25 Neurologic disorders in pregnancy

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From headache to neuromuscular disease to stroke and movement disorders, neurologic disorders are common. They occur in men and women. Pregnancy is no exception. In fact, pregnancy may have an effect on neurologic condition; in turn, neurologic disorders may have an effect on pregnancy or outcome of pregnancy. Treatment of neurologic disorders is another important aspect whereby knowledge of teratogenicity is important for the physician treating a pregnant woman. While this is an extensive area, an attempt will be made to cover some key areas. The coverage will include headache, multiple sclerosis (MS), neuromuscular disorders (NMDs), epilepsy, movement disorders, and stroke.

HEADACHES IN PREGNANCY

Headache is perhaps the most common complaint in medicine and is a common complaint during pregnancy. Most headaches during pregnancy are due to primary headache disorders (migraine, tension-type, and cluster headaches). Although these may be debilitating, they are almost always benign. Secondary headache disorders are those in which an underlying cause can be identified for the headache. These include headaches due to infection, trauma, vascular disorders, pre-eclampsia, or cerebrospinal fluid (CSF) derangement. This chapter will attempt to look at the diagnosis and treatment of the major primary and secondary headaches during pregnancy.

Primary Headaches

Migraine

Migraine headaches are usually a moderate or severe unilateral or bilateral throbbing or pulsating headache with associated increased sensitivity to light, noise, or physical movement and may be accompanied by nausea and vomiting. Migraine pain also commonly involves the neck and medial shoulders in addition to the head. The usual duration of a migraine headache is 4 to 72 hours. Up to 25% of migraine headaches may be preceded or accompanied by an aura. The aura is due to neuronal dysfunction that is thought to move through the cortex and is accompanied by decreased regional blood flow (1).

The most common migraine auras are visual and sensory. Visual auras may produce positive visual phenomena such as seeing lights, stars, shimmering lights (scintillating scotoma), and pixilated or mosaic vision. The visual dysfunction may gradually spread across the visual field. Negative visual phenomena may also occur such as dark visual scotoma. Somatosensory migraine auras may produce numbness in the face or arm and hand that may slowly travel over the affected

area. Less commonly, patients may report dysarthria or aphasia as a form of aura accompanying a migraine attack.

The typical migraine aura builds up over 10 to 20 minutes and usually completely resolves in 60 minutes. The conclusion of the migraine attack usually coincides with the onset of the migraine headache.

In most women, migraine usually improves during pregnancy. Migraine improves in up to 50% to 80% of women during pregnancy (2,3). Migraine may recur in the first postpartum week in up to 50% of migraineurs (4).

Treatment of Migraine During Pregnancy

Migraine headaches affect up to 18% of women during their lifetime and are common during the childbearing years. Treatment of migraine during pregnancy is geared toward providing headache relief for the mother and avoiding potential adverse effects on the developing fetus. Acetaminophen (650–1000mg po), codeine (30–60mg po with acetaminophen), and hydrocodone (5.0–7.5mg with acetaminophen) are considered safe to use for acute pain relief. Narcotics should be avoided in the third trimester because of the risk of neonatal dependence and withdrawal following delivery. Narcotic use should be restricted to several days a week to avoid development of medication overuse headache. Non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and naproxen are considered safe (pregnancy class B) in the first and second trimesters but should be avoided in the third trimester due to potential risks of inhibiting labor or premature closure of the ductus arteriosus. The jury is still out on use of triptans (pregnancy class C) such as sumatriptan during pregnancy (5). At this time, it is difficult to recommend triptan usage during pregnancy unless felt absolutely essential for the well-being of the mother.

Ergotamine and dihydroergotamine (pregnancy class X) are contraindicated in pregnancy as they are considered potential abortifacients.

Antiemetics such as prochlorperazine (10mg IV), metoclopramide (10mg IV or PO), or ondansetron (4mg IV) are considered relatively safe in pregnancy and are particularly useful in women who have significant nausea, vomiting, and dehydration accompanying their migraines. Metoclopramide and ondansetron are pregnancy class B.

Women who have prolonged, recurrent, or severe migraines, particularly when resistant to acute treatment, should be considered for preventative migraine treatment. Beta blockers (atenolol, nadolol, propranolol, and timolol), some tricyclic antidepressants (doxepin and protriptyline), fluoxetine [a selective serotonin reuptake inhibitor (SSRI)], verapamil (a calcium channel blocker) are all class C

pregnancy drugs. Tricyclic antidepressants should be stopped at least 2 weeks before delivery due to the potential of neonatal respiratory distress.

There is inadequate information regarding use of the newer anticonvulsants [lamotrigine, gabapentin (GBP), topiramate (TPM), oxcarbazepine and levetiracetam (LEV)] for migraine prophylaxis in pregnancy (6). Valproic acid (VPA; pregnancy category D) should be avoided in women actively seeking to become pregnant or in early pregnancy due to reports of risks of neural tube defects (NTDs) when taken early in pregnancy (7).

The safest migraine treatment in pregnancy encompasses good headache hygiene—regular meals and sleep, avoidance of known migraine triggers for a particular patient, and the avoidance of stress when possible. Behavioral therapy such as focused relaxation techniques and stress management when available can also provide safe alternatives to pharmacologic treatment. The same modalities can be beneficial for tension-type headache sufferers.

Tension-Type Headaches

Tension-type headaches are the most common recurring headaches during pregnancy. The headache pain is usually described as mild to moderate (less severe than the usual moderate to severe pain of a migraine headache). The pain quality is dull and aching and located diffusely throughout the head or in a band-like encircling pattern. They are not typically associated with increased sensitivity to light, noise, or physical movement and are not accompanied by nausea and vomiting. The duration of tension-type headaches is variable, but most last less than a day. Like migraines, they may be triggered by stress. The most common variety of tension-type headaches is those that occur episodically (1–10 episodes less than 15 days a month). Chronic tension-type headaches (more than 15 days a month) occur in a small percentage of patients and may be associated with medication overuse.

Tension-type headaches in pregnancy can be treated pharmacologically with acetaminophen or NSAIDs (ibuprofen or naproxen in the first or second trimesters). Mild tension-type headaches often respond to rest, relaxation, cold or hot packs, physical therapy, or even acupuncture. Chronic tension-type headaches, especially if associated with depression, can be treated with an SSRI such as fluoxetine.

Cluster Headaches

Cluster headaches are more common in men than women (3–5:1) and are seen uncommonly in pregnancy. The typical cluster headache is a unilateral orbital, supraorbital, or temporal head pain of rapid onset (5–15 minutes to reach peak severity) that lasts from 15 to 180 minutes and subsides rapidly and completely. The pain is very severe and is usually described as boring, claw-like, or exploding. Cluster headaches are usually accompanied by ipsilateral autonomic symptoms with some combination of ptosis, conjunctival injection, tearing, rhinorrhea, or forehead sweating. Cluster headaches may occur several times a day and may be triggered by the onset of rapid eye movement sleep, awakening patients within an hour after going to sleep. Patients are usually very restless during a cluster attack and frequently rock back and forth or pace. Lying down (as opposed to migraine) may

aggravate the pain. Patients may have one or more attacks a day for 1 to 3 months during a cluster period and then have a period of complete remission for one to several years. Cluster headaches can usually be treated effectively with O₂ inhalation at 7L/min for 10 minutes by a non-rebreathing face mask. Up to two of three patients may obtain significant relief in 5 to 10 minutes (8).

Breast-Feeding Following Delivery

Drugs that are safe during pregnancy are safe to use in breast-feeding mothers. Acetaminophen and NSAIDs are considered safe for acute migraine and tension-type headaches. Short-acting triptans such as sumatriptan (half-life 2.5 hours) can be used by women who pump and store breast milk prior to triptan use. Beta blockers, verapamil, and narcotics (codeine and morphine) are also relatively safe.

Secondary Headaches

Secondary headaches in pregnancy include a number of disease states with potentially serious morbidity of the mother. These include subarachnoid hemorrhage, cerebral venous thrombosis (CVT) and stroke, pre-eclampsia, central nervous system (CNS) infections, and pseudotumor cerebri.

Subarachnoid Hemorrhage

Subarachnoid hemorrhage usually presents with a sudden onset, severe headache that patients frequently describe as the “worst of their life.” Pregnancy does appear to increase the risk of aneurysmal and arteriovenous malformation (AVM) rupture with the greatest risk later in pregnancy, at the time of delivery, and in the puerperium (9). Most subarachnoid hemorrhages can be diagnosed with the use of MRI or CT scanning. A small percentage however may have negative cranial imaging and require analysis of CSF for detection of the hemorrhage. The risk of subarachnoid hemorrhage is estimated at 1 to 2 per 10,000 pregnancies.

CVT and Stroke

The risk of CVT is increased both during pregnancy and in the puerperium. Many conditions such as thrombophilias (factor V Leiden and prothrombin gene mutations, deficiencies of protein C or S, or presence of high titers of antiphospholipid antibodies), red blood cell disorders such as sickle-cell anemia or polycythemia, local infections (meningitis, cerebral abscess, sinus or inner ear infections), and dehydration among others can predispose to CVT. When the superior sagittal sinus is involved by thrombosis, the intracranial pressure may be raised producing headaches and papilledema. If the cerebral cortical veins are involved, cerebral hemorrhages, strokes, and seizures may occur. Diagnosis of CVT is made by magnetic resonance imaging (MRI) and MR venography (MRV). Treatment of CVT is anticoagulation with heparin. Warfarin is contraindicated in pregnancy due to the risk of fetal hemorrhage and malformation.

The risk of stroke appears to be increased in pregnancy. The exact risk is not known but is estimated to be at least several fold (10). Most strokes in pregnancy are due to arterial occlusions and be accompanied by headache in up to 29% of patients (11). Hemorrhagic strokes can also occur in pregnancy and may be accompanied by headache in up to

57% of patients (11). Pregnancy itself appears to be accompanied by a hypercoagulable state predisposing to both arterial and venous thrombosis. Cardiac embolic disease, systemic or cerebral vasculitis, hematologic disorders, and thrombophilias are the common causes of secondary strokes, although in up to a third of cases, no clear cause can be identified. A reasonable diagnostic approach to a stroke in pregnancy includes cerebral imaging with an MRI of the brain, a carotid and cerebral MR angiogram, a transthoracic echocardiogram with saline contrast injection to look for a right to left cardiac shunt, and blood work to help rule out hematologic, metabolic, infectious, and inflammatory causes. Treatment of stroke in pregnancy must be individualized.

Pre-eclampsia

Pre-eclampsia usually occurs in the third trimester and may be seen in up to 7% of pregnancies (12). Pre-eclampsia may present with headache and may at times be the only symptom of the condition. Other signs and symptoms of pre-eclampsia include hypertension (BP of 140/90 or greater), proteinuria of greater than 300mg/dL, and blurred vision or non-formed visual hallucinations. If left untreated, pre-eclampsia may lead to a seizure (eclampsia), due to small cortical or subcortical hemorrhages. Treatment of pre-eclampsia consists of antihypertensives to control the hypertension, and if seizures are present, use of anticonvulsants (fosphenytoin or possibly LEV) to control the seizures.

CNS Infections

CNS infections may present with headache, fever, and neck stiffness, but are relatively uncommon during pregnancy. Suspected CNS infections should be evaluated with MRI brain imaging, followed by an analysis of spinal fluid obtained by lumbar puncture. CSF analysis should include cultures for bacteria, fungi, and acid-fast bacillus, and herpes simplex virus polymerase chain reaction.

Idiopathic Intracranial Hypertension (Pseudotumor Cerebri)

Women may present with raised intracranial pressure (idiopathic intracranial hypertension—IIH) during pregnancy. The risk is higher in obese women. The usual clinical manifestations are pressure like or dull, throbbing, generalized headache, blurred vision, or tinnitus. The optic disc margins may be blurred or frank papilledema may be present. Following an MRI brain, a lumbar puncture shows an opening pressure of 20 to 25 cm or higher. Treatment consists of serial lumbar punctures or treatment with acetazolamide (500–2000 mg a day). Acetazolamide may be used in the second half of pregnancy. Occasionally optic nerve sheath decompression may be necessary to help preserve vision (13).

Diagnostic Evaluation of Headache in Pregnancy

Evaluation of a pregnant patient with the complaint of headache starts with a detailed history and thorough physical examination. The history should include a full characterization of the headache, any history of previous headaches, any history of recent trauma, a general medical history, and a history of concomitant drug use (including prescription, nonprescription, and illicit drugs). Both a careful neurologic examination and a physical examination should be

performed with attention to vital signs, the cranial nerves (especially the eyes), the motor and sensory systems, and the cardiovascular system. If the fetus is of viable age (24 weeks or greater), fetal monitoring should be performed. Appropriate blood work would include a complete blood count and differential, comprehensive metabolic profile, erythrocyte sedimentation rate, and thyroid function studies. MRI procedures (MRI brain, MR angiogram of the cerebral and cervical circulation, and MRV) for visualization of the venous sinuses with gadolinium are the procedures of choice for suspected cerebral or cerebrovascular pathology. If MRI is not readily available, noncontrast CT scanning with abdominal shielding poses very limited risk to the developing fetus. As noted above, lumbar puncture should be considered for pregnant patients with suspected CNS infection, suspected subarachnoid hemorrhage with negative neuroimaging, or idiopathic intracranial hypertension.

In summary, the diagnosis and treatment approach to headaches during pregnancy should be directed toward providing relief and comfort for the mother and safety for the developing fetus.

MS IN PREGNANCY

MS is an immune-mediated demyelinating disease of the CNS. Up to twice as many women are affected by MS compared with men. Up to 80% of women affected by MS develop clinical evidence of the disease between the ages of 20 and 40, the prime childbearing years.

Epidemiology of MS

There is extensive literature on the epidemiology and genetics of MS, which can be briefly summarized as follows:

- **Gender:** As noted above, MS is more common in females by a 2:1 margin. Women tend to present earlier than men. Women also tend to have less severe disease course overall compared with men.
- **Race:** Caucasians have the highest rates of MS, particularly those of Northern European ancestry (especially those of Scandinavian descent). The risk of African-Americans is about half of that of Caucasians in the same geographic area. In the United States, Asians and Native Americans have the lowest rates of MS.
- **Geographic distribution:** The prevalence of MS is the greatest in temperate climates and increases with increasing distance from the equator. The areas of greatest prevalence contain a proportionally higher Caucasian population.
- **Migration:** Epidemiologic studies have shown migration affects the development of MS, especially if immigration occurs from a low-risk to a high-risk area before the age of 15. When migration occurs after the age of 15, people tend to maintain the risk of their native country. Children of immigrants from low-risk to high-risk areas (or vice versa) tend to acquire the risk of their new homeland (14).
- **Familial occurrence:** First-degree family members of MS patients have a significantly increased risk (10–15 times) of development of the disease. The risk of

development of MS for children with one affected parent is 1.8%. The concordance rate for the development of MS is at least six times higher in monozygotic twins compared with dizygotic twins (31% compared with 5%) (15).

- **Genetics:** Numerous genes have been evaluated as possible causes or markers for MS. The strongest association with MS has been found in individuals who possess certain HLA (human leukocyte antigens) genes found on chromosome 6. Specifically, the presence of HLA-DW2 haplotype is found in up to 50% to 70% of northern Europeans with MS. The presence of these genes is currently thought to confer an increased susceptibility for the development of MS. Multiple other sites on the human genome involved in immune function and modulation are being examined for their possible role in MS (16).

Types of MS

Several different subtypes of MS have been identified.

- **Relapsing–remitting MS (RRMS):** The most common type of MS accounting for up to 60% of patients. RRMS patients have discrete attacks of neurologic dysfunction (relapses or exacerbations) lasting weeks to a few months. Recovery from relapses may be incomplete and patients may accumulate increasing disability over time. Patients tend to have relative stability of disease between relapses.
- **Secondary progressive MS (SPMS):** Many patients with RRMS develop a gradually progressive course although they may continue to have occasional relapses. SPMS may account for up to 30% of MS cases.
- **Primary progressive MS (PPMS):** Accounting for up to 9% to 10% of MS cases, patients with PPMS have a continuous downhill course from onset of the disease without relapses.
- **Progressive relapsing MS (PRMS):** These patients have a progressive course from onset with intermittent relapses with continuing progression between relapses. This pattern can be seen in up to 5% of MS cases.

Clinical Features of MS

The clinical manifestations of MS are due to lesions in the CNS, from lesions in the brain, or spinal cord. Although the initial lesions are due to demyelination and may be reversible, demyelinating lesions may progress to axonal loss and gliosis producing permanent neurologic deficits. MS can produce a wide range of neurologic dysfunction. The most common clinical manifestations are reviewed below.

- **Motor symptoms:** Muscle weakness is common in MS and may be a major source of disability. Muscle weakness in MS usually involves the legs to a greater degree than the arms or hands and may be the greatest in the proximal legs. Hyperreflexia,

ankle clonus, and extensor plantar responses (Babinski signs) are frequently seen in the legs. Spasticity (increased muscle tone) is common in the legs and patients may have both flexor and extensor spasms in the legs. The motor symptoms of MS are frequently worsened after exposure to increased environmental temperature and worsen later in the day.

- **Sensory symptoms:** Patients with MS often complain of numbness, tingling, or burning sensations. The distribution of symptoms usually does not correspond to a particular nerve root or dermatomal pattern. Shock-like or electric-type sensations may occur in the neck or back with neck flexion (Lhermitte's symptom). On examination, patients may have areas of impaired sensation to light touch, temperature, vibration, or position sense. Bilateral leg pain is another common complaint in MS.
- **Brainstem symptoms:** Cranial nerve dysfunction is commonly seen in MS. Patients may complain of blurred vision or diplopia and, on examination, may have horizontal, vertical, or rotary nystagmus. Many patients have an internuclear ophthalmoplegia due to a lesion of the medial longitudinal fasciculus in the brainstem. In this condition, examination reveals an ipsilateral adduction paralysis with nystagmus of the contralateral eye. Dysarthria and dysphagia may be seen in MS, particularly late in the disease. Although hearing loss is unusual in MS, vertigo is a fairly common complaint. Trigeminal neuralgia and both central and peripheral (Bell's palsy) facial palsy may also be seen.
- **Fatigue:** Fatigue is one of the most common complaints in MS patients and at times may be a major source of disability (17). Sleep complaints are also common in MS and poor-quality sleep may contribute to fatigue.
- **Cognitive and psychiatric dysfunction:** Many patients with MS complain of difficulty with memory, thinking, and concentration. Formal neuropsychologic testing may reveal deficits that patients are unaware of. Depression may be seen in up to 75% of patients at some time during the disease (18).
- **Autonomic disturbance:** Many MS patients complain of difficulty with bowel and bladder or sexual dysfunction. Most patients have constipation but bowel incontinence and fecal urgency may occur. Bladder frequency and urgency is also common in MS. Urodynamic studies may be necessary to define bladder dysfunction. Up to 50% of female MS patients may report sexual dysfunction, which may be due to decreased libido, vaginal dryness, or impaired perineal sensation.

Diagnosis of MS

The diagnosis of MS can be challenging. As with all medical conditions, a careful history is mandatory and should focus on current neurologic symptoms, any history of previous neurologic dysfunction (possibly indicating a previous unrecognized relapse), and inquiry as to other significant medical

conditions. A thorough physical examination should be performed with a full neurologic examination with emphasis on the mental status, visual system, motor and sensory systems, gait and balance, and reflexes.

- **Neuroimaging:** MRI of the CNS is the most sensitive test for determining the presence of demyelinating lesions. As up to 10% of MS lesions occur in the spinal cord, the cervical and thoracic spinal cord should be imaged in addition to the brain. Unless contraindicated, MRI imaging should be performed with gadolinium enhancement to look for evidence of active or acute demyelinating lesions. MRI is positive in at least 95% of patients with clinically definite MS. Typical MRI lesions in MS are seen in the periventricular regions, in the corpus callosum, and in the brainstem. Spinal cord MRI lesions in MS are often ovoid and involve two or less spinal segments. Spinal cord atrophy may also be seen.
- **CSF:** CSF analysis provides important information in MS and should be considered to help confirm a diagnosis of MS. The CSF may be abnormal in up to at least 80% of MS patients, although a normal CSF examination does not rule out the disease. Immunoglobulin G (IgG) in the CSF can be compared with levels in the serum and may be elevated in the CSF of patients with MS (IgG index and IgG synthesis rate). CSF electrophoresis may also reveal the presence of oligoclonal bands, which are due to IgG synthesis in the CNS. Elevated levels of myelin basic protein indicating myelin damage may also be seen in MS. None of the above CSF abnormalities are specific for MS although their presence in the setting of a typical clinical history can aid in making a diagnosis.
- **Evoked potentials:** Visual evoked potential (VEP) and brainstem auditory evoked potentials (BAEP) studies are useful at times in the diagnosis of MS as they can show subclinical lesions in the visual (VEP) and auditory (BAEP) pathways.

Ultimately, the diagnosis of MS is clinically based and usually rests on a clinical history of attacks of neurologic dysfunction in different areas of the brain or spinal cord at different times supported by evidence of positive findings on MRI, in the CSF, or on evoked potential testing.

Treatment of MS

Currently, a number of drugs have been shown to modify the natural history of MS and are approved to treat both the relapsing–remitting and the secondary progressive form of the disease. The interferons, glatiramer acetate, and natalizumab are approved for the relapsing forms of the disease. These drugs alter immune responses and have been shown to decrease relapse rates by up to 30% to 50% and are thought to retard disease progression over the long term. None of the drugs are indicated for use during pregnancy, and it is recommended that these drugs be stopped when a woman becomes pregnant or ideally 3 months prior to attempting to become pregnant.

The Course of MS in Pregnancy

Currently, pregnancy is not thought to impact the long-term progression of MS. Multiple studies have shown no adverse effects on pregnancy outcome in women with MS (19,20). Studies have also shown a significantly reduced rate of relapses during pregnancy (by 60–70%). Following pregnancy, there appears to be an increase in the relapse rate up to 3 months postpartum (21). Additionally, breast-feeding has not been shown to have a significant impact on exacerbation rates (22). In short, pregnancy does not appear to influence long-term disability in MS and a woman with MS who desires pregnancy should not be discouraged from pregnancy if her general health is adequate.

Finally, a woman who does have a significant MS exacerbation during pregnancy can be considered for treatment with glucocorticoids (methylprednisolone—pregnancy class C) only if the potential benefit to the mother outweighs potential risk to the fetus. Mild or moderate exacerbations are probably left best untreated in pregnancy.

In summary, women with MS who are contemplating pregnancy or who have become pregnant should be reassured that pregnancy does not adversely affect their long-term course of the disease.

NEUROMUSCULAR DISEASES (NMDs) IN PREGNANCY

NMDs are traditionally divided into diseases of anterior horn cell, peripheral nerves, neuromuscular junction, and skeletal muscles. In a pregnant woman, these may be approached as two categories: (i) pregnancy-related NMD including disorders with increased incidence or occurring as specific complications during pregnancy, delivery, or postpartum period, and (ii) chronic NMD that may influence maternal morbidity and mortality as well as fetal outcome. Following discussion focuses on the common NMDs encountered during pregnancy and puerperium.

Pregnancy-Related NMDs

Carpal Tunnel Syndrome

Incidence of carpal tunnel syndrome (CTS) is two to three times in pregnant women as compared with nonpregnant women of childbearing age (23). Gestational CTS is more common during third trimester. Various factors such as edema, weight gain, and abnormal hand position with need to sleep on side may contribute to increased incidence (24,25). Symptoms of burning pain and paresthesia in median nerve distribution or whole hand are typically worse at night and may be bilateral in 60% of patients. Loss of sensation or weakness in median nerve distribution, and Tinel or Phalen signs may be seen. Electrodiagnostic testing helps to confirm the diagnosis and distinguish it from nonspecific paresthesia of hands during pregnancy. Spontaneous resolution of symptoms occurs in majority in the immediate postpartum period, and therefore conservative treatment with wrist brace, physical therapy, and modification of activity is recommended (23,24). Patients with severe symptoms may benefit from corticosteroid injection. Women with the onset of symptoms in early part of pregnancy may be more likely to fail conservative treatment and need decompressive surgery on follow-up (24,26).

Lumbar Radiculopathy

Low back pain affects about 50% of pregnant women. Incidence of sciatica-type pain, however, is only 1% and clinical signs of radiculopathy are rare, occurring in 1:10,000 pregnancies (27). Women with prior history of back pain and sciatica are more prone to have recurrence during pregnancy. Lumbar lordosis, laxity of ligaments due to relaxin hormone, and pressure of gravid uterus may contribute to high incidence of lumbar pain (24). Lateral disc herniation commonly affects L5 or S1 nerve root and central disc herniation may cause cauda equina compression. MRI without the use of contrast agent is the investigation of choice, but care should be taken to interpret MRI abnormality in relation to clinical deficits. Most women respond to conservative treatment with analgesics and physical therapy (24,27). Decompressive surgery may be indicated for uncontrolled pain and neurologic deficits, and has been safely performed during pregnancy (28).

Meralgia Paresthetica

Lateral femoral cutaneous nerve is prone to entrapment or stretch during third trimester due to expanding abdominal wall and lordosis (23,29). Symptoms of pain, tingling, and numbness over lateral aspect of thigh may be unilateral or bilateral. Compression may also occur due to thigh flexion during delivery or pressure from the retractor during caesarian section. Treatment consists of reassurance for spontaneous resolution, and topical Lidoderm patches or local anesthetic injection in severe cases (24). Use of GBP or amitriptyline is preferably avoided during pregnancy. Intercostal neuralgias may also occur due to stretch injury and lead to chest or abdominal wall pain in a dermatomal pattern (23).

Bell's Palsy

Risk for Bell's palsy is three times higher during late pregnancy and early puerperium, probably related to increased tendency for reactivation of herpes virus infection. Corresponding incidence is lower in early pregnancy and therefore overall frequency of Bell's palsy is unaffected during pregnancy (30). Typical presentation is unilateral acute facial weakness, which progresses over 3 to 7 days. Increased lacrimation, alteration of taste, or hyperacusis may be present. There is no increase in recurrence rate during subsequent pregnancies. Gestational facial palsy is associated with increased occurrence of hypertension and pre-eclampsia, and close monitoring of affected women is recommended (30,31). Standard treatment with short course of prednisone, 1mg/kg for 5 days and acyclovir 400mg five times daily for 10days, is recommended except in the first trimester of pregnancy. Lubricating eye drops and eye patching are used to prevent corneal injury. Prognosis for recovery is excellent in patients with incomplete facial weakness; however, worse prognosis during pregnancy, noted in some reports, may reflect higher chance of severe facial palsy in third trimester.

Neuralgic Amyotrophy

Predilection for occurrence of brachial neuritis (neuralgic amyotrophy or Parsonage–Turner syndrome) in immediate postpartum period is well recognized (32). Clinically, acute onset of shoulder/upper arm pain is followed by patchy weakness and wasting commonly in the distribution of upper

and middle trunks. The disorder may be sporadic or hereditary (autosomal dominant) and has possible immunologic basis. Bilateral and recurrent episodes are common in familial type. The onset may be within a few hours to weeks after the childbirth. Mode of delivery does not seem to impact the susceptibility. Spontaneous improvement with good motor function over 1 to 2years is reported in 80% (27). Management in acute phase includes pain control, range of movement, and active physical therapy as tolerated. Intravenous methylprednisolone or intravenous human immunoglobulin (IVIG) may reduce the intractable pain but do not affect the course of the disease (33).

Guillain–Barré Syndrome

Guillain–Barré syndrome (GBS) is an acute or subacute predominantly motor, immune-mediated demyelinating polyneuropathy. Increase in risk for GBS is noted in postpartum period although overall incidence during pregnancy is similar to general population (27). Diagnosis is based on clinical features of generalized weakness, areflexia, elevated protein in CSF without pleocytosis, and abnormal electrophysiologic studies. Antecedent infection is seen in about two-thirds of patients. Significant association with *Campylobacter jejuni*, cytomegalovirus, and human immunodeficiency virus is described, and recognition of these infections in pregnancy may have important implications for maternal and fetal health. Pregnant women with GBS may be more prone to respiratory compromise due to elevated diaphragm and about 35% may need ventilatory support (34). Preterm labor may be more frequent, and caution should be exercised in the use of tocolytic agents to avoid autonomic complications. Vaginal delivery is possible, and caesarian section is performed for obstetric indications only (24). Efficacy and safety of plasmapheresis and intravenous immunoglobulin therapy for GBS during pregnancy are similar to nonpregnant population. General management includes respiratory and hemodynamic monitoring, prevention of thromboembolic complications, adequate nutrition, and physical therapy.

Maternal Obstetric Nerve Injuries

Lumbosacral plexus and its branching nerves are susceptible to injury during labor and delivery. The overall incidence of intrapartum nerve injuries has declined with present-day obstetric care, but is still fairly significant at 1% of live births (29). The predisposing factors include primiparity, short stature, dystocia, prolonged labor, and improper positioning (29). Injury to the components of lower plexus (L4-5, S1) presents as postpartum foot drop, while injury to the upper plexus (L2-4) causes mainly femoral and/or obturator nerve palsy. Pudendal nerve injuries are related to pelvic floor trauma.

Lumbosacral Plexus Injury

Lumbosacral trunk is unprotected as it crosses the pelvic brim to enter the true pelvis and is prone to compression by the fetal head or forceps. Rarely sciatic nerve itself may be compressed. Injury to lumbosacral plexus or sciatic nerve predominantly affects the peroneal nerve component. Foot drop is noted immediately postpartum. There is weakness of dorsiflexion, inversion and eversion of the foot, and

sensory impairment corresponding to L5 dermatome. Ankle reflex is preserved with L4–5 trunk lesion but is absent with sciatic nerve injury. Differential diagnosis is from lumbar radiculopathy and peroneal nerve compression at the fibular neck. Electrophysiologic studies help distinguish by findings of denervation in paraspinal muscles in lumbar radiculopathy and focal nerve conduction abnormality at fibular head in peroneal neuropathy. When difficult to distinguish from lumbar radiculopathy, MRI of lumbar spine is warranted.

The lesion is usually neurapraxic with variable axonal involvement. Significant spontaneous improvement is seen within 3 to 6 months. Patients with more than 50% axonal injury show slower and incomplete recovery. Treatment is symptomatic with physical therapy and ankle-foot orthosis. Caesarian section should be considered in subsequent pregnancies to avoid further compromise (23,29). Rarely, idiopathic or inherited lumbosacral plexopathy akin to brachial neuritis may occur in postpartum period.

Peroneal Neuropathy

External compression of peroneal nerve at fibular head is uncommon during labor and may be due to improper positioning in stirrups, manual pressure, or prolonged squatting. Women who receive epidural anesthesia may be more prone as they are not aware of pain and fail to change position to prevent prolonged pressure (35). Patients report pain and paresthesia over the anterior–lateral aspect of leg and dorsum of foot. Foot drop, weakness of dorsiflexion, eversion, and toe extension are noted. Normal inversion strength distinguishes from L5 radiculopathy and lumbosacral plexopathy. Nerve conduction demonstrates focal slowing and conduction block of peroneal nerve at the fibular head. Prognosis for recovery is good.

Femoral and Obturator Neuropathy

Incidence of femoral neuropathy in parturients has considerably declined with modern obstetric care. Branches of the lumbar plexus (L2–4) do not enter the true pelvis; the compression of femoral nerve therefore usually occurs at the inguinal ligament due to prolonged lithotomy position (29). Findings include difficulty walking and knee buckling, weakness of quadriceps femoris, absent patellar reflex, and impaired sensation in saphenous nerve distribution. Weakness of iliopsoas when present indicates a more proximal lesion due to nerve stretch from abduction and external rotation of hip or injury from instrumentation. Proximal part of femoral nerve has poor blood supply and is also prone to ischemia. Prognosis is favorable in majority of patients consistent with neurapraxic injury.

Obturator neuropathy is much less frequent as the nerve is deep within the pelvis and medial thigh. There is weakness of thigh adduction and sensory deficit over the medial thigh. A combined lesion of femoral and obturator nerves points to lumbar plexus involvement. Imaging of pelvis with computed tomography or MRI should be performed if intrapelvic pathology such as hematoma is suspected.

Various strategies that may help prevent nerve injuries in a parturient include avoiding prolonged thigh flexion and

extreme abduction and external rotation, frequent changing of the position of lower extremities, and reducing the active pushing time (29,35).

Pregnancy and Chronic NMDs

Motor Neuron Diseases

Late-onset spinal muscular atrophy (SMA), poliomyelitis/post-polio syndrome, and amyotrophic lateral sclerosis (ALS) may affect women of childbearing age. Pregnancy is rare in ALS, but severe exacerbation of ALS and respiratory failure are likely during pregnancy. Respiratory function should be closely monitored. Patients with severe SMA may be advised to avoid pregnancy. Presence of kyphoscoliosis and respiratory compromise are the major concerns in pregnant SMA patients. There may be increased incidence of premature labor in SMA and ALS, but fetal outcome is reported to be satisfactory (24,36,37).

For female survivors of poliomyelitis, spine deformity and cephalopelvic disproportion pose risks in pregnancy and parturition. Study of a large cohort of women with old poliomyelitis showed higher risk of complications during pregnancy and delivery, higher rate of caesarian section, and low birth weight of infants (38).

Peripheral Neuropathies

Chronic Inflammatory Demyelinating Polyneuropathy

Chronic inflammatory demyelinating polyneuropathy (CIDP) is autoimmune acquired demyelinating polyneuropathy presenting as relapsing or chronic progressive forms. CIDP is three times more likely to relapse in pregnancy particularly during third trimester and early postpartum period (23,27). This is attributed to relative suppression of cellular immunity and stimulation of humoral immunity during gestation. Fetal outcome is not affected (39). Treatment with prednisone can be maintained, but other immunosuppressive agents should be avoided. Exacerbation is treated with plasmapheresis or IVIG.

Hereditary Neuropathy

Charcot–Marie–Tooth disease (CMT) is the most common hereditary NMD. Worsening of disease is noted in 50% of affected pregnant women, especially in those with childhood onset of CMT. Endoneurial edema and local pressure from gravid uterus may be the contributory factors (24). Some resolution of worsening may occur in about one-third of patients after delivery, but remaining continue to have progressive course. Women with CMT may have increased risk for fetal malpresentation, postpartum bleeding, and higher incidence of assisted delivery or caesarian section (40).

Myasthenia Gravis

Myasthenia gravis (MG) occurs predominantly in women of reproductive years with peak incidence in third decade (41). Management of MG in a pregnant woman is a unique challenge needing many therapeutic decisions at different stages. The course of MG during pregnancy is unpredictable with exacerbation in about 40%, remission in 30%, and no change in the remaining (24,42,43). The risk of worsening is the greatest during first trimester and early puerperium, and in

women with recent diagnosis of MG (31). Women with MG who are considering pregnancy should be instructed on optimal disease control, minimizing oral immunosuppressants, and risks to mother and fetus. Elective thymectomy if being considered should be done before pregnancy as the benefit of thymectomy is delayed (24,41). Treatment with acetylcholinesterase inhibitors (pyridostigmine, edrophonium) and prednisone is safe during pregnancy. Immunosuppressive agents such as azathioprine and mycophenolate mofetil are contraindicated (41,43). Aggressive treatment is needed in patients with bulbar or respiratory involvement. Plasmapheresis or intravenous immunoglobulin therapy can be used for control of severe symptoms and in myasthenic crisis (41). Maintenance IVIG therapy can help to avoid the use of immunosuppressive agents. There is higher risk of maternal mortality in myasthenic women especially within 1 year of diagnosis (42). It is advisable for MG women to delay childbirth for 2 years after the onset of illness.

MG has no significant effect on fertility, course of pregnancy, or mode of delivery (31,43). During labor, MG does not affect the uterine contraction; however, myasthenic weakness may limit active pushing necessitating assisted delivery. Parenteral cholinesterase inhibitors can be used during labor to tide over the myasthenic fatigue. Neostigmine 1.5 mg intramuscularly or 0.5 mg intravenously is equivalent to 60 mg oral dose of pyridostigmine. Magnesium sulfate as well as neuromuscular blocking agents should be avoided as these can aggravate weakness or precipitate myasthenic crisis (43). Care is also needed while managing pain, infection, and hypertension to avoid medications that may potentiate muscle weakness in MG.

Fetal/neonatal complications in myasthenic pregnancies include higher perinatal mortality (6–8%), stillbirth (2%), pulmonary hypoplasia, polyhydramnios, neonatal MG (10–20%), and arthrogryposis multiplex congenita (AMC) (31,41,42). Neonatal MG is related to placental transfer of acetylcholine receptor antibody. The neonate may develop hypotonia, poor sucking and swallowing, and respiratory difficulties. The onset is within 1 to 4 days and weakness resolves over 4 to 6 weeks. Intrauterine exposure to acetylcholine receptor antibody is also the basis for poor fetal movement and consequent AMC (27). There is a high risk of recurrence of AMC in subsequent pregnancies.

Muscle Diseases

Myotonic Dystrophy Type 1

An autosomal dominant, trinucleotide (CTG) repeat disorder is the most common muscular dystrophy of adulthood (24). Pregnancy in DM1 carries multiple risks for mother and fetus. The course of disease may be accelerated with increasing muscle weakness, congestive heart failure, and respiratory compromise. There is increased risk of spontaneous abortion, polyhydramnios, preterm labor, uterine atony, and postpartum hemorrhage (27,44). Perinatal loss may be up to 15%. Congenital myotonic dystrophy is a maternally transmitted condition and is reported in 6% to 20% of infants (24,44). Prenatal diagnostic testing is available. At times, the mother is first diagnosed with DM1 when she delivers an affected child. During pregnancy and delivery, use of tocolytic agents,

pentobarbital, and neuromuscular blocking agents should be avoided.

DM Type 2

This follows a more benign course than DM1 (45,46). Pregnancy may unmask or exacerbate the symptoms of DM2 in affected women. There may be predisposition to pre-term labor but no increase in fetal or perinatal loss is reported. Congenital myotonic dystrophy does not occur with DM2.

Other Rare Inherited Muscle Diseases

Some of these are likely to be encountered in a pregnant woman: facioscapulohumeral muscular dystrophy and various forms of congenital and metabolic myopathies. Vaginal delivery is possible in majority of the affected women. Increased muscle weakness during pregnancy, low birth weight, need for operative delivery, and presence of AMC are variably reported (24,27,47). Inhaled anesthetics are contraindicated as these may precipitate malignant hyperthermia (48).

Inflammatory Myopathy

Polymyositis and Dermatomyositis

This can affect women of childbearing age. Pregnancy may worsen the disease course. Women in clinical remission of polymyositis/dermatomyositis (PM/DM) carry no increased risk for obstetric complications. Active disease during pregnancy, however, is linked to poor outcome with almost 50% chance of fetal death and 33% incidence of intrauterine growth retardation (49). Corticosteroids are the mainstay of treatment. IVIG has been used for exacerbation or as maintenance treatment (50). Caution is needed while using chemotherapeutic agents. Assisted vaginal delivery or caesarian section is recommended to avoid maternal exhaustion and to reduce the risk of rhabdomyolysis.

EPILEPSY AND PREGNANCY

Epilepsy is a neurologic disorder that causes recurrent unprovoked seizures. There are an estimated 50 million people with epilepsy worldwide. Many issues in the treatment of epilepsy are sex specific. In women, this is not only related to maternity issues such as pregnancy and delivery, but also to puberty, menstruation, and contraception. The care of women with epilepsy (WWE) requires an understanding of anti-epileptic drug (AED) pharmacology, and the neuroendocrine changes during the menstrual cycle and pregnancy. This review will be divided into three parts: WWE before pregnancy (preconceptional), pregnancy and epilepsy, and postpartum care of WWE.

WWE Before Pregnancy (Preconceptional)

Every woman with childbearing capability should receive preconceptional care and counseling with her neurologist. The woman should be asked about her seizure type and frequency and response to AED therapy, as well as side effects. Additional information should include the menstrual cycle, method of contraception, plans for pregnancy, and history of birth defects or major malformation. This section will discuss the basic principles of AED therapy before pregnancy, oral

contraception, the interaction of AEDs, sex steroid hormones and seizures, and teratogenicity of AEDs.

Seizure Management Before Pregnancy

In every epilepsy patient, the first goal is the optimization of AED treatment with no seizures and side effects (51–53). It is advisable to give the lowest possible AED dose or sub-toxic dose. The appropriate drug is based on the epilepsy syndrome and seizure type (generalized vs. partial seizures). Each epilepsy patient is different in their dosage requirement, tolerance, and side effects. Preferably, AED monotherapy should be used. When seizures are controlled, it is important to obtain a baseline preconceptional (or prepregnancy) AED level. A trough or pre-dose AED level, which is before the first morning dose, should be measured. This AED serum level will serve the *individual's* therapeutic level and this may be within or outside the therapeutic range reported by the laboratory. This can also serve as an important marker for drug compliance, and to monitor serum drug fluctuations during menstruation, pregnancy, or hormonal contraception. Poorly controlled seizures despite multiple AED therapy should prompt a referral to an epilepsy center for comprehensive evaluation.

If a woman with epilepsy plans to become pregnant and is taking a drug with high teratogenic potential, attempts can be made to switch her to a drug with a more favorable teratogenic profile. However, these medication changes should be completed at least 6 months before a planned conception, if possible, to avoid fetal damage from a breakthrough seizure. When the seizures are controlled, the woman should be advised not to discontinue or lower the dose of the AED if she desires to become pregnant or if she discovers to be pregnant. WWE are also advised not to switch an AED indiscriminately without notifying their neurologist or family physician. Discontinuation of AEDs is appropriate if the patient is seizure free for 2 to 5 years, has a normal EEG, normal neurologic examination, and with a single seizure type. Some women who have not satisfied all these conditions may also wish to try discontinuing AEDs because of concerns about teratogenic effects or interference with hormonal contraception. Before doing so, the risk of seizures must be carefully considered. The risk of seizure recurrence is the greatest within the first 6 months after discontinuation (51).

Oral Contraception and Antiepileptic Medications

Beginning in adolescence, it is important to be sure that all female patients have full information regarding effective contraception (54–56). Contraceptive management requires careful consideration and is closely tied to epilepsy management. However, only 3% of pregnant women saw an obstetrician in the 3 months before conception, whereas another survey found that one-third had never been counseled regarding the issues of pregnancy and seizures. A number of safe and effective methods of contraception are available. Like all women, WWE must carefully consider their best contraceptive option; however, they need additional information regarding the possible interaction of their epilepsy medication and contraceptive choice. Most studies have shown that estrogen-based contraceptives do not affect seizure frequency. Most current guidelines suggest that the combination oral

contraceptive (COC) pills give a sufficient dose of estrogen to inhibit ovulation, generally 35 µg or greater. It is the progestin component that prevents breakthrough bleeding and is only indirectly involved in contraceptive efficacy. In the ideal situation, oral contraceptive (OC) is highly reliable with an annual failure rate of <1%. The annual failure rate of OC with AED use is about 6%. Enzyme-inducing AEDs (EIAEDs) affect the efficacy of COC. The EIAEDs include phenytoin (PHT), primidone (PMD), phenobarbital (PB), carbamazepine (CBZ), TPM, felbamate, and oxcarbazepine. They do this by inducing enzymes, that is, CYP3A4 component of the hepatic cytochrome P450, leading to faster clearance of steroid hormones and by increasing the production of sex hormone-binding globulin (SHBG) (51,55). For WWE taking EIAEDs, COCs containing 1 mg of norethindrone, 0.150 mg of levonorgestrel, or 0.300 mg of norgestrel are recommended. COCs with at least 50 µg of the estrogen component are recommended. If there is breakthrough bleeding, the estrogen dose may be increased to 75 to 100 µg daily. Other methods of contraception are barrier methods (e.g., condom, diaphragm, cervical cap). EIAEDs reduce the contraceptive efficacy of levonorgestrel implant but not with intramuscular medroxyprogesterone. It is recommended that injections be administered every 10 weeks instead of the usual 12 weeks for WWE. If the “morning after pill” containing levonorgestrel postcoital contraception is used after unprotected sexual activity, some practitioners recommend that the first dose should be doubled to two pills. IUDs that contain progestin or Mirena coil that secrete levonorgestrel hormone locally and copper IUDs are not known to be affected by EIAEDs. The rhythm method is not a reliable method of birth control for WWE. EIAEDs also affect the efficacy of transdermal contraception. There is no additional risk of OC failure with non-EIAEDs. AEDs that do not induce cytochrome P450 3A4 enzymes include VPA, GBP, LEV, tiagabine (TG), vigabatrin (VG), zonisamide (ZON), and pregabalin (PG). Vagal nerve stimulators, which are used in refractory epilepsy, have no effect on sex hormone metabolism.

There is a special situation where seizure exacerbation may occur among women taking lamotrigine and OCs (55). It has been found that lamotrigine levels, when adjusted for dose and body weight, were found to be reduced by 50% in a group of 22 women taking lamotrigine and an OC that combined ethinyl estradiol and levonorgestrel compared with women taking lamotrigine alone. Further evaluation of this interaction has shown that it is the ethinyl estradiol component that produces the interaction; the progestin component has no effect on lamotrigine levels. The mechanism of this interaction is the induction of uridine diphosphate-glucuronyl-transferase 1A4 by ethinyl estradiol, which is the main metabolic enzyme for lamotrigine. The lamotrigine–OC interaction is further complicated by the risk that lamotrigine levels will increase during the OC placebo or pill-free week, which in most regimens occurs every fourth week. There are reported increase in lamotrigine levels of 27% on the 3rd placebo day, 63% on the 5th, and 116% on the 7th placebo day relative to lamotrigine levels during OC administration. There is also a bidirectional interaction for OCs and lamotrigine, in which lamotrigine was associated with a small decrease in levels of progestin, levonorgestrel, by 12% (54–56).

Sex Hormones, Reproductive Function, and Seizures

To understand the far-reaching effects of epilepsy and AEDs on hormones and vice versa, the reader must review the normal physiologic mechanisms of the hypothalamic–pituitary–gonadal axis (HPGA). In the female, the gonadotropin-releasing hormone (GnRH) is secreted by the hypothalamus. This stimulates the anterior lobe of the pituitary leading to the release of the follicle-stimulating hormone (FSH) and the luteinizing hormone (LH). FSH and LH, in turn, stimulate the formation of ovarian follicles, hence stimulating the release of estrogen (estradiol). This phase is the follicular or preovulatory phase; the phase occurs when LH stimulates the preovulatory follicular theca cells to secrete androstenedione, which aromatizes into estradiol. Estradiol binds to the SHBG, a glycoprotein that acts as a carrier in the bloodstream. This feeds back to the hypothalamus with high levels of estrogen; the hypothalamus increases the release of GnRH, which increases the amount of LH and FSH. A spike of FSH and LH from the pituitary results in ovulation and the follicle transforms into the corpus luteum. This marks the luteal phase in which the corpus luteum produces both estrogen and progesterone. Progesterone feeds back to the hypothalamus and inhibits GnRH secretion and thus the decrease in FSH and LH from the anterior pituitary. As the corpus luteum breaks down, the inhibition of the hypothalamus lessens and the cycle begins again (57).

There is an interaction between steroid sex hormones (estradiol, progesterone) and neurons. Estrogen is known as a proconvulsant and progesterone, a potent anticonvulsant. Overall, the ovarian sex steroids act at the level of the neuron in the CNS and alter the frequency and severity of seizures. It has been shown in WWE that intravenous administration of conjugated estrogens activates epileptiform discharges and may result in seizures. Estradiol also potentiates glutamate receptor-mediated excitatory post-synaptic potentials and excitatory post-synaptic currents on hippocampal CA1 pyramidal cells. Progesterone exerts an inhibitory effect via metabolites such as allopregnanolone, which is a GABA-A-receptor-modulating neurosteroid. Progesterone increases seizure threshold and also has anti-anxiety and sedating effect. The effect of sex hormones and neuronal excitability may explain the pattern of seizure exacerbation during menstruation. Seizures have been reported to occur in a cyclic pattern in between 5% and 70% of WWE, for example, catamenial epilepsy. About 35% of WWE will have significant (> two times) increase in seizure frequency around menstruation. Women with localization-related epilepsies may have an increase in seizures at the time of menarche. Treatment with progesterone may be helpful and the average decline in seizure frequency is about 55%. The possible side effects of progesterone treatment include sedation, depression, weight gain, breast tenderness, and breakthrough vaginal bleeding. This is managed by discontinuing the progesterone or lowering the dose (57).

WWE are at risk for altered neuroendocrine regulation (56,57). Epilepsy can affect the various aspects of sexual and reproductive functioning. The most common symptoms are hyperandrogenism, menstrual disorders, ovarian failure, polycystic ovary syndrome (PCOS) with or without divalproex (VPA) therapy, hyperinsulinemia, and weight gain especially with VPA therapy. An unusually high number of WWE will

have some degree of sexual or reproductive dysfunction, which can include difficulty with libido, arousal, orgasm, and menstrual irregularities. Menstrual disturbances are more frequent with epilepsy as compared with women without epilepsy. This is particularly common with temporal lobe epilepsy. About 30% to 50% of women will have menstrual irregularities, reduced fertility, irregular bleeding, and anovulation. Aside from catamenial epilepsy, another reproductive hormone-related disorder in WWE is PCOS. It is characterized by polycystic ovaries on ultrasound, hirsutism, obesity, acne, endocrine disturbance, elevated LH/FSH ratio, chronic anovulation, and increased risk of endometrial cancer and breast cancer (54). The prevalence of PCOS in the general population is approximately 17% to 22% of women. Up to 15% of females with primary generalized or partial seizures may exhibit features of PCOS. With the frequent disruption of the normal function of the HPGA caused by ictal and interictal epileptiform discharges, a whole cascade of events happens. The LH/FSH rates are elevated, and follicular maturation is disrupted leading to elevation in androgens, leading to hyperandrogenism. The fertility rate of WWE is about 60% to 80% of the normal population, the major contributing factor being PCOS. Anovulatory cycles are more frequent in women with idiopathic generalized epilepsy and those taking VPA. The management of PCOS should be symptom focused and individualized, such as encouraging weight loss if body mass index $>25\text{kg/m}^3$ or fasting glucose tolerance is above normal and the insulin level is elevated. Hirsutism can be managed by laser treatments, electrolysis, waxing, and bleaching to improve hair growth. Hyperandrogenism can be treated with a combination of estrogen only and combined contraceptives, which are used in the first 21 days of the menstrual cycle and antiandrogen acetate (50–100mg), used for the first 10 days of menstruation. OCs are useful in adolescents to prevent unwanted pregnancy but may worsen insulin resistance associated with PCOS. Spironolactone with antiandrogenic properties can be tried in young women where oral contraception is contraindicated (54).

AEDs and Teratogenicity

Rates of congenital malformations range from 2.3% to 18.6% (combined risk about 7%) in infants of WWE versus 2% to 3% in the general population (58–65). Estimates of risk vary, but a recent study indicates 4.5% frequency for AED monotherapy in utero exposure and 8.6% for AED polytherapy. The most common major congenital malformations are heart malformations (e.g., ventricular septal defect), urologic defects Z (e.g., hypospadias), skeletal abnormalities (e.g., radial ray defects, phalangeal hypoplasia), and NTDs (e.g., spina bifida) (58–65). Congenital malformations are physical defects that warrant medical or surgical intervention and cause major functional problems. Most major and minor malformations have been reported with the older AEDs such as PHT, CBZ, PB, and VPA largely because they are the most widely used AEDs globally. Exposure in the first trimester poses the highest risk. Barbiturates have been found to be associated with major congenital malformations. PHT has been associated with facial clefts, congenital heart defects, and urogenital defects. There have also been reports of dysmorphic facial features and distal phalangeal hypoplasia with PHT. CBZ has been associated

with NTDs, heart defects, hypospadias, hip dislocations, and inguinal hernia. PHT, CBZ, and PB are folic acid antagonist, so their teratogenicity may be attributable to their folate deficiency. VPA has been shown to carry a high risk of spina bifida aperta, cardiovascular complications, urogenital malformations, and skeletal defects. Association of VPA with congenital defects is dose dependent and is most likely when VPA is used with polytherapy and monotherapy above the doses of 1000mg/day. Minor anomalies are deviations from the normal morphology, but do not threaten health, impair function, or require intervention. Examples include hypertelorism (widely spaced eyes), low set ears, and distal phalangeal hypoplasia. Minor anomalies occur at a rate of up to 30% in the offspring of WWE taking AEDs versus 15% in newborns of matched controls without epilepsy.

Knowledge of the effects of newer generation AEDs is incomplete. Data on GBP, OXC, PG, TG, and TPM are very limited. One study did find an association between OXC and a major malformation. LTG has the most data available at this time, primarily from the Lamotrigine Registry and the UK Epilepsy and Pregnancy Registry. When LTG and VPA are given together, there is a higher frequency of major malformations. Emerging data from a pregnancy registry suggest an association between LTG and nonsyndromic oral cleft lip/palate 24 times greater than expected. Data on ZON are quite limited. Very few pregnancy outcomes have been reported with LEV, but it has been speculated that LEV may have a favorable profile for pregnant women because it has <10% protein binding and is eliminated primarily via renal excretion and extrahepatic hydrolysis. Renal blood flow increases in early pregnancy and persists throughout; LEV elimination has been found to be enhanced with this increased renal blood flow. Preliminary studies have noted a good pregnancy safety profile with LEV; however, more data are needed before it can be said to be non-teratogenic.

There are different pregnancy registries in epilepsy with varying results in the rate of major malformations (58). The North American Registry with over 3000 women enrolled while having AED during pregnancy has reported that PB (6.5%) and valproate (10.7%) have increased rates for major malformations. There is also a specific risk for cleft lip/palate (0.89%) for lamotrigine and CBZ (0.57%). The UK registry with 3607 pregnancy outcomes found higher major malformation rate for valproate (6.2%) and increased risk for lamotrigine at higher dose. LEV was associated with major malformation in 2.7%. The Australian Registry with 555 outcomes reported malformations in 5% of live births and additional 1% in induced abortions. Valproate monotherapy in the first trimester at doses above 1100mg/day was associated with significantly higher risk (38.5%) of malformations than other AEDs, which were 3.8% for CBZ, 0% for lamotrigine, and 5.9% for PHT. Both the Swedish and Finnish Birth Registries reported higher malformation rates for valproate. Valproate effect was dose dependent in the Finnish study. The International Lamotrigine Pregnancy Registry reported 2.9% risk for malformation, which was not dose dependent.

Animal studies have demonstrated that in utero AED exposure can produce behavioral defects at dosages lower than those required to produce somatic malformation (59,61,63,65). Cognitive studies in humans are less clear.

There has been no evidence that children exposed to CBZ produced IQ impairment or autistic spectrum disorder. By contrast, valproate in utero exposure was associated with lower IQ scores and impairment of verbal/language skills. The effect of valproate was dose dependent. Prospective population-based studies give no definite evidence that CBZ or PHT fetal exposure impair intelligence. Data on fetal PB exposure are insufficient. AED polytherapy in utero exposure results in higher risk for cognitive/behavioral teratogenesis. There is no information to suggest whether some combination would be safer or more hazardous than others, except that polytherapies with valproate appear to be at higher risk. Overall, polytherapy is associated with more negative effects on cognitive functioning than monotherapy.

The mechanism underlying adverse AED effects on development is uncertain. Teratogens interact with genotype to produce both anatomic and behavioral defects (59). Whether a defect occurs depends on susceptible genotype and may involve interaction of multiple liability genes. Proposed mechanisms underlying teratogenicity of AEDs include folate, ischemia, neuronal suppression, reactive intermediates (e.g., epoxides or free radicals), and AED-induced neuronal apoptosis. Neuronal dysfunction short of apoptosis or migration disorders may also contribute. Mechanisms of anatomic and behavioral teratogenesis may well differ since it appears that anatomic defects result from first-trimester AED exposure while behavioral defects arise from third-trimester exposure. A leading hypothesis of anatomic teratogenesis involves oxidative macromolecular damage from free radicals formed as reactive intermediates of AED metabolism. AED-induced apoptosis has been proposed as a possible mechanism for the behavioral deficits. Widespread neuronal apoptosis in animals occurs as a result of exposure to clonazepam, diazepam, PB, PHT, VG, or valproate in neonatal rats. The effect is dose dependent, occurs at therapeutically relevant blood levels, requires only a relatively brief exposure, and can be synergistic suggesting possible increased polytherapy risk. Similar apoptotic effects were not seen at therapeutic dosages for CBZ, LEV, lamotrigine, or TPM monotherapy. Further, fetal exposure of GABAergic AEDs such as valproate and VG can result in hippocampal and cortical dysplasia secondary to impaired migration and neuronal death.

Folate Supplementation

Folate is a water-soluble coenzyme that occurs naturally in food (e.g., green leafy vegetable, dried beans, fruits). In addition, fortified foods like ready-to-eat cereals are fortified with 100% of the recommended daily allowance for folate. Even so, most women do not consume enough folate that is provided in supplements and added to fortified foods. Folate helps produce and maintain new blood cells and is necessary for proper CNS development. This is especially important during periods of rapid cell division and growth as early in the first trimester of pregnancy. Folate-deficient women who become pregnant are at greater risk of giving birth to lower birth weight premature infants. Folate deficiencies have been implicated in the development of certain birth defects, particularly NTDs. Neural tube closure occurs at about day 26 of pregnancy, often before a woman is aware that she is

pregnant. Neural tube and cardiac defects occur in the first 28 days following conception, so folate supplementation should begin before conception is attempted and continue throughout the pregnancy. If folate supplement is begun more than 30 days after conception, it will not provide protection against NTD. About 40% to 50% of pregnancies with epilepsy are not planned and, hence, it is reasonable to recommend routine use of folate supplement for any women of childbearing age considered to be at risk for pregnancy. Evidence is mounting that folic acid protects developing fetuses against NTDs. There have been studies that have failed to demonstrate a neuroprotective effect for periconceptual folate supplementation. Folic acid supplementation may enhance PHT metabolism and thus lower PHT blood levels, placing women at risk for breakthrough seizures. EIAEDs have been shown to decrease serum folic acid levels by increasing the metabolism of circulating folic acid. The appropriate dosage for folate is probably dependent on a variety of factors including AED/no AED therapy, whether AED is taken, maternal age, and other concurrent medication. For any sexually active woman of childbearing potential, recommended daily allowances of folic acid have been increased to 400 µg/day for nonpregnant women, 600 µg/day for pregnant women, 600 µg/day for pregnant women and those contemplating pregnancy, and 500 µg/day for lactating women. Many epileptologists recommend higher doses (800 µg/day to 4 mg/day) for WWE. In most cases, folate intake should not exceed 1000 µg daily to avoid provoking seizures or masking the hematologic effects of B₁₂ deficiency and pernicious anemia. However, for women with a family history of NTDs, 4 mg/day is the recommended dosage and vitamin B₁₂ levels should be checked (54).

Epilepsy Care During Pregnancy

WWE can be reassured that having epilepsy should not prevent them from having children. About 1 million WWE in the United States are of childbearing age, and about 20,000 babies are born to WWE each year. It is probably not helpful to change an AED during pregnancy with the goal of using a less teratogenic drug, because of the critical phases of embryologic development occur very early in pregnancy. Despite the increased risk of maternal and fetal complications, around 90% of pregnant WWE deliver healthy newborns. Close medical care, however, is essential. A multidisciplinary approach is recommended, involving a patient's primary care, an obstetrician who specializes in high-risk pregnancies, and a neurologist (60).

EPILEPTIC SEIZURES DURING PREGNANCY

Epilepsy per se does not pose a teratogenic risk. Most WWE have no change in seizure frequency during pregnancy or even develop fewer seizures. Only 15% to 33% have more seizures during pregnancy (51,66–68). AED pharmacokinetics is altered during pregnancy. Serum drug concentrations are reduced by increasing maternal blood volume, a phenomenon that reaches its nadir at term (69,70). However, seizure frequency increases as early as the first trimester and not necessarily around term, so reduced AED levels only partially explain the phenomenon. Hormonal changes may also contribute: the ratio of estrogen (which lowers seizure threshold) to progesterone (which raises seizure threshold)

increases during pregnancy reaching its peak between weeks 8 and 16. Other factors that may contribute to a lower seizure threshold include stress, anxiety, and sleep deprivation. Also some women stop therapy because of the fear of teratogenic effects. Generalized tonic clonic seizure during pregnancy can result in fetal intracranial hemorrhage, transient fetal bradycardia, heart beat variability, fetal hypoxia, and stillbirth. Status epilepticus resulted in 30% maternal mortality and 50% infant mortality. There is no evidence that non-convulsive seizures during pregnancy adversely affect outcome apart from trauma.

Therapeutic Drug Monitoring During Pregnancy

Several published guidelines recommend monitoring serum AED concentration at the beginning of every trimester and 1 month after delivery (69,70). Monitoring *free* drug concentration has been recommended for both highly and moderately protein bound drugs such as PHT, PB, CBZ, and sodium valproate. Additional monitoring should be considered if adverse effects or poor seizure control are seen, or if non-adherence is suspected. In view of the large inter- and intra-individual variation of drug concentrations, some have recommended monthly serum AED concentration monitoring, particularly for lamotrigine. Since well-defined therapeutic ranges have not been established for the newer AEDs, including lamotrigine, it is suggested that an optimal therapeutic range should be established for each particular individual before conception and that this be used to guide dosage adjustment during pregnancy. Identifying an individual therapeutic range prior to pregnancy is similarly useful for older AEDs, as the clinical response to similar doses and serum drug concentrations can be highly variable. If AED doses have been increased during pregnancy, they should be readjusted after delivery, as concentrations normalize quickly in the postpartum period. At this time, AED toxicity may occur and serum concentrations may be a useful guide for reestablishing the correct dose.

By contrast, the unpredictability and variability of serum drug concentration have prompted others to recommend a more conservative approach, with alterations in dosage being made on clinical grounds. The practical limitations of free drug concentration monitoring and lack of a population target range make adjustments made on clinical grounds a more attractive and pragmatic approach. In fact, current evidence has failed to show that routine adjustment of AED doses during pregnancy based on serum concentration improves seizure control. There are no studies comparing seizure control in pregnancy in those with serum monitoring and those without. Additionally, increases in dose may potentially harm the fetus. While most changes in the dose are made in the second and third trimesters of pregnancy, when organogenesis is complete, there is concern that the potential longer term adverse effects of AED exposure in utero may be more likely to be related to exposure in the latter half of pregnancy. Women should have the opportunity to discuss the pros and cons of routine AED dose adjustment, and their views of the relative risk of seizures and potential adverse fetal outcomes should be taken into account. In practical terms, routine monitoring of serum AED concentration in pregnancy is not useful unless directed at answering a specific clinical question.

For example, if seizures increase or are likely to increase, serum AED concentrations may be useful to plan or anticipate the extent of the change (69).

Prenatal Screening for Fetal Malformations

All WWE should be offered prenatal screening for fetal malformation: maternal serum alpha-fetoprotein testing at 14 to 16 weeks of gestation and structural ultrasonography at 16 to 20 weeks of gestation (51). Performed together, these tests have more than 95% sensitivity in detecting open NTDs. Patients with equivocal results should undergo amniocentesis, which increases the sensitivity to more than 99%. Cardiac anomalies can also be diagnosed prenatally with detailed sonographic imaging of the fetal heart (18–20 weeks of gestation), which is 85% sensitive. The accuracy of ultrasonography for the prenatal diagnosis of cleft lip is less well established. The screening test has inherent ethical implications and may lead to difficult choices if a problem appears to be present.

Vitamin K Supplementation

Some case series have found that newborns exposed to EIAEDs have a higher risk of hemorrhagic disease of the newborn, a condition that has a mortality rate of up to 30%. When it occurs, bleeding usually happens within the first day of life and affects internal organs such as the lungs, abdomen, and brain. It is not clear whether the alteration of vitamin K metabolism caused by some AEDs is the only mechanism at work.

It is suggested that oral vitamin K supplementation at 10 to 20 mg/day be prescribed during the last month of pregnancy and 0.5 mg administered intramuscularly immediately after delivery for WWE. This is particularly important for women taking EIAEDs. Vitamin K is recommended for all neonates at birth; however, neonates born to WWE should be monitored for bleeding. The recommended dosage for neonates is 1 mg intramuscularly or intravenously at birth. If a woman has not taken vitamin K before beginning labor, it can still be administered during labor (51,53).

Labor and Delivery

About 95% of WWE have a safe vaginal delivery, without a seizure during, or in the 24 hour following, delivery (51,53). Women with generalized epilepsy are more at risk for seizures during delivery than are those with partial epilepsy. It is important to remind WWE to bring their AEDs to the hospital during labor and to take regular doses during this period under the supervision of hospital staff. Subtherapeutic or barely therapeutic AED concentrations can be a cause of seizures during labor and delivery. Intravenous or intramuscular AEDs may be needed if the woman is not able to keep down oral medication. Sleep deprivation can provoke a seizure, so in some cases, obstetric anesthesia may be indicated prior to delivery. WWE are more likely than the general population to have labor induced, although epilepsy is not an indication for induction. Cesarean sections and mechanically assisted delivery are also more common in WWE.

Epilepsy Care After Pregnancy

Postpartum Care and Breast-Feeding

New mothers with epilepsy should be encouraged to breast-feed their babies. Most experts believe that the benefits to the mother and baby outweigh the risk (54,67). All AEDs cross into breast milk, but only the free fraction—that which is not bound to maternal serum binding proteins—is available to cross. Breast-feeding conveys substantial benefits to the infant, and these benefits to the mother and infant outweigh any risk from AED exposure. AED concentrations in breast milk are far less than maternal serum levels; however, serum half-life of AEDs is longer in the neonate than in the mother. Nevertheless, the American Academy of Neurology supports breast-feeding for infants whose mothers are taking AEDs. Caution is advised if the mother is treated with PB, ESM, or PRM. For infants of women taking high-dose LTG, drug levels and adverse events in the infant should be monitored. Parents should alert their pediatricians if increased lethargy is noted. When the baby is born, an appointment for a neurologic evaluation should be made for age 4 to 6 weeks (67).

AED levels should be monitored closely in the weeks following delivery. During this period, AED levels may increase gradually. The increase in postpartum plasma levels of EIAEDs starts about 10 to 14 days postpartum. The levels of drugs that are excreted renally such as LEV, OXC, and LTG increase within days of delivery. Thus, some women require dose adjustment immediately following delivery.

Parenting Issues and Safety

WWE need to organize their lives to minimize fatigue in the weeks following delivery in order to minimize the occurrence of seizures precipitated by fatigue. They may also have an increased risk for breakthrough seizures due to stress. Napping is encouraged and asking help from other adults to do nighttime feedings can help with fatigue. For women who are breast-feeding, this can be accomplished either with expressed breast milk or with supplementary formula.

Each woman needs to assess her particular seizure pattern and to make appropriate arrangements for her own safety and that of her baby. For example, if her seizures make her fall, she may wish to rely on a stroller or carriage in the house rather than carrying the infant. If she tends to drop things, perhaps a baby harness is appropriate. Baby care such as changing diapers and clothing can be done on a blanket on the floor rather than on a high changing table, especially during the immediate postpartum period when AED levels fluctuate. A second person should be present during baths to avoid the danger than even a momentary lapse in alertness can pose (54).

MOVEMENT DISORDERS AND PREGNANCY

Disorders of human motor control are common neurologic problems. Although the majority of these disorders are more common in the older postmenopausal age groups, a few can be seen in women of childbearing age. Human motor control is achieved through complex interactions of many CNS regions but intimately involve regions of the brain known as the basal ganglia. The basal ganglia utilize a variety of neurotransmitters to achieve the desired sequencing of motor activity and

production of normal movement. The effects of progesterone and estrogen on the basal ganglia are unclear as experiments with rat models have produced improvement in dopamine function, whereas in humans either no effect or deleterious effects have been reported (71,75).

Rarely, abnormal movements known as choreas appear during gestation, typically following the first trimester known as chorea gravidarum. The chorea is generally seen only on half of the body and is known as a hemichorea. The incidence is said to be 1:139,000 pregnancies (76). It was previously associated with rheumatic fever; however, in the United States, the virtual elimination of this disorder has made this association less likely. More often now, it is linked to systemic lupus erythematosus or anti-phospholipid antibody syndrome (77,78). The chorea typically resolves spontaneously, often after delivery. Rarely, the movements are so severe as to induce rhabdomyolysis and hyperthermia (79). Treatment is typically by using dopamine receptor blockers. Due to concerns involving the fetus, haloperidol is preferred since of all of the medications available, it is the least likely to cause harm (80). Similar choreiform movements may occur following institution of birth control pills as well. These typically resolve after discontinuation of OC pills.

Dystonias

Dystonias are uncommon disorders that involve sustained muscle contraction and abnormal posturing. They can be associated with twisting and repetitive movements as well (81). Only very rare cases of dystonias being induced by pregnancy exist (authors' personal experience). More often, a preexisting dystonia may be seen to complicate pregnancy or delivery. The majority of medications used to treat dystonias have a high probability of being associated with fetal malformation; however, the exception to this is dopa-responsive dystonias treated with levodopa. Although experience with this levodopa in pregnancy is limited, small series and case reports published to date do not suggest any fetal malformations occurring while the mother is taking this medication (75). More recently, botulinum toxin injections have been used, and occasional case reports (82) suggest that this treatment is effective for the mother, and not harmful to the fetus.

Essential Tremor

Essential tremor is the most common movement disorder in the general population and is frequently seen in younger patients. This movement disorder more likely than any others to be encountered by a treating obstetrician. It involves action tremors of the hands, head, voice, and occasionally legs or trunk, and frequently runs in families. The tremor occurs when the patient is using the extremity; however, the head tremor occurs with any upright posture. There is no other impairment of neurologic function or cognition. The disorder follows a benign course and is generally only socially disabling; however, in more severe cases, it can be very difficult to eat or write. The most effective treatment for this disorder involves the use of PMD and propranolol. Other medications have been used with varying success. Given the unclear danger to the fetus of these medications, as well as the benign nature of the disorder, it is probably wise to counsel the mother to take no

medication for this condition while she is pregnant or breastfeeding. If the mother's tremor is so severe that it precludes reasonable normal daily function, the choice of medications should be discussed between the obstetrician and the neurologist to determine which medication is felt to be least likely, at that time, to cause harm to the fetus and most effective for that patient.

Tourette's Syndrome

Tourette's syndrome is also quite common, and since it begins in childhood, this disorder will be frequently seen in the obstetric population. Tourette's syndrome involves the combination of motor and vocal tics, which evolve and fluctuate over time. A tic is a brief un-voluntary movement or sound that can include throat clearing, coughing, sighing, or making sounds or words. The tics can be suppressed voluntarily but take a great deal of effort from the patient to do so. For this reason, they are called un-voluntary rather than involuntary. Patients with Tourette's syndrome also frequently have attention deficit disorder and obsessive-compulsive disorder. The tics typically respond to dopamine receptor blockade, and haloperidol is a very effective treatment. As discussed previously, this medication is felt to be the safest choice for the fetus (80).

Huntington's Disease

Huntington's disease occasionally presents during child-bearing years, although classically presents in the patients' 30s or 40s at a time when many women have already had children. Although not caused or necessarily exacerbated by pregnancy, the Huntington's patient presents several unique challenges. The first is treatment of a pregnant patient with significant symptoms. The symptoms of Huntington's disease include chorea, dementia, and psychiatric disorders. All treatment is symptomatic, as no neuroprotective or preventive therapies currently exist. The safest option for treatment of chorea or psychosis is dopamine blockade using haloperidol and the treatment for depression felt to be least harmful for the fetus is fluoxetine (80). A more common scenario is that a woman who has already delivered children will later develop the symptoms of Huntington's disease. The disorder is an autosomal dominant genetic disease that can be predicted by an expanded CAG repeat in the region that codes for the Huntington protein on chromosome four. Adult patients with symptomatic parents have the option of genetic testing to determine whether they will develop this disease, although not all will choose to do so. Genetic testing should not be carried out lightly, and the physician ordering this test must be prepared to properly counsel the asymptomatic adult patient. This responsibility is usually best carried out by a neurologist with expertise in Huntington's disease or a geneticist. The children of an affected parent have a 50% chance of developing the disorder, and some parents choose to proceed with pregnancy whether or not they expect to develop the disease themselves (83). For the affected patients who choose not to conceive naturally, techniques for artificial insemination or in vitro fertilization of donor ova could be considered as appropriate.

Parkinson's Disease

Because Parkinson's disease is more common over age 50, it is only rarely found in the age group likely to conceive children. Very little experience exists with this condition in the reproductive age group, although a small series (84) of patients suggests that levodopa is not associated with any significant fetal malformations or birth problems. Other antiparkinsonian medications appear to be associated with variable risks to the fetus in many cases and probably should be avoided if at all possible (80). Parkinson's disease is a neurodegenerative disorder that generally begins with increased muscle tone or resting tremor on one side of the body progressing to the other side over a variable length of time. Gait problems and significant problems with activities of daily living and self-care are later findings. Young people with Parkinson's disease often have a more aggressive progression of disease, but hopefully would be able to be adequately maintained throughout pregnancy on levodopa monotherapy. Consultation with a movement disorder neurologist would be very helpful with this patient group.

Wilson's Disease

Wilson's disease is a very rare disorder involving disordered copper metabolism. Clinically, there is a wide variability in the age of onset as well as presentation. In children, it more commonly presents with symptoms of liver disease, but in young adults psychiatric or movement disorders tend to predominate. The clinical picture consists of liver cirrhosis, a wide variety of abnormal involuntary movements, and psychiatric illnesses. The most common treatment for this disorder is the copper chelator penicillamine, which is known to be teratogenic. Trientine is another chelating agent sometimes used, but may also be associated with fetal malformations. More recently, the therapy with zinc acetate has been shown to be effective in the treatment of Wilson's disease (85), and a small case series suggests only a mildly elevated birth defect rate compared with the general population (86). The authors of that paper conclude that zinc acetate is a preferable treatment for Wilson's disease in pregnant women.

In this section, we have reviewed movement disorders that appear to have a direct link with sex hormones as well as those that are preexisting and may change their manifestations during pregnancy or otherwise complicate pregnancy in some fashion. Movement disorders induced by pregnancy are rarely seen, and the majority of experience is from cumulative case reports from many authors. The rarity of these disorders in the childbearing age group makes it unlikely that any single physician will have much experience with the management of these conditions during pregnancy, and referral to a movement disorder neurologist would be appropriate.

STROKE AND PREGNANCY

Cerebrovascular disorders, which include ischemic and hemorrhagic stroke, are an uncommon but feared complication of pregnancy contributing to 5% to 12% of all maternal deaths (87). Eclampsia occasionally shares presentation similar to stroke but importance of prompt recognition of either cannot be overemphasized. For the sake of clinical management, the issue of stroke in pregnancy has been divided into

cerebrovascular risk factors before pregnancy, during pregnancy, and in immediate puerperium.

Stroke Risk Before Pregnancy*Contraception in Relation to Stroke*

Contraceptives containing more than 80 µg of estrogen are linked to increased risk of stroke. This risk increases for hemorrhagic stroke if smoking is combined with estrogen intake.

Stroke Risk During Pregnancy

Incidence: Though studies have shown variable rates, most agree (88) that risk of cerebral infarction is the same in pregnancy as compared with age-matched controls though risk of intracranial hemorrhage is about 2.5 times higher during pregnancy. Witlin et al. reviewed the incidence of stroke in pregnancy and only reported 20 strokes in 130,000 women who delivered over a period of 10 years (88). Overall, for either type of stroke during or within 6 weeks after pregnancy, the adjusted relative risk is about 2.4 (95 % confidence interval, 1.6 to 3.6), and the attributable, or excess, risk is 8.1 strokes per 100,000 pregnancies (95% confidence interval, 6.4 to 9.7). The prevalence of hypertension, diabetes mellitus, and current smoking was found to be lower among pregnant women with stroke than among nonpregnant women with stroke in Baltimore–Washington Cooperative Young Stroke Study (89).

Pregnancy As a Risk Factor

Pregnancy is a relatively hypercoagulable state with markedly increased levels of fibrinogen, total body, and plasma levels of factors VII, X, and XII. The increased activity of factors of hemostasis is accompanied by an increase in activity and concentration of ATIII and acquired activated protein C resistance predisposing to thromboembolic events (90).

Many other physiologic changes occur in pregnancy that may impact the pathogenesis and management of stroke during pregnancy (91). Blood pressure decreases during the second and third trimesters due to decreased peripheral vascular resistance. Cardiac output, systemic blood pressure, and vascular resistance contribute to cerebral perfusion. Dramatic shifts in hemodynamics coupled with alterations in coagulation profile underscore the clinical significance of the physiologic adaptations in cerebral endothelial permeability and pressure. Middle cerebral artery perfusion pressure has been shown to increase steadily during gestation.

Presentation

The clinical features of arterial ischemic strokes during pregnancy are not unique, except for those of eclampsia-associated ischemic strokes, which comprise seizures and/or impairment of consciousness, in addition to focal deficits. CVT presents with a wide spectrum of symptoms and signs and can be confused with other diseases, in particular with eclampsia, encephalitis, intraparenchymal hemorrhage, and even with post-lumbar puncture headache. The differential diagnosis of hemorrhagic strokes includes eclampsia, pituitary necrosis, and CVT. It is noteworthy that hypertension and albuminuria, two main features of eclampsia, have been observed in about a third of intracranial hemorrhage caused by a ruptured vascular malformation during pregnancy (92).

Table 1 Causes of stroke in pregnancy

Generic causes of stroke during pregnancy	Causes of stroke unique to pregnancy
Premature atherosclerosis	Eclampsia
Hypertension	Caesarean delivery (88)
Cardiac disease	Choriocarcinoma
Hyperlipidemia	Postpartum cerebral angiopathy
Diabetes	Postpartum cardiomyopathy
Arterial dissection	Amniotic fluid embolus during labor
Takayasu's disease	<i>Associations of stroke in pregnancy</i>
Vasculitis	Migraine headache
Antiphospholipid antibody syndrome	Blood transfusion
Systemic lupus erythematosus	Anemia
Sickle cell disease	Age more than 35 years
Thrombotic thrombocytopenic purpura	Non-white race
Coagulopathies	Bromocriptine mesylate (used in postpartum for suppression of lactation)
Tobacco	Methylergonovine maleate (used in postpartum hemorrhage caused by uterine atony)
Cocaine or drug abuse	
Thrombophilic states	
Protein C and S deficiencies	
Antithrombin III deficiency	
Factor V Leiden mutation	
Hyperhomocysteinemia	
Mutations in the prothrombin gene	
Lupus anticoagulant	
Anticardiolipin antibody	

Etiology of Stroke

Causes of stroke in pregnant females are usually the same as causes in nonpregnant females. Though associations of migraine headaches and blood transfusion have been suggested, their exact etiologic role is unclear (87). Transfusion increased the risk of stroke more than 10-fold. Although the need for transfusion is increased in conditions that place a woman at an increased risk of stroke, such as severe pre-eclampsia, postpartum hemorrhage, and sickle cell anemia, transfusion itself may be a risk factor for stroke. Storage and preservation of red blood cells increases their aggregability, possibly increasing the risk of thrombosis (87). Age greater than 35 years and African-American race have also been found to be significant risk factors. Eclampsia is the main pregnancy-specific cause, which may be associated with focal neurologic deficits of sudden onset, consistent with a clinical diagnosis of stroke. The two other pregnancy-specific conditions (choriocarcinoma and amniotic fluid embolism) are rarely responsible for focal cerebral ischemia. Table 1 lists the causes of stroke in pregnancy grouped under generic causes, pregnancy specific causes, and associations of stroke in pregnancy that may not necessarily have an etiological role.

Pregnancy-Related Complications

Gestational diabetes and hypertension are both associated with increased risk of stroke (93).

Complications of pregnancy such as severe pre-eclampsia, eclampsia, infection, hyperemesis, and fluid and electrolyte imbalance are significant risk factors for pregnancy-related stroke (87).

Pre-eclampsia and Eclampsia

Pre-eclampsia is known to be an important risk factor for pregnancy-associated stroke. One-fourth of the

pregnancy-related infarcts are associated with eclampsia or pre-eclampsia. The hypercoagulable state of normal pregnancy is further potentiated in pre-eclampsia. There is increased expression of procoagulant proteins, such as tissue plasminogen activator, PAI1, von Willebrand factor, fibronectin, homocysteine, and thrombomodulin, and reduced levels of anticoagulant proteins, including antithrombin III, protein C, and protein S in women with pre-eclampsia (93). Beyond increasing risk of stroke during pregnancy, women with pre-eclampsia were 60% more likely to have a stroke in the months and years that followed their pregnancy.

Neurologic features of the pre-eclamptic–eclamptic syndrome include headaches, visual abnormalities owing to retinal or occipital lobe lesions, impairment of consciousness, seizures, or focal deficits of sudden onset (92). The clinical and neuroimaging findings are more consistent with edema, which is thought to result from a rapid increase in blood pressure with vasospasm of cerebral arterioles, subsequent loss of autoregulatory capacity, and disruption of the blood–brain barrier. Angiograms in patients with eclampsia have also shown segmental narrowing consistent with vasospasm of large and medium-sized cerebral arteries. Several causes of altered vascular reactivity, including increased sensitivity to normally circulating pressor agents, deficiency of vasodilating prostaglandins, and endothelial cell dysfunction, have been reported in eclampsia. MRI in pre-eclampsia or eclampsia may show nonspecific hyposensitivities in posterior regions, finding often labeled as posterior reversible encephalopathy syndrome.

Ischemic Stroke

During pregnancy, risk of cerebral infarction is the same as age-matched control subjects. Exacerbations of systemic lupus

erythematosus and Takayasu's disease may occur during pregnancy and may manifest as ischemic strokes. Pregnancy is classically associated with an increased risk of rheumatic disease recurrence.

Antibiotic prophylaxis has been advocated for all pregnant patients with a history of rheumatic fever, especially those with a history of rheumatic heart disease. The high risk of thromboembolism in gravid patients with prosthetic heart valves emphasizes the need for effective anticoagulation throughout the pregnancy, despite the potential fetal and maternal adverse effects of this treatment. Bioprosthesis do not seem to be associated with an increased risk of thromboembolism during pregnancy and may not require anticoagulant therapy.

Hemorrhagic Stroke

Eclampsia and ruptured vascular malformations are the most frequent causes of intraparenchymal hemorrhage (92). The risk of hemorrhagic stroke during pregnancy is more than the risk of ischemic stroke though it increases further 6 weeks postpartum. Common associations of intracranial hemorrhage in pregnancy are eclampsia, bleeding diathesis, cocaine, bacterial endocarditis, sickle cell disease, and metastatic choriocarcinoma. Aneurysmal subarachnoid hemorrhage may be life threatening and warrants urgent correction.

AVMs

The increased tendency of an aneurysm to bleed with advancing gestational age suggests that hemodynamic, hormonal, or other physiologic changes of pregnancy may play a role in aneurysmal rupture (92).

Risk of hemorrhage from an unruptured AVM is estimated to be around 3.5%. The optimal time to wait to conceive after surgical correction is controversial. For previously ruptured AVMs, risk of hemorrhage outweighs risk from surgical corrections. Surgical treatment might be considered before planning pregnancy. Women with repaired AVMs can undergo vaginal delivery under epidural, caesarean may be preferred for partially repaired or untreated AVMs. Stereotactic radiotherapy is not used in pregnant women. No data are available concerning embolization of AVM in pregnancy (92).

Neuroimaging Modalities

Computed tomography may harm the fetus or embryo both by exposure to ionizing radiation and by administration of iodine-based contrast material, if contrast is used. During head CT examination, only head is directly irradiated. Fetus is exposed only to radiation scattered throughout the body and shielding the abdomen does not significantly reduce the minimal fetal radiation dose. The teratogenic risk linked to radiation exposure is limited to the embryogenesis period, which runs from the second to fourth week of gestation. Iodinated contrast though not shown to have adverse effects except neonatal hypothyroidism is categorized as B class by FDA. Digital angiography procedures decrease the X-ray exposure and the amount of administered iodine if deemed necessary. Pregnancy does not modify the maternal tolerance to iodine. Good maternal hydration is needed to avoid fetal dehydration. After 6 months, there is a risk of fetal hypothyroidism, which can be diagnosed and treated at birth with an excellent prognosis (92).

Though longitudinal studies are lacking, MRI is generally considered safe during pregnancy. American College of Obstetricians and Gynecologists have reported no adverse fetal effects but still advise against the use of MRI in first trimester. Risk of gadolinium to fetus is not known; it is classified as category C by FDA. Magnetic resonance angiography might avoid the risk of radiation associated with computed tomography and angiography while evaluating blood vessel in stroke or AVM.

Pregnancy does not contraindicate radiologic procedures if they are deemed necessary. In case of acute stroke, CT head noncontrast may not detect acute strokes less than 6 to 8 hours in onset. MRI sequences including diffusion weight imaging (DWI) are currently the most accurate imaging test available for acute ischemia with sensitivity and specificity approaching 100%. Intravenous contrast is not required for DWI or magnetic resonance angiography.

Treatment Modalities

The potential benefits of antithrombotic drugs should be weighted against the potential risks to the mother and the fetus. Aspirin should be used for same indications as for stroke as in nonpregnant female. It has not been reported to cause any harmful effects in the second and third trimesters. Low-dose aspirin (60–150 mg/day) have been largely administered by obstetricians during the second and third trimesters of pregnancy in women at risk for pregnancy-induced hypertension without evidence of fetal or maternal adverse effects. The potential adverse effects of aspirin consumption late in pregnancy are maternal and fetal hemorrhage, premature closure of the ductus arteriosus, prolongation of labor, and delay in the onset of labor (92).

Warfarin is known to be teratogenic and causes congenital malformations in fetus by causing micro-hemorrhages in the fetal brain. Fetal warfarin syndrome is a well-reported entity. When therapeutic anticoagulation is warranted, heparin (unfractionated or low molecular weight) should be used. It does not cross the placenta and its short half-life makes dose adjustment easier in case of overdose, bleeding, or premature delivery. Heparin therapy may cause a persistent anticoagulant effect (for up to 28 h after the last injection of heparin) at the time of delivery, which increases the risk of bleeding and contraindicates epidural analgesia.

When anticoagulants are indicated during pregnancy, two schemes of anticoagulant treatment have been recommended: (i) heparin throughout pregnancy or (ii) heparin until week 13 followed by warfarin until the middle of the third trimester followed by heparin. Heparin should be discontinued immediately before delivery. Anticoagulation treatment is started again after delivery (92).

Partum–Postpartum Period

Kittner et al. in Baltimore–Washington Cooperative Young Stroke Study registry found that the risks of both cerebral infarction and intracerebral hemorrhage are increased in the 6 weeks after delivery but not during pregnancy itself (89). The extremely high relative risk of stroke during the postpartum period suggests a causal role for the large decrease in blood volume or the rapid changes in hormonal status that follow a live birth or stillbirth, perhaps by means of hemodynamic,

coagulative, or vessel-wall changes. A causal role for pre-eclampsia and eclampsia does not fully explain the much stronger associations with stroke found for the postpartum state than for pregnancy itself.

Postpartum Cerebral Angiopathy

Postpartum cerebral angiopathy is characterized by the rapid occurrence of severe headaches, nausea or vomiting, seizures, and less often focal neurologic signs with a delay varying from a few hours to 1 month after a normal pregnancy. This picture may suggest the diagnosis of a subarachnoid hemorrhage, but the CSF is normal or shows a moderate pleocytosis. Eclampsia may present with similar features, but in postpartum angiopathy patients do not necessarily have hypertension or proteinuria. Rapid spontaneous clinical recovery occurs in the vast majority of cases. Angiography shows transient focal vasospasm. In most reports cases, ergot alkaloids or other sympathomimetic drugs had been given in the preceding days or hours, hence inclusion of the disease in the category of Call-Fleming syndrome (92). Outcomes are variable though rapid spontaneous clinical recovery has been generally reported.

CVT

CVT presents with headaches, seizures, stroke-like symptoms, or mental status changes. Peak incidence is in immediate postpartum period though its occurrence during pregnancy is also known. CVT may lead to ischemic infarction or to intraparenchymal hemorrhage. MRI usually shows hemorrhagic infarcts and magnetic resonance venography may show thrombus in major sinuses or cerebral veins. Conditions that may present with similar symptoms like eclampsia, meningitis, or cerebral mass should be excluded.

Caesarian section and age greater than 25 are risk factors for CVT. Hypercoagulable state of pregnancy, preexisting coagulopathy like protein C or S deficiency, factor V Leiden mutation or antithrombin III antibodies, dehydration, or infection are usual causes. Heparin anticoagulation should be considered with similar indications as in nonpregnant female. Efficacy of venous thrombolysis or venous stenting is not established in pregnancy.

Traumatic damage to the endothelial lining of cerebral sinuses and veins during labor, hypercoagulable state, and stasis of intracerebral blood flow are the most likely explanations for the occurrence of most CVT in the puerperium. Puerperal infections and dehydration may contribute to the high frequency of CVT in developing countries.

Mode of Delivery and Outcomes

Risk of stroke in relation to the full range of outcomes of pregnancy (spontaneous or induced abortion, stillbirth, and live birth) has not been adequately studied. Caesarean delivery by itself is a risk factor for stroke accounting to the risk of thromboembolism from surgery (88).

Mode of delivery has not been adequately shown to affect outcomes in the history of gestational stroke though series have found higher incidence of caesarian deliveries in such patients (88). James et al. (87) reported several complications associated with pregnancy-related stroke—postpartum hemorrhage (OR 1.8), pre-eclampsia and gestational hyper-

tension (OR 4.4), fluid and electrolyte imbalance (OR 7.2), transfusion (OR 10.3), and the highest, pregnancy-related infection (OR 25.0). Case fatality rate for pregnancy-related stroke have been reported to be anywhere between 4.5% and 24% (87). Stroke during one pregnancy by itself is not a risk factor for stroke during subsequent gestation.

CONCLUSION

Stroke during pregnancy or shortly thereafter is etiologically heterogeneous and, as with stroke in any young patient, requires systematic evaluation (88). Prompt neuroimaging and neurologic consultation are recommended in any pregnant or postpartum female who presents with new neurologic symptoms suggestive of stroke.

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