningeal enhancement suggesting slowed intravascular flow | • Emergency C-section due to rapidly respiratory worsening                                             | • Posterior reversible encephalopathy syndrome |
| • Brain CT scan and CT angiography were normal                                             | • Maintenance sedation with propofol, fentanyl, midazolam, and atracurium                             | • Critical COVID–19-ARDS        |
| • Hydroxychloroquine, azithromycin, ceftriaxone, lopinavir/ritonavir, and enoxaparin     | • Intubation and mechanical ventilation, maintenance of sedation with propofol, fentanyl, midazolam, and atracurium |                                |
| • Emergency C-section due to eclampsia suspicion                                          | • Intubation and ventilation for less than 24 h                                                       |                                |
| • Magnesium sulfate                                                                       | • Metiprednisolone                                                                                     |                                |
| • Labetalol; enalapril and amlodipine                                                     | • Intubation and ventilation with intermittent sedation                                               |                                |
| • Visual recovery in 48 h after C-section                                                 | • Tocilizumab; Levetiracetam                                                                          |                                |
| • Date of discharge not reported                                                          | • Labetalol; captopril and amlodipine                                                                  |                                |
| • Suspected posterior reversible leukoencephalopathy                                       | • Magnesium sulfate, mannitol, anti-hypertensives, 3 packed cell volume transfusion                    |                                |
| • Mild COVID-19                                                                           | • Enoxaparin                                                                                          |                                |

(Continues)
| Case ID | First author, date of publication, number of cases | Clinical presentation | SARS-CoV-2 diagnostics | Relevant blood tests and radiology findings |
|---------|---------------------------------------------------|-----------------------|------------------------|---------------------------------------------|
| 05      | Sripadma, 2020 Dec 1 case—India                   | • 25-year-old woman   | • RT-PCR positive      | • Neutrophilic leukocytosis, mildly increased liver enzymes, CPR, and D-dimer levels |
|         |                                                   | • Age of gestation not reported |                        | Chest CT-scan showed bilateral symmetrical ground-glass opacities |
|         |                                                   | • G1 P0                |                        |                                             |
|         |                                                   | • 12 h after delivery, fever and cough |                        |                                             |
|         |                                                   | • 1 day later, headache, hypertension and, subsequently, generalized tonic-clonic seizures and drowsiness |                        |                                             |
| 06      | Gama, 2021 Aug 1 case—Brazil                      | • 34-year-old woman   | • RT-PCR positive      | • Mild anemia, leukopenia, thrombocytopenia, increased D-dimer, CRP, and ESR levels |
|         |                                                   | • 26 weeks of gestation |                        | Chest CT-scan showed bilateral ground-glass opacities |
|         |                                                   | • Obstetric history not reported |                        |                                             |
|         |                                                   | • Persistent headache and respiratory symptoms; acute respiratory failure after 5 days |                        |                                             |
|         |                                                   | • Hyperactive delirium and left-side motor focal seizures with progression to bilateral seizure |                        |                                             |
|         |                                                   | • Left hyperreflexia and left homonymous hemianopsia |                        |                                             |
| 07      | Gunduz, 2021 Mar 1 case—Turkey                     | • 22-year-old woman   | • RT-PCR positive      | • Increased fibrinogen and D-dimer levels, low platelet count |
|         |                                                   | • 35 weeks of gestation |                        | Chest CT-scan showed findings compatible with COVID-19 pneumonia after surgery |
|         |                                                   | • Obstetric history not reported |                        |                                             |
|         |                                                   | • Transient right-side weakness with no respiratory complaints |                        |                                             |
|         |                                                   | • 4 days of progressive throbbing headache, accompanied by nausea and vomiting; 12 h of progressive right-sided weakness after waking up in the morning |                        |                                             |
|         |                                                   | • Mild motor aphasia, muscle strength was 3/5 in the upper and 2/5 in the lower right extremities with extensor response |                        |                                             |
|         |                                                   |                         |                        | Cerebral venous sinus thrombosis |
|         |                                                   |                         |                        | Moderate COVID-19 pneumonia |
|         |                                                   |                         |                        |                                             |

**TABLE 1 (Continued)**
| Neurological investigations                                                                 | Management, progression, and outcome                                                                 | Neurological diagnosis, WHO COVID–19 disease severity                                      |
|--------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|
| Electroencephalogram showed left occipital sharp waves with no signs of electrographic seizures | Spontaneous vaginal delivery at term                                                                    | Atypical posterior reversible encephalopathy syndrome                                     |
| Brain CT scan showed symmetrical parieto-occipital hypodensities suggestive of vasogenic edema with small bilateral hemorrhages | Hydroxychloroquine, oseltamivir, piperacillin-tazobactam, and azithromycin  Intubation and mechanical ventilation for 6 days  Benzodiazepines, labetalol and levetiracetam  Intermittent pneumatic compression device  Progressive improvement, discharged after 12 days  Newborn evolved without complications | Critical COVID–19–ARDS                                                                    |
| Brain CT angiography and venography was normal                                                |                                                                                                         |                                                                                           |
| CSF analysis showed normal cell count and mildly elevated protein                           |                                                                                                         |                                                                                           |
| Brain MRI showed bilateral posterior predominant subcortical T2 hyperintensities with no restricted diffusion suggestive of vasogenic edema with small bilateral hemorrhages | Intubation and mechanical ventilation  Route of delivery not reported  Fetal death after delivery  Oral anticoagulants and oxcarbazepine  Progressive improvement, discharged after 45 days with good clinical recovery | Ischemic stroke  Critical COVID–19 – ARDS                                                  |
| Brain MRI showed signs of an infarct in the right frontoparietal lobes with a cingulate gyrus hematoma | Discharged from the emergency department to follow up at home  Anticoagulation with low molecular weight heparin  Nifedipine and betametasone but labor could not be stopped  Emergency C-section due to signs of increasing intracranial pressure  Headache complaints decreased, and speech became fluent after surgery  Hydroxychloroquine and ceftriaxone  Progressive improvement, no more headaches after 3 days, and muscle strength was 4-5/5 in the right side after 10 days | Cerebral venous sinus thrombosis  Moderate COVID–19 pneumonia                                |
| Brain MRI angiography showed subtle asymmetry in the right middle cerebral artery             |                                                                                                         |                                                                                           |
| Chest CT scan showed bilateral ground-glass opacities                                       |                                                                                                         |                                                                                           |
| Transthoracic echocardiography showed a moderate reduction in left ventricular systolic function suggestive of myocarditis |                                                                                                         |                                                                                           |
| Brain MRI showed signs of an infarct in the left parietal region                              |                                                                                                         |                                                                                           |
| Brain MRI venography showed widespread loss of flow in superior sagittal sinus and right transverse sinus; partial venous thrombosis in the left transverse sinus |                                                                                                         |                                                                                           |
| Discharged from the emergency department to follow up at home  Anticoagulation with low molecular weight heparin  Nifedipine and betametasone but labor could not be stopped  Emergency C-section due to signs of increasing intracranial pressure  Headache complaints decreased, and speech became fluent after surgery  Hydroxychloroquine and ceftriaxone  Progressive improvement, no more headaches after 3 days, and muscle strength was 4-5/5 in the right side after 10 days | Cerebral venous sinus thrombosis  Moderate COVID–19 pneumonia                                |

(Continues)
The most common method of delivery was cesarian section; in 11 out of 17 cases (64.7%), seven were due to fetal distress associated with a worsening maternal respiratory status, three due to obstetrical indications (two cases of suspected preeclampsia, and one twin pregnancy with rupture of membranes), and one due to increased intracranial pressure associated with cerebral venous sinus thrombosis (CVST). There was no difference in the frequency of cesarian section when comparing CNS or PNS involvement.

Only one out of 18 women (5.6%) presented a poor neurologic outcome and remained with disabilities related to a diagnosis of Guillain-Barré syndrome. There were no maternal deaths. Three out of 13 cases (23.1%) presented a poor fetal outcome, one spontaneous abortion at 12 weeks of gestation, and two fetal deaths possibly due to prematurity. No association was observed between the clinical parameters and maternal or newborn outcomes.

### 3.1 Central nervous system involvement

Central nervous system involvement was reported in nine cases\(^{20-28}\) (*Table 1*): delirium\(^{20}\) (*n* = 1); posterior reversible encephalopathy syndrome\(^{21-24}\) (PRES) (*n* = 4); cerebrovascular disease\(^{25,26}\) (CVD) (*n* = 2), one case of arterial involvement and one of venous; acute cerebral demyelinating disease\(^ {27}\) (ADEM) (*n* = 1); and acute necrotizing encephalopathy\(^ {28}\) (ANE) (*n* = 1).

Among the five cases presenting with encephalopathy (delirium and PRES), four patients presented with altered behavior and mental status or impaired consciousness\(^{20,22,24}\); three with headache\(^{20,21,24}\); three with generalized seizures\(^{21,23,24}\), and one patient with bilateral blindness.\(^ {23}\) All these findings indicate diffuse brain injury, and one case also presented with signs of focal brain deficit: hemiparesis and aphasia.\(^ {22}\)

While none of the four cases of PRES had previously been diagnosed with chronic hypertension, they all presented episodes of hypertension.\(^{21-24}\) Notwithstanding, in just one case report of PRES there was reference to a suspicion of preeclampsia, although this woman showed no brain CT scan abnormality.\(^ {23}\) All the other three cases of PRES presented abnormalities in the brain MRI, including two cases of asymmetrical lesions, one with posterior predominance\(^ {21}\) and one with anterior,\(^ {22}\) and there was also one case of symmetrical, posterior lesions with an atypical finding of hemorrhages.\(^ {24}\) One case also demonstrated leptomeningeal enhancement, suggesting a slow blood flow.\(^ {22}\) Only one case repeated the brain MRI, which revealed a complete reversion of the lesions.\(^ {21}\) None of these three cases were diagnosed with preeclampsia. The only woman diagnosed with delirium was also...
diagnosed with preeclampsia and presented a normal brain CT scan. Angiographic studies were undertaken in three cases of PRES, which demonstrated no abnormalities. The CSF analysis on one woman with PRES revealed elevated protein levels with no signs of infection.

Both women with cerebrovascular disease presented with headaches and signs of focal brain lesions, including, in both cases, unilateral motor signs, hemianopsia, or aphasia. The women diagnosed with ischemic stroke also presented focal seizures; the brain image revealed an extensive infarct with a hemorrhagic component and a possible lesion in the related arterial trunk. The brain image of the other case also presented an infarct associated with extensive venous thrombosis, and she went on to develop increased intracranial pressure.

Two women were diagnosed with inflammatory brain diseases: the first patient was diagnosed with ADEM due to tetraparesis, noted after an improvement of the critical status during the fourth week of COVID-19. Images revealed bilateral, asymmetric cerebral lesions suggestive of brain demyelination and no spinal cord lesions, and the CSF analysis ruled out infection with a negative test for SARS-CoV-2. The second patient with ANE, after 1 week of COVID-19, showed bilateral, asymmetric cerebral lesions suggestive of brain inflammation with bleeding and no vascular involvement. A CSF tap was not undertaken in this last case due to the risk of complications. Both women presented good outcomes.

### Neurological investigations

| Neurological investigations                                                                 | Management, progression, and outcome                                                                 | Neurological diagnosis, WHO COVID-19 disease severity       |
|-------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|-----------------------------------------------------------|
| • Brain MRI showed multiple T2 hyperintense lesions with restricted diffusion involving the corpus callosum, bilateral cerebral white matter, right pons, and the bilateral ventral medulla, no hemorrhage; the most extensive lesion in the body of the corpus callosum (3 cm) showed some contrast enhancement. • Spinal cord MRI was unremarkable. • CSF analysis showed an increased level of protein with normal cell count and glucose level, negative oligoclonal bands with RT-PCR negative for SARS-CoV-2. | • Emergency C-section due to rapidly respiratory worsening and fatal distress. • Intubation and ventilation for 16 days. • Hydroxychloroquine, zinc and convalescent plasma therapy. • Intravenous dexamethasone. • Progressive improvement of strength with intact cognition after 50 days. • Newborn outcome not reported. • Date of discharge not reported. | • Acute demyelinating encephalomyelitis. • Critical COVID-19-ARDS. |
| • Brain CT scan showed bilateral thalamic hypodensities. • Brain CT angiography and venography were normal. • Electroencephalogram showed signs of severe encephalopathy. • Brain MRI showed T2-FLAIR hyperintensities in bilateral thalami and caudate nuclei with hemorrhage and restricted diffusion, and hyperintensities in bilateral hippocampi, right parietal deep white matter, and bilateral posterior frontal white matter. | • Aggressive isotonic fluids and bicarbonate infusions; high-dose thiamine. • Intubation and emergent bedside C-section due to fatal distress. • Neonate was intubated and transferred to ICU. • 5-days of methylprednisolone followed by a prednisone taper. • Gradual improvement, discharged after 22 days with complete neurological recovery. • Newborn discharged with healthy condition. | • Acute necrotizing encephalopathy. • Critical COVID-19-ARDS. |

**3.2 Peripheral nervous system involvement**

Peripheral nervous system involvement was reported in nine cases (Table 2): GBS (n = 5), among which, one case also presented vestibular neuritis; Bell’s palsy (n = 3); and rhombodomyelitis (n = 1).

The first symptoms of GBS developed during the first week of COVID-19 in three cases and after the first month in 2 cases. One patient was diagnosed with GBS with no further investigations, while all the other four cases had been investigated. These last cases presented with sensory complaints, including low back pain and distal paraesthesia. Three patients also reported a decreased sensation with no sensory level. All four cases presented motor impairment, including unilateral or bilateral facial paresis; ascending tetraparesis; and areflexia. Two women presented manifestations of dysautonomia, including hypertension, dysphonia, dysphagia, or dyspnea.
TABLE 2  Peripheral nervous system involvement in pregnant women with COVID-19

| Case ID | First author, date of publication, number of cases | Clinical presentation | SARS-CoV-2 diagnostics |
|---------|--------------------------------------------------|-----------------------|------------------------|
| 10      | Algeri, 2020 Jul 2 out of 5 cases—Italy Case #4 | • 30-year-old woman  
• 37 weeks and 3 days of gestation  
• G1 P0  
• Fever, dyspnea, desaturation, and reduced fetal movements  
• Ascending Guillain–Barre syndrome at 1-month follow-up | • RT-PCR positive |
| 11      | Tekin, 2021 Feb 1 case—Turkey                     | • 34-year-old woman  
• 36 weeks and 4 days of gestation  
• “Multiparous”  
• Mild cough at admission  
• Progressive 1-week history of low back pain, ascending weakness, and numbness that started in lower extremities  
• Readmission after 16 days  
• Right-side facial paresis, muscle strength of 1/5 in lower and 4/5 in upper limbs with absent deep tendon reflexes | • RT-PCR positive |
| 12      | Garcia, 2021 May 1 case—Philippines               | • 22-year-old woman  
• 20 weeks of gestation  
• G2 P0, one abortion  
• 1 week of cold and non-productive cough  
• Acroparaesthesia followed by progressive, bilateral lower to upper extremities weakness, dysphonia, and dysphagia  
• Bilateral facial weakness, poor gutturals, hypotonic areflexic quadriparesis, and decreased sensation over the distal arms and legs; proximal muscle strength was 3/5 and distal muscle strength of 1/5  
• Hypertension without other signs of dysautonomia | • RT-PCR positive |
| 13      | Mahajan, 2021 Aug 1 case—India                    | • 31-year-old woman  
• 12 weeks of gestation  
• G2 P0, one abortion  
• Rheumatoid arthritis; history of pulmonary tuberculosis  
• 5 days of fever, dry cough, diarrhea, myalgia, and fatigue  
• 4 days of progressive tingling and prickling sensation followed by weakness in her upper and lower limbs, and eventually developed sensory loss up to thigh and elbows and had difficulty walking independently and standing without support in the next 8 days  
• Bilateral facial weakness, muscle strength of 4/5 in upper and 3/5 in lower limbs, with absent deep tendon reflexes in lower limbs, depressed in upper limbs; there was no demarcated sensory level | • RT-PCR positive |
| Relevant blood tests and radiology findings | Neurological investigations | Management, progress, and outcome | Neurological diagnosis, WHO COVID−19 disease severity |
|--------------------------------------------|----------------------------|-----------------------------------|-----------------------------------------------------|
| Chest CT-scan showed interstitial pneumonia | CSF analysis showed an increased level of protein and no white blood cells with RT-PCR negative for SARS-CoV-2  | C-section due to fetal distress 1 day after admission | Guillain–Barré syndrome |
|                                            | Nerve conduction studies showed decreased amplitude of compound muscle action potentials and no response of sensory action potentials except right sural nerve; F responses could not be recorded | Hydroxychloroquine and azithromycin | Critical COVID-19-ARDS |
|                                            |                             | Discharged after 5 days following a negative RT-PCR test for SARS-CoV-2 | Moderate COVID-19 pneumonia |
|                                            |                             | Intravenous immunoglobulin; enoxaparin, and pregabalin after readmission | |
|                                            |                             | Initial worsening of the motor symptoms with development of shortness of breath and dysphagia | |
|                                            |                             | Gradual improvement, discharged after 12 days of readmission with muscle strength of 3/5 in lower and 5/5 in upper extremities | |
| Chest CT-scan consistent with COVID-19 pneumonia | CSF analysis showed no white blood cells and normal protein level  | Electrolyte correction | Guillain–Barré syndrome |
|                                            | Nerve conduction studies showed signs of a predominantly demyelinating pattern of polyradiculoneuropathy with secondary axonal loss | Intravenous immunoglobulin | Mild COVID-19 |
|                                            |                             | Oral methyl dopa and aspirin | |
|                                            |                             | Progressive improvement, discharged with 25 weeks of gestation with proximal muscle strength of 4/5 and distal muscle strength of 2/5 after 33 days | |
|                                            |                             | Progressive improvement 1-month post-discharge | |
|                                            |                             | Normal progression of pregnancy and assisted-vaginal delivery at 37 weeks of gestation | |
|                                            |                             | Newborn evolved with no reported complications | |
| Low serum potassium level, increased liver enzymes | CSF analysis showed elevated cell count with normal protein and glucose level | Intravenous immunoglobulin | Guillain–Barré syndrome |
|                                            | Nerve conduction studies showed sings of mixed (predominantly demyelinating) sensorimotor polyradiculoneuropathy involving the four limbs | Antibiotics, heparin, steroid, and hydroxychloroquine | Moderate COVID-19 pneumonia |
|                                            | Brain and spinal cord MRI were normal | Spontaneous abortion within the 13th week of gestation | |
|                                            | Biopsy of the superficial peroneal nerve did not show active vasculitis | Progressive improvement, discharge against medical advice with mild distal sensory loss and weakness, she was able to walk independently after 25 days | |
| Case ID | First author, date of publication, number of cases | Clinical presentation | SARS-CoV-2 diagnostics |
|---------|--------------------------------------------------|-----------------------|------------------------|
| 14      | Aasfara, 2021 Jan 1 case—Morocco                | 36-year-old woman     | RT-PCR negative        |
|         |                                                  | 37 weeks of gestation  | Antibodies positive    |
|         |                                                  | Obstetric history not reported |                   |
|         |                                                  | SARS-CoV-2 test positive 6 weeks before admission |                   |
|         |                                                  | 1-day onset of sudden vertigo, nausea, and vomiting, left-sided facial weakness, and fullness of the right ear with tinnitus |                   |
|         |                                                  | Reduced tendon reflexes in lower limbs with preserved strength, spontaneous horizontal and rotatory left-beating nystagmus, and left peripheral facial palsy |                   |
|         |                                                  | Right peripheral facial weakness and asymmetric distal numbness in the lower limbs and left fingers |                   |
| 15      | Algeri, 2020 Jul 2 out of 5 cases—Italy Case #5 | 40-year-old woman     | Antibodies positive    |
|         |                                                  | 35 weeks and 6 days of gestation |                   |
|         |                                                  | G3 P0                 |                       |
|         |                                                  | Dichorionic-diamniotic twin pregnancy admitted for rupture of membranes |                   |
|         |                                                  | Bell’s palsy 1 week before |                   |
|         |                                                  | Chest pain, desaturation, and Bradycardia with no fever |                   |
| 16      | Figueiredo, 2020 Aug 1 case—Portugal            | 35-year-old woman     | RT-PCR positive        |
|         |                                                  | 39 weeks and 6 days of gestation |                   |
|         |                                                  | G1 P0                 |                       |
|         |                                                  | Optimal blood control |                       |
|         |                                                  | 2-days of progressive left-side peripheral facial palsy |                   |
|         |                                                  | No respiratory symptoms |                     |
| 17      | Kumar, 2021 Mar 1 case—India                    | 28-year-old woman     | RT-PCR positive        |
|         |                                                  | 36-weeks of gestation  |                       |
|         |                                                  | G1 P0                 |                       |
|         |                                                  | Polycystic ovarian disease |                 |
|         |                                                  | 3-days of anosmia with dysgeusia and 1-day of fever |                   |
|         |                                                  | High blood pressure after admission |               |
|         |                                                  | Sudden-onset of generalized weakness on the day after surgery and right-side peripheral facial palsy |                   |
|         |                                                  | Steroid-induced diabetes |                     |
| Case ID | First author, date of publication, number of cases | Clinical presentation | Neurological investigations | Management, progress, and outcome | Neurological diagnosis, WHO COVID-19 disease severity |
|---------|--------------------------------------------------|-----------------------|-----------------------------|----------------------------------|--------------------------------------------------|
| 14 Aasfara, 2021 Jan | 1 case— Morocco | • 36- year- old woman • 37 weeks of gestation • Obstetric history not reported • SARS-CoV-2 test positive 6 weeks before admission • 1- day onset of sudden vertigo, nausea, and vomiting, left-sided facial weakness, and fullness of the right ear with tinnitus • Reduced tendon reflexes in lower limbs with preserved strength, spontaneous horizontal and rotatory left-beating nystagmus, and left peripheral facial palsy • Right peripheral facial weakness and asymmetric distal numbness in the lower limbs and left fingers | • “Diagnostic workup” negative • Negative IgM and positive IgG antibodies | • Intravenous immunoglobulin associated with intravenous steroids • Complete recovery of the right facial palsy and the sensorineural hearing loss, but persistent tingling in the lower limbs and left facial palsy 2 weeks later • Normal pregnancy progression and spontaneous vaginal delivery at 40 weeks of gestation • Newborn evolved without complications • Date of discharge not reported | • Bifacial palsy variant of Guillain–Barré syndrome • Acute vestibular neuritis • Mild COVID-19 |
| 15 Algeri, 2020 Jul | 2 out of 5 cases— Italy | • 40- year- old woman • 35 weeks and 6 days of gestation • G3 P0 • Dichorionic-diamniotic twin pregnancy admitted for rupture of membranes • Bell’s palsy 1 week before • Chest pain, desaturation, and bradycardia with no fever | • Antibodies positive • Low platelet count, elevated liver enzymes, and increased creatine level • Negative IgM and positive IgG antibodies at 2-months follow-up • Chest CT-scan showing a 30% interstitial pneumonia • Progressive prolongation in QT interval | • Oral deltacortene • C-section • Antibiotic therapy; enoxaparin; and cortisone • Progressive improvement, discharged after 9 days • Twin newborns evolved without complications | • Bell’s palsy • Moderate COVID-19 pneumonia |
| 16 Figueiredo, 2020 Aug | 1 case— Portugal | • 35-year-old woman • 39 weeks and 6 days of gestation • G1 P0 • Optimal blood control • 2-days of progressive left-side peripheral facial palsy • No respiratory symptoms | • RT-PCR positive • Mild leucocytosis, with relative lymphopenia and relative neutrophilia; increased CRP level | • Oral prednisolone • Physiotherapy • Normal labor progression and vaginal delivery • Slightly improvement after 15 days • Newborn evolved without complications • Date of discharge not reported | • Left-side Bell’s palsy • Mild COVID-19 |
| 17 Kumar, 2021 Mar | 1 case— India | • 28-year-old woman • 36-weeks of gestation • G1 P0 • Polycystic ovarian disease • 3-days of anosmia with dysgeusia and 1-day of fever • High blood pressure after admission • Sudden-onset of generalized weakness on the day after surgery and right-side peripheral facial palsy • Steroid-induced diabetes | • RT-PCR positive • Mild drop in hemoglobin level and leucocytosis after surgery | • Emergency C-section due to high blood pressure • Oral valacyclovir and prednisolone • Physiotherapy • Subcutaneous insulin • Significant improvement, discharged after 10 days • Newborn evolved without complications • No residual neurological deficits 2 weeks post-discharge | • Right-side Bell’s palsy • Mild COVID-19 |

(Continues)
Two cases had undergone brain and spinal cord imaging exams, which proved to be unremarkable.32,33 All four patients underwent complementary investigations: the CSF analysis demonstrated no cells30,31 normal33 or increased32 cell counts, along with elevated30,33 or normal31,32 protein levels; the CSF of two cases was tested for SARS-CoV-2 with a negative result30,33; nerve conduction studies demonstrated signs of generalized polyradiculoneuropathy30–32 or mononeuropathies33 with predominantly demyelinating pattern31–33 and axonal loss.30–32 A nerve biopsy was performed, which, in one case, ruled out vasculitis.32

One case with GBS also presented unilateral findings of hearing loss and vestibular impairment, including fullness of the ear, tinnitus, vertigo, and nystagmus, which was confirmed by otoneurologic tests and videonystagmography.33

Bell’s palsy was diagnosed in three patients with no further investigations being conducted.19,29,34 Anosmia and dysgeusia were reported by one woman, along with fever and generalized weakness.34

Just one case was diagnosed with rhabdomyolysis based on laboratory findings after a long, complicated period in ICU. However, no further investigations were carried out to rule out neuropathy or myopathy.35

4 | DISCUSSION

In this scoping review, we found few case reports of neurologic complications of COVID-19 in women during pregnancy or the postpartum period, considering that until June 2020 there were more than ten thousand patients reported with neurologic involvement in the general population with COVID-19.15

Neurologic signs and symptoms are more prevalent than specific neurologic conditions in the general population with COVID-19 (86.3% and 13.7%, respectively), and these complications are more common in the inpatient setting.15 Moreover, neurologic conditions are more frequent in patients aged over 60 years and in those with severe COVID-19.11,36 Notwithstanding, it would be expected that pregnant women in their second to fifth decade of life would not commonly be affected by neurologic complications of COVID-19, mainly because most of them are either asymptomatic or they present with mild respiratory symptoms,5 and also because they are younger and have fewer comorbidities than non-pregnant women.6

Although pregnant women have a higher risk for mechanical ventilation and the need for ICU than non-pregnant women, outcomes and mortality of COVID-19 appear to be no different in pregnant women.6,37 However, the risk of surgical delivery and preterm birth was higher among pregnant women with COVID-19 compared with the general pregnant population.37 In our review, CNS involvement was associated with ICU admission, but overall, outcomes were good, and the method of delivery was chosen due to the neurologic complication in just one patient. We found no research regarding neurologic complications and pregnancy outcomes in COVID-19 patients.

Overall, almost 15% of patients with COVID-19 and neurologic symptoms presented some specific entities of nosology or clinical conditions affecting the nervous system, with encephalopathy and stroke being the most common conditions in CNS involvement and
Guillain–Barré syndrome in PNS involvement. These were also the most common conditions in the cases summarized in our review.

Encephalopathy may be the predominant disorder in the initial presentation of COVID-19. Many patients had no brain imaging findings or presented with PRES or features of hemorrhagic necrotizing encephalopathy. One of the reported cases of pregnant women with COVID-19 presented with delirium with no evident brain injury. There were also four cases of PRES, and only one of these women presented no abnormalities in the brain image.

The cause of delirium is usually multifactorial, including a stress response to infection or physical and psychiatric modifications linked to pregnancy and puerperium. However, it has become a rare disorder because of current perinatal care. Moreover, delirium may be the presenting feature of PRES, a condition that disrupts autoregulatory brain vascular mechanisms due to the direct or indirect effects of SARS-CoV-2 over the brain endothelium.

Posterior reversible encephalopathy syndrome is usually linked to preeclampsia, which is approximately twice as frequent in COVID-19 pregnant women, even those who have no respiratory symptoms. Interestingly, only one of the four reported cases of PRES presented suspected preeclampsia, although all of them presented episodes of hypertension. The women with delirium were also diagnosed with preeclampsia.

Acute cerebral demyelinating disease is a rare, immune-mediated syndrome of multifocal demyelination of the CNS that typically occurs weeks after a viral infection in children and presents with acute encephalopathy and multiple focal neurologic signs and symptoms. It has been described in association with other coronaviruses. Until May 2021, 46 cases had been reported in association with COVID-19, most of them with symptomatic respiratory illness with severe features, developing ADEM after 15–30 days. The majority of these cases presented with encephalopathy, focal neurologic signs, seizures, normal or mildly inflammatory CSF analysis, and multiple cerebral and spinal cord lesions. Interestingly, one-third presented findings of the severe variant of acute hemorrhagic leukoencephalitis. The pregnant women were diagnosed with ADEM due to tetraparesis, observed after 21 days of severe respiratory COVID-19, and the patient with ANE was diagnosed soon after the respiratory symptoms. The other three cases of ANE related to COVID-19 also presented with early neurologic symptoms after the viral infection, and recent reports of ANE have also demonstrated good outcomes.

Until November 2020, there were 760 stroke cases among patients with COVID-19, of which most were ischemic strokes. In this study, the estimated prevalence was 1.11% (1.03%–1.22%) for ischemic stroke and 0.46% (0.40%–0.53%) for hemorrhagic stroke. Commonly, older men with hypertension, hyperlipidemia, and diabetes mellitus were affected with stroke as a complication of COVID-19, and their mean National Institutes of Health Stroke Scales (NIHSS) scores were high. At least two-thirds presented respiratory symptoms, and their common stroke indicators were unilateral motor deficits (67%), altered consciousness (66%), and headache (11%). Admission to ICU, ventilatory assistance, and mortality rates were higher for COVID-19 patients who suffered any type of stroke. The outcomes were better for young patients in the fifth decade of life and poor in severe COVID-19 cases. Although the only pregnant woman with an ischemic stroke presented a severe form of COVID-19, her outcome was good possibly because she was...
young and had no previous medical conditions.25 Interestingly, half of the patients with intracranial hemorrhage were on anticoagulation medication as part of the treatment for COVID-19,42 similar to the report of pregnant women.

The other pregnant women with a cerebral venous infarct presented no hemorrhagic complications.26 Until December 2020, 57 cases of CVST were reported in patients with COVID-19, and the estimated prevalence was 0.08% (0.01%–0.50%).43 One-third of these cases had a common risk factor for CVT besides SARS-CoV-2 infection, and none had preexisting thrombophilia or a history of previous events of venous thromboembolism. Most presented with respiratory symptoms, encephalopathy, focal deficits, or epileptic seizures. Multiple venous vessel involvement and hemorrhagic lesions are common, and mortality is high. The pregnant woman with CVST was diagnosed with thrombophilia after the stroke and had a good outcome.26 With this patient, there was also a risk of thrombotic events related to a transient prothrombotic state, which occurs during pregnancy and puerperium.

Guillain–Barré syndrome is an acute polyradiculoneuropathy characterized by rapidly progressive, asymmetrical limb weakness, areflexia on examination, sensory symptoms, and, in some patients, facial weakness, although there are several variants.38 Until February 2021, 109 patients were identified with GBS in association with COVID-19.44 These patients were mostly males in the sixth decade of life, who commonly presented with fever and respiratory symptoms, and developed neurologic complications 2 weeks after being diagnosed with COVID-19. These patients most frequently presented tetraparesis or paraparesis with areflexia; facial palsy; sensory symptoms; elevated protein levels with a normal cell count in the CSF analysis; and a demyelinating sensorimotor pattern in the nerve conduction studies. In some cases, image studies revealed contrast cranial nerve or spinal nerve root enhancement and anti-ganglioside antibody positivity. Three of the pregnant women with GBS developed early neurologic symptoms,30–32 and all investigated cases presented typical features of GBS.30–33

Until January 2021, there were 56 patients reported with COVID-19 and cranial nerve involvement, of which two-thirds were isolated cranial neuropathies.45 Except for trochlear and accessory nerves, all other cranial neuropathies were described in patients with COVID-19, most with unilateral involvement of the facial nerve, oculomotor nerves (III and VI), or the optic nerve.45 The three cases of cranial nerve involvement in pregnant women were classified as Bell’s palsy and were all unilateral.19,29,34 The only case of vestibular neuropathy was associated with GBS.33 Cranial neuropathies in patients with COVID-19 were often associated with GBS,44,45 and bilateral cranial nerve involvement in COVID-19 was also commonly associated with GBS.45

Muscle injury due to COVID-19 may manifest as an asymptomatic elevation of creatine kinase to severe rhabdomyolysis. This is possibly due to myositis, which can cause myoglobinuria and acute kidney disease. Patients may present with generalized weakness. There are a few individual case reports of rhabdomyolysis associated with COVID-19,46 including one case in a critically ill patient similar to the pregnant women reported.35 In both cases, ICU complications, such as other infections, drug interactions, hypoxemia, and extremes of body temperature, should also be implicated in the muscle injury beyond the SARS-CoV-2 infection.35,46

Before COVID-19, there were several epidemic outbreaks of other respiratory viruses, most notably related to the SARS-CoV in 2002, the influenza virus A (H1N1) in 2009, and the Middle East respiratory syndrome (MERS)-CoV in 2012.47,48 Respiratory viruses are common worldwide and present from mild-to-severe disease, including systemic manifestations and neurologic complications.49 High rates of hospitalization and the need for ICU, a severe clinical course, poor obstetric outcomes, and death have been associated with infections due to the influenza virus and coronavirus in pregnant women.47,48

Several other respiratory viruses are neurotropic and neuroinvasive, especially in vulnerable populations. These viruses may directly damage the cells in the nervous system or induce autoimmune responses, as with other well-recognized neuroinvasive viruses (mainly herpesvirus, arbovirus, and enterovirus).50 Infection with the influenza virus may cause encephalopathy, encephalitis, and GBS and tend to affect children more often.48 We found no cases of neurologic complications in pregnant women with influenza. Although the MERS-CoV was the leading cause of severe cases in pregnant women before COVID-19,47 we only found one published article reporting a 32-year-old woman in the 26th week of gestation with SARS-CoV-2 evolving with generalized seizures possibly associated with CNS involvement.50

4.1 | Mechanisms

Pathophysiologically, it is possible that SARS-CoV-2 directly infects the brain through nasal epithelial cells or brain endothelium, given the prevalence of ACE2 expression in both locations.36 Moreover, neurologic complications of COVID-19 may also be due to the secondary effects of infection, including hypoxia, drugs, toxins, metabolic derangements,39 or hyperimmune responses, often referred to as “cytokine storm.”36

The detection rate of SARS-CoV-2 RNA and proteins in brain specimens is not related to neurologic symptoms, and inflammatory infiltrates are more frequently associated with neurologic impairment.51 Therefore, immune responses may be an essential pathophysiological factor for brain injury, causing encephalopathies and encephalitis in COVID-19 patients, especially those who become severely ill. It is thought that the proinflammatory state induced by the cytokine storm may be responsible for glial cell activation and the subsequent demyelination.27

Risk factors for CVD, such as age, hypertension, and obesity, among others, are also the most frequent comorbidities among COVID-19 patients with neurologic manifestations. Additionally, the viral infection of the endothelial cells leading to inflammation and a disruption of vascular homeostasis and coagulation or endotheliopathy associated with severe COVID-19, with no evidence
of endothelial infection, have been reported as potential causes of CVD.\textsuperscript{36}

SARS-CoV-2 has a high affinity for ACE2 receptors expressed by endothelial cells and arterial smooth muscle cells throughout the body, including the brain.\textsuperscript{25,36} Inflammation, platelet activation, endothelial dysfunction, and blood flow stasis associated with COVID-19 predispose patients to thrombotic events, mainly associated with the transient prothrombotic state of pregnancy and puerperal period.\textsuperscript{26}

The binding of SARS-CoV-2 to ACE2 also impairs the conversion of angiotensin II, which has vasoconstrictive and proinflammatory effects. It is possible that this is the way in which COVID-19 increases the risk of vasomotor dysfunction related to preeclampsia,\textsuperscript{7} as well as other vascular complications.

4.2 | Limitations

In the few case reports summarized in this scoping review, none of them used standard guidelines to report scientific data, such as CARE guidelines. Thus, essential information may be lacking. Furthermore, it seems evident that neurologic complications were underestimated during the COVID-19 pandemic among pregnant women. Therefore, a significant proportion of young and previously healthy pregnant women may have progressed with non-severe COVID-19, leading to mild neurological manifestations and complications. In addition, the overlapping of preeclampsia and eclampsia features could have contributed to low identification rates of specific neurologic conditions.

5 | CONCLUSION

It was only possible to find 18 case reports of pregnant women with both COVID-19 and a neurologic complication published until November 2021 and was possibly underestimated. The central nervous system and the peripheral nervous system were equally affected, but acute respiratory distress syndrome due to COVID-19 and ICU admission were more frequent among women with central nervous system conditions. Only one case presented a poor neurologic outcome.

CONFLICT OF INTEREST

The authors report no conflict of interest.

AUTHOR CONTRIBUTION

JEM and PASRF contributed to conception and study design; acquisition and analysis of data; and drafting of the manuscript and tables.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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