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Pregnancy and neurologic complications of COVID-19: A scoping review

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While neurologic complications are frequently reported among patients with COVID-19 in the general population, they are unknown in pregnant women. This paper summarizes the case reports of pregnant women with confirmed SARS-CoV-2 infection plus a specified neurologic diagnosis. Until November 2021, 18 case reports were found. Both the central and peripheral nervous systems were equally affected: delirium (n = 1), posterior reversible encephalopathy syndrome (n = 4), cerebrovascular disease (n = 2), acute cerebral demyelinating disease (n = 1), acute necrotizing encephalopathy (n = 1), Guillain-Barré syndrome (n = 5), including one patient who also had vestibular neuritis, Bell's palsy (n = 3), and rhabdomyolysis (n = 1). The median maternal age was 32.5(25-35) years, the median gestational age was 34(30-36.5)weeks, and 38.9% presented previous medical conditions. Respiratory symptoms were reported in 76.5%, and 76.5% received immunotherapies to treat the COVID-19 or the neurologic complications. Half the women required admission to ICU and, more often, were those with central nervous system involvement (77.8% vs. 22.2%; Chisquare test, p = .018). For 64.7% of women, the most common method of delivery was surgical, although just one case was due to the neurologic complication. There were reports of one spontaneous abortion, two fetal deaths, and no maternal deaths. Only one case presented a poor neurologic outcome. It is possible that our findings are underestimated, considering that there are thousands of reports regarding neurologic complications in the general population with COVID-19.

KEYWORDS

COVID-19, neurologic complications, pregnancy, puerperium, women

| INTRODUCTION 1

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.¹ The overall rate of a COVID-19 diagnosis in pregnant and recently pregnant women who have been tested is 10% (7%-12%).² However, population data analyses on pregnant women have reported a 1.03% prevalence of COVID-19 in England³ and 2.2% in the USA.⁴

Most pregnant women with COVID-19 present with no symptoms or mild respiratory complaints,⁵ possibly because pregnant women are younger and healthier than non-pregnant women.⁶ However, severe COVID-19 has been associated with pregnancy,⁶ especially among women with certain neurologic complaints, such as fatigue, myalgia, and headache.⁵ The severity of COVID-19 is also associated with preeclampsia,⁵ and this obstetric complication

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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.^{11,16,17}

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," "myelopathy," "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.

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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 hydroxy-chloroquine 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.

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TABLE 1 Central 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	Relevant blood tests and radiology findings
01	Mahajan, 2020 Dec 1 case—India	 34-year-old woman 30 weeks of gestation 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 	RT-PCR positive	 Low hemoglobin value Minimal pleural effusion (image method not reported)
02	Shankar, 2021 Jun 1 case—India	 34-year-old woman 32 weeks of gestation G1 P1 3 days of hypertension and headache, presenting with generalized tonic-clonic seizures Disoriented, confused, and irritable; hypoxemia and extreme agitation 	RT-PCR positive	 Elevated liver enzymes, LDH, interleukin-6, procalcitonin Chest radiographic study showed bilateral symmetrical peripheral opacities suggestive of COVID-19 pneumonia
03	López-Pérez, 2020 Jul 1 case—Spain	 24-years-old woman Gestational age not reported 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 	RT-PCR positive	 Chest radiographic study showed findings suggesting bilateral interstitial pneumonia Increased interleukin-6, CPR, and procalcitonin values
04	Garcia-Rodrigues, 2020 Oct 1 case—Spain	 35-year-old woman 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 	RT-PCR positive	 Increased LDH and D-Dimer levels, normal creatinine values

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Neurological investigations	Management, progression, and outcome	Neurological diagnosis, WHO COVID–19 disease severity
Brain CT scan was normal	 Dinoprostone gel, vaginal delivery Magnesium sulfate, mannitol, anti-hypertensives 3 packed cell volume transfusion Restrainment; midazolam and haloperidol Gradual improvement Neonatal death after 31 days due to extreme prematurity Discharged after 31 days 	DeliriumMild COVID-19
 Brain MRI showed several areas of altered signal intensity in the left temporal lobe, occipital lobes, and basal ganglia Control brain MRI was normal after 8 days 	 Magnesium sulfate Intravenous midazolam and labetalol Intubation and mechanical ventilation, maintenance of sedation with propofol, fentanyl, midazolam, and atracurium C-section Intravenous convalescent plasma, methylprednisolone, antibiotics, and low molecular weight heparin Extubation after 4 days Oral antihypertensives Progressive improvement, discharged after 14 days Newborn intubated during 5 days, discharged after 14 days 	 Posterior reversible encephalopathy syndrome Critical COVID-19-ARDS
 Brain CT scan was normal Brain CT angiography was normal CSF analysis showed normal cell count, protein, and glucose levels 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 	 Hydroxychloroquine, azithromycin, ceftriaxone, lopinavir/ritonavir, and enoxaparin Emergency C-section due to rapidly respiratory worsening Maintenance sedation with propofol and remifentanil Intubation and ventilation for less than 24 h Metiprednisolone Reintubation and ventilation with intermittent sedation Tocilizumab; Levetiracetam Labetalol; enalapril and amlodipine Progressive improvement, discharged after 18 days Newborn outcome not reported Readmission after 2 days due to obnubilation, no follow up reported 	 Posterior reversible encephalopathy syndrome Critical COVID-19-ARDS
• Brain CT scan and CT angiography were normal	 Emergency C-section due to eclampsia suspicion Magnesium sulfate Labetalol, captopril and amlodipine Enoxaparin Visual recovery in 48 h after C-section Neonate history not reported Date of discharge not reported 	 Suspected posterior reversible leukoencephalopathy Mild COVID-19

mutation was found

¹⁰ WILEY Neurologica TABLE 1 (Continued)

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 Age of gestation not reported G1 P0 12 h after delivery, fever and cough 1 day later, headache, hypertension and, subsequently, generalized tonic-clonic seizures and drowsiness 	• RT-PCR positive	 Neutrophilic leukocytosis, mildly increased liver enzymes, CPR, and D-dimer levels Chest CT-scan showed bilateral symmetrical ground- glass opacities
06	Gama, 2021 Aug 1 case—Brazil	 34-year-old woman 26 weeks of gestation 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 	• RT-PCR positive	 Mild anemia, leukopenia, thrombocytopenia, increased D-dimer, CRP, and ESR levels Chest CT-scan showed bilateral ground-glass opacities Transthoracic echocardiography showed a moderate reduction in left ventricular systolic function suggestive of myocarditis
07	Gunduz, 2021 Mar 1 case—Turkey	 22-year-old woman 35 weeks of gestation 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 	RT-PCR positive	 Increased fibrinogen and D-dimer levels, low platelet count Chest CT-scan showed findings compatible with COVID-19 pneumonia after surgery Antinuclear antibodies were positive, and prothrombin heterozygous

Neurological investigations

- Electroencephalogram showed left occipital sharp waves with no signs of electrographic seizures
- Brain CT scan showed symmetrical parieto-occipital hypodensities suggestive of vasogenic edema with small bilateral hemorrhages
- 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
- Brain MRI showed signs of an infarct in the right frontoparietal lobes with a cingulate gyrus hematoma
- Brain MRI angiography showed subtle asymmetry in the right middle cerebral artery

- Management, progression, and outcome
- Spontaneous vaginal delivery at term
- Hydroxychloroquine, oseltamivir, piperacillintazobactam, 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

Neurological diagnosis, WHO COVID-19 disease severity

- Atypical posterior reversible encephalopathy syndrome
- Critical COVID-19-ARDS

- 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 a cortical 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

TABLE 1 (Continued)

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Case ID	First author, date of publication, number of cases	Clinical presentation	SARS-CoV-2 diagnostics	Relevant blood tests and radiology findings
08	McCuddy, 2020 Sep 1 out of 3 cases— United States of America Case #1	 37-year-old woman 30 weeks of gestation Obstetric history not reported Hypertension, type II diabetes, and obesity Progressive cough, chest pain, fever, and shortness of breath evolving to acute respiratory failure After 22 days, diffuse weakness perceived post-extubation Plegic in the legs bilaterally, significant, symmetric weakness in the arms, brisk deep tendon reflexes, no clonus or Babinski's sign; preserved mental status and sensation 	RT-PCR positive	_
09	Breit, 2021 Jul 1 case—United States of America	 19-year-old woman 33 weeks of gestation G2 P1 Obesity, previous gestational hypertension 1 week of chest pain, tachypnea, dyspnea, and reduced appetite with nausea and vomiting 1 day of mental confusion Tachycardia and tachypnea with increased work of breathing evolving with respiratory distress Awake, global aphasia, right homonymous hemianopsia, left gaze preference, and reduced movement on the right upper extremity 	RT-PCR positive	 Low hemoglobin, hematocrit, and albumin levels; increased LDH and D-dimer levels; metabolic acidosis, and increased protein and ketones levels in the urine tests



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 obstetric 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 cases²⁰⁻²⁸ (Table 1): delirium²⁰ (n = 1); posterior reversible encephalopathy syndrome²¹⁻²⁴ (PRES) (n = 4); cerebrovascular disease^{25,26} (CVD) (n = 2), one case of arterial involvement and one of venous; acute cerebral

demyelinating disease²⁷ (ADEM) (n = 1); and acute necrotizing encephalopathy²⁸ (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 predominance²¹ 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

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 fetal 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 fetal 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

diagnosed with preeclampsia and presented a normal brain CT scan.²⁰ Angiographic studies were undertaken in three cases of PRES, which demonstrated no abnormalities.²²⁻²⁴ The CSF analysis on one woman with PRES revealed elevated protein levels with no signs of infection.²⁴

Both women with cerebrovascular disease presented with headaches and signs of focal brain lesions, including, in both cases, unilateral motor signs,^{25,26} hemianopsia,²⁵ or aphasia.²⁶ 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.²⁵ 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.²⁶

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-2.²⁷ The second patient with ANE, after 1 week of respiratory symptoms, presented with mental confusion, aphasia, and paresis of the right arm. Images revealed bilateral, symmetric lesions suggestive of brain inflammation with bleeding and no vascular involvement.²⁸ A CSF tap was not undertaken in this last case due to the risk of complications. Both women presented good outcomes.

3.2 | Peripheral nervous system involvement

Peripheral nervous system involvement was reported in nine cases^{19,29-35} (Table 2): GBS²⁹⁻³³ (n = 5), among which, one case also presented vestibular neuritis³³; Bell's palsy^{19,29,34} (n = 3); and rhab-domyolysis³⁵ (n = 1).

The first symptoms of GBS developed during the first week of COVID-19 in three cases³⁰⁻³² and after the first month in 2 cases.^{29,33} One patient was diagnosed with GBS with no further investigations,²⁹ while all the other four cases had been investigated. These last cases presented with sensory complaints, including low back pain³⁰ and distal paraesthesia.³⁰⁻³³ Three patients also reported a decreased sensation with no sensory level.³¹⁻³³ All four cases presented motor impairment, including unilateral³⁰ or bilateral³¹⁻³³ facial paresis; ascending tetraparesis³⁰⁻³²; and areflexia.³⁰⁻³³ Two women presented manifestations of dysautonomia, including hypertension,³¹ dysphonia,³¹ dysphagia,^{30,31} or dyspnea.³⁰ 14 WILEY- Neurologica Scandinavica

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	_	 Emergency C-section due to rapidly worsening and fetal distress Intubation, ventilation, and prone positioning Extracorporeal circulation Transferred to a long-term supporting center Newborn evolved without complications 	 Guillain-Barré syndrome Critical COVID-19-ARDS
• Chest CT-scan consistent with COVID-19 pneumonia	 CSF analysis showed an increased level of protein and no white blood cells with RT-PCR negative for SARS-CoV-2 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 	 C-section due to fetal distress 1 day after admission Hydroxychloroquine and azithromycin Newborn presented transient tachypnea and stayed at ICU, but the outcome was not reported Discharged after 5 days following a negative RT- PCR test for SARS-CoV-2• 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 	 Acute motor- sensory axonal neuropathy variant of Guillain-Barré syndrome Moderate COVID-19 pneumonia
• Low serum potassium level, increased liver enzymes	 CSF analysis showed no white blood cells and normal protein level Nerve conduction studies showed signs of a predominantly demyelinating pattern of polyradiculoneuropathy with secondary axonal loss 	 Electrolyte correction Intravenous immunoglobulin Oral methyldopa 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 	Guillain-Barré syndromeMild COVID-19
 Low hemoglobin level, increased liver enzymes, and increased interleukin-6, D-dimer, LDH, and CRP levels Antinuclear antibody, anti-dsDNA, anti- cardiolipin, anti-beta2- glycoprotein I, and lupus anticoagulant were positive; rheumatoid arthritis factor was negative Chest CT-scan showed findings suggestive of sequelae of COVID-19 pneumonia 	 CSF analysis showed elevated cell count with normal protein and glucose level Nerve conduction studies showed sings of mixed (predominantly demyelinating) sensorimotor polyradiculoneuropathy involving the four limbs Brain and spinal cord MRI were normal Biopsy of the superficial peroneal nerve did not show active vasculitis 	 Intravenous immunoglobulin Antibiotics, heparin, steroid, and hydroxychloroquine Spontaneous abortion within the 13th week of gestation Progressive improvement, discharge against medical advice with mild distal sensory loss and weakness, she was able to walk independently after 25 days 	 Guillain-Barré syndrome Moderate COVID-19 pneumonia

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TABLE 2 (Continued)

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 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 	 RT-PCR negative Antibodies positive
15	Algeri, 2020 Jul 2 out of 5 cases—Italy Case #5	 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
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
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

Relevant blood tests and radiology findings	Neurological investigations	Management, progress, and outcome	Neurological diagnosis, WHO COVID–19 disease severity
 "Diagnostic workup" negative Negative IgM and positive IgG antibodies 	 Oto-neurological tests showed severe right sensorineural hearing loss Videonystagmography showed complete right vestibular areflexia Brain and spinal cord MRI were normal Nerve conduction studies showed findings supporting the diagnosis of isolated right tibial and peroneal nerves demyelinating acute neuropathy CSF analysis showed an increased level of protein and normal cell count with PCR negative for SARS-CoV-2 	 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
 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
• 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
• 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 palsyMild COVID-19

TABLE 2 (Continued)

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Case ID	First author, date of publication, number of cases	Clinical presentation	SARS-CoV–2 diagnostics
18	Kolkova, 2020 Jul 1 case—Sweden	 27-year-old woman 32 weeks and 1 day of gestation G2 P1 Extreme obesity, type-1 diabetes, and hypothyroidism; preeclampsia in the previous pregnancy 7 days of fever, lower abdominal pain, malaise, headache, cough, dyspnea, and polyuria Decrease in oxygen saturation with acute respiratory failure, metabolic acidosis; evolved with acute renal injury 	RT-PCR positive

Abbreviations: ARDS, acute respiratory distress syndrome; CRP, C-reactive protein; C-section, cesarean section; CSF, cerebrospinal fluid; CT, computed tomography; eGFR, estimated glomerular filtration rate; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase; MRI, magnetic resonance image; WHO, World Health Organization.

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 cells,^{30,31} normal³³ or increased³² cell counts, along with elevated^{30,33} or normal^{31,32} protein levels; the CSF of two cases was tested for SARS-CoV-2 with a negative result^{30,33}; 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

Relevant blood tests and radiology findings	Neurological investigations	Management, progress, and outcome	Neurological diagnosis, WHO COVID–19 disease severity
 Neutrophilic leukocytosis, increased ferritin, CRP, procalcitonin, fibrinogen, interleukin-6, LDH, liver enzymes, and lactate levels; a progressive increase of myoglobin and urea levels, with progressive decrease of eGFR Chest CT-scan showed bilateral diffuse ground- glass opacities with no signs of pulmonary embolism 		 Preventive acetylsalicylic acid; tinzaparin, and betamethasone Intubation and mechanical ventilation Emergency C-section at 32nd week of gestation due to critical condition Preventive piperacillin/tazobactam Prone positioning and muscle relaxant; aerosolized dornase-alfa Continuous renal replacement therapy Meropenem due to nosocomial superinfection Prolongated ICU stay with lack of contact during wake-up tests Tracheostomy performed after 19 days Diagnosis of rhabdomyolysis after 21 days Extubation after 30 days Neonate needed mechanical ventilation, extubated after 24 h Date of discharge not reported 	 Rhabdomyolysis Critical COVID-19-ARDS

Guillain-Barré syndrome in PNS involvement.¹⁵ 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.^{11,15} Many patients had no brain imaging findings or presented with PRES or features of hemorrhagic necrotizing encephalopathy.¹⁵ One of the reported cases of pregnant women with COVID-19 presented with delirium with no evident brain injury.²⁰ There were also four cases of PRES,²¹⁻²⁴ and only one of these women presented no abnormalities in the brain image.²³

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.²⁰ 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.²¹⁻²⁴

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.⁷ Interestingly, only one of the four reported cases of PRES presented suspected preeclampsia,²³ although all of them presented episodes of hypertension.²¹⁻²⁴ The women with delirium were also diagnosed with preeclampsia.²⁰

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.^{27,38} It has been described in association with other coronaviruses.²⁷ 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.³⁹ 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-19,²⁷ and the patient with ANE was diagnosed soon after the respiratory symptoms.²⁸ 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.²⁸

Until November 2020, there were 760 stroke cases among patients with COVID-19, of which most were ischemic strokes.⁴⁰ 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.⁴⁰ At least two-thirds presented respiratory symptoms, and their common stroke indicatives were unilateral motor deficits (67%), altered consciousness (66%), and headache (11%).⁴¹ Admission to ICU, ventilatory assistance, and mortality rates were higher for COVID-19 patients who suffered any type of stroke.⁴⁰⁻⁴² The outcomes were better for young patients in the fifth decade of life and poor in severe COVID-19 cases.⁴¹ Although the only pregnant woman with an ischemic stroke presented a severe form of COVID-19, her outcome was good possibly because she was

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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, symmetrical 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 antiganglioside 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 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).⁴⁹ 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,³⁸ 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 $\ensuremath{\mathsf{CVD}}\xspace{.}^{36}$

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.^{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.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,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.

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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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