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Chapter 105

Neurology of pregnancy

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Pregnancy presents a unique set of physiologic conditions, upon which certain diseases are seen either in a specific manner or with increased frequency. This chapter will not attempt to reduplicate the entire field of neurology, but will focus predominately upon clinical features that are unique to pregnancy. Whenever possible, mechanisms of disease will be described to facilitate a deeper understanding of contributory role of pregnancy.

STROKE DURING PREGNANCY AND THE PUERPERIUM

Stroke during and shortly after pregnancy may be caused by a unique set of physiologic conditions that are distinct from stroke occurring in the young nonpregnant adult. It is beyond the scope of this section to discuss all causes of stroke in young patients. The following will describe stroke syndromes unique to pregnancy, along with a detailed description of underlying mechanisms that may produce stroke in this context.

Stroke during pregnancy can be divided into three main groups: ischemic stroke (IS), hemorrhagic stroke (HS), and from cerebral venous thrombosis (CVT). Some strokes may demonstrate both ischemic and hemorrhagic features.

Epidemiology

Ischemic and hemorrhagic stroke most commonly occurs in the third trimester and up to 6 weeks postpartum. The estimated incidence excluding subarachnoid hemorrhage (SAH) is 8.1–34.2 cases per 100 000 pregnancies. Third trimester IS relative risk in one study was not found to be elevated. However, in another study one fifth of all strokes occurred in the third trimester. Postpartum IS relative risk was 8.7. HS adjusted relative risk was 2.5 during pregnancy, rising to 28.3 in the first 6 weeks postpartum (Kittner et al., 1996; Skidmore et al., 2001; James et al., 2005; Roger et al., 2012).

Underlying mechanisms producing stroke syndromes unique to pregnancy

Several stroke syndromes are unique to pregnancy. They occur through multiple factors which have a common final action upon vascular endothelium, hemodynamic and clotting function.

The role of vascular endothelium

Vascular endothelial dysfunction has a central role in many cerebrovascular disorders of pregnancy. A continuous monolayer lining blood vessels, vascular endothelium creates a surface area of more than 1000 m^2 in the adult, and serves multiple roles in hemostasis, fibrinolysis, and vascular reactivity with maintenance of blood pressure (Sagripanti and Carpi, 2000).

The role of clotting function and fibrinolysis

Pregnancy produces a relative hypercoagulable state for several reasons. Firstly, in the placental architecture, blood flows through intravillous spaces and exchanges molecules across the trophoblastic lining, which creates the potential for hemorrhage. Placental trophoblast cells express procoagulant factors (Lanir et al., 2003). A second function is to prevent hemorrhage when the placenta separates at term. During normal pregnancy, fibrinogen concentrations increase, protein S decreases by 60% of control values by the 10th week of pregnancy, protein C activity falls in conjunction with a rise in natural fibrinolytic activity (t-PA and type I plasminogen activator activity, the latter increasing by 31st week of gestation).

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Shortening of the prothrombin time (PT) begins in the 20th week of pregnancy, likely due to increased factor VII levels. Procoagulants including fibrinogen begin to increase at the 30th week and remain stable until delivery. Prothrombin fragments 1+2 increase throughout pregnancy and fall in the puerperium. Factors VII and VIII increase and factor X remains stable or increases. The activated partial thromboplastin time (aPTT) and factor X, factor XI and factor XII levels remain unchanged. D-dimer gradually increases during pregnancy, consistent with fibrinolytic activity. In summary, while there is both an increase in procoagulation factors and fibrinolysis, the relative imbalance favoring the former supports a net hypercoagulable state in pregnancy (Comeglio et al., 1996; Cerneca et al., 1997).

The role of immunity

An embryo is semi-allogenic, necessitating adjustments in maternal immunity. The immune system interacts with the aforementioned placental coagulation factors. Derangements in this delicate immune balance can produce hemostatic abnormalities and contribute to pre-eclampsia, miscarriage, recurrent spontaneous abortion and intrauterine growth retardation (Li and Huang, 2009).

The role of vascular hemostasis

The kidney-based renin–angiotensin system (RAS) is well known for its effects upon arteriolar vasoconstriction and fluid and electrolyte homeostasis necessary to maintain blood pressure. Additionally, the renin–angiotensin system is also found in the uteroplacental unit, serving a role in the placentation of normal pregnancy. Derangements of pregnancy can upset the delicate equilibrium of RAS signaling, which has been implicated as contributory to the development of pre-eclampsia, with its associated edema and hypertensive component (Irani and Xia, 2008).

Maternal physiologic changes during pregnancy

To meet the physiologic needs of the developing fetus, cardiac output, heart rate and stroke index increase, with decreased systemic vascular resistance, pulmonary vascular resistance and mean arterial blood pressure. There is increased regional blood flow in the uterus, kidneys, extremities, skin, and breasts with essentially unchanged blood flow in the brain and liver (Roach et al., 2010).

Vascular endothelial dysfunction syndromes of pregnancy

Several important cerebrovascular syndromes of pregnancy have common features which appear to represent expression along a spectrum of maternal vascular endothelial dysfunction. The commonality of clinical and laboratory features seen in pre-eclampsia, eclampsia, reversible cerebral vasoconstriction syndrome (RCVS), postpartum cerebral angiopathy and reversible encephalopathy syndrome suggest a final common action affecting vascular endothelium. While these conditions are likely multifactorial, we propose classification under the heading vascular endothelial dysfunction syndromes of pregnancy (VESOP) to foster a greater understanding from a mechanistic rather than purely syndromic basis. While the biophysiology has not been completely defined, a brief overview of the physiologic changes that occur during pre-eclampsia will create a framework for understanding the aforementioned unique pregnancy-related syndromes.

Pre-eclampsia and eclampsia

A multitude of cerebrovascular and systemic vascular sequelae of pregnancy occur as a manifestation of pre-eclampsia and eclampsia. Understanding common mechanisms leading to the development of pre-eclampsia creates a framework for understanding the mechanisms producing these vascular complications, including those that occur long after the completion of pregnancy.

Pre-eclampsia is characterized by the new onset of arterial hypertension $\geq$140/90 mmHg measured on two separate occasions and proteinuria $\geq$300 mg/24 hours after 20 weeks of pregnancy. Edema and excessive third trimester weight gain (>2 pounds/week) can occur, but are not necessary for the diagnosis. Pre-eclampsia occurs in 5–8% pregnancies and accounts for 50 000 annual deaths worldwide. Risk factors for pre-eclampsia include obesity, prior pre-eclampsia or eclampsia, insulin resistance, hyperlipidemia, hypertension, renal disease, and thrombophilia. Neurologic symptoms include headache, confusion, visual disturbances, and IS or HS. Systemic manifestations may also include renal failure, pulmonary edema, epigastric or right upper quadrant pain, hemolysis, elevated liver enzymes and low platelets (HELLP syndrome). Pre-eclampsia-induced HELLP is associated with activation of blood coagulation resulting in macroscopic fibrin deposits in various organs in severe cases. Such peripartum hemostatic emergencies may occur in 1–5% of patients with disseminated intravascular coagulation (DIC), producing abruptio placenta and retained dead fetus syndrome (Levi, 2009). Fetal growth restriction may occur.

Eclampsia is defined after a seizure occurs in a pre-eclamptic patient in the absence of other provocation (ACOG Practice Bulletin, 2002). The cornerstone of treatment includes magnesium sulfate. While magnesium sulfate has been demonstrated to generally be more efficacious in preventing recurrent seizures than phenytoin and diazepam (Duley, 1995), seizures that do not initially respond to magnesium sulfate may necessitate the addition of a benzodiazepine such as diazepam or lorazepam. Long-term anticonvulsant management following delivery is generally not needed. Hydralazine or labetalol can be used for hypertension not controlled by magnesium sulfate. Delivery often is curative. However, delayed postpartum eclampsia occurs in 10–45% of women with eclampsia between 2 and 48 days following delivery, and may be associated with other conditions such as postpartum angiopathy (aka reversible cerebral vasoconstrictor syndrome, see below).

Pre-eclampsia begins in the placenta and affects the maternal multiorgan vascular endothelium (Powe et al., 2011). In 1988, Rogers first proposed that multiorgan dysfunction occurring in pre-eclampsia was due to endothelial dysfunction (Rogers et al., 1988). The following year, additional information suggested that poorly perfused placental tissue triggered a dysfunctional cascade of systemic factors producing such endothelial injury causing vasoactive, coagulation and intravascular fluid redistribution (Roberts et al., 1989). Subsequently, the origins of eclampsia can be traced to two major factors: abnormal development of the placenta that subsequently produces an imbalance of humoral factors which affect vascular endothelial function, most notably angiogenic versus antiangiogenic peptides.

The role of the placenta in pre-eclampsia

The placenta is necessary to develop pre-eclampsia; a fetus is not. Maternal hypertension and/or proteinuria occurring before 20 weeks gestation can occur in a molar pregnancy. This is caused by either an extra set of paternal chromosomes producing a fertilized egg and a growing mass of cysts rather than a viable fetus (complete molar pregnancy) versus malformed nonviable embryo and some normal placenta (incomplete molar pregnancy) (Mutter and Karumanchi, 2008). Removal of the placenta generally cures pre-eclampsia. Under normal circumstances, differentiation of epithelial stem cells (cytotrophoblasts) and their invasion into the uterine arterioles occurs at approximately the end of the first trimester. The uterine spiral arteriolar vascular bed is composed of small, low-flow, high-resistance vessels and is relatively hypoxic. This induces production of vascular endothelial growth factor, allowing the cytotrophoblasts embedded in the smooth muscle and endothelial maternal decidual arterial layers to remodel into a large-caliber, high-capacitance vascular bed which allows for a steep rise in the oxygen tension gradient. When cytotrophoblasts cannot gain access to a supply of richly oxygenated maternal arterial blood there is impairment in the ability to differentiate into fully invasive cells (Zhou et al., 1997; Genbacev et al., 1997).

The role of humoral factors in pre-eclampsia

Circulating soluble fms-like tyrosine kinase-1 (sFlt-1) is a circulating antiangiogenic protein made by placenta. Vascular endothelial growth factor (VEGF) triggers angiogenesis. Pre-eclampsia occurs when the relative functional activity sFlt-1 exceeds that of VEGF. Renal capillary endothelium is very sensitive to VEGF, needed to maintain normal fenestration of glomerular endothelial cells. This may explain why pre-eclampsia-induced renal dysfunction characterized by proteinuria and hypertension (in part) is an important and early marker of the disease. A second soluble factor, endoglin (Eng), is highly expressed in vascular endothelial cells and syncytiotrophoblasts, which amplifies the antiangiogenic effect of sFlt-1. Endothelium-derived nitrous oxide (NO) produces vascular relaxation and contributes to regulation of systemic blood pressure, vascular permeability, and angiogenesis. The combination of sFlt-1 and Eng has an effect upon endothelial nitric oxide synthetase and is the cause of abnormalities of vascular tone observed in pre-eclampsia as well as inducing multiorgan dysfunction which produces hemolysis, elevated liver enzymes, and low platelets (HELLP syndrome), which can predispose to maternal hemorrhage. Like sFlt-1, Eng begins to rise 6–10 weeks before the clinical symptoms of pre-eclampsia, and falls following completion of pregnancy. Multiple small studies have confirmed measurable disproportionally high circulating antiangiogenic factors in pre-eclamptic patients, as early as the first and second trimester (Koga et al., 2003; Levine et al., 2004, 2006; Rana et al., 2007; Singhal et al., 2009). If these findings are confirmed by large-scale studies, such ELISA-based screening of all pregnant patients may one day be used to predict patients at risk for pre-eclampsia and eclampsia long before the appearance of clinical symptoms.

The long-term effects of pre-eclampsia and eclampsia on maternal health in later life

Women who have pre-eclampsia have an increased risk of future cardiovascular disease. Pre-eclampsia is associated with asymptomatic global left ventricular dysfunction and abnormal geometry during the acute phase of the disorder. One year postpartum, asymptomatic left ventricular moderate-severe dysfunction and

hypertrophy were significantly higher in preterm eclampsia (56%) compared to term pre-eclampsia (14%) or matched controls (8%). There was also a significant risk of developing hypertension within 2 years (Melchiorre et al., 2011). Bellamy and colleagues performed a meta-analysis of studies published between 1960 and 2006 encompassing almost 3.5 million women. Almost 200 000 were affected by pre-eclampsia and almost 30 000 were affected by cardiovascular disease and cancer. Women who experienced pre-eclampsia had an absolute risk of cardiovascular events: 17.8% by the age of 59 and 30.7% by the age of 69 in comparison to women who did not experience pre-eclampsia (8.3% and 14.2% respectively). More specifically, following pre-eclampsia the increased risk of future hypertension was 3.7, ischemic heart disease 2.16, stroke 1.81, and venous thromboembolism 1.79. Breast cancer risk was not found to be significantly increased. All-cause mortality risk was 1.49 (Bellamy et al., 2007). Similarly, Brown et al. found that women who experienced pre-eclampsia were 60% more likely to have a nonpregnancy-related ischemic stroke (Brown et al., 2006). Staff, Dechend and Redman have hypothesized that oxidative stress of the placenta presents an inflammatory burden to the mother even in normal pregnancies. Pre-eclampsia further stresses the uteroplacental circulation to the point of decompensation based upon the histologic finding of acute atherosis (defined as subendothelial lipid-filled foam cells, fibrinoid necrosis, and leukocyte infiltration resembling early atherosclerosis) in placental spiral arteries of women suffering from pre-eclampsia. While not seen in all women with pre-eclampsia or unique to pre-eclampsia, its presence may suggest that there may be a subset of women that have an augmented risk for future atherosclerosis (Staff et al., 2013).

Following the observation of decreased incidence of breast cancer and other solid tumors in women with a history of pre-eclampsia, it has been hypothesized that there may be chronic residual antiangiogenic balance that may confer partial protection from growth and metastases of certain vascular solid tumors (Cohn et al., 2001; Vatten et al., 2002; Aagaard-Tillery et al., 2006).

Of note, a mutation in the gene that encodes Eng is responsible for causing hereditary hemorrhagic telangiectasia type I (Osler–Weber–Rendu syndrome), which produces abnormal multiorgan vasculogenesis that can produce cerebral hemorrhage in pregnancy (Venkatesha et al., 2006).

Pre-eclampsia, hypertension, and stroke-risk mitigation

Hypertension in pre-eclampsia can precipitate cerebral hemorrhage. While not studied prospectively, blood pressure elevation values > 150–160/105–110 mmHg are commonly considered by various consensus reports to be the initial threshold to initiate antihypertensive treatment (JNC 7, 2004). However, Martin and colleagues found that only 12.5% of patients experiencing pre-eclamptic-mediated stroke (mostly hemorrhage) exhibited diastolic blood pressures at or above 110 mmHg before experiencing a stroke, but all patients experienced stroke when the systolic blood pressure was greater than 155 mmHg. They recommended initiation of antihypertensive therapy to prevent pre-eclampsia-mediated cerebral hemorrhage if the systolic blood pressure exceeded 155–160 mmHg even without diastolic hypertension (Martin et al., 2005). These observations deserve evaluation in a larger prospective series.

Ischemic strokes

Cardiogenic embolism

As in the nonpregnant patient, cardiogenic embolization may occur from a multitude of disorders including cardiac valvular disease, atrial fibrillation, left ventricular thrombi, paradoxical embolization via intracardiac shunt, congenital heart disease, infective and noninfective endocarditis, etc. Availability of antibiotic therapy has reduced but not completely eliminated the incidence of rheumatic heart disease. Similarly, advances in cardiac surgery have allowed women with congenital heart defects to survive into childbearing age. Transthoracic echocardiography has demonstrated attenuated cardiovascular adaptation with reduced systolic function and progressive diastolic function during pregnancy which persists for 6 months after pregnancy, placing them at risk for adverse cardiovascular outcomes (Cornette et al., 2012).

Peripartum cardiomyopathy (PPCM) produces heart failure with left ventricular systolic dysfunction, occurring with an estimated incidence of 18–333 cases per 100 000 live births. Mortality may be as high as 20%. PPCM typically occurs in the last month of pregnancy or within 5 months of delivery. No clear etiology has been proven, but there may be an association with pre-eclampsia mediated through cleavage of the prolactin molecule. It is a diagnosis of exclusion after other causes of heart failure have been ruled out. It may recur with subsequent pregnancies. In conjunction with the hypercoagulable nature of pregnancy, reduced left ventricular ejection fraction (LVEF) < 35% increases the risk for left ventricular thrombus, at which point therapeutic anticoagulation should be considered. While many patients spontaneously recover cardiac function, women with LVEF ≤25% are at greater risk for nonrecovery and may need cardiac transplantation (Reuwer et al., 2010; Blauwet and Cooper, 2011).

Reversible cerebral vasoconstriction syndrome

A unique syndrome of *intracranial* arterial vasospasm may occur during pregnancy, pre-eclampsia or postpartum (aka: postpartum angiopathy, PPA, Call–Fleming syndrome) (Call et al., 1988). Reversible cerebral vasoconstriction syndrome (RCVS) is often heralded by thunderclap headache followed by focal neurologic signs, visual disturbances, and occasionally one or more seizures. Aneurysmal SAH, arterial dissection and primary angiitis of the central nervous system (PACNS) need to be rapidly sought and excluded. Cerebral infarction may occur, often in a watershed distribution. Cortical SAH involving one or several sulci has a radiographic appearance distinct from aneurysmal SAH (Fig. 105.1). Concurrent impairment of vascular endothelial cell function may cause disruption of the blood–brain barrier with vasogenic edema (posterior reversible encephalopathy syndrome, PRES). Cerebroispinal fluid (CSF) is generally normal or may only show mild elevation of protein and white cells. Initial cerebral arteriography may be normal, but within 1 week demonstrates multifocal arterial segmental constriction, often in a widespread distribution. The hallmark of RCVS is the radiographic resolution of the intracranial vasconstriction, generally in less than 12 weeks (Calabrese et al., 2007). While outcome is generally

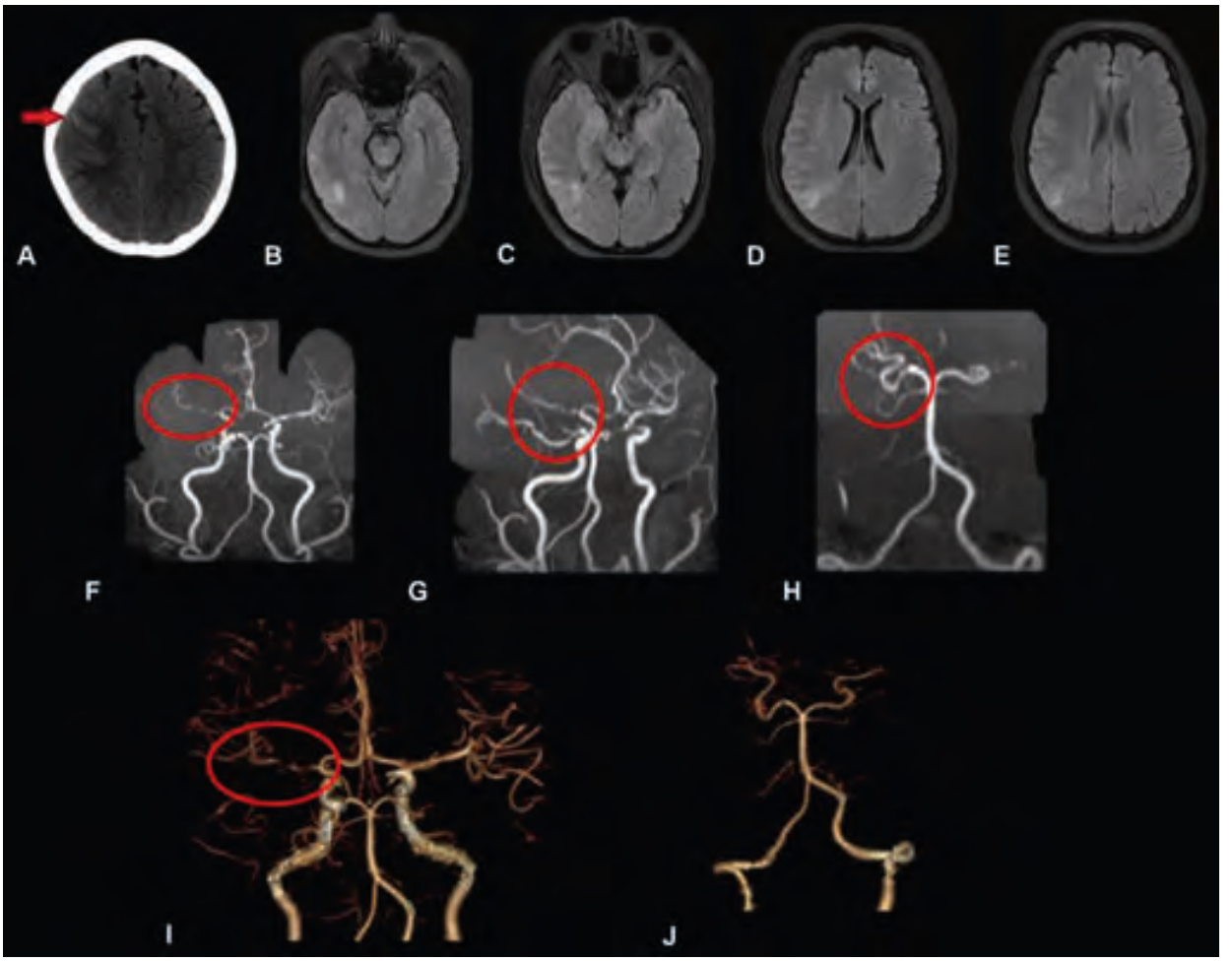

Fig. 105.1. A 27-year-old right-handed woman, G1, P1 with history of gestational diabetes and pre-eclampsia had acute onset of "marching" left face and left hand numbness associated with slurred speech and nonpostural posterior head pain following delivery. Examination showed a blood pressure of 160/101 mmHg and bilateral pitting edema of her legs. Neurologic examination was unremarkable. Unenhanced CT (**A**) showed a focal cortical right frontal SAH (arrow). MRI (**B**, **C**, **D**, **E**) showed areas of abnormal signal intensities on the right posterior frontal and anterior parietal regions. MRA (**F**, **G**, **H**) demonstrated diffuse, bilateral areas of arterial narrowing and dilation more pronounced on the right middle cerebral artery (MCA) (oval and circles). CTA (**I**) corroborated areas of intracranial arterial narrowing (oval). Post-treatment CTA (**J**) showed resolution of the diffuse intracranial vasoconstriction. Final diagnosis was RCVS (postpartum angiopathy) in a pre-eclamptic patient.

favorable, fatalities have been reported (Singhal et al., 2009; Fugate et al., 2012a).

Two-thirds of the cases of PPA begin in the first week following delivery after a normal pregnancy or one complicated by proteinuria and HELLP, suggesting an overlap with eclampsia. Patients with PPA may have a more severe manifestations and a potentially worse outcome. Up to 40% may experience a cerebral hemorrhage. In so far as the initial CTA, MRA, or cerebral arteriogram may be negative, a high index of suspicion and a repeat study are recommended (Ducross, 2012; Fugate et al., 2012a, b).

Hemorrhage may occur in one-third of patients, most commonly in a cortical sulcus, and less commonly in the brain parenchyma or subdural space. In contrast to vasospasm near an aneurysmal SAH, cases of RCVS-induced cortical SAH have more widespread vasospasm.

RCVS is a syndrome of various conditions with similar outward expression, but without a definitive understanding of the underlying cause. One proposed mechanism involves sudden alteration of cerebrovascular tone. Constriction or dilation of peripheral cortical pain-sensitive small distal arteries triggers the thunderclap headache. Subsequently, abnormal vessel reactivity spreads more centrally within the brain to involve medium- and large-sized arteries responsible for ischemic events (Ducross et al., 2007; Werring, 2010).

Triggers of RCVS include exposure to medications that affect vascular reactivity including sympathomimetic, serotonergic, dopaminergic agonists, illicit drugs, etc. No cause can be found in approximately one half of cases.

Various treatments to mitigate vasospasm have been tried, including magnesium sulfate, calcium channel blockers, intracranial angioplasty, etc. However, there has been no proven treatment that influences outcome. Initial seizures generally do not produce epilepsy, and do not require a long-term antiepileptic therapy.

Antiphospholipid syndrome

Antiphospholipid syndrome (APS) is an autoimmune disorder which can produce arterial or venous thrombosis, recurrent miscarriages, stroke and a myriad of other symptoms described below. The hallmark of the condition is antiphospholipid antibodies (aPL), of which anticardiolipin antibodies (aCL), β-2 glycoprotein 1 and a lupus anticoagulant (LA) have been observed most commonly associated with various clinical syndromes. Antibodies to other phospholipids currently play an uncertain role in APS.

Diagnosis and treatment of patients with suspected APS should be approached with caution. Twenty-six years after the first clinical description of APS was published (Hughes et al., 1986) the potential mechanisms producing various clinical symptoms have not been fully elucidated. Clinical symptoms as described below can occur either with or without the detection of currently recognized biomarkers; conversely, biomarker positivity can occur in the absence of symptomatology. The American Heart Association (AHA) published proposed criteria for the evaluation of novel biomarkers of cardiovascular risk (Hlatky et al., 2009). Among other attributes, the biomarker should be able to correlate with specific clinical symptoms, distinguish between subjects with and without a specific outcome, provide predictive information over standard risk markers, predict future events which would predict out, or influence management, etc. De Groot and Urbanus methodically detail the current limitations in the predictive power of the aforementioned three biomarkers, which are limited in their ability to predict the risk of recurrence with a high degree of confidence. A more complete understanding of the clinical manifestations to characterize APS is needed as well as new assays to provide tailored therapies and prognostic value (deGroot and Urbanus, 2012). The following highlights the literature thus far.

Geoepidemiology of APS has been elegantly reviewed (Biggioggero and Meroni, 2010). To briefly summarize, primary APS occurs in the absence of underlying autoimmune disease. Secondary APS most commonly occurs with systemic lupus erythematosus (SLE), other autoimmune disorders, inflammatory diseases, neoplasia, infections, and medications. It can also be found in asymptomatic patients. Between 30% and 40% of patients with aPL have a history of thrombosis of which 30% is arterial, most predominantly in the cerebral circulation producing stroke or TIA, and involves the coronary arteries to a lesser degree. Deep venous thrombosis (DVT) occurs in up to 30% of patients. In addition to fetal loss, aPL is associated with preeclampsia, eclampsia, intrauterine growth retardation, HELLP syndrome, oligohydramnios, uteroplacental insufficiency, and premature birth due to pregnancy-induced hypertension.

How to interpret the antibody positivity. A single positive test may not be associated with thrombosis. aPL and β-2 glycoprotein 1 antibody positivity has a modest association with thrombosis and a low recurrence rate. Currently, triple antibody positivity has the highest correlation with clinical symptoms of APS. β-2 Glycoprotein 1 antibodies are more specific and related to thrombosis, especially if the titer is high (Devreese, 2012). All three antibodies need to be drawn. To omit aCL or anti-β-2 glycoprotein 1 antibody testing would lead to the failure to diagnose APS and 9.5% and 29.4% of patients respectively (Gardiner et al., 2013).

Antiphospholipid effect upon the hemostatic mechanism is complex, and not completely elucidated. There is protein C resistance, inhibition of protein S,

antithrombin and tissue factor pathway inhibition, impairment of fibrinolysis by inhibiting tPA, interacting with the antiplasmin and activating factor XI. Activated complement C3a and C5a activate monocytes and macrophages and trigger inflammatory process. Following cell death, small detached membrane microparticles rich in phospholipids may lead to thrombin formation and thrombosis. The mechanism has not been established for antiphospholipid cognitive dysfunction and demyelination.

Criteria manifestations of APS. Stroke and TIA occur in younger patients, more frequently women. Twenty percent of patients under 45 years have APS, and antiphospholipid antibodies are found in 6.8% of stroke patients. Sneddon syndrome is a progressive noninflammatory arteriopathy with cerebrovascular disease and livedo reticularis (aka: livedo racemosa), affecting small- and medium-sized arteries in the skin and brain. Antiphospholipid antibodies are found in 41%. Pregnancy loss may occur early or late. While the definition of APS includes fetal loss as described above, the literature supporting APS-induced early fetal loss demonstrates conflicting and inconsistent findings, and deserves further study. Clark and colleagues (2012) outlined biologic false positives and inconsistencies in reported study methodology over the past 25 years. Antiphospholipid antibodies in recurrent pregnancy loss without SLE varied depending upon the antiphospholipid antibody measured. The association of anticardiolipin IgG and IgM appeared variable dependent upon the titer and gestational age. Prospective human data on the relationship of antiphospholipid antibodies and recurrent pregnancy loss are lacking and the mechanism for uteroplacental insufficiency is not completely understood. Furthermore, up to 30% of pregnancies end before the first trimester, mostly due to chromosomal abnormalities. The current criteria for the diagnosis of APS do not include fetal chromosomal assessment, only ultrasound or direct examination of the fetus. Hence, it is difficult to ascribe the early fetal loss in the presence of an antiphospholipid antibody solely upon the latter. In late fetal loss, lupus anticoagulant positivity was a strong predictor but β-2 glycoprotein 1 antibodies and high anticardiolipin antibody titers were not. They further note that inconsistent with the current classification criteria for APS, there was not a consistent correlation between the presence of antiphospholipid antibodies and the clinical manifestations of the syndrome. A majority of women with early recurrent pregnancy loss, DVT and stroke are negative for antiphospholipid antibodies. Additionally, women with uneventful pregnancies were found to have antiphospholipid antibodies. They reference the recommendations from the 13th International Congress on Antiphospholipid Antibodies (2010) to treat aPLs as a risk factor marker rather than a diagnostic focus. Given the inconsistent presence of aCLs, they also recommend redefinition of the criteria for early fetal loss (distinct from late fetal loss and early delivery with placental infarction).

Non-criteria manifestations associated with APS. Multiple sclerosis (MS)-like syndrome may resemble MS both clinically and radiographically, with the presence of white matter lesions. However, white matter hyperintensities on long TR-weighted pulse sequences perpendicular to the lateral ventricles (Dawson's fingers) are more common in MS. This may produce sensory or motor dysfunction, optic neuritis, or transverse myelitis. MS, primary APS and neuropsychiatric SLE with or without APS are all multisystem autoimmune diseases with similar relapsing-remitting courses, affecting the same population of patients and may produce multifocal white matter lesions on MRI. Seizures may be caused by SLE or APS associated with SLE. They are likely due to hypercoagulable-induced cortical infarction. Chronic intermittent headaches may be migraine-like in character. Proximal stabbing headaches have been described in various autoimmune disorders (Rampello et al., 2011). Chorea is rare with SLE and/or APS, but strongly associated with aPL. Precipitating factors include estrogen-containing oral contraceptives, pregnancy and the early postpartum period. Cognitive dysfunction is poorly understood. Poor memory, difficulty with concentration and attention may be related to cerebral ischemia. Livedo reticularis and Raynaud's phenomenon represent cutaneous manifestations. Mitral and aortic valve disease, including valvular vegetations, thickening and dysfunction to be present. Platelet counts less than 100,000/mm^3 may produce bleeding complications.

Catastrophic APS is a rare, rapidly evolving and life-threatening variant, occurring in approximately 1% of patients with APS, associated with high levels of aPL. The condition is manifest as a multiorgan thrombotic microangiopathy and exists along a continuum with other similar conditions including thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), and HELLP syndrome, and has an associated higher incidence of DIC-related hemolysis. Diagnosis may be difficult to establish in view of similarities from false positive aPL from infection or anticoagulation (positive lupus anticoagulant test), other microangiopathic thrombotic states as described above and heparin-induced thrombocytopenia. Manifestations include pulmonary emboli, intra-alveolar hemorrhage, renal microangiopathy with infarction producing acute renal failure, livedo reticularis, purpura, skin ulcerations, liver failure, stroke, encephalopathy, seizures, headache, silent brain infarctions, and CVT. Given its

infrequent occurrence, a registry was established in 2000 (Cervera, 2012). From the first 280 patients, 72% were women, with a mean age of 37 years, 46% suffered from primary APS, 40% SLE, 5% lupus-like disease and 9% other autoimmune disease. In almost half of patients with catastrophic APS, this was their first presentation. It is most commonly triggered by infection, surgery, oral anticoagulation withdrawal, medications, obstetric complications, and neoplasia and SLE flares. Diagnostic criteria were initially published in 2003 (Asherson et al., 2003) and updated in 2010 (Erkan et al., 2010). Criteria include involvement of three or more organs, symptom onset in less than 1 week, biopsy confirmation of small vessel occlusions and laboratory confirmation of the presence of a LA and/or anticardiolipin antibody. Treatment consists of corticosteroids, anticoagulant therapy, plasma exchange (PLEX) and/or intravenous immunoglobulin (IVIG).

Seronegative APS may produce clinical features of APS, with persistently negative testing for LA, ACL and anti-β-2 glycoprotein. Rodriguez-Garcia compared the clinical manifestations of SLE-seronegative APS (SN-APS) with seropositive APS. There was no significant difference in the occurrence of DVTs, pulmonary emboli, transient ischemic attacks, early spontaneous abortions, stillbirths, prematurity and pre-eclampsia. Additionally, both groups developed recurrence of arterial and venous vascular events following withdrawal of anticoagulation. They question whether other antibodies directed against other phospholipids (prothrombin, and phosphatidyl ethanolamine, annexin V, and vimentin/Cardiolite and complex) might have a contributory influence, and suggest it deserves further study (Rodriguez-Garcia et al., 2012).

Treatment of CNS manifestations of APS. Risk stratification for recurrent thrombosis can be estimated based upon the clinical presentation (arterial versus venous, etc.), involved antibodies, and underlying risk factors. Les and associates have outlined the intensity and duration of anticoagulation therapy in APS (Les et al., 2012). In severe cases, combined anticoagulation and immunosuppression/immunomodulation may be needed. Underlying triggers including infection need to be sought and treated. In mild disease low-dose aspirin and hypertension control may be adequate. In SLE and secondary APS, consider low-dose steroids, hydroxychloroquine or chloroquine. In difficult cases of thrombosis and nonthrombotic CNS-APS, high-dose oral or intravenous corticosteroids, Cytoxan, plasma exchange and/or or IVIG may be needed. Insofar as anticoagulation is a nonselective therapy, not effective in all patients and carries a risk of bleeding, investigation into targeted immunomodulatory therapies is ongoing, assessing the efficacy of hydrochloroquine, statins, B cell suppression such as rituximab, certain antiplatelet agents, anticytokine therapies, etc. (Comarmond and Cacoub, 2013).

Anticoagulant considerations in pregnancy. Various conditions may require anticoagulant therapy, including both primary and secondary hypercoagulable states, atrial fibrillation, CVT, cardiac valvular disease and prosthetic mechanical heart valves (especially in the mitral position), mural thrombi, APS, DVT, etc. Vitamin K antagonists (VKA) such as warfarin are teratogenic between 6 and 12 weeks of pregnancy, producing intellectual disability, facial and limb deformities. Several malformations have been associated with VKA exposure at any time during pregnancy, including agenesis of the corpus callosum, Dandy–Walker malformations, midline cerebellar atrophy, and optic atrophy.

Current anticoagulant guidelines from the American College of Chest Physicians (Bates et al., 2012) are based upon observational studies and deserve further investigation. Various recommendations are based upon the underlying condition. In general, unfractionated (UFH) or low molecular weight heparin (LWMH) may be used throughout pregnancy as they do not cross the placenta. VKA should be avoided in the first trimester, but may be considered in the second trimester, followed by conversion back to a heparin product, which should be discontinued at least 24 hours before anticipated delivery or cesarean section. VKA can be initiated after delivery, and is not present in breast milk. UFH poses a risk for heparin-induced thrombocytopenia and osteoporosis. LMWH does not carry these risks. The optimal dosage of LMWH has not been established. Measurement of trough and peak anti-Xa levels may guide dosing (Goland and Elkayam, 2012; McClintock, 2013).

Direct thrombin inhibitors and factor Xa inhibitors have not been adequately studied in human pregnancy and should be avoided. Table 105.1 illustrates FDA categories in drug safety in pregnancy.

Hemorrhagic strokes

Subarachnoid hemorrhage

Subarachnoid hemorrhage (SAH) may occur during pregnancy from a variety of conditions. In addition to intracranial aneurysmal rupture, a variety of nonaneurysmal conditions can also produce SAH. These include trauma, CVT, pre-eclampsia and eclampsia, hypertension of pregnancy, and inherited and acquired thrombophilias. Intracerebral hemorrhages with subarachnoid extension may be caused by various conditions such as hypertensive hemorrhage, hemorrhagic infarction, occult cerebrovascular malformation, Moyamoya disease, RCVS (postpartum angiopathy). Infective endocarditis and metastatic choriocarcinoma may produce infective (mycotic), or oncotic aneurysms.

Table 105.1

US Food and Drug Administration categories for the use of medications in pregnancy

FDA pregnancy category	Description
A	Controlled studies on animals and humans have shown no risk in the first trimester, and possible fetal harm is remote
B	Either animal studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women, or animal studies have shown an adverse effect that was not confirmed in controlled studies in women in the first trimester
C	No controlled studies in humans have been performed, and animal studies have shown adverse events, or studies in humans and animals or not available; give if potential benefit outweighs the risk
D	Positive evidence of fetal risk is available, but the benefits may outweigh the risk if life-threatening or serious disease
X	Studies and animals or humans show fetal abnormalities; drug contraindicated

Radiographically, acute SAH is generally detected by either unenhanced cerebral CT or MRI FLAIR imaging. However, it should be kept in mind that other conditions can mimic the radiographic appearance of SAH, including meningitis, leptomeningeal metastases, leptomeningeal melanosis, status epilepticus, supplemental oxygen administration, intravenous anesthetic agents, prior administration of radiographic contrast agents and artifacts (Cuvinciuc et al., 2010).

In the general population, SAH from ruptured intracranial aneurysms accounts for approximately 5% of all strokes. The overall incidence of SAH for women varies geographically, typically ranging between 7 and 13 per 100 000 person-years. However, the incidence in Japan and Finland is substantially greater (22.7 and 19.7 per 100 000 person-years, respectively) and increases with age (de Rooij et al., 2007). The true incidence may even be greater due to pre-hospital death.

In addition to the modifiable risk factors of SAH which include excessive alcohol consumption, hypertension, and smoking (Feigin et al., 2005), a possible contribution of hormonal factors in aneurysmal SAH has been suggested, but a clear mechanism has not been strongly established. This is based upon the observation that women have a greater incidence of SAH than men (1.24, range 1.09–1.42), which begins at age 55 (de Rooij et al., 2007).

Noncontraceptive hormonal replacement therapy used at any time in life has been associated with a lower incidence of SAH (Mhurchu et al., 2001; Feigin et al., 2005; Algra et al., 2012). The risk of SAH in a woman that has taken oral contraceptives is unclear. Some studies have demonstrated little or no increased incidence of SAH, while other meta-analyses have suggested otherwise (Johnston et al., 1998; Mhurchu et al., 2001; Algra et al., 2012).

The risks of SAH are lower in older women with a first pregnancy (Mhurchu et al., 2001), and greater with earlier age of menarche (<13 years) and nulligravidity (Okamoto et al., 2001).

In some series, the risk of aneurysmal SAH was reported not to be increased during pregnancy, labor or puerperium (Tiel Groenestege et al., 2009; Algra et al., 2012). In contrast, using insurance data from the Nationwide Inpatient Sample of Health Care Cost and Utilization Project, Agency for Health Care Research in Quality, Bateman and colleagues identified 639 cases of pregnancy-related SAH in over 11 million deliveries and more than 12.8 million pregnancy-related admissions between 1995 and 2008 for an annual incidence of 5.8 per 100 000 deliveries. The incidence in their referral center was 17.1 per 100 000 deliveries. Nonaneurysmal SAH was more common than aneurysmal SAH, with lower mortality rates. Most SAHs occurred in the delivery/postpartum period. Pregnant African American women were 3.3 times more likely, and Latino women were 1.4 times more likely to experience SAH than Caucasian women. Rates of hemorrhage were substantially greater for women between 35 and 44 years old in comparison to women less than 25. Modifiable risk factors included smoking, and drug and alcohol abuse (Bateman et al., 2012).

In general, aneurysms larger than 7 mm are more likely to bleed. The prospective phase II International Study of Unruptured Intracranial Aneurysms described the 5 year cumulative rupture rates of nonruptured anterior circulation aneurysms as 0 (<7 mm), 2.6% (7–12 mm), 14.5% (13–24 mm) and 40% (≥25 mm). Over the same interval, in aneurysms of the posterior circulation and posterior communicating arteries, 5 year rupture rates were 2.5% (<7 mm), 14.5% (7–12 mm), 18.4% (13–24 mm) and 50% (≥25 mm) (Wiebers et al., 2003). However, smaller aneurysms have also been described to bleed (Lu et al., 2013; Wong et al., 2013).

Aneurysmal SAH (aSAH) has a mortality rate reported as high as 67% (Nieuwkamp et al., 2009), making it imperative to secure the aneurysm as soon as safely possible.

Treatment of an intracranial aneurysm must be individualized, but need not be delayed until after delivery. Treatment decisions should be based upon aneurysm size, location, and progressive enlargement, especially if the patient has become symptomatic. Endovascular obliteration of the aneurysm with detachable platinum coils represents an alternative to open craniotomy and carries lower morbidity. The International Subarachnoid Aneurysm Trial demonstrated the benefit of endovascular treatment including independent survival at 1 year, with similar case fatality in comparison to open craniotomy for aneurysm neck clipping (Molyneux et al., 2002). Following endovascular aneurysmal occlusion the potential for regrowth of the aneurysm exists if it is not completely occluded. This possibility should be described when obtaining informed consent, which necessitates periodic radiographic surveillance (Molyneux et al., 2002; Tarnaris et al., 2011).

Patients that have experienced a SAH with an initially negative cerebral arteriogram may experience a more favorable clinical course and outcome in comparison to patients that experienced aSAH. However, they deserve follow-up cerebrovascular imaging to look for a bleeding source not initially evident. Etiologies include intracranial aneurysm, cerebral vasculitis, intracranial arterial dissections, hemorrhagic infarction, RCVS, PRES, etc. Additionally, a diffuse distribution of subarachnoid blood was more likely to be associated with an occult intracranial aneurysm, in comparison to patients with subarachnoid blood in the perimesencephalic or cortical locations (Lin et al., 2012).

Pregnancy-induced hypertension may produce nonaneurysmal SAH, hypothesized to be caused by rupture of small pial blood vessels, possibly venous, either singly or in conjunction with suspected failure of cerebral autoregulation (Shah, 2003).

Vertebral artery dissections that occur rostral to the foramen magnum may produce hemorrhage that is not solely confined to the arterial wall as is seen in extradural carotid and vertebral artery dissections. This can produce SAH, which may be fatal (Tuluc et al., 2006).

SAH can also occur from extracranial bleeding sources, and has been reported with vascular malformations of the spinal cord and aneurysms of the anterior spinal artery (Garcia et al., 1979).

The more general aspects of intracranial aneurysm management are beyond the scope of this chapter. The reader is directed to the recently published evidence-based guidelines from the American Heart Association/American Stroke Association (Connolly et al., 2012).

Carotid cavernous fistula (CCF) occurs when an aneurysm of the high-pressure cavernous carotid artery ruptures into the surrounding low-pressure cavernous venous sinus. CCF accounts for 2–9% of all intracranial aneurysms and produces sudden eyelid ptosis, periorbital swelling, orbital pain, ophthalmoplegia from compression of the intracavernous third, fourth and sixth cranial nerves, conjunctival injection and potentially visual loss. Most of the ruptured cavernous carotid aneurysms occur in women under the age of 40 during pregnancy. Radiographically, there is engorgement of the cavernous sinus, superior ophthalmic vein and unilateral congestion of the extraocular muscles. Differential diagnosis includes orbital or preseptal cellulitis, acute sinusitis and orbital pseudotumor. Cavernous carotid artery aneurysm rupture during pregnancy is suspected to be caused by the effects of third trimester estrogen rise upon blood vessels. Treatment may include endovascular aneurysm obliteration, either singly or in combination with surgical decompression (Rashkind et al., 1977; Toya et al., 1981; Dogan et al., 2012).

Intracerebral hemorrhage

Intracerebral hemorrhage (ICH) in the pregnant patient occurs with a frequency of approximately six cases per 100 000 deliveries at-risk person-years, compared to five per 100 000 in the nonpregnant population. Most ICH occur postpartum with the exception of AVMs that bled 92% antepartum and 8% postpartum in one series. One in five patients dies and 30% were discharged to a chronic care facility. Independent risk factors, in decreasing order, include coagulopathy (including HELLP), pre-existing hypertension either with or without pre-eclampsia or eclampsia, advanced maternal age, and smoking. Other risk factors include infective and noninfective aortic aneurysms, including mycotic aneurysms due to metastatic choriocarcinoma. Amniotic fluid embolism can produce either cerebral hemorrhage or infarction, in conjunction with a DIC-like picture and hypotension. Vessel abnormalities may be caused by cerebral vasculitis, cerebral vessel reactivity from vasoactive drugs such as cocaine, moyamoya disease, and brain arteriovenous malformations (AVMs). Risk factors for AVM hemorrhage include prior bleed, deep venous drainage, and deep location. Outcomes following cerebral aneurysm mobilization are better than AVM surgical intervention following ICH. In one series, cerebral cavernous malformations did not have an increased risk of bleeding during pregnancy compared to the nonpregnant population (Dias and Sekhar, 1990; Bateman et al., 2006; Gross and Du, 2012; Witiw et al., 2012).

Pituitary apoplexy (Sheehan syndrome)

Postpartum necrosis of the anterior pituitary (pituitary apoplexy, Sheehan syndrome) may produce either infarction, or hemorrhage or both within the gland.

The condition can lead to visual loss and has the potential to become life-threatening. It may be difficult to recognize due to its variable and sometimes subtle initial presentation. In the general nonobstetric population the condition has been described to occur between the first through ninth decades of life with a peak in the fifth decade (Biousse et al., 2001).

The anterior lobe of the pituitary secretes thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), growth hormone (GH), adrenocorticotropic hormone (ACTH), and α-melanocyte-stimulating hormone (α- MSH). The posterior lobe of the pituitary secretes vasopressin (ADH) and oxytocin. Abnormalities of the pituitary can cause hyposecretion of any of the aforementioned hormones. Tumors of the pituitary can produce hormonal hypersecretion or hyposecretion due to encroachment upon specific cellular populations. Pituitary tumors of any size can undergo hemorrhage with apoplexy (Biousse et al., 2001). Clinical syndromes depend upon the specific hormone-producing cells affected.

The pituitary receives its blood supply from two branches of the internal carotid arteries. The inferior hypophyseal artery perfuses the infundibulum and posterior pituitary. The superior hypophyseal artery forms a network of capillaries between the hypothalamus, infundibulum, and anterior pituitary to carry hypothalamic releasing hormones that trigger release of anterior pituitary hormones. This is a low perfusion pressure arterial network, and is susceptible to both arterial hypotension and venous congestion. The pituitary progressively enlarges in all directions during normal pregnancy, reaching a maximal volume by the third postpartum day (vertical height 9.6 mm through term, 10.2 mm by the third postpartum day for maximal volume growth of 120–136%) and then gradually recedes over the ensuing 6 months (Gonzalez et al., 1988; Dinc et al., 1998). In the nonpregnant state, the pressure within the sella turcica is estimated to be 10 mmHg (Tessnow and Wilson, 2010). The enlarging pituitary may increase the pressure within the sella turcica.

Clinical presentation can be variable ranging from sudden and severe to mild or subclinical chronic symptoms. Pituitary apoplexy should be considered in any patient with sudden severe headache, altered mental status, visual symptoms such as diplopia or visual diminution, and hypotension. Polyuria, excessive thirst not improved with rehydration and hypernatremia may suggest diabetes insipidus. Adrenal insufficiency may be life-threatening, necessitating rapid measurement of serum cortisol and ACTH followed by glucocorticoid replacement. In conjunction with severe headaches it may simulate hyperemesis gravidarum. More subtle chronic presentations include amenorrhea and inability to lactate, hypotension, or hypoglycemia (Weston et al., 2005; Tessnow and Wilson, 2010; Bamfo et al., 2011).

Pituitary apoplexy has been described to be caused by four discrete mechanisms: (1) hypotension, in conjunction with the relatively low infundibular artery perfusion pressures may predispose to pituitary infarction. Similarly, Valsalva maneuver from coughing, sneezing, or positive pressure ventilation may increase intracranial and venous pressure and congestion, especially if there is an underlying pituitary adenoma; (2) acute increased pituitary blood flow such as in malignant hypertension has been associated with both pituitary infarction and pituitary hemorrhage; (3) stimulation of the enlarged pituitary of pregnancy (especially if there is a coexisting pituitary tumor) by therapeutic or provocative diagnostic administration of estrogens, gonadotrophins, TRH, dexamethasone, bromocriptine, after increased endogenous steroid production following systemic stresses such as myocardial infarction, surgery, etc.; (4) conditions that predispose to bleeding such as therapeutic anticoagulation, thrombophilia, thrombocytopenia of any cause including HELLP syndrome, during thrombolysis (Shirataki et al., 1988; Biousse et al., 2001; Semple et al., 2007; Murao et al., 2011).

Management of pituitary apoplexy is predicated upon the clinical presentation. Hemorrhage into the pituitary may produce rapid enlargement and optic chiasm or optic nerve compression with visual loss. Transsphenoidal surgical decompression may save vision. Sometimes more than one pituitary hormone may be deficient requiring all of the pituitary hormone levels to be measured. The sequence of replacement therapy may be critical. If both adrenal insufficiency and hypothyroidism are present, to avoid adrenal crisis glucocorticoid therapy should be replaced before thyroxine, as the latter increases the metabolic clearance rate of cortisol (Tessnow and Wilson, 2010).

Cerebral venous thrombosis

Thrombosis of intracranial veins accounts for 0.5% of all strokes. There is a 3:1 female predominance. Various causes include dehydration, infection, estrogen-containing oral contraceptives, pregnancy and the postpartum state, various thrombophilias such as factor V Leiden mutation or prothrombin 20210A gene mutation, hyperhomocysteinemia, etc. Headache is the presenting feature in over 80% of patients at onset, and subsequently occurs in 90–95% of all patients. Impaired venous drainage may produce elevations in intracranial pressure. In severe cases transient visual obscurations or visual loss may occur. Hemorrhagic infarction of the cerebral cortex adjacent to the thrombosed venous sinus

may occur, but does not represent a contraindication to anticoagulation. Seizures may occur. During the acute phase, the death rate is approximately 4%. Subsequently, death and dependency rise to 15%, often following delayed diagnosis and general medical complications (Bousser and Crassard, 2012). In many, the prognosis is favorable. Anticoagulation is the treatment of choice, in an effort to arrest further thrombosis while allowing the natural fibrinolysis to gradually recanalize the vessel. In the nonpregnant patient, warfarin may be used, which is not an option in the first trimester due to the risk of fetal harm. LMWH has been shown to have greater efficacy and safety then UFH (Coutinho et al., 2010). The duration of anticoagulant therapy is based upon the underlying cause, which typically ranges between 3 and 6 months. The exception is malignancy, which should be indefinitely anticoagulated unless the malignancy resolves. At that point, 3–6 months of anticoagulant therapy is advised (Caprio and Bernstein, 2012). In patients that continue to deteriorate following elevated intracranial pressure and impending herniation, escalating therapy with thrombolytics and/or mechanical clot retrieval delivered to the thrombosed vein has been proposed. In severe cases, decompressive surgery may also be considered (Khan et al., 2010). Meta-analysis of 15 studies evaluating 156 patients who received thrombolytics for CVT revealed a significant risk of major bleeding complications, including intracranially (Dentali et al., 2010). This is being further studied in the ongoing TO-ACT trial which will compare thrombolysis and endovascular clot retrieval against anticoagulation (Coutinho et al., 2012).

PREGNANCY AND EPILEPSY

The natural physiologic changes that occur in pregnancy may affect antiepileptic drugs (AED)and excretion with the potential for reduced seizure control. Some AEDs may be teratogenic.

Women with epilepsy (WWE) have a significant (>2-fold) risk for premature contractions, labor and delivery, observed predominantly in women that smoke. There is a moderate (1.5–2-fold) increased possibility of the need for cesarean section. There are insufficient data to determine if there is a greater risk of pre-eclampsia or pregnancy-induced hypertension (Harden et al., 2009a).

Infants exposed to AED are twice as likely to experience birth defects, with malformation rates approximately 4–6%, increased from 2–3% in the general population. Folic acid is necessary for red and white blood cell and central nervous system development. Folic acid depletion may be caused by nutritional deficiencies or may be valproate-induced producing neural tube defects (NTD) which include spina bifida, myelomeningocele, and anencephaly, necessitating folic acid supplementation in all pregnant women. Other deficiency states producing NTD include glutathione, folate, vitamin C, riboflavin, zinc, cyanocobalamin, selenium as well as excess exposure to vitamin A (Yerby, 2003). Multiple anticonvulsant agents increases the risk of major congenital malformations (MCM). Whenever possible, monotherapy is advised. Phenytoin (PHT) and carbamazepine (CBZ) may produce cleft palate. Phenobarbital (PB) may cause cardiac malformations. Cognitive impairment may be caused by valproic acid (VPA), phenytoin, and phenobarbital. VPA may also produce neurodevelopmental disorders, of which autistic spectrum disorders occur most often. They may be seen in conjunction with fetal valproate syndrome, characterized by major and minor congenital malformations and dysmorphic features (Bromley et al., 2013). There is double the expected rate of low birthweight neonates in the context of maternal anticonvulsant use. There is no substantially increased perinatal death. Reduced 1 minute Apgar scores of <7 were seen at twice the expected rate (Harden et al., 2009b). PB, primidone (PRM), PHT, CBZ, levetiracetam (LVT) and VPA probably cross the placenta and gabapentin (GBP), LTG, oxcarbazepine (OXC) and topiramate (TPM) possibly cross the placenta in significant concentration to affect the fetus. VPA and lamotrigine (LTG) may produce teratogenesis in a dose-dependent fashion. Hence, VPA should not be used as a first-line anticonvulsant if at all possible. As LTG, PHT, OXC, CBZ have increased clearance, anticonvulsant levels should be measured frequently as they may change during various stages of pregnancy with an increased risk of seizures (Harden et al., 2009c). Based upon pregnancy outcome data, CBZ appears to be relatively safe as a drug of first choice in localization-related epilepsy. In idiopathic generalized epilepsy, LTG appears to be relatively safe, but may be affected by pharmacokinetic changes with the risk of breakthrough seizures. There are insufficient data for the use of LVT and TPM (Tomson and Battino, 2009).

Breast-feeding is generally felt to be safe during pregnancy, withAED concentrations lower than transferred to the fetus *in utero*. PRM, LVT, GTB, LTG, and TPM may be secreted in breast milk. There is a small chance of infant thrombocytopenia from LTG. Postpartum, anticonvulsants such a VPA, PB, PHT, and CBZ that are highly protein bound are less likely to be secreted in breast milk. Women taking felbamate should not breast-feed due to the risk of aplastic anemia. Clonazepam and clobazam may produce fetal sedation. There is insufficient information as to whether other anticonvulsants transferred to the baby by breast milk may produce a symptomatic effect (Harden et al., 2009c; Klein, 2012).

With regard to seizure recurrence during pregnancy, women who were seizure free for at least 9 months prior

to pregnancy remained seizure free during pregnancy between 84% and 92% of the time. They EURAP Epilepsy Pregnancy Registry found that 58.3% remained seizure free during pregnancy. Recurrent seizures are more often due to localization-related epilepsy or the need for polytherapy (EURAP Study Group, 2006; Harden et al., 2009a).

Eclampsia may represent a risk factor for hippocampal sclerosis and temporal lobe epilepsy, but this observation needs further study (Lawn et al., 2004).

The clinician should be mindful that nonepileptic seizures may also occur. Pregnancy and the postpartum state may be extremely stressful. Nonepileptic seizures may initially represent a diagnostic and therapeutic dilemma (DeToledo et al., 2000).

Lastly, in WWE there should be significant attention directed to maternal wellbeing. Postpartum depression in WWE is reported to be greater than in the general postpartum population without epilepsy. Adequate rest to prevent breakthrough seizures is necessary. WWE should be counseled to place the baby in a safe place if a seizure is preceded by aura. Similarly, myoclonic jerks may cause the mother to drop the baby (Klein, 2012).

MULTIPLE SCLEROSIS DURING PREGNANCY

Pregnancy does not pose a long-term risk or enhance multiple sclerosis (MS) progression or disease disability. For many patients, MS relapse rates fall during pregnancy. There is no impact on fertility or neonatal condition. Dahl and colleagues found that among 649 Norwegian births compared to a control population of 2.1 million births, there were smaller neonates for gestational age with a normal head circumference. Apgar scores, perinatal mortality, and birth defects did not differ. There was some increased incidence of slow progression of labor requiring physician assistance including cesarean section (Dahl et al., 2005).

Relapse rates in multiple sclerosis

In 1998 the Pregnancy in Multiple Sclerosis Group (PRIMS) published the relapse rate of 269 pregnancies in 254 women across 12 European countries. There was a significant reduction from prepregnancy relapse rate (0.7 per woman per year), to 0.5 in the first trimester, 0.6 in the second trimester and 0.2 in the third trimester. In the first 3 months after pregnancy it rose to 1.2, then down to 0.9 from postpartum months 4–9, then 0.6 in months 10 through 12, similar to the prepregnancy rate. They observed that the natural pregnancy MS recurrence rates were lower than that observed from any therapeutic benefit modality (Confavreux et al., 1998).

Can multiple sclerosis relapse be predicted, and in whom?

In 2004, the PRIMS study group tried to identify clinical predictors of multiple sclerosis relapse for 2 years postpartum using a logistic regression model and multivariate analysis. Only 28% of the cohort had a relapse during this timeframe. In retrospect, two factors increase the likelihood of a relapse in the first 3 months postpartum: the number of relapses before and the number of relapses during pregnancy. However, mathematical models could not reliably predict which individual might develop a relapse, especially in the first 3 months, precluding the ability to tailor individualized therapy. They also found that breast-feeding did not have a protective effect on disease activity in the postpartum period (Vukusic et al., 2004).

However, clinical symptoms alone may not tell the entire story. There is MRI evidence of increased MRI T2, gadolinium and ADC lesions appearing in the third trimester and 4–5 weeks postpartum, which may suggest earlier late pregnancy and postpartum activation of MS than had been observed clinically (Paavilainen et al., 2007). Similarly, measurement of a rise in specific T cell subsets and cytokines in women demonstrating reactivation of MS may one day be used on a large scale to detect preclinical MS disease activation. This biomarker may help identify patients that might benefit from early treatment (Iorto et al., 2008).

Management of disease-modifying therapies

Currently, there are no reports of completed high-quality prospective studies of disease-modifying therapies (DMTs), and none of the therapies have been placed in the safest pregnancy risk category. In an effort to minimize fetal risks, both the US Food and Drug Administration (FDA) and the National Multiple Sclerosis Society have recommended discontinuing DMTs prior to planned pregnancy and during breast-feeding. However, a substantial number of pregnancies are unplanned. None of the DMTs have achieved FDA class A safety classification. Several published studies (Lu et al., 2012; Houtchens and Kolb, 2013) have reviewed the strength of published evidence for risk of each of the following agents, which are summarized. Glatiramer acetate (GA) is FDA class B, and has not been associated with teratogenicity or higher rate of miscarriage. Current evidence supports no definitive conclusions for the therapeutic efficacy of GA in pregnant women. Interferon β-1a and interferon β-1b have not been proven to be teratogenic in humans, but the former may be associated with low birthweight babies in some, but not all series. Fingolimod is FDA pregnancy category C following

the observation of visceral malformations in rats. Registry data are insufficient to arrive at conclusions regarding safety in humans. Natalizumab is FDA category C and also has insufficient data to establish a recommendation in humans. Mitoxantrone is a cytotoxic chemotherapeutic agent and is FDA pregnancy category D; consider teratogenic.

Impact of DMTs upon fertility. Neither GA nor the interferons have known effects on human fertility. Fingolimod and natalizumab have not been found to affect experimental animal fertility. Mitoxantrone has been shown to produce infertility and amenorrhea.

Breast-feeding

The data for GA and interferon transfer into breast milk is limited, but appears to be significantly reduced in comparison to the maternal concentration. Fingolimod, natalizumab, and mitoxantrone are excreted into breast milk. Corticosteroids are felt to be generally safe, but there shoul be at least 2 hours between steroid ingestion and breast-feeding in order to minimize exposure to the baby. Coyle has recommended withholding MS therapy if a choice is made to breast-feed. If pulse IVIG or pulse steroids for 3–6 months are needed, breast-feeding should be delayed 4–6 hours after steroids. DMT may be resumed following completion of pregnancy if a decision not to breast-feed has been made (Coyle, 2012).

Houtchens and Kolb have recommended monthly high-dose steroid treatment to coincide with the menstrual period in women attempting conception off of DMTs. Interferons and GA should be discontinued at least 1 month before attempting conception and 2–3 months cessation of natalizumab, fingolimod, and mitoxantrone are advised. Natalizumab should be used only during pregnancy if the maternal benefit justifies potential risks to the fetus. Intravenous prednisone, prednisolone and methylprednisolone are moderately safe in the second and third trimester of pregnancy for serious acute exacerbations. With unexpected pregnancy, DMTs should be discontinued, especially mitoxantrone and fingolimod. Patients exposed to high-risk approved medications or off-label compounds in the first trimester should be referred for high-risk maternal-fetal care.

Vigilance should be directed towards nonambulatory women with MS, which places them at greater risk for deep venous thrombosis. Additionally, neurogenic bladder may increase the risk of urosepsis.

Since there is an increased incidence of MS relapse in the first 3 months postpartum, 1 g single dose prophylactic intravenous methylprednisolone administered after delivery reduced the relapse rate to 17.9% from 46.2% in a control population that did not receive postpartum steroids. A larger randomized controlled prospective trial is needed (Avila-Ornelas et al., 2011).

NEUROMUSCULAR DISEASES IN PREGNANCY

Upper extremity mononeuropathies and radiculopathies

Carpal tunnel syndrome (CTS) is the most common peripheral nerve disorder of pregnancy. Sensory and motor branches of the median nerve traverse the relatively crowded carpal canal formed by carpal bones along the dorsal surface and a transverse carpal ligament over the palmar surface. Also traversing the carpal canal are the finger flexor tendons. This segment of the median nerve can be compressed by flexor tendon swelling, edema, focal mass lesions, cysts, etc. In pregnancy, it is suspected that tissue fluid retention may contribute to the median nerve compression. The mechanism of median nerve injury initially consists of focal demyelination. As compressive focal demyelination worsens, loss of nerve conduction ensues, ultimately causing the nerve to stop conducting (focal motor conduction block). If the compression is not relieved, secondary axonal loss can occur. Typical symptoms include paresthesias of the thumb, index, middle and radial aspect of the fourth fingers followed by sensory loss and ultimately motor weakness of the abductor pollicis brevis. Patients can also experience an ill-defined nondermatomal aching sensation in the forearm which may extend proximally. Differential diagnosis should consider median nerve pathology proximal to the carpal canal, abnormalities of the brachial plexus lesions and cervical radiculopathy.

The incidence of pregnancy-related CTS varies widely between 0.34% in a retrospective chart review up to 59% (Stolp-Smith et al., 1998; Padua et al., 2002).

This wide variation may in part be explained by many published studies using symptoms and examination signs without electrodiagnostic confirmation. While characteristic symptoms may suggest CTS, electrodiagnostic evaluation is important to confirm the diagnosis and determine severity, which should be used as a guide for treatment planning. CTS nerve conduction study techniques are well described (Werner and Andary, 2011). Many pregnant patients will benefit from conservative treatment which includes neutral position wrist splints, salt reduction, carpal canal corticosteroid injection, etc. (Weimer et al., 2002). While symptoms occurring early in pregnancy and following substantial weight gain may predict lower chance for spontaneous improvement after delivery (Padua et al., 2002), one-half of the patients will experience spontaneous symptomatic improvement in the first year and two-thirds by the third

postpartum year (Weimer et al., 2002; Mondelli et al., 2007; Padua et al., 2010).

Carpal canal decompression may be considered in several circumstances: (1) patients with severe intolerable sensory symptoms that do not improve with conservative management; (2) patients with focal motor conduction block across the carpal ligament that do not improve following delivery, as there is an increased likelihood of secondary axonal loss to the abductor pollicis brevis.

Other mononeuropathies of the upper extremities occurring as a manifestation of pregnancy are rare, and are more typical of the type seen in the general population. Of note, bilateral ulnar and radial mononeuropathies occurred in a woman in labor using a wooden birthing stool supported from behind by her husband with his hands/fingers holding her axilla for 2 hours. The prolonged compression against the intra-axillary segments of the ulnar and radial nerves produced transient sensory and motor weakness (Buckley and Davis, 1983).

Lower extremity mononeuropathies and radiculopathies

In a series of 6757 live births, 56 women experienced lower extremity peripheral nerve injuries (Wong et al., 2003). They found that lower extremity mononeuropathies and radiculopathies occur during delivery with an incidence as high as 0.92, with the following nerves affected, listed in decreasing order: lateral femoral cutaneous nerve of the thigh, femoral, common peroneal, lumbosacral plexus, sciatic, obturator and lumbar or sacral root. Most often, they occur with prolonged pushing during the second stage of labor, high fetal station (defined as the presenting part of the baby relative to the ischial spines, the narrowest part of the pelvis) and semi-Fowler lithotomy positions with the legs flexed at the hips, abducted, and externally rotated. Regional anesthesia associated with longer second stage labor with sensory blockade may preclude patients from perceiving an impending nerve injury. In many circumstances, nerve compression or stretch are implicated.

The lateral femoral cutaneous nerve may be stretched or compressed as it traverses the inguinal ligament in the anterior superior iliac spine, especially during maternal pushing in the thigh-flexed posture. The nerve may also be transected during a wide Pfannenstiel incision at the time of cesarean section or stretched by a retractor. It has also been described with laparoscopic surgery, abdominoplasty, and total abdominal hysterectomy-bilateral salpingo-oophorectomy (Peters and Larner, 2006). A pure sensory nerve injury can produce paresthesias, sensory loss and occasional pain along the lateral thigh (meralgia paresthetica) which can be treated with a local anesthetic block of the nerve adjacent to the anterior superior iliac spine, TENS unit, topical lidocaine patch or gabapentin, reserving surgical exploration for medically intractable cases. The femoral nerve may be compressed at the inguinal ligament during thigh flexion, external rotation and abduction, as well as from intraoperative retraction of the psoas muscle (Bradshaw and Advincula, 2010). If there is weakness of iliopsoas function, the nerve lesion may be more proximal within the pelvis. The saphenous sensory nerve arises from the femoral nerve and causes sensory loss along the anterior thigh and leg. Common peroneal mononeuropathy producing foot drop has been described following extrinsic compression from obstetric stirrups, after prolonged squatting during labor, after excessive manual pressure by delivery room attendants holding a patient's knees, following external compression with forceful knee flexion while pushing during vaginal delivery, and after one woman held her distal posterior thigh while under epidural anesthesia. The latter produced compression against the common peroneal nerve proximal to the knee (Babyev et al., 1998; Sahai-Srivastava and Amezcua, 2007; Radawski et al., 2011).

The sciatic nerve comprises discrete muscle fascicles of the common peroneal and posterior tibial nerves. Injury may produce weakness in muscles innervated from both nerve distributions, but there may be disproportionate involvement, more commonly affecting the peroneal nerve fascicles. Hence, sciatic nerve injuries, lower segment lumbosacral plexopathies and L5 radiculopathies may selectively or disproportionally affect peroneal nerve- innervated musculature and mimic a common peroneal mononeuropathy that may cause a foot drop. Electromyography may be helpful in distinguishing between these possibilities.

Obturator mononeuropathies are rare. In 38 patients seen at the Mayo Clinic with a clinically suspected obturator mononeuropathy over 24 years, EMG demonstrated an alternate site of abnormality in 15 patients (lumbar root, lumbar plexus, or femoral nerve). EMG confirmed an obturator nerve injury in 22 patients. The most common reported symptom was pain in the medial thigh or groin, followed by weakness of obturator nerve-innervated musculature. Etiologies, in decreasing order, included: total hip arthroplasty, pelvic surgery, pelvic trauma, femoral artery procedure, metastatic disease to the operator canal, bilateral total knee arthroplasty with prolonged high tourniquet, diabetes, and myositis ossificans. The prognosis is often favorable with conservative management (Sorensen et al., 2002). MR imaging T2 hyperintensity in denervated muscle, and MR neurography may be useful in excluding other structural abnormalities of the nerve (Nogajski et al., 2004).

Plexopathy

Intrapartum maternal lumbosacral plexopathy is rare. Katirji and colleagues reported seven cases with EMG confirmation. Cephalopelvic disproportion, maternal short stature, and prolonged/arrested labor contributed to the fetal head pressing against the lumbosacral trunk at the pelvic brim. Most patients experienced severe foot weakness, predominantly in L5 innervated musculature, with recovery occurring in 3–5 months (Katirji et al., 2002).

Bilateral lumbosacral plexus ischemia, paraplegia, and gluteal necrosis have occurred following bilateral internal iliac artery embolization for severe postpartum hemorrhage, which may be mitigated by more selective embolization of branch vessels (Al-Thunyan et al., 2012).

Careful body and limb position on the delivery table can mitigate brachial plexus stretch injury and ulnar nerve compression at the elbow (Bradshaw and Advincula, 2010).

Low back pain is commonly experienced in both pregnancy and the general population. Pain-sensitive structures include ligaments, tendons, lumbar facets, lumbar disc capsule, sacroiliac joint, and myofascial tissue. Lumbar disc herniation may produce either focal low back pain and/or radicular pain. Atypical symptoms or clinical features such as fever, radicular pain, elevated sedimentation rate or leukocytosis deserve radiographic investigation. MRI without contrast enhancement is relatively safe in pregnancy. Primiparity and advancing maternal age may increase the risk of lumbar disc herniations. In uncomplicated lumbar disc disease, patients can be managed conservatively until after delivery. However, with cauda equina compression producing leg weakness and bowel or bladder retention or incontinence, urgent management may be needed. The mode of delivery (i.e., vaginal versus cesarean section) in this context is controversial, but some have recommended cesarean section to avoid Valsalva during labor that may worsen neurologic dysfunction (LaBan et al., 1995). In atypical cases, the clinician should be mindful of less common etiologies such as postpartum septic sacroiliitis (Liu et al., 2010), inferior vena cava (IVC) obstruction with engorgement of lumbar epidural veins producing radiculopathy (Paksoy and Gormus, 2004), and compressive sciatic mononeuropathy (Mumby and Hartsilver, 2012).

Myasthenia gravis

Myasthenia gravis (MG) is an autoimmune disorder with antibodies against skeletal muscle acetylcholine receptors (Anti-AchR ab). Batocchi and colleagues (1999) followed 64 pregnancies in 47 myasthenic women over 19 years. There were 55 live births and 10 abortions (six voluntarily induced, three spontaneous, one ectopic pregnancy). Only one of the 10 women worsened following an induced abortion. Forty of 47 women demonstrated Anti-AchR ab positivity (85%). The course of myasthenia is highly variable. Some 17% of women in remission before conception experienced a mild myasthenic relapse during pregnancy, most in the first trimester. Of those receiving pharmacologic therapy, 39% experienced marked improvement of myasthenic symptoms during pregnancy, 42% were unchanged, and 19% had clinical worsening. After delivery, MG worsened in 28%. Premature delivery occurred in 7.4% (32–35 weeks gestation). Similar to the nonmyasthenic Italian population, cesarean section was performed in 30%, mostly for nonmyasthenic reasons such as cephalopelvic disproportion, malpresentation, failure of progression of labor, prior cesarean delivery, etc. One woman with severe myasthenic symptoms experienced severe dyspnea prompting caesarean section. Neonatal myasthenia (NMG) occurred in 9%, with no correlation between maternal disease severity or maternal Anti-AchR ab titers. The condition can produce hypotonia, potential respiratory insufficiency, and difficulty feeding. All babies with NMG were Anti-AchR ab positive, but a larger number of seropositive babies were asymptomatic. All 55 babies were followed between 1 month and 20 years and were in good health. Transmission of maternal Anti-AchR ab from myasthenic mothers can produce congenital joint contractures from decreased *in utero* fetal movement, arthrogryposis multiplex congenita (AMC). Of note, AMC can also occur without clinical expression of maternal myasthenia gravis. Studying maternal sera of affected neonates, Riemersma and colleagues (1996) found high levels of maternal antibodies which inhibited α-bungarotoxin binding to fetal acetylcholine receptors, without symptoms of maternal MG.

A review of the Norwegian Medical Birth Registry from 1967 to 2000 (Hoft et al., 2003) evaluated 127 births of myasthenic mothers compared to a control population of 1.9 million births. There was a threefold increased incidence of preterm rupture of amniotic membranes, suspected to be corticosteroid-induced. Other labor and obstetric complications also occurred more frequently, which included injuries in the birth canal, postpartum bleeding, obstruction of the birth process and umbilical cord complications. Cesarean sections were performed twice as frequently. While five neonates (3.9%) experienced severe anomalies with three deaths, the overall mortality was not significantly different from the control population.

Over half of pregnant women suffering from MG can be treated with anticholinesterase inhibitors such

as pyridostigmine bromide and neostigmine chloride. Medication has been safely used in pregnancy for over 50 years (Djelmis et al., 2002). Some myasthenic women may require additional medications which include corticosteroids either singly or in combination with immune suppressants. Several of the latter have the potential for fetal harm and are reviewed below. In circumstances of rapid decompensation of muscular strength, IVIG and PLEX may be needed. Both are relatively safe in pregnancy. Potential risks include IVIG-induced allergic reactions and PLEX-induced hypotension and electrolyte disturbances.

Stage 1 labor depends upon uterine smooth muscle, and is not affected by MG. Second stage labor is dependent upon maternal pushing of abdominal striated muscle and may fatigue, potentially worsening myasthenia. If necessary, supplemental intravenous neostigmine may be needed. Sedatives, opioids and tranquilizers can potentiate respiratory depression and should be used with caution. Magnesium sulfate used to treat preeclampsia and eclampsia may worsen myasthenia or trigger a myasthenic crisis due to altered calcium flux at the neuromuscular junction (Da Silva et al., 2011).

Acquired inflammatory polyradiculoneuropathy

Acquired inflammatory polyradiculoneuropathy (AIDP) (aka: Guillain–Barré syndrome, GBS). AIDP is an autoimmune-mediated demyelinating neuropathy which can produce ascending weakness, sensory loss, respiratory insufficiency, autonomic dysfunction, and ocular/bulbar palsies. Isolated involvement of any of the aforementioned can occur, as well as variants such as the Miller Fisher variant producing opthalmoplegia, ataxia, and areflexia. AIDP occurs with manual incidence of 0.75–2 cases/100 000 people/year, and two-thirds follow an infection (Roper, 1992). These include *Campylobacter jejuni* (32%), cytomegalovirus (13%), Epstein–Barr virus (10%), mycoplasma pneumonia (5%), *Haemophilus influenzae* (1%), parainfluenza 1 virus (1%), adenovirus (1%), herpes simplex virus (1%), and varicella zoster virus (1%). *C. jejuni* associated with anti-GM1 and anti-GD1b antibodies and a severe pure motor form of AIDP. CMP associated with anti-GM 2 antibiotics may produce severe motor-sensory deficits (Jacobs et al., 1998). The incidence was no greater in the pregnant population (Cheng et al., 1998). In a Swedish population-based study from 1978 to 1993, GBS occurred more frequently in the second and third trimesters and first weeks of the postpartum period (Cheng et al., 1998). Chan and colleagues reviewed 30 case reports of AIDP during pregnancy from 1985 to 2001. While none experienced *Campylobacter jejuni* colitis, which is the most common infectious etiology of GBS, 13% had CMV, the second most common infectious agent associated with GBS. One-third required ventilator support. Twenty-two patients received IVIG, plasmapheresis or both, without complication. All patients experienced substantial improvement, some with full recovery. One patient relapsed requiring repeat IVIG treatment. One patient who initially recovered ultimately expired at home, probably due to a tracheoesophageal fistula. Three patients underwent termination of pregnancy, which did not hasten recovery. Vaginal delivery was achieved even in a ventilator-dependent tetraplegic patient. Delivery by cesarean section was performed for a variety of reasons in 14 patients, including birth canal infection, nonprogression of labor, and rapidly deteriorating maternal neurologic condition (Chan et al., 2004). In view of bedbound patients with diminished mobility, there should be meticulous attention to thrombosis prophylaxis and infection.

Chronic inflammatory demyelinating polyradiculoneuropathy

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) occurs infrequently during pregnancy. Patients with CIDP were found to have an increased rate of relapse during pregnancy, often in the third trimester and immediate postpartum period (McCombe et al., 1987). The condition can be treated with corticosteroids, IVIG, and PLEX (Eftimov et al., 2009).

Multifocal motor neuropathy

Also a demyelinating neuropathy, multifocal motor neuropathy (MMN) often presents asymmetrically, and is associated with elevated titers of IgM anti-GM1 antibodies and to a lesser extent other glycolipids including asialo-GM1, GD1a, and GM2. The disorder is electrophysiologically characterized by noncompressive multifocal motor conduction blocks. Clinically, it resembles motor neuron disease with muscle weakness and if chronic, muscle atrophy, but without pyramidal tract signs. Differential diagnosis should include mononeuritis multiplex, but with slower progression and without sensory signs. EMG diagnostic consensus criteria (Onley et al., 2003) are described. Discussion of additional variants (Lewis-Sumner syndrome, multifocal axonal loss neuropathy, acute motor axonal neuropathy and acute motor-sensory axonal neuropathy) is beyond the scope of this chapter. Chaudry described three pregnant women with MMN that experienced relapse during pregnancy, affecting both previously involved and new muscle groups (Chaudry et al., 2002). MMN responds to intravenous immunoglobulin, especially if anti-GM1 antibodies are present. Failure to improve and even clinical worsening have been described following treatment

with corticosteroids and PLEX (Nobile-Orazio et al., 2005; van Schaik et al., 2005).

Inflammatory myopathies

Dermatomyositis is uncommon in childbearing years. However, fetal prognosis worsens with maternal disease activity. Corticosteroid therapy can be effective, but exposes the mother and fetus to potential side-effects including premature rupture of membranes, gestational diabetes, hypertension, and others. In patients that have not improved with corticosteroids alone, IVIG can be safely used as a second-line agent in conjunction with steroids (Linardaki et al., 2009; Elovaara and Hietaharju, 2010). Polymyositis has not been well studied with IVIG, but may be considered as a treatment option for patients not responding to first-line immunosuppressant therapy.

Various hereditary neuropathies, dystrophies, and myopathies

Charcot–Marie–Tooth

Charcot-Marie-Tooth (CMT) is one of the most common hereditary neuropathies. Its generally slow progression allows individuals to adapt to distal lower and upper extremity weakness and atrophy. Hoff reviewed 108 births of Norwegian mothers with CMT within a general population at 2.1 million births between 1967 and 2002. There was double the rate of postpartum bleeding (suspected to be caused by adrenergic degeneration-induced uterine atony) and presentation abnormalities (breech and cephalic). Forcep deliveries were three times more common (Hoft et al., 2003).

Myotonic dystrophy type I

Myotonic dystrophy type I (DM1) can occur in three forms, congenital, childhood (first decade of life), and adult (third and fourth decades of life). Fertility in the mother is variable. First symptoms often occur during pregnancy for the postpartum period with either weakness or producing a child with congenital myotonic dystrophy. Such children experience respiratory distress, hypotonia, generalized weakness, poor feeding, and mental retardation. They have a high mortality rate of 25% by 18 months and 50% by adulthood. There is a tenfold increased incidence of fetal loss, premature delivery, and polyhydramnios. Myotonic dystrophy type II (DM 2) does not produce congenital phenotypic expression. In most women affected, the presentation is beyond the reproductive stage of life. However, in some, first symptoms may be experienced (possibly triggered) by pregnancy. There is no polyhydramnios. While there is no increased obstetric risk, women who experience symptoms prior to or during pregnancy have an increased risk of fetal loss and prematurity. The combination of fetal club feet and polyhydramnios in congenital DM1 is associated with a high risk of maternal blood loss at delivery (Rudnik-Schoneborn et al., 2006; Sax and Rosenbaum, 2006; Norwood and Rudnik-Schoneborn, 2012).

Fascioscapulohumeral muscular dystrophy (FSHD) and congenital nemaline rod myopathy often have uncomplicated pregnancies apart from limitations caused by physical deformities. Limb-girdle dystrophies (LGMD) experienced worsening of muscle strength during pregnancy (Rudnik-Schoneborn et al., 1997).

Malignant hyperthermia may occur in King syndrome/Native American myopathy (myopathy, susceptibility to malignant hyperthermia and congenital facial and skeletal anomalies in the Lumblee Indian population of south-central North Carolina) (Stamm et al., 2008). Mutations in the *RYR1* gene, which is necessary for skeletal muscle excitation-contraction coupling and calcium homeostasis, are responsible for producing central core myopathy, multiminicore disease, and a congenital myopathy (CM). Following specific provocations, malignant hyperthermia manifest as skeletal muscle hypermetabolism, myofilament activation, respiratory and metabolic acidosis, hyperthermia, muscle rigidity, and rhabdomyolysis may occur (Habib et al., 2003; Robinson et al., 2006).

Mitochondrial disorders. Carnitine palmitoyltransferase 1 deficiency is a mitochondrial disorder of fatty acid β oxidation which has been described to produce a myopathy following pregnancy due to carnitine depletion. The severe weakness improved following carnitine replacement (Angelini et al., 1978). Ylitalo reported a 25-year-old woman who had experienced four episodes of hypoglycemia, metabolic acidosis, hepatomegaly and ALT elevation elevated serum ammonia, elevated triglycerides, and fatty liver biopsy since the first year of life. She was previously diagnosed as having Reye's syndrome. At 34 weeks gestation, she developed fatigue and mild anemia, nausea and vomiting. By 37 weeks she developed pre-eclampsia followed by HELLP syndrome. A healthy baby was delivered by cesarean section. The following day the patient developed life-threatening uterine bleeding, elevated serum ammonia, hypoglycemia, metabolic acidosis, and coma. A CPT1 deficiency was diagnosed. Her symptoms resolved following a diet enriched with medium chain triglycerides, essential fatty acids, and fat-soluble vitamins (Ylitalo et al., 2004).

Pregnancy outcomes of women with hereditary neuromuscular disorders

Awater and colleagues reviewed the obstetric outcomes of 178 women with hereditary neuromuscular disorders (DM1, DM2, CMT, spinomuscular atrophy, LGMD,

FSHD and CM). The number of miscarriages and the rate of hypertensive disease during pregnancy were not increased. Preterm deliveries ranged between 12% and 30%. Chairbound patients with DM1 and LGMD had abnormal fetal presentations. Clinical worsening of muscle strength suspected to be related to pregnancy occurred in approximately half of patients with LGMD, one-third of those with SMA and in one fifth of those with CMT. Apart from two newborns with congenital DM1 that died shortly after birth, neonatal outcomes were typically favorable. The authors emphasized the need for regular multidisciplinary follow-up during pregnancy to include an obstetrician, neurologist, geneticist, anesthetist, respiratory and general medical specialists, as appropriate, to follow potential cardiac or pulmonary complications that may be related to the underlying condition (Awater et al., 2012).

Immunosuppressant treatment for neuromuscular disease in pregnancy

Corticosteroids. Prednisone and its active metabolite prednisolone are metabolized by placental 11β-hydrosteroid dehydrogenase, with less than 10% reaching the fetus, which acts to protect the fetus against high levels of maternal cortisol (Benediktsson et al., 1997). Prednisone is considered relatively safe in pregnancy. Fluorinated corticosteroids (betamethasone and dexamethasone) are completely metabolized by 11β-hydrosteroid dehydrogenase and cross the placenta. The medication may be used for specific conditions to protect the fetus such as preterm respiratory distress. However, Benediktsson notes that dexamethasone administered to pregnant rats produces low birthweight offspring. Low birthweight in humans has been correlated with the later development of noninsulin-dependent diabetes mellitus, hypertension, and metabolic syndrome X. It is uncertain whether dexamethasone administered in human pregnancy may produce an actual or theoretic risk to the neonate in later life, but the aforementioned suggests caution and careful consideration of the choice of steroid administered. Breast milk of women taking prednisone produces only a small elevation of infant circulating cortisol and may be mitigated by timing the breast-feeding 3–4 hours after the steroid dosage. Prednisone FDA category C.

Under certain circumstances, disease activity may not be adequately controlled with corticosteroids alone, requiring other immune suppressants. Their safety is described below.

Azathioprine. Azathioprine is metabolized to 6-mercaptopurine and 6-thiouric acid which cross the placenta. In a detailed review of azathioprine to treat inflammatory bowel disease, Gisbert (2010) notes that multiple studies have demonstrated an increased risk of adverse birth outcomes which may be related to the underlying disease activity rather than from azathioprine. While the medication is excreted in breast milk within 4 hours of ingestion, the infant exposure is less than 1% of the maternal dose, and felt to be of low risk (Gisbert, 2010; Elliott and Chakravarty, 2010). (FDA category D.)

Ciclosporin. Ciclosporin crosses the placenta. In laboratory rats and rabbits at standard human dosages used for renal transplantation, there have been no mutagenic or teratogenic effects. In substantially greater dosages it has been found to be teratogenic in animals. From the population of patients treated for inflammatory bowel disease and following transplants, it has not been proven to increase human fetal malformations. Potential adverse effects, which include premature births, low birthweight, seizures, hypertension, lowered resistance to infection including JC-induced progressive multifocal leukoencephalopathy (PML), suggest that the drug should be used if disease activity is advanced and other options for immunosuppressionare limited. Breastfeeding is contraindicated (Batocchi et al., 1999; Gisbert, 2010). (FDA category C.)

Methotrexate. Methotrexate is a folic acid antagonist and is highly teratogenic and can also induce miscarriages. Methotrexate has been demonstrated to be present within red blood cells up to 3–32 weeks after discontinuation, prompting the need for meticulous contraception of women taking this agent, with a substantial drug-free interval before a planned pregnancy (Dalrymple et al., 2008). Folic acid supplementation is also necessary. (FDA category X.)

Mycophenolate mofetil. This immunosuppressive agent produces inhibition of purine synthesis. It is teratogenic in humans, producing a distinctive embryopathy tetrad with the acronym EMFO (Ear: microtia and auditory canal atresia; Mouth: cleft lip and palate; Fingers: brachydactyly, hypoplastic toenails; Organs: heart, kidney, brain, diaphragm and eyes) (Merlob et al., 2009). The severity may be dependent upon dosage and timing in pregnancy, especially in the first trimester which can produce spontaneous abortion (Ang et al., 2008). (FDA category D.)

HEADACHE DURING PREGNANCY AND PUERPERIUM

Headaches during pregnancy can be either benign or associated with life-threatening conditions. This section will review the unique characteristics of headache during pregnancy and in the postpartum state.

Headaches are classified as primary or secondary headaches. Primary headaches include tension-type headache, and migraine headache and cluster headache.

Secondary headaches are caused by other conditions distinct from primary headaches. A detailed history and physical examination is critical to identify a treatable life-threatening process.

Primary headaches. Tension-type headaches (episodic and chronic) are the most common headache type, often characterized by a dull holocranial steady squeezing, nonpulsatile sensation. Often they do not change in frequency compared to the prepregnancy state. The role of reproductive hormone levels in triggering muscle contraction headaches is uncertain. Migraine headaches can occur with or without aura. They are frequently unilateral and pulsatile. Fluctuations in the estrogen level rather than the absolute level may trigger a migraine. Both during pregnancy and after menopause migraines without aura tend to improve due to the stable level of estrogen. Sances and colleagues found that migraine without aura significantly improved in over 87% of patients by the third trimester with complete remission in almost 79%. Breast-feeding reduced migraine recurrence within the first month after childbirth to 50% of patients in comparison to 86% that bottle-fed. The benefit lasted for 6 months. One year after delivery, 80% of both populations had experienced recurrence of headache (Hoshiyama et al., 2012). Menstrually-related migraine before pregnancy often predicted lack of headache improvement during pregnancy (Sances et al., 2003). Migraine that occurs for the first time during pregnancy necessitates a detailed history, physical examination and radiographic or laboratory tests as appropriate to exclude secondary causes of headache which may resemble migraine (see below). Migraine is also associated with an increased risk of hypertensive disorders of pregnancy.

Although a detailed discussion of management of migraine headache during pregnancy is beyond the scope of this chapter, it should be noted that the following medications used to treat migraine in the nonpregnant patient carry increased risk to the fetus. Valproate may produce neural tube defects due to inhibition of folic acid metabolism. Other medications to avoid include topiramate, lithium, phenobarbital, angiotensin receptor blockers and second-generation angiotensin-converting enzyme inhibitors, atenolol, paroxetine, methysergide, certain nonsteroidal agents in the first trimester, and ergot alkaloids (McGregor, 2012).

Secondary headaches. While migraine and tension-type headaches do not have a negative impact upon pregnancy directly (albeit conditions like hyperemesis gravidarum can produce dehydration which may lead to a cerebral venous thrombosis), the following differential diagnostic considerations should always be kept in mind. Many of these disorders have been discussed previously in the cerebrovascular disease section of this chapter. Differentiating features will now be reviewed. The clinician should inquire about the character of the headache (acute onset? severe?), lack of similar headaches in the past, change in headache pattern and progressively worsening or persistent headache. On examination the clinician should be vigilant for focal neurologic findings, decreased level of consciousness, emesis or syncope at the onset of headache, convulsion, fever and meningismus (Bateman et al., 2012). Headache onset may be gradual or sudden and severe with maximal intensity in less than 1 minute ("thunderclap headache"). The differential diagnosis of thunderclap headache, especially with meningismus, includes SAH, RCVS, PRES, postpartum angiopathy (PPA), postpartum eclampsia, meningitis, encephalitis, systemic infection, cervical artery dissection, pituitary or pineal apoplexy, some ischemic strokes, colloid cyst of the third ventricle with sudden obstructive hydrocephalus, sinusitis, cough headache, exertional headaches, some migraine and tension headaches, hypertension, etc. Progressive, insidious dull headaches may occur with cerebral venous thrombosis and primary angiitis of the central nervous system (Calabrese et al., 2007). Evaluation of all headaches in a pregnant woman deserves measurement of the blood pressure and urinary protein for possible pre-eclampsia.

Lastly, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) may present during pregnancy. CADASIL is a hereditary small artery disease of the brain characterized by migraine with aura and recurrent ischemic infarctions occurring in young individuals in their twenties and thirties, ultimately producing a vascular dementia. It is caused by a mutation in the *NOTCH3* gene. The first clinical occurrence of CADASIL symptomatology may occur during pregnancy. Roine and colleagues described the clinical features of 25 CADASIL patients during pregnancy and the puerperium. The mean age was 31.6 years. In one half of the 78 pregnancies, expectant mothers experienced complications of pregnancy. Some 82% experienced neurologic symptoms and pre-eclampsia as their first clinical manifestation. Neurologic features included hemiparesthesias (76%), aphasia (65%), hemiparesis (36%) and visual symptomatology (47%). Confusion and dysarthria were found less frequently. Migraine headaches lasted for hours to many days. The incidence of pre-eclampsia occurred twice as often in CADASIL than the general population (10.3% versus 3–5%). Patients known or suspected to have CADASIL should be carefully followed during pregnancy (Roberts et al., 1989; Roine et al., 2005).

BRAIN TUMORS IN PREGNANCY

The occurrence of primary intracranial neoplasms during pregnancy has not been found to be greater than

non-pregnant women of childbearing age (Haas et al., 1986). While certain inherited neurocutaneous syndromes (tuberous sclerosis complex, neurofibromatosis type 1 and 2), nevoid basal cell carcinoma syndrome, Li–Fraumeni, multiple endocrine neoplasia type 1 (MEN-1), and a variety of syndromes involving adenomatous polyps have been associated with a predisposition to primary brain tumors, there is no evidence that pregnancy predisposes women to the development of primary or metastatic brain tumors (Simon, 1988).

More than 120 types of brain tumor have been described; glial tumors account for approximately 35% of all intracranial tumors, meningiomas account for 18% of all intracranial tumors, while pituitary tumors account for 10–15% of all primary brain tumors (Simon, 1988; Burger and Scheithauer, 2007; Louis et al., 2007). Although the incidence of brain metastases remains difficult to ascertain, lung cancer, breast cancer, melanoma, renal and colon cancer account for the majority of brain metastases. Women have a lower incidence of gliomas and a greater incidence of meningiomas. Although the incidence of meningiomas in pregnant women is comparable to nonpregnant women of the same age group, meningiomas have been found to increase in size during pregnancy (Fig. 105.2) regress after delivery, and recur during subsequent pregnancies (Kanaan et al., 2003; Olivi et al., 2011). Clinical flare of meningiomas during pregnancy has been attributed to the presence of sex hormone receptors in tumor cells, water retention, and engorged vessels. Likewise, enlargement of hemangioblastomas, and pituitary adenomas, particularly macroadenomas, during pregnancy is well established. Furthermore, enhanced pituitary vascularity may increase the risk of hemorrhage within the pituitary gland (see pituitary apoplexy).

Brain tumors in pregnancy have been associated with adverse pregnancy outcomes, although neurosurgical interventions do not appear to enhance the risks. Moreover, brain tumors in pregnancy have been associated with higher rates of caesarean delivery (Terry et al., 2012). Thus, a sensible approach is for multidisciplinary and individualized management. The reader is referred to standard neuro-oncology and neurosurgery texts for further details on current thoughts on anesthesia, surgery, radiation therapy, radiosurgery, and chemotherapeutic approaches for these patients.

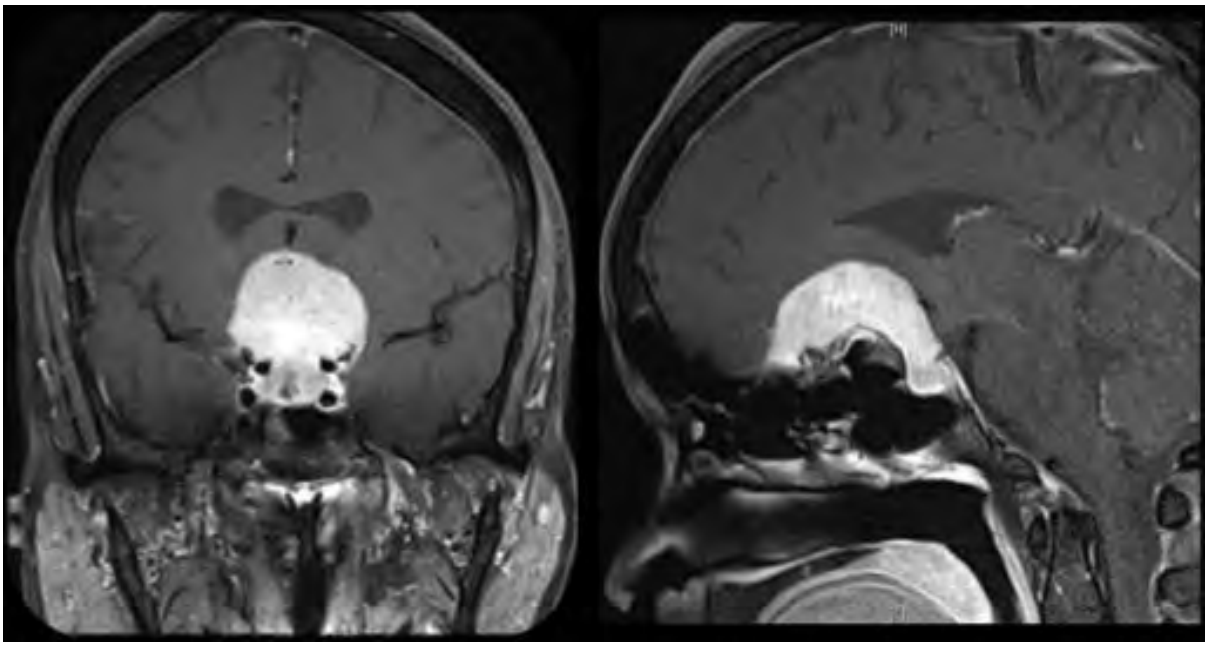

Fig. 105.2. A 37-year-old woman, with an estimated gestational age of 37 weeks, presented to our hospital with protracted headaches and bilateral, nonpostural visual blurring. Neurologic examination was remarkable for anosmia, no light perception OS, 20/20 visual acuity OD, pale disc OS, blurred nasal margins of the OD, and a left relative afferent pupillary defect (APD). T1-weighted, postcontrast, MRI of the brain (coronal and sagittal views) obtained post delivery, demonstrate an avidly enhancing extra-axial mass lesion arising from the region of the planum sphenoidale and fovea ethmoidalis with posterior extension to the suprasellar cistern and inferior extension to contact the pituitary gland. There is a suggestion of encasement of the left optic nerve and partial encasement of the right optic nerve. The lesion abuts the supraclinoid carotid arteries but without obvious encasement. Surgical pathology corroborated an olfactory groove meningioma (WHO Grade 1). The tumor was positive for progesterone receptors and the Ki-67 proliferation index overall is less than 1%.

Spinal cord tumors and other disorders of the spine and spinal cord

Tumors of the spinal cord may be intramedullary, extramedullary, or involve the vertebrae. In the general population, primary spinal cord tumors represent 2–4% of all neoplasms of the CNS (Grimm and Chamberlain, 2009). While pregnant women may experience tumors of the spinal cord, they are rare, with an estimated incidence of 1/11460 in one series (Podceichowski et al., 2003). Scattered case reports are noted in the literature, without tumors that are unique to pregnancy. Notable is an unrecognized ependymoma that hemorrhaged following attempted spinal anesthesia for anticipated cesarean section producing paraplegia (Jaeger et al., 2002). Breast cancer is rare during pregnancy; a case of poorly differentiated scirrhous breast cancer with negative hormone receptors metastatic to spine was discovered in the 29th week of gestation, treated with chemotherapy (trastuzumab and ibandronate) successfully during pregnancy, producing anhydramnios and a healthy fetus (El-Safadi et al., 2012).

Vascular malformations of the spinal cord include arteriovenous malformations, arteriovenous fistulas, dural AV fistulas, epidural vascular malformations, cavernous malformations, and complex vascular malformations. These malformations may present with myelopathy, radicular pain, and spine pain. Between 10% and 15% may be associated with cutaneous angiomas. These malformations may produce subarachnoid or parenchymal hemorrhage, arterial steal, venous hypertension or mass effect upon the spinal cord or exiting nerve roots. Spinal cord dural arteriovenous fistulas (DAVF) are the most common type (80%) of spinal cord vascular malformations, are more commonly observed in men (>80%) with a predilection for the lower spinal segments, and are the most amenable to treatment . Spinal DAVFs may have protean clinical manifestations. They may produce an insidious and progressive myelopathy or an acute or subacute myelopathic exacerbation due to severe venous congestion (hypertensive venous myelopathy). Symptoms may worsen with physical exertion. Upper extremity involvement is rare (Caragine et al., 2002).

Hemangiomas of the vertebrae are commonly observed as incidental, asymptomatic radiographic findings. Less than 1% of vertebral hemangiomas cause neurologic symptoms due to spinal cord or nerve root compression. During pregnancy the gravid uterus may compress the inferior vena cava producing venous obstruction and redistribution of blood flow through the vertebral venous plexus. Hemangiomas may then become expansile producing rapid onset of symptoms by compressing the spinal cord. It may also produce a vascular steal phenomenon (Chi et al., 2005; Kiroglu et al., 2009).

CONCLUSION AND FUTURE DIRECTIONS

Pregnancy creates alterations in maternal physiology which predispose to unique neurologic disorders. We discussed disease states occurring during pregnancy and their underlying mechanisms. Pre-eclampsia, eclampsia, certain types of ischemic and hemorrhagic stroke, RCVS, PRES, and thunderclap headaches all appear to share a common origin from vascular endothelial dysfunction, with overlapping clinical presentations. Such alterations of vascular endothelial dysfunction may persist for many years, with increased incidence of chronic vascular disease following pre-eclampsia. RCVS produces sudden severe headache, focal neurologic symptoms and signs, cortical SAH and angiographic evidence of multifocal intracranial segmental arterial narrowing with subsequent resolution. Peripartum cardiomyopathy occurring in the third trimester and early postpartum period may produce heart failure, reduced left ventricular ejection fraction, and cardioembolic stroke. APS is an autoimmune disorder which may produce stroke or transient ischemic attack, pregnancy loss, multiple sclerosis-like symptoms, chorea, and headaches. CVT may occur following dehydration (such as from hyperemesis gravidarum) thrombophilia, estrogen-containing oral contraceptives, and pregnancy. Unique aspects of anticoagulant management during pregnancy are reviewed, including warfarin teratogenicity. Intracerebral and SAH may occur following altered hemodynamics and pregnancy-related hypertension. MS often improves during pregnancy. Compression mononeuropathies may occur in the upper extremity to produce carpal tunnel syndrome, and in the lower extremity to affect the lateral femoral cutaneous nerve of the thigh, femoral, common peroneal, lumbosacral plexus, sciatic nerve, obturator nerve and lumbar or sacral nerve roots. MS is an autoimmune disorder directed against the postsynaptic terminal of the acetylcholine receptor. Stage 1 labor is dependent upon uterine smooth muscle and is not affected by MG. Second stage labor is dependent upon maternal pushing using abdominal striated skeletal muscle which may fatigue, requiring assisted delivery. Magnesium sulfate used to treat pre-eclampsia may worsen MG or an occasionally trigger myasthenic crisis. Maternal acetylcholine receptor antibodies may be transferred to the fetus causing decreased *in utero* movements and joint contractures (arthrogryposis multiplex congenita). Neonatal MG may transiently produce weakness after delivery due to the persistence of maternal antibodies. Various inflammatory peripheral neuropathies, dystrophies, and myopathies may occur during pregnancy; the safety of specific immune suppressants was reviewed. Headaches during pregnancy are classified as primary or

secondary to other neurologic processes, sometime sinister and life-threatening. Epilepsy does not have a significant effect upon the course of pregnancy, albeit there is a modest increase in the need for cesarean section. Certain AEDs may produce fetal malformations, most notably valproic acid. Alterations in AED volume of distribution, plasma protein binding and clearance may affect seizure control. Breast-feeding is generally safe when taking AEDs. Brain and spinal cord tumors are rare during pregnancy, but may increase in size due to activation of hormonal receptors on tumor cells surfaces, water retention, and engorged blood vessels, sometimes producing adverse neurologic outcomes.

Future research should be directed towards large-scale availability of biomarkers that predict pre-eclampsia early in pregnancy.

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