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REVIEW

Headache in challenging and special circumstances: Pregnancy and lactation

Zorlu ve özel koşullarda baş ağrısına yaklaşım: Gebelik ve laktasyon

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Summary

Headache has special importance during pregnancy and postpartum period. The health-care professionals and patients report headache management as challenging during pregnancy and lactation period. Cautions are recommended in pregnancy and lactation due to maternal and fetal/newborn risks. Most headaches in the first trimester are due primary headaches. Nevertheless, the incidence of secondary headaches increase in the last trimester and post-partum period. Red flags prompt early evaluation in a patient with headache. Assessment of headache patient requires a detailed history of the headache characteristics and performing appropriate examinations. Approach to headache and strategies to promote best practice in pregnancy and lactation will be reviewed.

Keywords: Diagnosis; migraine; primary headaches; red flags; secondary headaches; treatment.

Özet

Gebelik ve doğum sonrası dönemdeki baş ağrıları özel bir önem taşımaktadır. Bu dönemdeki baş ağrısı yönetimi sağlık çalışanları ve hastalar tarafından zorlayıcı olarak bildirilmektedir. Başağrısına doğru yaklaşım hem anne hem de fetal/yenidoğan risklerinin önlenmesi açısından önemlidir. İlk trimesterdeki baş ağrılarının büyük çoğunluğu primer baş ağrıları grubundadır. Gebeliğin son trimesteri ve doğum sonrası dönemlerde, sekonder baş ağrılarının sıklığı ise artmaktadır. Baş ağrısı hastalarında kırmızı bayrak belirti ve bulgularına dikkat edilmelidir. Baş ağrısı hastasının değerlendirilmesinde detaylı anamnez alınması; doğru ve eksiksiz olarak fizik ve nörolojik muayene yapılması yanında gerekirse ileri tetiklerin yapılması da önemlidir. Bu derlemede gebelik ve laktasyon dönemindeki baş ağrılarına yaklaşım ve en iyi medikal uygulama stratejileri gözden geçirilmektedir.

Anahtar sözcükler: Tanı; migren; primer baş ağrıları; kırmızı bayrak bulguları; sekonder baş ağrıları; tedavi.

Headache is the most common disease of admissions to the neurology outpatient clinics and the seventh highest cause of disability worldwide.[1] Pregnancy and lactation are unique conditions in which certain diseases are seen either in a specific manner or with increased frequency. Headache has special importance during pregnancy and postpartum period due to the negative impact on both to the mother and the baby. The International Classification of Headache Disorders classifies headaches as 1) primary headaches, 2) secondary headaches and 3) painful cranial neuropathies, other facial pains and other headaches.[2] Although most headaches in pregnancy are primary and benign, pregnant women may present with a secondary headache due to pregnancy- related conditions (e.g. role of clotting factors, vascular endothelium, hemodynamic functions, immunity etc.). Increased risk of certain secondary headaches during pregnancy seek for attentive evaluation and management.[3]

Assessment of a headache patient requires a detailed history of the headache characteristics and performing appropriate examinations. Headache history is mandatory and must include location of pain, severity of pain, quality of pain, duration of pain, headache attack characteristics, accompanying features, factors that precipitate/increase or al-

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leviate pain, etc.), medical history, and family history (genetic predisposition to headache etc.) should be obtained.[4] Red flags prompt early evaluation in a patient with headache. The sudden onset of worst headache ever experienced, headache that peaks in severity very quickly, new onset headache, change in previous headache characteristics or worsening of headache, headaches awakening a woman at night, headaches associated with blurred vision or pulsatile tinnitus, headaches precipated by valsalva, headache severity change with posture, headaches with prolonged auras or complicated features such as aphasia, weakness, or numbness, prolonged neurological symptoms, chronic persistent unilateral headaches, changes in the frequency and character of the headache, recent trauma, thrombophilia and headaches in anyone who are on anticoagulation therapy or history of malignancy, immune deficiency, HIV, pituitary tumour, hypertension prompt early evaluation.[5]

Most headaches in the first trimester are due primary headaches (most commonly due to migraine, tension-type and rarely cluster headache). Nevertheless, the incidence of secondary headaches increase in the last trimester and post-partum period.[6] A complete neurologic examination is crucial. In primary headache disorders, the general and neurological examination should be normal. Positive findings on fundoscopy (e.g.papiledema or hemorrhages), neck stiffness, fever, visual disturbances, altered consciousness, unsteadiness, weakness, sensory deficits, or any focal neurological deficit must be excluded. Headache is one of the most common cause for brain imaging during pregnancy.[7] If any red flag is present, neuroimaging and further additional studies (such as imaging of the vessels of the head and neck and lumbar puncture) may be offered to the severe headache patients.[6] Magnetic resonance imaging (MRI) is the preferred imaging modality during pregnancy. Gadolinium has a risk of passage through the placenta and may impair fetal renal function.[8] Although amount of radiation exposure to the fetus from a non-contrast maternal head computerized axial tomography (CT) is less than the amount of radiation that may cause fetal loss,[9] growth retardation or fetal anomalies are still considered as risk of a stochastic effect.[10] Thus, MRI is preferred over CT in pregnancy.

1. Approach to primary headaches in preganancy and lactation

a) Migraine

Migraine is more common in women and the prevalance peaks at reproductive years.[3] Fluctuations in estrogen levels influence migraine attacks.[11] Migraine is one of the commonest headache in pregnancy. The risk of prematurity, intrauterine growth restriction and fetal malformations are of concern in pregnant migraineurs.[3] In a review of 401 women with migraine, 71.6% confirmed that they searched informations about safetiness of usage of their previous antimigraine medications during their pregnancy and lactation. Nearly half of women who consulted through multiple sources reported that they experienced conflicting informations. More than third admitted to the study reported that they had stopped taking their drugs. These women clearly signified the demand of follow-up visits and easy accesibility to their healthcare professionals during their pregnancy and breastfeeding periods.[12]

Menstrually triggered migraine is reported to be more frequent in patients with migraine without aura.[11] Due to sex hormonal changes, pregnancy is in general reported to decrease the migraine attack frequency and this effect is reported to be more profound in patients with migraine without aura.[13] However, migraine may even worsen, particularly in the first trimester[3] when human chorionic gonadotropin levels are decreased.[11] Unfortunately, the frequent migraine attacks at the first trimester and usage of antimigraine treatments may represent a vulnerable time for fetal drug toxicity.[14]

Strategies of migraine treatment in pregnancy and lactation

General strategy is to start with behavioural/non-medical treatments.[15] The most frequently reported triggers for migraine are stress (mental or physical), irregular or inappropriate meals, high intake or withdrawal of coffee and other caffeine-containing drinks, dehydration, sleep disorders (too much or too little sleep), and reduced or excessive physical exercise.[16] Pregnant women with migraine should be encouraged to avoid skipping meals, take regular exercise, drink plenty of fluids, and maintain a regular sleep pattern. Alcohol and smoking are potentially harmful to the fetus and should be avoided dur-

ing pregnancy. Nonpharmacological therapies such as relaxation, biofeedback, and physical therapy are safe and may be effective in pregnancy.[17]

Acute migraine attack treatment options

Acetaminophen

Acetaminophen remains the first- line and safe treatment option for pain and fever in pregnancy. A large cohort study showed that acetaminophen, was used by 39.7% of women during the first 5 months of pregnancy.[18] Nevertless, reports from three independent studies[19] showed adverse neurodevelopmental effects[20] in children after long-term exposure (>28 days) in utero.[21] However, the European Medicines Agency (EMA) concluded that current evidence is still insufficient to support the association between paracetamol exposure in pregnancy and neurodevelopmental risks.[22]

Acetaminophen is excreted in breast milk in low concentrations and the metabolic capacity of paracetamol is about the same in neonates as in adults.[23] Acetaminophen is considered safe during breastfeeding.[24]

Nonsteroidal anti-inflammatory drugs (NSAIDs)

NSAIDs are frequently used for acute attack treatment.[25] In fetus, prostaglandins mediate relaxation of smooth muscle cells of the ductus arteriosus,[26] renal blood vessels and the systemic vasculature.[27] Adverse pregnancy outcomes following NSAIDs differ according to the trimester of the drug exposure.[28] NSAID usage in early pregnancy has been associated with miscarriages[29] and congenital malformations.[28] Use of NSAIDs at late pregnancy has been associated with premature closure of the ductus arteriosus,[30] neonatal intraventricular haemorrhage,[31] impaired renal function,[32] persistent pulmonary hypertension of the newborn[33] necrotising enterocolitis[30] and cerebral palsy.[31] As a conclusion, due to the increased risk of miscarriage and congenital malformations, NSAIDs should preferably be avoided in the first trimester. In the second trimester and the early part of third trimester, the use of single doses of NSAIDs for treating acute migraine attacks is justified when both nonpharmacological therapy and paracetamol are proven to be insufficient. Usage of NSAIDs closer to term should be avoided due to the increased risk of adverse fetal outcomes.[22]

In general, NSAIDs are considered compatible with breastfeeding. Particularly ibuprofen being the drug of choice owing to its short elimination half-life (about 2 hours), lack of active metabolites, and low excretion in milk.[34] As children exposed to salicylates have a theoretical risk of Reye syndrome, regular use of salicylates during breastfeeding should be avoided.[15]

Triptans

Triptans act as serotonin 5-HT1B/1D/1F receptor agonists. Triptans pass through placenta and 5-HT1B/1D receptors are reported to be present in the umbilical cord artery[35] and fetal brain.[36] Although accumulated data suggest that sporadic use of sumatriptan is probably safe during pregnancy, concern has been raised regarding the possibility that the vasoconstrictive effects of triptans could cause malformations related to vascular effects. For triptans other than sumatriptan, safety documentation remains limited. It is suggested that sumatriptan might be the first choice if triptans are considered necessary during pregnancy.[22]

The Summary of Product Characteristics for sumatriptan advises that breastfeeding should be avoided for 12 h after treatment. This precaution may be regarded as very conservative, given the drug's short elimination half-life of about 2 hours and its low oral bioavailability.[22] Eletriptan is suggested to be even safer than sumatriptan because its high plasma protein binding and lower concentrations in breast milk compared to sumatriptan.[37] Thus, eletriptan may be an option for the breastfeeding refractory migraineurs.

Antiemetics

Metoclopramide and domperidone have been widely used in acute migraine treatment. In pregnancy, metoclopramide is commonly used in the treatment of hyperemesis gravidarum, and no association with congenital malformations or other harmful fetal effects has been established.[38] Safety data for domperidone in pregnancy is lacking. However, electrocardiographic QT-prolongation in newborns and infants has been reported following paediatric use of domperidone.[39] Thus, domperidon should be avoided in pregnant women.[22]

No adverse effects with metoclopramide have been reported in breastfed infants.[40] Metoclopramide in

single dose may not cause harm in the infant, if necessary may be considered compatible with breastfeeding.[22]

Migraine preventive treatment options

Medications commonly used for migraine prophylaxis in the healthy adults include β-blockers, antiepileptic drugs, tricyclic antidepressants, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), calcium channel blockers and botulinum toxin type A (BTX-A).[22] During pregnancy, prophylaxis may only be advised in pregnant who have frequent (>3–4 attacks per month) and prolonged severe attacks, especially for those who do not respond to symptomatic treatment, or experience complications such as dehydration, anorexia and fetal stress.[34] Caution should always be taken according to the stage (trimester) of the preganancy.

β-blockers

If prophylaxis is considered necessary during pregnancy, the lowest effective doses of propranolol or metoprolol are the drugs of choice.[15] The metabolism of metoprolol is markedly enhanced during pregnancy[25] which could impair its clinical effect. The usage of β-blockers in the third trimester can induce fetal bradycardia, and newborns exposed to β-blockers close to delivery should be monitored for pharmacological effects such as bradycardia, hypotension and hypoglycaemia.[34]

β-blockers are suggested as first-choice medications during lactation if migraine prophylaxis is considered.[41] Propranolol is excreted into breast milk, but the amounts are considerably lower. Although symptoms caused by β-blockade (such as bradycardia and hypoglycaemia) have not previously been reported following exposure to propranolol or metoprolol via milk, some authors nevertheless recommend that exposed infants should be closely observed for these signs.[42]

Antiepileptics

Antiepileptic drugs are not recommended in pregnancy. In healthy adults, (except pregnants) valproate and topiramate are the two antiepileptic drugs with good efficacy in migraine prophylaxis.[42] Risk of fetal anomalies such as oral clefts are increased after exposure to topiramate in pregnancy.[43] Sodium valproate is associated with a high risk of fetal abnormalities such as neural tube defects, cardiovascular abnormalities and is contraindicated during pregnancy in the absence of refractory epilepsy.[44] Valproate binds highly to plasma proteins, thereby limiting its passage into breast milk.[45] Although infant plasma levels after exposure via breast milk are considerably low, it has been argued that valproate is best avoided owing to its teratogenic potential once the lactating mother become pregnant again.[46]

Antidepressants

Antidepressants are not usually recommended in pregnancy. Among the tricyclic antidepressants used in the prevention of migraine, amitriptyline has the best-documented effect.[34] Low-dose amitriptyline 10 mg/d to 25 mg/d may be an option. While data are conflicting regarding limb deformities associated with use of high doses of amitriptyline during pregnancy, no association has been reported with low doses between 10 and 50 mg/d which are recommended doses for pain management.[15] Exposure to antidepressants in late pregnancy may cause neonatal adverse effects such as drowsiness, jitteriness, hyperexcitability, and suckling problems.[37] Amitriptyline has been suggested as a second-line choice (after β-blockers) as preventive therapy in pregnant women.[41] Milk levels of amitriptyline and its active metabolite nortriptyline are low.[47] Adverse effects have not been reported in breastfed infants, and infant plasma levels have been reported to be very low. However accumulation cannot be excluded in premature and newborn babies.[34]

ACE inhibitors, ARBs and calcium channel blockers

ACE inhibitors, ARBs and Calcium Channel Blockers are not recommended in pregnancy. Intrauterine exposure to ACE inhibitors and ARBs are associated with increased risk of adverse outcomes in the fetus, including miscarriage, oligohydramnios, renal failure and death.[48] ACE inhibitors and ARBs are considered to be contraindicated at any stage of pregnancy.[49] The calcium channel blocker flunarizine should not be used during pregnancy owing to its insufficient safety data.[22]

Botulinum toxin type A

Data is not sufficient to recommend Botulinum toxin A in pregnancy. Botulinum toxin type A is adminis-

tered as intramuscular injections in the neck and head. Because of its high molecular weight, BTX-A is not expected to cross the placenta.[50] BTX-A may only be considered as an option in treatment-refractory cases. Botulinum toxin type A would consequently not be excreted into breast milk.[22] It should also be kept in mind that a black box warning information of "DISTANT SPREAD OF TOXIN EFFECT" is present in botulinum toxin products. We also do not recommend this toxin to our pregnant patients.

Magnesium and riboflavin

Magnesium may be used during pregnancy for migraine, constipation and pre-eclampsia.[51] One gram intravenous magnesium sulfate given over 15 minutes is an efficient, safe, and well-tolerated drug in the treatment of migraine attacks.[52] There are no indications of any untoward maternal or fetal effects after intrauterine exposure.

Riboflavin is a safe and well-tolerated alternative in migraine prophylaxis.[53]

Magnesium is normally found in breast milk. There is no reason to believe that surplus magnesium in breast milk would cause any substantial effects in the infant.[54] Neverthless, fewer data are available for riboflavin, this drug is also considered compatible with breastfeeding.[22]

Peripheral nerve blocks

Peripheral nerve blocks are practiced widely by headache specialists.[55] Common injection sites are upper cervical nerve branches (greater occipital nerve, lesser occipital nerve) and trigeminal nerve branches (auriculotemporal nerve, supraorbital nerve, supratrochlear nerve).[56] Lidocaine and bupivacaine which are well studied in pregnancy are commonly used in dentistry and obstetric anesthesia.[57] According to retrospective, uncontrolled case series none of the patients experienced any major maternal or fetal adverse effects related to these drugs. Peripheral nerve blocks are used for both short-term migraine prophylaxis as well as the treatment of status migrainosus.[58]

Non-pharmacological interventions

Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) is a noninvasive method by which weak electrical currents are induced in the brain by a rapidly changing magnetic field. When TMS is applied to the head, the magnetic field passes through the skull, inducing mild electric currents in the brain, which excite and depolarize neurons in the brain.[59] TMS is considered as a low risk technique with promise in the diagnosis, monitoring, and treatment of different types of neurological and psychiatric diseases in adults.[60] Several clinical studies have shown that single-pulse TMS (sTMS) is an effective and well tolerated treatment for migraine with or without aura, thus suggesting that sTMS may offer a nonpharmacologic, nonbehavioral therapeutic approach to the currently prescribed drugs for patients who suffer from migraine.[61] No adverse events were reported associated with repetitive transcranial magnetic stimulation application during pregnancy.[61] The Committee on the Possible Effects of Electromagnetic Fields on Biologic Systems, a committee of the National Research Council, reviewed exposures to electric and magnetic fields and concluded that reproduction and development in animals, particularly mammals, have not been shown to be affected by exposure to extremely low frequency electric or magnetic fields.[62]

Acupuncture

The Cochrane Collaboration review of 22 randomised controlled trials concluded that acupuncture is at least as effective as, or possibly more effective than, prophylactic drug treatment, and has fewer adverse effects. Acupuncture should be considered as a treatment option for patients willing to undergo this treatment.[63] The efficacy of prophylaxis thus demonstrated in nonpregnant women can probably be reached during pregnancy, with the added benefit that this treatment may not cause any harm to the fetus.[64]

Mind-body treatment options

The systematic review of 10 randomized clinical trials concluded that yoga has the potential for alleviating pain.[65] Prenatal yoga with a certified instructor may improve not only headache but also the overall health quality in pregnancy[66] and decrease comorbid conditions including depression, anxiety, and sleep disorders.[67,68]

b) Tension-type headache

Headaches that lack associated symptoms are likely

to be tension-type headaches. In most women, tension type headache will improve during pregnancy.[15] Symptomatic treatment with simple analgesics is appropriate for episodic attacks (fewer than 2 days per week).[69] Prophylactic medications are indicated when headaches regularly occur more than 2 to 3 days a week. Amitriptyline is the drug of first choice for prophylaxis of tension-type headache during pregnancy and lactation.[15]

c) Cluster headache

Cluster headaches are a series of relatively short but extremely painful headaches every day for weeks or months at a time. It is much more common in men than in women. It has stereotypical symptoms of strictly unilateral headache and autonomic symptoms lasting up to 2 hours in clusters typically lasting 6 to 8 weeks.[15] Acute treatment includes 100% nasal mask oxygen 7 L/min for 10 to 15 minutes at the onset or subcutaneous/intranasal sumatriptan.[70] Preferred preventive treatments during pregnancy and lactation are verapamil or prednisone/prednisolone. Verapamil can cause cardiac conduction problems. ECGs to assess PR interval prolongation should be undertaken at baseline, before each dose increment, and every 6 months during long-term treatment.[15]

2. Approach to secondary headaches in preganancy and lactation

a) Idiopathic intracranial hypertension (IIH)

Incidence of IHH is increasing, in parallel with the epidemic of obesity.[71] The common onset of IIH is in the first half of the pregnancy. Reccurrence of pre-existing IHH in pregnancy tends to ocur 20 weeks of pregnancy, reflecting the period of maximal weight gain.[72] Transient visual obscurations or dim outs and pulsatil tinnitus are predominant symptoms. Papilledema is important finding for the diagnosis.[73] Visual loss develops in 10%–20% of patients. Visual outcome is similar to non-pregnant state.[74] In suspected IIH patients, non-contrast Brain MRI and brain MR venography should be performed to exclude mimics, including mass lesions and cerebral venous thrombosis.[75] The next step is a lumbar puncture to check the opening pressure. After diagnosis of IIH, a referral to a neuro-ophthalmologist is warranted for close visual field monitoring. In pregnancy, controlled weight gain rather than weight loss is recommended. Medications such as acetazolamide and diuretics are usually avoided due to safety concerns. Although the complete safety of acetazolamide during pregnancy is not known, studies have shown favorable outcomes without fetal anomalies.[73] If vision is threatened, in conjunction and close monitorization with ophtalmology doctors, interventions such as serial lumbar punctures can safely be applied by specialist to control worsening of the symptoms.[76]

b) Pre-eclampsia and eclampsia

Pre-eclempsia and eclampsia are part of pregnancy specific dangerous conditions which remain significant risk of maternal/fetal morbidity and mortality. Preeclampsia occurs in about 2–8% of pregnancies, usually after 20 weeks' gestation time period and typically improves following delivery of the placenta.[77] However pre-eclampsia/eclampsia can occur in the postpartum period. Pre-eclampsia diagnosis requires arterial hypertension (>140/90 mm Hg) documented by two blood pressure readings at least four hours apart, or a rise in diastolic pressure of ≥15 mm Hg or systolic pressure of ≥30 mm Hg, coupled with urinary protein excretion >0.3 g/24 hours.[78] In addition, tissue edema, thrombocytopenia and abnormalities in liver function can occur. Eclampsia is defined by the onset of seizures in a woman with pre-eclempsia.[2] The neurological manifestations of pre-eclampsia/eclampsia reflect the areas of the brain affected. Seizures (in over 70%), hypertension (in 60%), confusion, headache and visual disturbances are common initial presentations.[79] Vision disturbances are common due to occipital and parietal lobe involvement including: cortical blindness, homonymous hemianopia, flashing lights, blurred vision, visual neglect or visual hallucinations.[80]

In the brain, the posterior circulation has less ability to autoregulate and is preferentially affected. Typically, brain imaging demonstrates posterior reversible encephalopathy syndrome, with bilateral white matter abnormalities, suggesting edema in the posterior regions of the cerebral hemispheres, but the changes may involve other cerebral areas including the brainstem or the cerebellum.[81] The diagnostic criteria for preeclampsia/eclampsia are listed by ICHD-III.[2] The management of pre-eclampsia/eclampsia includes: delivery of the baby, rapid control of blood pressure and seizure control. Hypertension

is usually managed with intravenous labetalol (beta blocker) or an intravenous calcium channel blocker such as nicardipine.[82] Seizures are safely treated by intravenous magnesium. In refractory cases or in status epilepticus, additional antiepileptic medications should be introduced. Fortunately, epilepsy is a rare consequence of pre-eclampsia/eclampsia, and long-term antiepileptic medications are generally not necessary.[83]

c) Cerebral venous thrombosis

Cerebral venous thrombosis is an uncommon cause of stroke, accounting for only 0.5%–1% of all strokes.[84] However pregnancy is a hypercoagulable state. This is a normal physiological adaptation to decrease the risk of blood loss at the time of delivery. There are increased levels of multiple procoagulant factors including factors II, VII, VIII, IX, X, XII and XIII, and a decrease in the anticoagulant proteins antithrombin III and protein S, as well as an acquired resistance to activated protein C. This prothrombotic state lasts up to 6 weeks post partum.[85] Two per cent of pregnancy-related strokes are attributed to cerebral venous thrombosis. The last trimester through the postpartum period has an increased risk. Additional risk factors include dehydration, caesarean section and older age.[86] Headache is the most common presentation of cerebral venous thrombosis. The headache may be of a thunderclap onset or more commonly may mimic IIH with gradual onset and features concerning for elevated intracranial pressure—worse on awakening with associated visual obscurations, papilloedema and sixth nerve palsy. Focal neurological signs or seizures may result from venous infarction or haemorrhage. Clues to the diagnosis of cerebral venous thrombosis include bilateral hemispheric involvement, haemorrhage in unusual locations and progressive symptoms.[87] Patients who have haemorrhage, stroke and involvement of the deep venous sinuses have the worst prognosis.[88] On MRI, venous sinus thrombosis can be seen directly as thrombus with signal characteristics appropriate to the time since onset (T1-isodense and T2-hypodense when acute, with T1 becoming hyperintense followed by T2 becoming hyperintense so that the thrombus is bright on both T1- and T2-weighted images at the late subacute phase). MR venography can also show the thrombosis as a filling defect, which does not require a contrast imaging.[89] After the diagnosis of cerebral venous thrombosis has been confirmed, other causes of a hypercoagulable states also needs to be excluded. Laboratory studies should include, full blood count, chemistry panel, prothrombin time and activated partial thromboplastin time. Testing for prothrombotic conditions, including protein C, protein S, antithrombin deficiency, antiphospholipid syndrome, prothrombin G20210A mutation, and factor V Leiden, are needed for the decision of long-term management. Testing for protein C, protein S and antithrombin deficiency is generally indicated 2–4 weeks following completion of anticoagulation.[87] Treatment is characterized by full heparin anticoagulation during the acute phase of cerebral venous thrombosis whether hemorrhage is present or not, and then a period of approximately 3 to 6 months of ambulatory anticoagulation.[89] Vitamin K antagonists, such as warfarin, are associated with fetal embryopathy and bleeding in the fetus; therefore, they are contraindicated in pregnancy. During pregnancy, low molecular weight heparin is the anticoagulant of choice. Postpartum low molecular weight heparin or a vitamin K antagonist can be used with a target international normalised ratio (INR) of 2.0–3.0.[90]

d) Reversible cerebral vasoconstriction syndrome (RCVS)

Reversible cerebral vasoconstriction syndrome (RCVS) is recently described combinations of clinical and radiological features: sudden, severe ("thunderclap") headache; transient, multifocal, segmental vasoconstriction of cerebral arteries lasting several weeks to months; and focal neurological symptoms, sometimes with stroke.[91] RCVS is commonly reported in post-partum period, usually within a week after delivery.[92] The exact pathophysiological process resulting in RCVS is unknown.[93] Brain MRI or CT angiography, may be normal in the first days of the process.[92] There is no consessus on the optimal treatment of RVCS.[93] Symptomatic pain relief and eliminating precipitating factors are recommended. Calcium channel blockers are often used to treat RCVS. The use of steroids are not recomended by most authorities.[94]

e) Pituitary apoplexy

Pituitary apoplexy is a rare but potentially life-threatening condition. It is due to haemorrhagic infarction of the pituitary gland and is more common with an

underlying pituitary adenoma. Acute changes in blood pressure, and stimulation of the gland by increased estrogen levels such as in pregnancy and coagulopathy are associated with pituitary apoplexy.[95] Headache is the most common presentation and may be severe, thunderclap in nature. The headache is often referred retro-orbitally due to irritation of the first division of the trigeminal nerve. Other features of pituitary apoplexy include changes in visual acuity and visual fields, change in mental status from a mild encephalopathy to coma, cranial nerve III, IV, and V involvements.[6] Pituitary apoplexy is a neuroendocrine emergency due to hormonal insufficiency. There are often multiple hormonal deficiencies including: adrenocorticotropic hormone, growth hormone, thyroid hormone and hypogonadotropic deficiency.[95] The most urgent issue is to assess for fluid and serum electrolyte imbalance and to replace corticosteroids. The role for surgery is controversial and generally restricted to patients with significant neurological impairment.[6]

f) Subarachnoid hemorrhage (SAH)

Subarachnoid hemorrhage (SAH) refers to extravasation of blood into the subarachnoid space between the piamater and arachnoid membranes. Subarachnoid hemorrhage without a preceding trauma is caused by the rupture of an intracranial aneurysm in 80% of cases; other causes include vascular malformations and vasculitis.[96] The etiologies of SAH in pregnancy are diverse and include ruptured saccular and mycotic aneurysms, ruptured arteriovenous malformations, intracranial venous thrombosis, pregnancy-induced hypertension leading to pial vessel rupture, intracranial vertebral artery dissection, Moyamoya disease, posterior reversible encephalopathy syndrome, and postpartum angiopathy, which is a form of the reversible cerebral vasoconstriction syndrome.[97] Mostly, pregnancy-related SAH are caused by aneurysmal rupture or bleeding from a vascular malformation.[98] Due to the increased vascular stress from expanded circulating blood volume and increased cardiac output, aneurysmal SAH is most commonly reported in the third trimester, and up to 6 weeks postpartum period.[99] Treatment include airway evaluation, blood pressure reduction, control of seizures and definitive treatment of the aneurysm once demonstrated.[100]

g) Postdural puncture headache (PDPH)

Parturients have approximately a 1.5% risk of an accidental dural puncture with epidural anaesthesia. Of these, about half will result in postdural puncture headache.[101] Headache occurrs within 5 days of a lumbar puncture, related with cerebrospinal fluid (CSF) leakage through the dural puncture. It is usually but not invariably orthostatic. Headache that significantly worsens soon after sitting upright or standing and/or improves after lying horizontally, accompanied by neck stiffness and/or subjective hearing symptoms.[2] Evidence of CSF leakage on contrats enhanced Brain MRI confirms the diagnosis. Independent risk factors post-dural puncture headache have recently been demonstrated: female gender, age between 31 and 50 years, a previous history of post-dural puncture headache and orientation of the needle bevel perpendicular to the long axis of the spinal column at the time of the dural puncture.[6] The headache location, severity and description are not helpful diagnostic features. Exercise and Valsalva manoeuvres can aggravate postdural puncture headache. Other symptoms can include nausea (73%) and dizziness (60%), horizontal diplopia, altered hearing and tinnitus, neck pain/stiffness and uncommonly visual field deficits.[102] Most women with PDPH improve spontaneously with bed rest, fluid intake, simple analgesics and caffeine.[103] Some may require parenteral treatment. In refractory cases, single epidural blood patch is highly effective with up to 90% response rate. Fever, infection on the back, coagulopathy and patient refusal are contraindications for epidural blood patch[6] In these cases, regional anesthetics (eg, occipital nerve block, sphenopalatine ganglion [SPG] nerve block) or alternative treatments (eg, acupuncture) may be offered.[104] Dural strech induced by low CSF volume may activate the trigemnal nucleus caudalis (TNC) causing increased activity in the trigeminal and greater occipital nerves. Greater occipital nerve block (GONB) results in interruption of pain transmission via occipital nerves to the TNC. The temporary reduction in afferent input to the TNC may cause a 'winding down' of the central sensitization, which provokes the headache.[105,106] The transnasal sphenopalatine ganglion block (SPGB) is a low-risk, noninvasive technique that is easily performed and could potentially be beneficial in the treatment of PDPH.[107] SPGB blocks the parasympathetic flow

to the cerebral vasculature through the sphenopalatine ganglion, allowing the cerebral vessels to return to normal diameter and thus relieving the headache.[108]

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