New-Onset Seizures in Pregnancy and Puerperium

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ABSTRACT

Seizures in pregnant women cause several maternal and fetal consequences. Eclampsia is usually diagnosed to be the etiology. However, seizures during pregnancy or puerperium could be caused by pre-existing epilepsy, the initial presentation of a non-pregnancy-related disorder or the new-onset pregnancy-related disorder. Therefore, thorough diagnostic evaluation is essential. Although the pathogenesis of new-onset pregnancy-related neurological disorders remains unknown, physiological changes during pregnancy and puerperium are believed to have a major role. Advanced neuroimaging of the brain and cerebral vessels can help in differentiating the specific causes of seizures in these patients.

Keywords: Seizure; pregnancy; postpartum

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INTRODUCTION

While seizures happen during pregnancy, they may disturb the placental circulation leading to fetal hypoxia and bradycardia during the maternal seizures and may cause postictal apnea in the mother. Moreover, several other consequences of seizures during pregnancy could happen including maternal traumatic injury, fetal injury, abruptio placentae and abortion. For these reasons, prompt diagnosis and treatment of seizures in pregnant women is undoubtedly crucial. Since preeclampsia is common, eclampsia is usually the default diagnosis of pregnant women who develop seizures. However, seizures in pregnant and postpartum women could be caused by two groups of disorders. First is the pre-existing seizure disorder i.e. epilepsy. Another group refers to new-onset seizure disorders that could be pregnancy-related or non-pregnancy-related conditions. A brain tumor is an example of the non-pregnancy-related disease. In this article, the author will focus on the pregnancy-related seizure disorders which include eclampsia, posterior reversible encephalopathy syndrome (PRES), reversible cerebral vasoconstriction syndrome (RCVS), cerebral venous thrombosis (CVT), and some rare conditions. Because these disorders have overlapping symptoms and signs encompassing seizures, headache, focal neurologic deficits, altered mental status, and so on, neuroimaging study is needed for accurate diagnosis. The aim of this article is to review the pathogenesis, incidence, clinical features, diagnosis and principle of treatment of individual pregnancy-related conditions including how to approach seizures in pregnancy and neuroimaging safety issues.

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Pathogenesis

The precise pathogenesis of the new-onset seizure disorders in pregnancy and puerperium remains unknown. However, several factors have been reported to be involved in the mechanism of these syndromes as Fig 1. The major factors include the physiological changes of normal pregnancy[1] and the abnormal placental implantation[2]. Minor factors comprise underlying disease, current medication, caesarean surgery, puerperal infection, postpartum hemorrhage, and so on[1]. The author will only focus on the major factors.

The physiological changes in pregnancy focus on the altered blood levels of hormones i.e. estrogen and progesterone. Both hormones are produced initially by the corpus luteum and later by the placenta. Estrogen level slightly increases in the first trimester and then rapidly rises in the second trimester with the maximum at the end of pregnancy. Progesterone level elevates faster than the estrogen level does in the first trimester and continuously rises toward the end of gestation. For this reason, the proportion of progesterone and estrogen level is not constant throughout the pregnancy i.e. 10:1 in early pregnancy and 4:1 in late pregnancy. Hence, this may explain why the influence of estrogen is highest at the end of gravidity[3].

The effect of increased estrogen level is to stimulate the procoagulant production in the liver[4]. This becomes the risk of thrombosis formation. Meanwhile, the increased estrogen also leads to the expansion of plasma and blood volume, or in other words, the hypertension risk[1]. The altered progesterone level has several impacts on cerebral vessels. The elevated progesterone could induce vasodilatation (especially the venous vessels) and also change the autoregulatory function. Moreover, it increases the risk of capillary leakages and subsequent vasogenic cerebral edema as well[1]. Owing to the known vasodilatation effect of progesterone, the postpartum plunge of its level may provoke the paradoxical vasoconstriction[5].

Abnormal placental implantation is believed to be an another culprit of the altered vascular function as well[6]. It may cause placental hypoxia and then secrete some vascular mediators leading to the vascular endothelial dysfunction and also

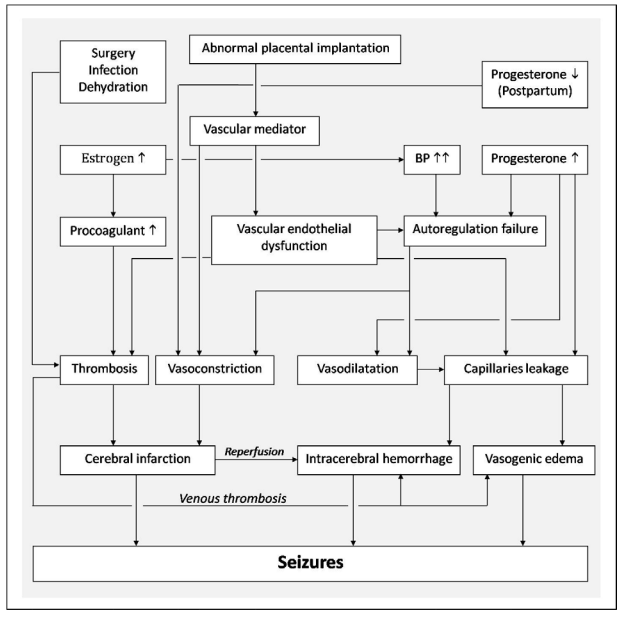

Fig 1. Pathogenesis of the new-onset neurological disorders in pregnancy and puerperium.

the autoregulatory dysfunction. This mechanism could bring several vascular changes including vasodilatation, vasoconstriction, vascular thrombosis and capillaries leakage.

All of the above mechanisms that cause vasoconstriction and vascular thrombosis can lead to brain ischemia or infarction. For the leaky capillaries, it can progress to vasogenic cerebral edema or even intracerebral hemorrhage. This final pathology could be a source of the hyperexcitable neuronal network which is the crucial component of epileptogenesis.

Individual disorders that cause new-onset seizures in pregnancy

Clinical features, imaging findings, and the principle of treatment of each condition are summarized in Table 1.

Eclampsia

Eclampsia refers to the occurrence of new-onset, generalized, tonic-clonic seizures in a patient with preeclampsia. The diagnostic criteria for preeclampsia comprise of two major elements. Firstly, new-onset hypertension (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg) after 20 weeks of gestation in a previously normotensive patient is a prerequisite. Secondly, proteinuria (urine protein ≥0.3 grams

TABLE 1. Comparison of clinical, imaging features and treatment between the selected pregnancy-related neurological disorders.

	Eclampsia	PRES	RCVS	CVT
Onset	Third trimester, intrapartum or postpartum	End of pregnancy or postpartum	Usually postpartum	Third trimester or postpartum
Key findings	Seizures, headache, blurred vision, photophobia, epigastric or right upper-quadrant pain; hyperreflexia, hypertension, proteinuria	Seizures, dull headache, blurred vision or visual hallucination; altered mental status	Thunderclap headache, recurrent; seizures, focal neurologic deficits, 50% of patients have positive CSF profile, slight pleocytosis and increased protein	Headache at onset, persistent and progressive, maybe thunderclap; seizures, focal neurologic deficits
Imaging findings	Same as for PRES, some have brain ischemia or intracerebral hemorrhage	CT positive in 50%, MRI shows T2-weighted and FLAIR hyperintensity in parieto-occipital lobes; intracerebral hemorrhage in 15% of patients	CT usually normal; CTA or MRA shows cerebral vasoconstriction, string-of-beads appearance; cervical arterial dissection or convexal SAH in small minority	CT may show intraluminal clot, cord sign or empty delta sign; MRI may show brain edema or intracerebral hemorrhage; CTV or MRV shows absence of flow
Principles of treatment	Left lateral position, oxygen supplement, blood pressure lowering, prevention of recurrent seizures with magnesium sulfate; prompt delivery	Blood pressure lowering, anticonvulsants if indicated; treatment of eclampsia if present	Supportive treatment, analgesics, anticonvulsants if symptom present	LMWH during antepartum, followed by LMWH or VKA with targeted INR 2-3

Abbreviations: PRES=posterior reversible encephalopathy syndrome. RCVS=reversible cerebral vasoconstriction syndrome. CVT=cerebral venous thrombosis. SAH=subarachnoid hemorrhage. FLAIR=fluid-attenuated inversion recovery. CTA=computed tomography angiography. CTV= computed tomography venography. MRA=magnetic resonance angiography. MRV=magnetic resonance venography. LMWH=low molecular weight heparin. VKA=vitamin K antagonist

in a 24-hour urine specimen or protein: creatinine ratio ≥0.3) or a sign of end-organ dysfunction (thrombocytopenia, elevated serum creatinine or elevated serum transaminases) is additionally required[7]. Eclampsia occurs in 2 to 3 percent of patients with severe features of preeclampsia and 0.6 percent of patients without severe features[8]. The incidence in developing countries varies from 6 to 157 cases per 10,000 deliveries[9]. The peak incidence is described in adolescence and early twenties. Most cases occur after 28 weeks of gestational age encompassing antepartum, intrapartum and postpartum especially in the first 48 hours. The precise cause of eclampsia is not clearly understood. The placental implantation abnormalities are believed to be the main

etiology. This abnormality leads to the release of some vascular mediators e.g. soluble fms-like tyrosine kinase-1 (sFlt-1) causing two important mechanisms i.e. the vascular endothelial dysfunction and the autoregulatory system breakdown. These mechanisms result in several consequences including abnormal cerebral vasoconstriction, vasodilatation, thrombosis or weakened vascular wall. The subsequent ischemic stroke, intracerebral hemorrhage or vasogenic cerebral edema may happen. Moreover, this vascular dysfunction can also provoke PRES which can coexist[10]. The brain pathology is most commonly located in occipital lobes, followed by parietal, frontal and temporal lobes successively[1]. Seizure is usually generalized tonic-clonic (GTC) type and lasts approximately 1 minute. Accompanying symptoms include headache (frontal or occipital), blurred vision, photophobia, abdominal pain (epigastric or right-upper quadrant) and altered mental status. Even though the characteristics of preeclampsia should be presented in eclampsia, one-third of eclamptic patients has blood pressure below 140/ 90 mmHg or no proteinuria.[11] Eclampsia is a clinical diagnosis based on the occurrence of new-onset GTC seizure in preeclampsia without persistent focal neurologic deficits, and no other causes of seizure are identified. The neuroimaging study is not necessary for the diagnosis. However, the brain imaging usually shows the same findings as PRES. The specific treatment of eclampsia is prompt delivery while prevention of maternal hypoxia and trauma during seizures is also crucial. Rolling a patient onto the left side, oxygen supplementation and raising the padded bed rails are among the management. Magnesium sulfate is the drug of choice for prevention of recurrent seizures. If severe hypertension is present, it should be treated to avoid subsequent cerebrovascular disease.

Posterior reversible encephalopathy syndrome

PRES is a clinical-radiographic syndrome of several various etiologies. PRES has been coincident with several medical conditions such as hypertensive encephalopathy, eclampsia and the use of immunosuppressive or cytotoxic drugs[12]. The exact incidence of PRES is not known. PRES can be found in all age-groups. Women are affected by PRES more commonly than men even with ifthe exclusion of eclampsia[13]. This condition most commonly occurs at the end of pregnancy or postpartum. Pathogenesis of PRES focuses on two mechanisms i.e. vascular autoregulatory failure and endothelial dysfunction[13]. Hypertensive emergency can cause the autoregulatory dysfunction - in other words, the cerebral vessels are not able to control blood flow in the normal range. This effect leads to vasodilatation, capillaries leakage and intracerebral hemorrhage. Both abnormal placental implantation in preeclampsia and cytotoxic drugs are among the etiologies of vascular endothelial injury. This injury can induce further capillaries leakage and vasogenic cerebral edema. Seizures are the prominent features of PRES. They can be partial or generalized forms. Headache, visual disturbance, and altered mental status are among the accompanying symptoms. Headache is usually bilateral and dull in quality. The visual symptoms can be hallucination, blurred vision, scotoma or even transient cortical blindness. The spectrum of altered mental status can range from drowsiness, confusion to coma. These characteristics rapidly progress in 12 to 48 hours. However, the visual disturbance generally returns to a normal state within hours or days[14]. There are no specific diagnostic criteria for PRES. The diagnosis depends on clinicoradiographic features combined with the syndrome of seizures, headache, and visual disturbance with abnormal neuroimaging. CT scan of the brain can demonstrate hypodense lesions in the white matter of bilateral occipital lobes. However, MRI is more sensitive than CT for detecting abnormalities. Increased signal intensity on T2-weighted and FLAIR sequences over bilateral parieto-occipital white matter areas are major findings on MRI brain as Fig 2. The Brain stem, cerebellum, cerebral cortex or basal ganglion lesions can also be seen. Involvement of anterior part of the brain may be present; however, the posterior brain lesions always exist[15]. Because the symptoms of PRES are not unique, the differential diagnosis should be recognized especially cerebral infarction from bilateral posterior cerebral arteries (PCA) occlusion. Unlike the PCA occlusion, lesions in PRES usually do not involve

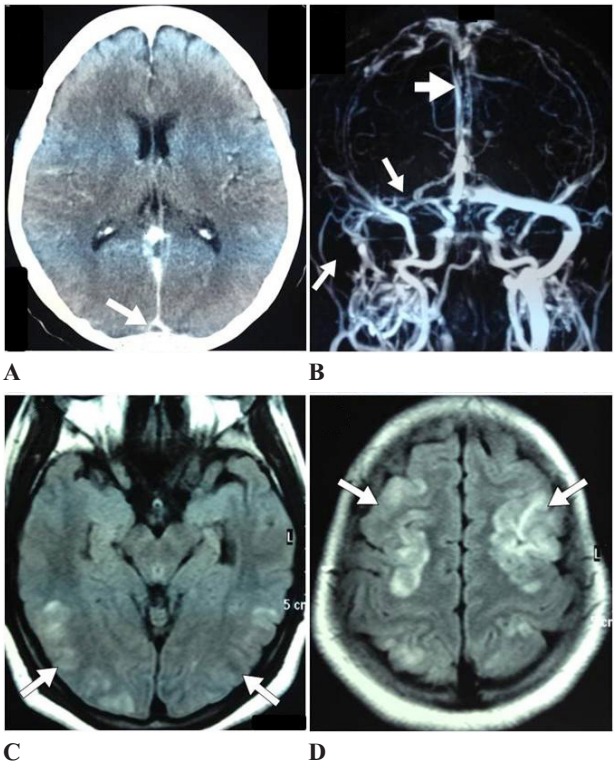

Fig 2. Neuroimages of the pregnancy-related neurolo-gical disorders

(A) Contrast CT scan of a patient with cerebral venous thrombosis shows hyperdensity lesion surrounding the central hypodensity lesion along the thrombosed superior sagittal sinus (arrow) or so-called empty delta sign. (B) Magnetic resonance venogram of the same patient demonstrates no flow of superior sagittal sinus (thick arrow), right transverse and sigmoid sinus (thin arrows). (C) FLAIR image on MRI shows hyperintensity in both temporo-occipital areas (arrows) with spare medial occipital cortex. (D) Bilateral frontal cortices are also involved in the same patient.

calcarine and paramedian parts of occipital lobes and are not confined to the only single arterial territory. Furthermore, MRI can help differentiating between these two conditions by diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) methods. The principle of management is to treat the associated conditions, for example, blood pressure lowering in hypertensive emergency, stopping the relevant immunosuppressive or cytotoxic drugs, prompt delivery and magnesium sulfate administration in coincident eclampsia. The antiepileptic drug is needed to prevent the seizure recurrence. Visual symptoms can improve within hours or days, although the radiologic abnormalities will subside in the later period.[16]

Reversible cerebral vasoconstriction syndrome

RCVS is characterized by the condition of reversible multifocal narrowing of cerebral arteries and clinical syndrome of thunderclap headache, focal neurologic deficits or seizures. The actual incidence of RCVS is unknown. However, it is believed that RCVS is more fre-quently recognized due to the availability of non-invasive angiography and the increasing use of vasoconstrictive medications[17]. The proportion of affected women to men varies from 2:1 to 10:1 depending on the studies. Mean age is 42 to 43 years even though all age-groups can be affected[18]. Several risk factors have been reported including pregnancy, migraine, the use vasoactive drugs, brain surgery, hypercalcemia and unruptured cerebral saccular aneurysm[19]. For pregnant women, RCVS most commonly occurs within the first week of postpartum. Despite the unknown pathogenesis of RCVS, several risk factors are believed to be the cause of inability to control vascular tone and severe cerebral vasoconstriction. In the early postpartum period, there are two mechanisms of RCVS. Firstly, the rapid plunge of progesterone level can lead to severe paradoxical cerebral vasoconstriction[5]. Secondly, sudden changes in blood volume and circulatory blood flow also result in abnormal vascular tone responsiveness. For this reason, severe cerebral vasoconstriction can occur and may lead to brain ischemia or infarction and even intracerebral hemorrhage from the mechanism of reperfusion injury. In addition to vasoconstrictive effect, the abnormal vascular tone in RCVS could cause convexal subarachnoid hemorrhage (SAH) or cervicocranial arterial dissection[19]. From other observations, the existence of temporary brain edema in RCVS and radiologic cerebral arterial vasoconstriction in PRES indicates the overlapping pathogenesis of these two disorders[20]. Thunderclap headache (TCH) is the pathognomonic symptom of RCVS. TCH is characterized by the most severe and sudden headache ever in life. The pain location might be generalized, occipital or at the vertex. Each episode of headache generally subsides within

minutes to hours and then recurs several times at intervals of days or weeks. Associated symptoms include vomiting, photophobia, confusion and visual blurring. Furthermore, subsequent seizures or focal neurologic deficits can be present. Until now, there has still been no valid diagnostic criterion for RCVS. The diagnosis mainly depends on the characteristics of clinical manifestations, cerebral angiographic images, and CSF profile. Cerebral angiography (i.e. contrast angiography, CT angiography or MR angiography) demonstrates multifocal narrowing of cerebral arteries in the "string of beads" appearance[21]. In the case of no SAH, CSF profile may be normal or show mild pleocytosis and slightly increased protein with normal glucose level[21]. The diagnostic confirmation of RCVS can be proved by the full recovery from cerebral arterial vasoconstriction which usually occurs around 3 months after onset. The natural history of RCVS is usually spontaneous recovery. Moreover, there has not been any treatment proven to be effective. For this reason, the principle of treatment is supportive and symptomatic treatments. Patients may be admitted to the hospital in order to observe any complications such as focal neurologic deficits. Appropriate analgesics e.g. opioids can be used for pain control, although triptans and ergot derivatives are contraindicated because of their vasoconstrictive properties[22]. The short-term antiepileptic drug is considered if the seizure is present.

Cerebral venous thrombosis

CVT is the presence of thrombosis in the dural venous sinuses or cortical veins. CVT is less common than other types of cerebrovascular disease. However, it is a serious condition that has various clinical spectrum and causes including inherited and acquired etiologies. In the US, only 2 percent of pregnancy-related strokes are caused by CVT, so, it is uncommon[23]. Nevertheless, more incidence is described during pregnancy, especially the third trimester and puerperium. The occurrence of CVT during the first trimester is usually caused by the preexisting thrombophilia[24]. Risk factors in pregnant women include caesarean section, dehydration, delivery injury, anemia, hyperhomocysteinemia and spinal anesthesia[25]. High estrogen level, especially at the end of pregnancy is the main factor of thrombosis formation. Estrogen stimulates the procoagulant production and also decreases the factor inhibiting coagulant production in liver[4]. Other risk factors including caesarean section, perinatal injury, infection and dehydration all can induce blood clotting formation. As a result of thrombosis formation, cerebral venous sinus backward pressure increases to the capillaries and then plasma or red blood cells can leak into brain parenchyma causing vasogenic edema and intracerebral hemorrhage. Moreover, the poor venous circulation due to sinus occlusion can cause brain ischemia and venous infarction. This impaired circulation also leads to increased intracranial pressure via the mechanism of decreased CSF absorption. Headache is the most common symptom at the onset. It is usually generalized, constant or progressive in severity. Mode of onset is subacute, although 10 percent of patients have TCH headache character[26]. Seizures can be found in approximately 40 percent of patients[19]. Furthermore, the focal neurologic deficits and altered mental status are occasionally present in CVT. The diagnosis of CVT relies on clinical features and positive radiologic test (Fig 2). Non-contrast CT (NCCT) scan could show vasogenic cerebral edema and even intracerebral hemorrhage that are not confined to an arterial vascular territory. The "cord sign" described as hyperdense lesion along the structures of cerebral venous sinus or cortical vein implies the existence of thrombosis in these vascular lumens. CT scan with contrast may demonstrate the filling defect or "empty delta sign" described as hyperdensity lesion surrounding the central hypodensity lesion along the thrombosed superior sagittal sinus. MRI can detect the vascular thrombosis as the CT does, although MRI is superior to CT in the detection of hemorrhage shown by the hypointensity in T2 gradient echo images. CT venography (CTV) or MR venography (MRV) shows no flow of the affected venous sinus. Nevertheless, this should be differentiated with the normal anatomic variant (20 percent of the normal population) which is hypoplasia of the transverse sinus[27]. For the CVT with and without intracranial hemorrhage, low molecular weight heparin (LMWH) is the main

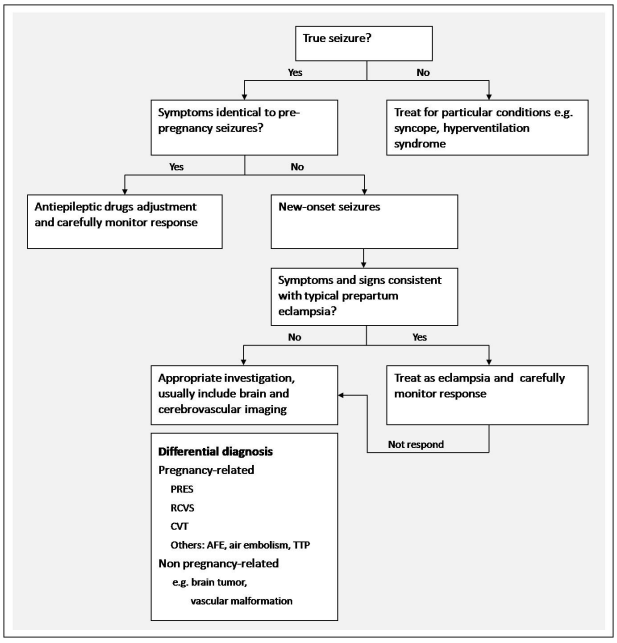

Fig 3. Diagnostic approach for pregnant and postpartum women who presents with seizures.

Abbreviations: PRES=posterior reversible encephalopathy syndrome. RCVS=reversible cerebral vasoconstriction syndrome. CVT=cerebral venous thrombosis. AFE=amniotic fluid embolism. TTP=thrombotic thrombocytopenic purpura.

treatment throughout the pregnancy. LMWH or vitamin K antagonist (VKA) with targeted INR should be continued for at least 6 weeks of the postpartum period. Moreover, the patient should receive any of these anticoagulants for at least 6 months in one course[23]. Other treatments encompass antiepileptic medication if indicated and intracranial hypertension management.

Approach to the new-onset seizure in pregnancy and puerperium

As described before, the seizures in pregnancy and postpartum can be manifestations of the pre-existing seizure disorders or the new-onset seizure disorders that include both pregnancy-related and non-pregnancy-related conditions. Therefore, it is necessary to emphasize that pregnant and postpartum women with seizures need the same diagnostic process for a seizure do all seizure patients (Fig 3).

Firstly, the symptom should be differentiated with other conditions presenting as transient loss of consciousness, for example, syncope, hyperventilation syndrome, and so on. These seizure mimics are not uncommon in pregnant women. If it is a true seizure, the next step is to find out whether it is identical to pre-pregnancy seizure disorder or not. The appropriate antiepileptic adjustment should be provided in case of a seizure from a pre-existing disorder. The author will not focus on this group.

For a new-onset seizure, eclampsia treatment needs to be started with careful response monitoring when the symptoms and signs are compatible with the typical prepartum eclampsia. If the clinical features are not consistent with typical prepartum eclampsia or the eclamptic patients do not respond to treatment, then thorough history taking and physical examination including appropriate investigation should be done. The clinical exploration should focus on the type of seizures (partial or generalized), associated features (fever, headache, focal neurologic deficits or visual disturbance), provoking factors, current medication and underlying physical and neurological diseases. Selection of the appropriate investigation depends on individualized clinical suspicion. For example, lumbar puncture is essential for diagnosing meningitis, or blood test is needed for detecting electrolyte disturbance, and so on. However, brain imaging should be done to every pregnant and postpartum women having new-onset seizures. The only one exception is the classic prepartum eclampsia as mentioned previously. If a pregnant-related seizure disorder (such as PRES, RCVS or CVT) is suspected, both brain and cerebrovascular imaging by MRI or CT will be needed to confirm the diagnosis.

Neuroimaging safety issues

Many clinicians and radiologists are usually concerned about radiology-associated risks when their pregnant patients need to do imaging. A basic principle of risks reduction is to minimize the ionizing radiation and intravenous contrast exposure. Because the MRI scan of the brain is generally more sensitive than the CT to detect abnormalities except for aneurysmal SAH, for this reason, the clinician may directly choose MRI rather than routine preceding CT scan[19].

CT scan uses the ionizing radiation passing through the body to create images. CT scan of the

brain is generally safe for pregnant women because the fetal radiation exposure is negligible[28]. Unlike the CT, MRI images are created by using electromagnetic radio waves. MRI in pregnant patients is thought to be safe, although the conclusive data is non-existent[28]. Until now, there have been no reports regarding the harmful effects for the pregnant woman or fetus from MRI with no more than 1.5 Tesla magnetic strength[29].

Even though both iodinated contrast and gadolinium can cross the placenta, there has been no clinical significance reported[30]. The US Food and Drug Administration classifies iodinated contrast as class B and gadolinium as class C. Nevertheless, iodinated agents could theoretically affect the fetal thyroid function, so infants should have their thyroid function checked after birth. Breast feeding in the pregnant women exposed to iodinated contrast or gadolinium is also regarded as safe because these agents are secreted in breast milk and absorbed by the baby's gut in subtle amounts.[28]

CONCLUSION

Although the pathogenesis of pregnancy-related seizure disorders remains unknown, physiological changes during pregnancy and puerperium are believed to play a major role. Several seizure disorders share overlapping pathogenesis and clinical features. Moreover, new-onset seizures in pregnant and postpartum women could be caused by pregnancy-related or non-pregnancy-related conditions. For this reason, a thorough assessment is needed for diagnostic accuracy and prompt treatment. Advanced neuroimaging including brain and cerebrovascular studies, have become the investigation of choice if the seizures are not compatible with typical prenatal eclampsia. MRI or CT scan of the brain including iodinated contrast and gadolinium are generally safe for the fetus, although they should be used only when there is an indication.

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