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MINI-REVIEW

Neurological complication during pregnancy, delivery and puerperium requiring intensive therapy management

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Abstract

Neurological complications during pregnancy, delivery and puerperium are relatively rare, but can lead to serious consequences and life-threatening situations. Clinical symptoms such as headache, weakness, seizures, sudden neurological deficits, or decreased level of consciousness should be the reasons for a prompt and careful consideration and neuroimaging to confirm the diagnosis and initiate treatment. In this article, we aim to describe the diseases and clinical situations that may manifest as neurological symptoms during pregnancy, delivery and puerperium. We also provide a more comprehensive descriptions of certain pregnancy-specific diseases and latest findings in literature and improvement in diagnostic approaches and treatment. Our primary objective is to emphasise the urgent need for prompt and accurate diagnosis and treatment in order to prevent life-threatening situations, not only for the mother, but also for the baby.

Keywords

Pregnancy; Neurological complication; Headache; Seizures; Stroke; Preeclampsia; Eclampsia; Posterior reversible encephalopathy syndrome; Reversible cerebral vasoconstriction syndrome; Cerebral venous thrombosis

1. Introduction

Neurological complications occurring during pregnancy, delivery and puerperium are relatively uncommon, but they can have devastating consequences for both the mother and the baby. Within the first week postpartum, nearly 40% of women experience headaches, with tension and migraine headaches accounting for more than three-quarters of those cases [1, 2]. However, it is important to recognise that some pregnant women and parturient may develop severe secondary headaches that can be life-threatening.

Our primary objective is to emphasise the urgent need for prompt and accurate diagnosis and treatment in order to prevent life-threatening situations for the mother and the baby.

Clinical symptoms such as headache, weakness, seizures, sudden neurological deficits or decreased level of consciousness require prompt and diligent diagnostic workup. The indications for neuroimaging are the same as in non-pregnant patients and can generally be performed safely during pregnancy [3, 4].

Managing neurologic complications requires a collaborative effort from obstetricians, anaesthetists, intensivists, neurologists, neuroradiologists and neurosurgeons, as no single physician possesses expertise in all aspects of care. However, there is a scarcity of literature on this subject, largely due to the exclusion of pregnant women from clinical trials [2].

Pregnancy entails numerous physiological changes that are necessary for normal development of the foetus and the mother's well-being [5]. Pregnancy and puerperium are physiological hypercoagulable states that prevent excessive bleeding in the mother but can in some circumstances also lead to thrombotic events [6]. On average plasma volume expands by 45% and is accompanied by a physiological anaemia, increased cardiac output, vasodilation, increased circulating permeability factors and seizure-provoking constituents [7, 8]. In late gestation, more vasoconstrictors are circulating. To maintain the normal ion and water balance, vascular permeability, and blood flow, the brain must counteract these physiological changes, which is unique in comparison with the adaptation of other organs. During pregnancy the upper and the lower limits of the cerebral blood flow (CBF) autoregulatory curve are extended and functional and structural changes occur in some cerebral vasculature segments whereas the permeability of the blood brain barrier is not changed [8]. Inadequate adaptation mechanisms can lead to some pregnancy-related neurological complications (*e.g.*, preeclampsia/eclampsia) or worsen some pre-existing neurological disorders (*e.g.*, epilepsy) [9, 10]. Plasma volume expansion, elevated renal clearance, and induction of hepatic metabolism have an impact on the pharmacokinetics of many drugs [5].

2. Epilepsy

Seizure disorders are the most frequent major neurologic complication in pregnancy, affecting 0.3% to 0.8% of all gestations [11]. The most common cause of seizures during pregnancy are previously diagnosed epilepsy and eclampsia.

The mortality rate for pregnant women with epilepsy (PWE) is approximately ten times higher than that of pregnant women without epilepsy, which places PWE at high risk for adverse outcomes [12, 13].

PWE have an increased risk of miscarriage, antepartum haemorrhage, postpartum haemorrhage, hypertensive disorders, a higher risk of induced labour, caesarean delivery, preterm labour, and intrauterine growth restriction [11, 14].

Optimizing epilepsy treatment before pregnancy by selecting the best anti-epileptic therapy (AED) for seizure type and using the lowest effective dose is recommended to minimize foetal exposure to AEDs, which is associated with an increased risk of congenital malformations and neurocognitive deficits and varies depending on the dosage [6, 11, 14, 15].

Conversely, certain physiological changes in pregnancy can reduce the level of AEDs in blood by more than 35%. A very careful adjustment of therapy is required to avoid epileptic seizures and potential harm to the foetus [16].

Generalised tonic-clonic seizures, in particular, can increase the risk of hypoxia, acidosis, blunt trauma injury, and other complications, which may have detrimental effects on the mother and the foetus [17].

There are several reasons why childbirth is associated with a relatively high risk of recurrent epileptic seizures: poor bioavailability and compliance with AEDs, sleep deprivation, anxiety, and hyperventilation in labour. The occurrence of seizures during labour may lead to an increased incidence of neonatal hypoxia and low Apgar scores in infants born to PWE, particularly in the case of generalized seizures [18].

Benzodiazepines are considered the first-line treatment for status epilepticus during pregnancy. Levetiracetam and phenytoin are recommended as second-line options. Valproic acid should be used only if other antiepileptic drugs have failed, and its use is preferably avoided during the first trimester of pregnancy [7]. For refractory status epilepticus, anaesthetic drugs, such as propofol and midazolam, and airway management with mechanical ventilation and haemodynamic stabilisation are required as described in Section 9 [19]. In cases of status epilepticus related to eclampsia, magnesium sulphate is the first-line therapy. If general anaesthetics fail, termination of pregnancy through delivery or abortion may be suggested [20].

3. Preeclampsia/eclampsia

Preeclampsia is a multisystem disorder with an occurrence rate of 3–8% of all pregnancies and incidence rate at about 5–7 cases per 10,000 deliveries in the developed countries of North America and Europe [21–23].

Preeclampsia refers to the new onset of hypertension and proteinuria or the new onset of hypertension in addition to a significant end-organ dysfunction with or without proteinuria in a previously normotensive patient. It typically occurs after 20 weeks of gestation or postpartum. During pregnancy, hypertension is characterized by a systolic blood pressure equal to or exceeding 140 mmHg and/or a diastolic blood pressure equal to or exceeding 90 mmHg, based on the average of two measurements [24, 25].

Preeclamptic patients may experience additional signs and symptoms, such as visual disturbances, headache, epigastric pain, thrombocytopenia, and abnormal liver function. They result from mild to severe microangiopathy of target organs [21, 26].

Traditionally eclampsia has been defined as the new onset of generalised tonic-clonic seizures or coma in women with preeclampsia. More recent opinions, however, suggests that seizures often occur in the absence of a preeclampsia syndrome, particularly in late postpartum eclampsia. Eclamptic seizures can occur antepartum, mostly after the 20th week of gestation, intrapartum, and postpartum [23].

While the pathogenesis of preeclampsia and eclampsia remains poorly understood, it is widely acknowledged that the placenta plays a crucial role in their development [26].

There is clear evidence that sustained, severe hypertension is associated with an increased risk of maternal morbidity, including cerebrovascular injury in the form of hypertensive encephalopathy with a massive increase in intracranial pressure and resultant cerebral oedema or intracranial haemorrhage [23, 27].

Acute treatment of severe hypertension is mandatory. Blood pressure should be lowered to $<$160 mmHg systolic and $<$110 mmHg diastolic. Initial antihypertensive therapy should be with nifedipine, hydralazine, or labetalol [23, 25]. Alternative antihypertensive medications include a nitro-glycerine infusion, oral methyldopa, oral labetalol, oral clonidine, and postpartum, oral captopril since angiotensin-converting enzyme inhibitors and angiotensin receptor blockers remain contraindicated in pregnancy. In pregnant women, first line intravenous treatment is labetalol or hydralazine, and second line an infusion of esmolol or nicardipine [7, 25].

Magnesium sulphate is recommended for the prevention and treatment of eclampsia in women with severe pre-eclampsia and it is preferred to other anticonvulsants. The recommended approach is to administer full intravenous or intramuscular magnesium sulphate regimens [25, 28]. In developed countries the Zuspan regimen is frequently utilised. This regimen includes a loading dose of 4 g intravenous over 20 minutes followed by a continuous infusion of 1 gram per hour starting during the period of observation and continuing until 24 hours postpartum [29].

If recurrent seizures occur, an additional bolus of 2 g magnesium sulphate can be administered over a period of 3–5 minutes. However, it is crucial to closely monitor for magnesium toxicity. If seizures persist even after two boluses of magnesium sulphate, alternative anti-seizure medication (*e.g.*, diazepam, lorazepam and midazolam) can be considered [20].

Delivery is the definitive treatment for preeclampsia and eclampsia, and the timing of delivery depends on the severity of the disease and the gestational age of the foetus. Induction of labour is recommended for women with severe pre-eclampsia at a gestational age when the foetus is not viable. However, in women with severe pre-eclampsia with a viable foetus before

36 (plus 6 days) weeks of gestation, a policy of expectant management may be considered if there are no uncontrolled maternal hypertension, increasing maternal organ dysfunction or foetal distress and close monitoring is possible. On the other hand, for women with severe or mild pre-eclampsia at term, early delivery is recommended [25].

In cases where the disease has resulted in serious complications, admission to the intensive care unit (ICU) is usually necessary, since they require close monitoring and intensive management as described in Section 9 [7, 20, 30, 31]. These complications can include refractory hypertension, neurological dysfunction (such as seizures, intracranial haemorrhage or elevated intracranial pressure), renal failure, liver rupture or failure, pulmonary oedema, the HELLP syndrome (haemolysis, elevated liver enzymes and low platelet count), and/or disseminated intravascular coagulation.

Overall, the prognosis for patients with preeclampsia and eclampsia who receive ICU management is favourable, with maternal mortality rates ranging from 0.5% to 5%. However, it is important to note that the risk of adverse outcomes is higher in patients with severe disease or associated complications [31].

4. Postdural puncture headache

Postdural puncture headache (PDPH) refers to a mild to severe headache that occurs after intentional or unintentional dural puncture. The headache (frontal and occipital) worsens when in an upright position and improves when lying down [32, 35]. Other accompanying symptoms may include neck pain/stiffness, nausea, tinnitus, hearing changes, diplopia and photophobia [33, 34, 37]. Two thirds of PDPH occur within 48 hours after dural puncture and 90% within 3 days [34, 35]. Accidental dural puncture during the insertion of a labour epidural catheter (incidence rate of up to 1.5%) results in PDPH in 50–80% of women [36].

The differential diagnosis of PDPH includes several serious conditions, such as preeclampsia, pregnancy associated stroke (PAS), intracerebral haemorrhage (ICH), subarachnoid haemorrhage (SAH), posterior reversible encephalopathy syndrome (PRES), reversible cerebral vasoconstriction syndrome (RCVS), cerebral venous thrombosis, intracranial tumour, infection, intracranial haemorrhage, brain herniation, and pneumocephalus [32, 34].

In rare cases, PDPH can lead to further complications, including seizures, subdural haematoma, cerebral venous sinus thrombosis, or brain herniation and death [35].

In majority of cases (90%), PDPH is self-limiting and resolves within one week [32]. Initial conservative measures include adequate hydration, bed rest and the use of caffeine [36]. In severe cases, epidural blood patch remains the gold standard [32, 35].

Rare complication of the epidural blood patch includes adhesive arachnoiditis, cauda equina syndrome, spinal or subdural haematoma, cerebral venous thrombosis, intracerebral haematoma, cerebral ischemia, pneumocephalus, and facial nerve palsy [35].

Patients experiencing serious complication related to PDPH or epidural blood patch require admission to the ICU for close monitoring and appropriate intensive therapy for their condition (Section 9).

5. Pregnancy-related stroke, pregnancy-related intracerebral haemorrhage and aneurysmal subarachnoid haemorrhage

Risk factors for cerebrovascular events during pregnancy and puerperium include pregnancy-related hypertension and its complications, the hypercoagulable state, autoimmune disorders, caesarean section, and hyperemesis resulting in haemoconcentration [37]. The incidence of pregnancy-related stroke (PAS) (3 per 100,000) is three times higher than in the non-pregnant population of the same age, with a high mortality rate of 1.4/100,000 deliveries [38]. It primarily occurs in the third trimester (40%) and puerperium (50%) [39, 40].

If PAS is suspected, it is of great importance to promptly confirm the diagnosis with neuroimaging and manage the patient in a setting where both the stroke unit and perinatal care are available [7]. The management of PAS is generally to that of non-pregnant patients, with the need of adjusting therapeutic measures depending on the severity of stroke, stage of pregnancy and potential issues regarding the foetus (Section 9) [38, 41]. Similarly, to other serious pregnancy-related diseases, maternal health takes priority [7, 41].

PAS, pregnancy related intracerebral haemorrhage (pICH) and aneurysmal subarachnoid haemorrhage (aSAH) present with similar clinical pictures as in non-pregnant patients. In PAS mechanical thrombectomy or thrombolysis should be considered and weighed against the potential risk of bleeding, particularly within the first 48 hours after delivery [41, 42]. pICH is associated with a poor prognosis, with an in-hospital mortality of 20% and an overall mortality rate of nearly 50% [39]. pICH is mostly linked to vascular malformations. The mainstay of therapy involves blood pressure management, coagulopathy reversal and mass effect therapy if needed (Section 9) [41]. Detailed descriptions of therapeutic options and related concerns regarding the mother and the foetus can be found in three excellent review articles [7, 37, 41].

6. Posterior reversible encephalopathy syndrome

Posterior reversible encephalopathy syndrome (PRES) is a clinico-radiological diagnosis.

Clinically it presents with subacute (hours to days) neurological symptoms such as headache, vomiting, visual disturbances (up to 39%), seizures, and other symptoms of encephalopathy. If seizures occur, they typically present early in the course of PRES (within the first 24–48 hours) and often become generalised [43, 44]. Confirmation of PRES is carried out with CT (computer tomography) or MRI (magnetic resonance imaging). These imaging modalities reveal subcortical white matter hyperintensities secondary to vasogenic brain oedema. In some patients, infarction areas may also be observed [45]. MRI offers the advantage of better resolution allowing for the detection of even small focal abnormalities, particularly in the posterior fossa and the absence of radiation exposure [46].

The oedema is typically observed in the white mater of the parietal, temporal, and occipital regions of the brain [47]. Symmetric distributed frontal and temporal lobe lesions can be present in up to 75% patients [48]. Intraparenchymal or subarachnoid haemorrhage can be observed in 10 to 25% of patients and microhaemorrhages may be present in up to 65% of patients [49]. Both clinical and radiological findings are generally reversible [45, 47].

The mechanism underlying PRES remains poorly understood. Sudden increases in systemic blood pressure cause endothelial injury. Consequently, the transudation of fluid into the tissue and petechial haemorrhages occurs [45, 50]. Impaired cerebral autoregulation causing hyperperfusion, endothelial dysfunction and reperfusion injury may also play a significant role [51].

Common risk factors for developing PRES include preeclampsia/eclampsia, renal failure, blood pressure fluctuations, autoimmune disorders, and the use of cytotoxic drugs [46, 52]. PRES is present in 75 to 98% cases of eclampsia and 46% cases of preeclampsia and is mostly occurring in the third trimester of pregnancy, especially after 36 weeks' gestation and in postpartum eclampsia patients [43, 45, 53, 54].

Currently there is no specific treatment for PRES and the primary approach to therapy is removing the underlying precipitating factor [46]. Most patients require admission to the ICU for close monitoring and prolonged infusions of antihypertensive drugs. Up to 40% may also require sedation, mechanical ventilation and management of increased intracranial pressure (ICP) in malignant PRES (declining alertness and/or Glasgow comma scale <8) as described in Section 9 [44, 46]. A target mean arterial blood pressure of 105–125 mmHg and a gradual reduction of blood pressure by 20%–25% are generally required [55]. There are no randomized controlled trials for treating hypertension in PRES. Labetalol (2–3 mg/min), nicardipine (5–15 mg/hour), and nimodipine are commonly used as first-line drugs, while sodium nitroprusside, hydralazine and diazoxide are considered as second-line agents [56].

The presence of severe encephalopathy, hyperglycaemia, elevated level of C-reactive protein, low cerebrospinal glucose, coagulopathy, involvement of corpus callosum, extensive brain oedema, haemorrhage, and restrictive diffusion on imaging are associated with a poor outcome, whereas the presence of preeclampsia/eclampsia is associated with a better prognosis [53].

7. Reversible cerebral vasoconstriction syndrome

Reversible cerebral vasoconstriction syndrome (RCVS) is an umbrella term for various rare syndromes that share similar clinical and radiological features with potential serious complications and is likely underdiagnosed [33, 57, 58]. RCVS presents with a hyperacute onset of a severe headache (peak intensity <1 min) or a severe recurrent headache with or without focal neurologic deficits and segmental cerebral vasoconstriction of medium-sized vessels of the circle of Willis or extracranial circulation on imaging in at least two different arteries without primary angiitis or aneurysmal subarachnoid haemorrhage [59]. One third of patients exhibit abrupt hypertension [53]. Headaches are typically bilateral and diffuse [59] and may be triggered or exacerbated by Valsalva manoeuvres, which are a normal part of labour [33, 59, 60]. Patients' symptoms often include nausea, vomiting, phonophobia and photophobia. Focal neurologic deficits are present in up to 45% of cases and seizures occur in up to 17% [59]. Vasculitis should be excluded through serology and cerebrospinal fluid analysis. Vasoconstriction resolves within days to weeks with complete resolution occurring no later than three months [61]. 70% of patients have a precipitating factor, vasoactive drugs (including ergot alkaloids), puerperium (10%–50%) or eclampsia being the most common, RCVS also can occur during pregnancy [33, 59, 60, 62, 63].

Postpartum RCVS accounts for approximately 1% of all postpartum headaches and can sometimes be misdiagnosed as postdural puncture headache [63]. Due to limited data, the incidence of reported preeclampsia/eclampsia varies widely (0%–39%) [51, 57].

To confirm the clinical suspicion of RCVS, multiple neuroimaging options are available. In clinical practice, CT and CT angiography should be immediately performed. Magnetic resonance imaging (MRI) and magnetic resonance (MR) angiography can provide a more detailed information, particularly regarding parenchymal lesions. The presence of "beading" or "pearls on a sting" in the cerebral arteries, indicative of alternating parts of intense vasoconstriction and vasodilation is characteristic of RCVS [59, 61]. If CT angiography does not reveal vasoconstriction, digital subtraction angiography (DSA) should be performed, however, this method is contraindicated in pregnant women and can lead to complications [15, 59]. Up to 20% of patients with RCVS may show no vasoconstriction in the initial angiography, since the vasoconstriction may primarily affect small vessel [64]. In such patients repeat angiography should be performed after 1–3 weeks (time of peak vasoconstriction) [59]. Once vasoconstriction is confirmed, transcranial doppler should be performed to obtain a baseline status and repeated for follow-up [61]. In every new neurological deterioration, consideration should be given to the DSA because of the possibility of intra-arterial intervention. To confirm the reversibility of a vasospasm, angiography should be repeated after 3 months [33].

Laboratory blood tests typically show normal results, the cerebrospinal fluid, however, may sometimes exhibit certain abnormalities (protein level <100 mg/dL, white blood cells <15 per mm^3, normal glucose level) [57].

The pathophysiological mechanism underlying RCVS is not completely understood. Cerebral vascular endothelial dysfunction may be a key factor, accompanied by increased oxidative stress, disruption of the blood-brain barrier, brain-derived neurotrophic factor polymorphism, reduced circulating endothelial progenitor cells, sympathetic hyperstimulation, and abnormal heart rate variability [59, 65, 66].

After confirming RCVS, the triggering factor should be removed without delay—Valsalva manoeuvre and vasoactive drugs. No guidelines regarding pharmacological treatment exists. Based on case reports and expert opinion, the recommended approach includes multimodal analgesia and calcium

channel blockers, while magnesium sulphate has also been used in certain cases [57].

Oral (30–60 mg every 4 hours) or intravenous nimodipine (1–2 mg/hour) over 4–8 weeks is the preferred drug, although no evidence suggests that nimodipine contributes to a better improved long-term outcome or prevention of complications [59]. It is considered safe in breastfeeding women and neonates [63].

Alternative treatment options include verapamil and nicardipine, administered orally over a period of 4–8 weeks [33]. Severe cases should be admitted to the ICU for close monitoring and treatment of hypertension and neurological deficits or seizures [57]. There are some case reports including non-pregnant patients, using intraarterial vasodilators including milrinone and angioplasty in most severe cases, although the experience is limited, and the benefit remains unclear [59, 67]. Non-steroidal anti-inflammatory drugs are not advised due to the potential to exacerbate RCVS. If necessary, antiemetics and antiepileptics should be administered. Patients with stroke, intracerebral haemorrhage, SAH or raised ICP warrant admission to the ICU and should be managed according to their condition as described in Section 9.

Approximately one third of patients with RCVS develop complications: PRES (8%–38%), subarachnoid or intraparenchymal haemorrhage, ischemic stroke, cervico-cephalic artery dissection [66]. The presence of aphasia/neglect/apraxia during the acute phase of the disease are identified as independent risk factors for residual neurological deficit after RCVS [33].

In general, the outcome in RCVS is good. An estimated 90%–95% of patients recover within weeks. Less than 10% of patients exhibit permanent neurological deficits [59].

8. Cerebral venous thrombosis

Cerebral venous thrombosis (CVT) is a relatively rare cause of stroke in the general population, however, it accounts for 80% of all stroke causes in younger adults (under 50 years) [68]. The thrombosis mostly affects the transverse sinus (86%) and superior sagittal sinus (62%), with thrombi extending into multiple sinuses in up to 90% [69, 70]. There is a strong female predominance (75%) since it is more commonly in association with pregnancy [69, 71].

Half of the patients exhibit multiple risk factors, *e.g.*, genetic thrombophilia, anaemia, obesity, severe inflammatory disease, and infections (*e.g.*, severe acute respiratory syndrome coronavirus type 2—SarSCov2 infection) [68, 72]. Regarding pregnancy the risk for CVT increases during the third trimester and during the first six weeks after delivery there is a 19-fold increased risk [68, 72, 73].

The clinical manifestation of CVT in peripartal period is not significantly different from that in the general population [71, 74]. More than 80% of patients' experience headache [75], and the most commonly observed signs and symptoms include elevated ICP, focal neurological deficits or encephalopathy [68]. In one third of patients, the onset of symptoms is acute, usually presenting with stroke-like symptoms or thunderclap headache [69, 76]. In two thirds of patients the onset of symptoms is subacute (>48 hours) and can include headache, seizures (in up to 40%), focal symptoms and a reduced level of consciousness [69, 76, 77].

To confirm CVT, neuroimaging is essential [75]. The European Stroke Organisation guidelines recommend CT or MR angiography (venography) [78]. A positive CVT diagnosis requires visualisation of a thrombus in a venous sinus or cerebral vein with absent blood flow. In the largest published prospective multinational cohort of patients with CVT—the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT) 64% of patients had parenchymal lesions [69].

The extent of brain injury can vary greatly ranging from mild vasogenic oedema to extensive intracerebral haemorrhage. Notably, juxtacortical flame-shaped lobar haemorrhages in the parasagittal frontal and parietal lobes were described as a pathognomonic finding, particularly in patients with superior sagittal sinus thrombosis [79].

In addition to neuroimaging, full blood count, coagulation profile and metabolic panel should be conducted [75].

The pathophysiology underlying CVT remains not fully understood and likely represents an interplay of hemodynamic changes and alterations in brain parenchyma [80]. CVT is nearly always associated with the triad of Virchow, additionally, hypovolemia due to postpartum haemorrhage and trauma during delivery (especially with Cesarean section) may further promote thrombosis [75].

The main goal of the treatment is to prevent the extension of thrombosis, the formation of new thrombi, restore antegrade drainage and prevent further damage of the brain tissue. Upon confirming the diagnosis of CVT prompt anticoagulation should be initiated even in patients presenting with intracerebral haemorrhage [78]. Neither standard heparin or low-molecular weight heparin (LMWH) cross the placenta [81, 82]. The European Stroke Organisation guidelines recommend therapeutic doses of LMWH administered subcutaneously due to slightly better outcomes, although the supporting evidence is limited [78, 83]. In situations that a neurosurgical procedure or a delivery by caesarean section is required and in patients with severely reduced kidney function, the administration of intravenous unfractioned heparin infusion in the therapeutic range may be the preferred approach [82, 84]. Since rapid venous recanalization could lead to improved outcomes in severe CVT, there have been numerous cases of endovascular approaches, but the consensus of criteria for recanalization is lacking [68, 74]. The European Stroke Organization guidelines recommend the use of endovascular therapy only for patients whose condition continues to deteriorate despite the use of first-line anticoagulation [78]. Recently, the TO-ACT trial that compared anticoagulation only to endovascular treatment in patients with at least one predictor of poor outcome (mental status disorder, coma state, intracerebral haemorrhage, or thrombosis of the deep venous system), was terminated prematurely due to futility. The clinical outcome did not differ significantly between the two groups of the 67 recruited patients [85].

In addition to anticoagulation, many patients need supportive care (headache management, hydration), along with treatment for raised ICP or seizures as described in Section 9 [68].

The primary cause of death in CVT is brain herniation.

Decompressive craniotomy may be lifesaving in patients with impending brain herniation, the decision should be made on a case-by-case basis [68, 76].

The results of the prospective DECOMPRESS-2 trial were presented at 2021 European Stroke Organization Conference but are yet to be published. More than half of the patients (58%) recruited for the DECOMPRESS-2 trial were comatose prior to surgery, and the trial found unfavourable outcomes [76].

According to our best knowledge, there is no clear data regarding the preferred delivery mode in pregnant women with stable CVT. Potential issues are as follows; CVT is more common in the puerperium, Cesarean delivery is a risk factor for developing CVT on the one side, on the other side vaginal delivery is related to increases in intracranial pressure which can worsen the neurologic outcome and can also result in massive bleeding and trauma which lead to additional coagulation disturbance.

Regarding general functional outcome, the prognosis of CVT is good. While 85%–90% of patients regain functional independence, many of them can experience long-term complaints such as cognitive impairment, mood disturbance, fatigue, and pain, all of which can have a significant impact on quality of live [76]. Approximately 10%–15% of patients present with neurological deficits or even die [86]. Following acute treatment, most patients require oral anticoagulation for a minimal period of six months and LMWH in subsequent pregnancies is recommended [76, 78].

9. General therapeutic measures of pregnant/patients during the puerperium needing intensive therapy

Pregnant women and parturient admitted to the ICU due to neurological complications often need intubation, mechanical ventilation and haemodynamic stabilisation.

Airway management can be challenging, and the risk of hypoxemia and aspiration of gastric content is high. A neuroprotective airway management should be provided [87]. There are no guidelines for optimal mechanical ventilation, but to prevent volutrauma, plateau pressure should be kept <24 cmH_2O and driving pressure <13 cmH_2O. Tidal volumes should be kept 6–8 mL/kg. Hypoxemia and hypocapnia should be avoided since they cause foetal ischemia [88].

The goals of analgesia and sedation should be the same as in non-pregnant patients and the depth of sedation should be monitored [88]. Short acting agents are preferred always considering the risk of potential foetal harm. Propofol, lorazepam, dexmedetomidine, remifentanil and fentanyl are probably the drugs of choice [88, 89].

Haemodynamic stability is one of the main goals in every critical ill patient and is the mainstay of adequate cerebral perfusion pressure (CPP). Hypovolemia should be promptly corrected with isotonic or hypertonic fluids if appropriate, and electrolyte disturbances corrected [88]. If needed, vasopressors and/or inotropes should be titrated to a target mean arterial pressure (MAP), according to the trimester/puerperium, and target CPP, always considering potential placental vasoconstriction and foetal ischemia [88, 90, 91]. Since placental vessels do not have autoregulatory capacity, the flow passively follows blood pressure [88]. Phenylephrine is the vasopressor recommended in pregnant women, since it does not cross the placenta. Due to its pure alpha 1 agonism, it causes reflex bradycardia and is a potent splanchnic vasoconstrictor [92]. It also may worsen systolic/diastolic function and ventriculoarterial coupling which may be important in a compromised foetus [93, 94]. Noradrenaline may be the better alternative since it has the potential to improve mother's cardiac output through its beta agonism [94, 95]. In pregnant patient, foetal monitoring should be done [88].

To date, none of the standard therapeutic interventions for controlling ICP have been evaluated in clinical studies regarding the safety and efficacy in pregnant women. Clinical presentation of elevated ICP is not different than in non-pregnant population [87, 96]. The diagnostic rule to predict elevated ICP based on clinical and CT data in non-pregnant population should also be applicable to pregnant women [97]. The same applies for the indications of invasive ICP monitoring, external cerebral fluid drainage and neurosurgical procedures [87, 88, 98].

A stepwise and additive therapeutic approach for non-pregnant patients with elevated ICP should be adapted to pregnant women considering known potential harm of specific therapies [88, 96]. If any clinical or ICP deterioration occurs, neuroimaging should be done. General measures are the same as in non-pregnant population: head position and avoiding potential causes of elevated ICP [87, 99].

Adapted to physiological changes of pregnancy, the target values of the so-called physiological neuroprotection are as follows; normovolaemia, central temperature <37.5 °C, haemoglobin 7–10 g/L, serum sodium 135–145 mEq/L, serum glucose 110–150 mg/dL, SaO_2(oxygen saturation of arterial blood) $>92\%$, PaO_2(partial pressure of oxygen) >70 mmHg and $PaCO_2$ (partial pressure of carbon dioxide) 30–32 mmHg [88]. The target value of ICP <23 mmHg and CPP 50–60 mmHg should be maintained [88, 100].

Regarding osmotherapy, hypertonic saline should be preferred in pregnant women, since mannitol crosses the placenta and causes foetal dehydration, hypovolemia, hypoxia, bradycardia, and changes in acid-base status secondary to maternal hyperosmolarity [88].

Hyperventilation should only be used in case of brain herniation and lethal elevation of ICP for the shortest possible time and under strict foetal monitoring [88].

In general, barbiturates and hypothermia should be avoided in pregnant women, since they cause multiple complications in both the mother and the foetus [88, 101].

10. Conclusion

Neurological clinical symptoms that manifest during pregnancy, delivery and puerperium require immediate and accurate diagnosis and treatment to prevent the serious consequences or even death, safeguarding not only the health of the mother but also that of the baby.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

AUTHOR CONTRIBUTIONS

AMP—designed the study. AMP and JS—performed the literature research. All authors wrote the manuscript and contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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