Review Article

Neurologic and Psychiatric Syndromes Associated With Pregnancy: A Review

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Abstract

Certain neurologic and psychiatric syndromes are characteristically associated with pregnancy. This review provides an insight into the pathogenesis, clinical features, diagnosis, treatment, and outcome of these conditions.

The conditions such as posterior reversible encephalopathy syndrome, cerebral venous sinus thrombosis, postpartum angiopathy, thrombotic thrombocytopenic purpura, eclamptic seizures, acute fatty liver of pregnancy, chorea gravidarum, restless legs syndrome, dystonia, Wernicke's encephalopathy, Bell's palsy, compression neuropathies (meralgia paresthetica, carpal tunnel syndrome, obturator neuropathy, and iliohypogastric neuropathy), depression, and postpartum psychosis are discussed.

The benefits of radiologic tests and prescription of drugs for these conditions have to be weighed against the potential harm that they can cause during pregnancy. It is imperative for physicians and gynecologists to be well-versed with these conditions for timely diagnosis, treatment, and appropriate referral to improve the outcome.

Key Words: Cerebral venous thrombosis, posterior reversible encephalopathy syndrome, thrombotic thrombocytopenic purpura, seizures, acute fatty liver of pregnancy, restless legs syndrome, neuropathy, depression, psychosis, pregnancy

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Introduction

Pregnancy is associated with certain physiologic changes that put women at risk of certain ailments that are either unique to pregnancy or are more prevalent among pregnant women compared with that in the general population. This narrative review provides an insight into the pathogenesis, diagnosis, clinical features, management, and outcomes of certain neurologic and psychiatric syndromes (Figure 1), which may initially be encountered by gynecologists and need multidisciplinary management.

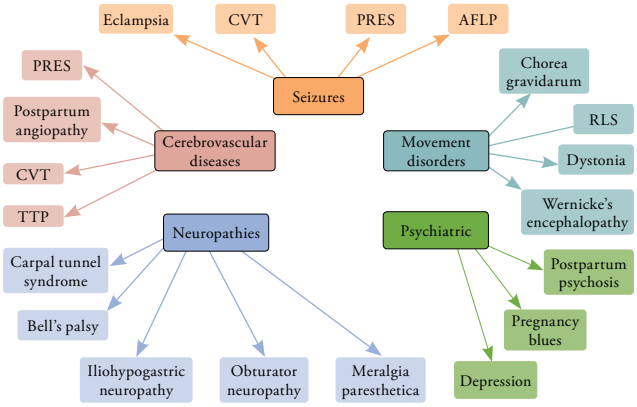

Figure 1. A Map Showing the Conditions Discussed in This Review Article

AFLP, acute fatty liver of pregnancy; CVT, cerebral venous thrombosis; PRES, posterior reversible encephalopathy syndrome; RLS, restless legs syndrome; TTP, thrombotic thrombocytopenic purpura.

Cerebrovascular Diseases

The incidence of both ischemic and hemorrhagic stroke is higher in pregnant women than in the general population, particularly in the perinatal period. In a large retrospective study that was conducted in the United States, the incidence of stroke in pregnant women was found to be 34.2 per 100,000 deliveries, and the risk factors included age > 35 years, African ancestry, and presence of migraine, systemic lupus erythematosus (SLE), hypercoagulable states (eg, antiphospholipid syndrome, thrombophilias, and malignancies), cardiac disease, sickle cell anemia, and thrombocytopenia.[1] Pregnancy itself is a hypercoagulable state, with an increased incidence of thromboembolic events including ischemic stroke.[2] This is because of the physiologic increase in certain procoagulant factors such as fibrinogen and factors II, VII, VIII, X, XII, and XIII and the decrease in anticoagulant protein S. The conventional risk factors for stroke such as diabetes, hypertension, smoking, dyslipidemia, and atrial fibrillation are relevant in pregnancy also. Stroke itself is not an indication for cesarean delivery, and mode of delivery has to be based on the case.

The hypertensive disorders—preeclampsia, eclampsia, and hemolysis, elevated liver enzymes, and low platelets syndrome (HELLP syndrome)—account for a majority of strokes in pregnancy. High blood pressure can lead to intracranial hemorrhage. Marked hypertension or swift blood pressure fluctuations can lead to failure of the cerebral blood flow autoregulatory mechanism, which culminates in the breakdown of the blood–brain barrier, causing vasogenic edema that is most prominent in the area of posterior circulation.[3] This is known as posterior reversible encephalopathy syndrome (PRES). It is generally reversible and requires strict and gradual blood pressure control (avoiding more than 25% reduction in the mean arterial pressure in the first hour) and individualized supportive therapy with cerebral antiedema measures and antiepileptic drugs. Rarely, hemorrhagic transformation may occur within the affected area, which can lead to long-term neurologic disability and even death.[4] The onset of PRES is abrupt, and its clinical features include headache, nausea, vomiting, loss of consciousness, seizures, vision loss, and focal motor or sensory deficits. The lesions are visible on magnetic resonance imaging (MRI) as a hyperintense signal on T2/fluid attenuated inversion recovery (FLAIR) sequence and as a hypointense to isointense signal on diffusion-weighted imaging (Figure 2).

Postpartum angiopathy is a syndrome of reversible diffuse or segmental cerebral vasoconstriction that is detected on conventional angiography, computed tomography (CT), or magnetic resonance (MR) angiography.[5] It presents after delivery with sudden-onset severe headache (thunderclap headache) and neurologic defects. Although generally benign, cases of secondary infarction or hemorrhage with a fatal outcome have

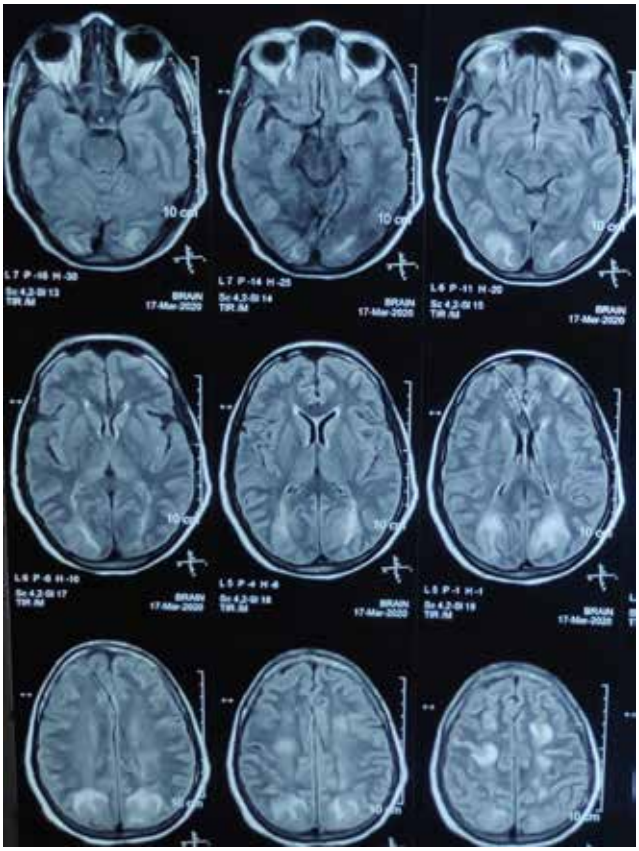

Figure 2. Axial Sections of T2/FLAIR Sequence of Brain MRI in PRES, Secondary to Eclampsia, Showing Hyperintensities, Predominantly in the Region of Posterior Circulation

FLAIR, fluid attenuated inversion recovery; MRI, magnetic resonance imaging; PRES, posterior reversible encephalopathy syndrome.

been reported. Elevated blood pressure is not a universal finding, and up to 39% of the cases are associated with preeclampsia or eclampsia.[6] Management involves blood pressure control and supportive care.

Cerebral venous thrombosis (CVT) is characterized by thrombosis of blood in the dural venous sinuses, leading to venous obstruction and subsequently brain infarction, disruption of the blood–brain barrier, and impaired cerebrospinal fluid (CSF) absorption.[7] The risk factors include pregnancy, use of oral contraceptive pills, dehydration, malignancies, and hypercoagulable states. The incidence of CVT in the general population is very low, but it is a very frequent cause of stroke during pregnancy. In a study of 240 pregnant women with cerebrovascular complications who were followed up postpartum, 56.7% of the cases were attributed to CVT, 26.7% to ischemic stroke, and 16.6% to intracerebral hemorrhage.[8] Patients with CVT had the best outcome. Its incidence was the highest in the first trimester and second and third week postpartum. In another study, 22.4% of the strokes in pregnancy and the puerperium period were due to CVT, and the incidence was the highest in the puerperium period.[9] The nonspecific clinical features include headache, mental status change, and seizures.[10] In the superior sagittal sinus, thrombosis, monoparesis, or hemiparesis can occur. In cavernous sinus thrombosis, proptosis and palsy of the oculomotor, trochlear, and abducens cranial nerves lead to ophthalmoplegia. Lateral sinus thrombosis leads to aphasia and multiple cranial palsies with resultant ophthalmoplegia and bulbar palsy. Findings on an early CT scan can be completely normal or show subtle changes such as a dense triangle sign (triangular hyperdensity in the posterior part of the superior sagittal sinus on noncontrast CT) or an empty delta sign (triangle with contrast-enhancing walls in the posterior part of the superior sagittal sinus on a contrast-enhanced CT).[10] A CT done after a few hours or early MRI can reveal bilateral infarcts with or without hemorrhagic transformation. The diagnosis is confirmed on CT or magnetic resonance venography, which shows filling defects in the cerebral venous system. CVT is treated by anticoagulation, even in the presence of hemorrhagic transformation.[11] Unfractionated heparin or low-molecular-weight heparin (LMWH) such as enoxaparin is started initially and later bridged to warfarin to maintain the international normalized ratio between 2 and 3. In early pregnancy, warfarin is contraindicated; hence, LMWH is administered twice daily, subcutaneously. LMWH may safely be used throughout pregnancy. The treatment is generally continued for 3 to 6 months postpartum, but it may be extended if an underlying hypercoagulable state is detected.

Thrombotic thrombocytopenic purpura (TTP) is a type of thrombotic microangiopathy, that is, a condition characterized by occlusion of small blood vessels with platelet microthrombi and downstream organ damage.[12] It is classically described as a

pentad of microangiopathic hemolytic anemia, thrombocytopenia, acute kidney injury, fever, and neurologic dysfunction. The underlying pathologic feature is a hereditary or acquired (due to autoantibodies) deficiency of ADAMTS13, a metalloproteinase enzyme that is synthesized in the liver and cleaves the von Willebrand factor (VWF) multimers into small units. The accumulated multimers promote the formation of platelet thrombi over the vascular endothelium. The risk factors of TTP include pregnancy, malignancies, bone marrow transplant, and intake of drugs such as cyclosporine, tacrolimus, mitomycin, and quinine. Martin et al[13] reviewed 166 cases of pregnancy-associated TTP that were published over 50 years. TTP occurred in 55.5% of the women during the second trimester, in 32.8% of them during the third trimester or postpartum, and in 11.7% of them during the first trimester. They documented a reduction in mortality from 58.1% (before 1980) to 9% (after 1996) due to the development of effective treatments and early diagnosis. The risk of death is higher when TTP is accompanied by preeclampsia, eclampsia, or HELLP syndrome. Fetal death can be due to thrombosis of decidual arteries that leads to placental infarction. Diagnosis requires a high index of suspicion as the initial clinical features are nonspecific. Thrombocytopenia, reduced hemoglobin, bleeding manifestations, elevated lactate dehydrogenase levels, reticulocytosis, renal dysfunction, schistocytes in blood film, fever, and neurologic dysfunction in the form of altered mental status, seizures, PRES, and stroke are cardinal features, although not all of these may be seen together. The diagnosis can be confirmed by documenting an ADAMTS13 activity of < 10% of the normal.[12] Plasma exchange (PEX) forms the mainstay of treatment, and it should be initiated as early as possible. It removes the autoantibodies and replenishes the normal levels of ADAMTS13 and VWF multimers to normalize the platelet function. Corticosteroids are also used as an adjunct to suppress more antibody production. Supportive care is given in the form of packed red cell or platelet transfusions, antiepileptic drugs (AEDs), and dialysis, when indicated. Caplacizumab, a novel humanized monoclonal recombinant antibody, has recently been developed and is found to be effective in the treatment of TTP.[14] It acts by reducing platelet aggregation, and it has been used in addition to PEX in trials, with promising results.

Seizures

Pregnancy-associated disorders that can lead to new-onset seizures include preeclampsia/eclampsia, CVT, PRES, TTP, and acute fatty liver of pregnancy (AFLP). Patients with preexisting epilepsy are at a slightly increased risk of having breakthrough seizures due to sleep deprivation and emotional stress that can occur in pregnancy. CT scans are contraindicated to evaluate seizures before delivery due to the exposure to ionizing radiation; MRI is safe. If MRI is not available, a low-radiation CT scan can be done using a lead apron, to minimize the risk to the fetus. Although gadolinium-based MRI contrasts had traditionally been contraindicated in pregnancy because of their ability to cross the placenta and because of lack of data on their long-term effects, the latest evidence indicates that they can be used safely at any stage of pregnancy when they are expected to provide significant diagnostic information; otherwise, a plain MRI can be done.[15]

Pathogenesis of seizures and coma in eclampsia involves cerebral dysfunction due to breakdown of the blood–brain barrier, hyperperfusion, endothelial dysfunction, vasoconstriction, and vasogenic or cytotoxic cerebral edema.[16] Overall, 2% to 3% of the patients with severe preeclampsia who do not receive magnesium sulfate prophylaxis develop seizures, and hence, eclampsia.[17] In a review, seizures occurred in 59%, 20%, and 21% of the cases before delivery, intrapartum, and postpartum, respectively.[18] Before the onset of seizures, many patients have premonitory symptoms such as headache, visual loss, or abdominal pain. Brain imaging reveals features consistent with PRES in most of the cases. The maternal seizures are accompanied by loss of fetal heart rate variability and short-lasting decelerations along with risk of placental abruption.[19] Fetal lung maturation is hastened by administering glucocorticoids (2 doses of betamethasone at 12 mg, administered intramuscularly [IM], given 24 hours apart, or 6 doses of IM dexamethasone given 12 hours apart). The AED of choice is magnesium sulfate, and other drugs such as

phenytoin can be added in refractory cases. Magnesium sulfate is initially loaded by an IV infusion of 4 g over 3 to 5 minutes along with 5 g IM in each buttock. The maintenance dose is 1 to 2 g per hour by IV infusion or 5 g IM every 4 hours on alternate buttocks, and it is continued for 12 to 24 hours postpartum.[20] The adverse effects include hypotension, vomiting, loss of knee jerk reflex (useful to detect toxicity early), respiratory suppression, and arrhythmias. Calcium gluconate, at an initial dose of 10 mL of 10% solution administered IV over 5 minutes, can effectively antagonize the cardiac toxicity. Immediate delivery and control of blood pressure are other important aspects for the management of eclampsia.

AFLP is a very rare syndrome of fatty infiltration of hepatocytes and acute liver failure, which occurs in the third trimester or the immediate postpartum period.[21] Defective mitochondrial fatty acid metabolism due to certain enzyme deficiencies, with their consequent accumulation during pregnancy, is responsible for this catastrophic condition. The most authenticated association is with fetal deficiency of long-chain 3-hydroxyacyl CoA dehydrogenase. The risk factors include a history of AFLP, hypertensive disorders, multiple gestation, male fetus, and low body mass index of the mother.[21,22] Patients mostly present after 30 weeks of gestation with a nonspecific prodrome of anorexia, nausea, vomiting, and abdominal pain. This is quickly followed by hepatic decompensation in the form of jaundice, encephalopathy, and coagulopathy. They may develop seizures, coma, hypoglycemia, bleeding manifestations, ascites, renal failure, cerebral edema, and eventually, multiorgan dysfunction, with a very high mortality if untreated. Patients require critical care and immediate delivery, regardless of fetal maturity. Failure of improvement in hepatic function after delivery is an indication for liver transplantation, although it is rarely required if timely management is done.[22]

Seizures during pregnancy are associated with fetal bradycardia and hypoxemia, abortion, preterm labor, and placental abruption. Patients with preexisting epilepsy should receive adequate counseling, as proper planning of pregnancy can help in better outcomes by prior optimization of treatment.[23] Most AEDs reduce the effectiveness of oral contraceptive pills by their hepatic enzyme–inducing property. Intrauterine devices, barrier methods, and IM depot medroxyprogesterone acetate are the ideal contraceptives.[24] Folic acid supplementation (at least 0.4 mg/d) should be started before conception and should be continued throughout the pregnancy to reduce the incidence of neural tube defects. A comprehensive neurology consultation should be sought to review the control of epilepsy and need for any change in AEDs.[25] In general, if the disease is well-controlled, AEDs are not altered unless valproate is being taken. This is because changing AEDs with the intent of reducing neural tube defects places the patient at risk of seizures. Valproate carries an unacceptably high risk of congenital malformations and should be used only as the last resort and in the minimum possible dose when other AEDs have failed. Serum AED levels should be monitored, if possible, to maintain the target level and reduce breakthrough seizures.[26] The safest AEDs are lamotrigine and levetiracetam. Carbamazepine can also be used, especially if the seizures are focal. These drugs are also preferred in new-onset seizures during pregnancy. Seizures that occur during the intrapartum period are terminated using a lorazepam bolus. Maternal barbiturate (primidone and phenobarbital) or benzodiazepine use can lead to neonatal sedation and poor feeding, necessitating close monitoring.[27]

Movement Disorders

Chorea is an abnormal involuntary movement disorder characterized by rapid, brief, jerky, unpredictable, and dancelike movements that can only partially be suppressed by the patient consciously.[28] It is due to a lesion in the caudate nucleus of the basal ganglia. The etiologies include acute rheumatic fever, stroke, Wilson's disease, Huntington's disease, encephalitis, SLE, and antiphospholipid syndrome. Occurrence of chorea in pregnancy is called chorea gravidarum. Symptomatic improvement can be achieved by administration of tetrabenazine, haloperidol, or chlorpromazine.

Restless legs syndrome (RLS) is characterized by an uncomfortable urge to move legs when the patient

is rested, especially during evenings. It leads to social embarrassment and disturbed sleep. It has familial predisposition, and the exact etiology is unclear. RLS is very strongly associated with iron deficiency, renal failure, and peripheral neuropathy. A quarter of all pregnant patients suffer from RLS.[29] It is often more severe in advanced pregnancy and resolves after delivery in > 90% of the cases.[30] Mild cases can be managed by physical exercise, avoiding prolonged immobility, and iron supplementation. When RLS is severe and disabling, clonazepam and levodopa can be used.

Wernicke's encephalopathy is an acute syndrome of ataxia, confusion, and ophthalmoplegia. It is due to vitamin B1 (thiamine) deficiency and is classically described in malnourished alcoholic patients. The condition is reported in pregnancy as a complication of hyperemesis gravidarum.[31] The treatment involves supplementation with a high dose of parenteral thiamine.

Acute dystonic reactions can occur when antiemetics having antidopaminergic action, such as metoclopramide and prochlorperazine, are used for the management of vomiting in pregnancy.[28] These can manifest in various forms as torticollis, laterocollis, oculogyric crisis, and blepharospasm. Rarely, death can also occur from airway compression. Treatment modalities include administration of anticholinergics (eg, procyclidine and biperiden), antihistamines (eg, pheniramine and trihexyphenidyl), or benzodiazepines (eg, clonazepam).[32]

Neuropathies

Carpal tunnel syndrome is very common in pregnancy, and studies report an incidence rate of 34%.[33] The symptoms peak in the third trimester, and most patients experience resolution over several months following delivery. Bilateral affliction is also common. This may be due to certain hormonal changes and fluid retention in pregnancy that leads to compression of the median nerve within the carpal tunnel in the wrist. The presenting features of carpal tunnel syndrome include numbness and burning or tingling sensation in the lateral half of the hand (thumb, index, and middle fingers). The symptoms are worst during the night, and patients often wake up with pain; shaking the hands provides relief. Weakness and wasting of the thenar muscles present later. Diagnosis can be made by observing the clinical features and can be confirmed by a nerve conduction study, although it may reveal no abnormality in the early stages. The initial treatment is with paracetamol, and wrist splints can be advised to reduce pressure on the median nerve.[34] When these are not effective, a local corticosteroid injection can be given. In the third trimester, neuropathic agents such as amitriptyline and gabapentin can be prescribed with caution.

Bell's palsy is an idiopathic, lower motor neuron type of paralysis of the facial nerve. The incidence of Bell's palsy in the third trimester and 2 weeks postpartum is 2 to 4 times higher than that in the general population, and the long-term outcome (in terms of incomplete recovery or aberrant reinnervation) is also worse.[35,36] There is weakness of facial muscles on the affected side and incomplete closure of the eyelids, with or without the loss of taste. The treatment involves a short course of oral corticosteroids and corneal protection using lubricants and eye pads.

Meralgia paresthetica is a common condition in pregnancy, and it is due to the compression of the lateral femoral cutaneous nerve under the inguinal ligament, leading to a burning or tingling sensation in the lateral part of the thigh.[37] It can also be due to injury during labor or cesarean section.

Obturator neuropathy is rare, and it is due to compression of the fetal head by forceps application during recovery. It leads to pain and weakness in the medial aspect of the thigh. Damage to the iliohypogastric nerve can be due to injury during cesarean section or during the third trimester, due to a rapid increase in abdominal girth.[37] It leads to pain in the inguinal and the suprapubic regions. Treatment of these conditions involves neuropathic agents or a lidocaine patch. Recovery is generally good and depends on the extent of injury.

Psychiatric Disorders

Although many pregnant women may have depressed mood not requiring treatment (pregnancy blues), the risk of major depression (that fulfills the diagnostic

criteria described in the Diagnostic and Statistical Manual of Mental Disorders IV) during pregnancy is the same as that in the general population; however, it increases in the postpartum period.[38] The risk factors include history of major depression, unwanted pregnancy, distressed relationship with the partner, poor economic status, and lack of social support.[39] Antenatal depression is associated with a slightly increased risk of abortion, bleeding, and preterm birth.[40] Postpartum depression is associated with subnormal mental development of the child.[41] Patients who have previously been treated successfully for depression should be treated with the same drug. New-onset antenatal depression is managed by psychotherapy and selective serotonin reuptake inhibitors (SSRIs).[42] SSRIs are generally safe, and sertraline is preferred because of abundant evidence on its effectiveness and safety during pregnancy and lactation. Citalopram and escitalopram are acceptable alternatives. Paroxetine is specifically avoided because of a possible increase in the incidence of congenital heart defects. Neonates having in utero exposure to SSRIs may suffer from neonatal adaptation syndrome during the first few weeks of life.[43] It is characterized by agitation, excessive crying, poor feeding, hypothermia, and insomnia. If SSRIs fail, other pharmacotherapy options include tricyclic antidepressants, duloxetine, bupropion, and mirtazapine, but data on their safety in pregnancy are less. Electroconvulsive therapy (ECT) is reserved for patients with refractory depression, psychotic features, catatonia, malnutrition, and a high risk of suicide.[44] The possible pregnancy-specific adverse effects of ECT include vaginal bleeding, preterm labor, and fetal bradycardia.

Postpartum psychosis is less common than postpartum depression. The incidence is 1 per 1000 births.[45] The risk factors are first pregnancy, schizophrenia, and personal or family history of postpartum psychosis.[46] The clinical features of delusions, hallucinations, and disordered behavior appear 2 to 3 weeks postpartum. The patient should be admitted and special arrangements should be made for the care of the neonate. The antipsychotics of choice are risperidone, olanzapine, and quetiapine as they have been proven to be safe during lactation; however, they can lead to maternal weight gain, hyperglycemia, and hyperlipidemia.[47] Excessive agitation can be controlled with benzodiazepines. Older antipsychotics such as haloperidol are less often used and can lead to extrapyramidal side effects (eg, tardive dyskinesia, tremors, and rigidity). Treatment is continued for a year after remission to prevent relapse.

Conclusion

Pregnancy could put one in a unique physiologic state, and there are certain neurologic and psychiatric disorders associated with it. Some of these can adversely affect the fetus and even necessitate termination of pregnancy. The approach to these disorders is different from that in the general population and demands extra care. The benefits of radiologic tests and prescription of drugs have to be weighed against the potential harm that they can cause. It is imperative for physicians and gynecologists to be well-versed with these conditions for timely diagnosis, treatment, and appropriate referral to improve the outcome.

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