Neurological Disorders in Pregnancy

A Comprehensive Clinical Guide

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Foreword

The journey into the complex world of neurological disorders in pregnancy is an exploration that bridges neurosurgery, neurology, and obstetrics. This textbook, meticulously crafted by experts in these fields, serves as a guidepost to navigate the intricate landscape where maternal health and neurological well-being intersect.

Pregnancy is a transformative period in a woman's life where profound physiological changes and adaptations occur in support of the developing fetus. In some instances, the emergence or exacerbation of neurological disorders complicates the care of the obstetric patient. To provide the best possible care, it is necessary to understand the delicate balance between maternal health and fetal development.

In this comprehensive textbook, the authors explore both common and uncommon neurologic conditions affecting pregnancy. The interdisciplinary approach taken by our contributors brings together the latest insights from neurology, neurosurgery, neuroradiology, and obstetrics, ensuring a holistic understanding of these conditions and their management. The insights shared are valuable not only for healthcare professionals but also for researchers, educators, and students seeking to expand their knowledge in this specialized field.

Our hope is that this textbook will serve as an indispensable resource, fostering interdisciplinary collaboration, and ultimately improving the care and outcomes for women facing neurological challenges during pregnancy.

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Preface

This book is a product of an extraordinary team effort. The multidisciplinary management of any pregnant patient with neurological disorders includes experts in this field from neurosurgery, neurology, high-risk obstetrics—maternal fetal medicine, and neuroradiology.

The knowledge about the pathophysiology of neurological conditions in pregnancy can be complex. As we encounter a significant number of pregnant patients with varied spectrum of neurological disorders, we realized that the management of such conditions is loosely based on old and outdated evidence and not supported by well-defined or systematic literature reviews or meta-analysis. For instance, pregnant patients with certain neurological conditions, e.g., diagnosis of brain aneurysm in pregnancy, are being managed with elective cesarean section even though there is data suggesting that in most uncomplicated cases, the patient should be allowed to deliver vaginally without an associated increase in fetal or maternal morbidity/mortality. Taking motivation from our successful management of pregnant cases with neurological disorders at Rutgers Robert Wood Johnson Medical School and Hospital, we decided to pen this book to help guide our medical community in better management of these perplexing issues. It is an attempt to encourage "evidence-based practices" in treating such patients.

New Brunswick, NJ, USA — Gaurav Gupta

Acknowledgments

‘Neurological Disorders in Pregnancy- a comprehensive clinical guide’ is the work of a multi-disciplinary team a at Rutgers-Robert Wood Johnson Medical School in New Brunswick, New Jersey, USA. The team consists of dedicated physicians and experts in this field who have contribute from their knowledge, experience, and evidence mased medicine to guide us towards better management of pregnant patients with neurological disorders. I would like to thank my colleagues Dr Todd Rosen (High risk Maternal Fetal Medicine) Anil Nanda (Neurosurgery), Drs Priyank Khandelwal and Dr Fawaz Al-Mufti from Neurology, and Dr Sudipta Roychowdhury from Neuro-radiology. I would like to thank my Associate Editors- Michael Rallo, who is an MD, PhD candidate in training at Rutgers Robert Wood Johnson Medical School, and Dr Sanjeev Sreenivasan, our clinical research fellow at Rutgers Neurosurgery. I would also like to thank all the authors who have contributed to this text.

Thank you,
Gaurav Gupta

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Jessica C. Fields and Todd Rosen

Introduction

Pre-conception Planning for All Patients

In general, pre-conception planning is imperative to maximize successful and healthy pregnancy outcomes for both mothers and babies. A discussion of patient health care before conception provides the opportunity to review lifestyle, medical conditions and medications, immunizations, and nutrition and weight to make changes to improve pregnancy.

While it is important to screen reproductive-aged patients for interest in pursuing pregnancy [1], pre-conception planning should be a priority for all care because health status and risk factors continually change, and pregnancies are often unintentional. Furthermore, the American College of Obstetricians and Gynecologists (ACOG) and American Society for Reproductive Medicine (ASRM) are both proponents of coverage for and access to pre-conception counseling and services [2]. In addition to individualized care, all patients should be offered genetic counseling if desired and be recommended initiation of folic acid every day starting at least 1 month prior to conception with continuation for the entire pregnancy to prevent fetal malformations [3, 4]. Counseling should be provided on the importance of a healthy diet, regular exercise, attainment of a normal body mass index, and smoking cessation to enhance pregnancy outcomes.

Pre-conception Planning for Patients with Specific Neurological Disorders

For those with neurological disorders, pre-conception planning provides an opportunity for discussion of pregnancy impact on disease, the effect that disease impairment may have on pregnancy, and use of treatment for disease control during pregnancy. Pre-conception counseling plays an integral role because neurologic disease holds potential for significant contribution to morbidity and mortality in pregnancy. It is crucial to identify possible risks and reduce harm for the patient, fetus, and neonate [5]. Planning not only allows for optimization of neurologic health but also fosters patient education about pregnancy risks and provides time and integrated care to intervene for ultimate pregnancy success [6].

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The key integral components of preconception assessment for patients with neurological disorders include understanding patient history, performing a physical exam, and reviewing neuroimaging and medications. Additional considerations may be important for the postpartum period or breastfeeding. Moreover, it is critical that all women with pre-existing neurological disorders have excellent communication between all involved physicians. Counseling and risk assessment should involve a multidisciplinary care team such as obstetricians, neurologists, neurosurgeons, anesthesiologists, geneticists, and neonatologists.

Given that various neurological disorders have intricacies to their impact on pregnancy, specific neurological disorders will each be discussed separately to address all unique planning tools and concerns.

Spinal Cord Injury

Women with spinal cord injury (SCI) who are considering pregnancy should have preconception counseling and planning [7–9]. It is important to start with an understanding of a patient's history given that there are concomitant chronic medical problems and adaptations associated with SCI. The approach to patients with neurotrauma, including SCI, is discussed in detail in Chap. 25.

There is increased risk of complications with SCI in pregnancy including anemia (i.e., from iron deficiency, anemia of chronic disease, and chronic renal insufficiency), asymptomatic bacteriuria, lower urinary tract infections (up to 35% incidence), pyelonephritis, decubitus ulcers, and respiratory problems. Risk of pre-term birth ranges from 8 to 13%, which is similar to the general population [10–14]. Given the association with urinary tract infections, serial or frequent urine cultures or antibiotic suppression is recommended, although there is no definitive evidence to suggest this management [14–16]. Additionally, due to risk for pulmonary compromise, baseline pulmonary function studies, specifically vital capacity, should be performed pre-pregnancy and serially re-assessed during pregnancy to determine which patients may need ventilatory support in labor; this is especially important for those with high thoracic or cervical spinal lesions, typically above T5 [7, 14, 16]. Frequent skin exams and position changes to prevent decubitus ulcers as well as stool softeners and a high fiber diet to aid with worsening constipation in pregnancy are recommended [16].

Additionally, venous thromboembolism (VTE) incidence is higher in this population at about 8%, yet there is insufficient data to recommend universal thromboprophylaxis during pregnancy or postpartum [7, 17]. Each case must have an individualized risk assessment with stronger consideration of mechanical or pharmacologic prophylaxis if a patient has additional risk factors [18]. Range of motion exercises in the lower extremities, leg elevation, and leg stockings can be utilized for VTE prevention as well as upper body exercises to improve strength for those who are not quadriplegic [15, 18, 19].

A multidisciplinary team should involve specialists including but not limited to maternal-fetal medicine subspecialists, anesthesiologists, spinal rehabilitation physicians, physiotherapists, occupational therapists, lactation consultants, and neonatologists [15, 20]. Specifically, a discussion about risk for autonomic dysreflexia should occur pre-conception since this is the most serious of pregnancy complications, is potentially fatal, and affects about 90% of those with SCI lesions at or above level T6 [11, 21]. The most common sign is often severe systemic hypertension and this must be monitored for closely.

Patients should understand that they are not at higher risk than the general obstetric population for congenital malformations or fetal death [22]. Pregnancies may be at increased risk for small for gestational age infants and serial fetal growth ultrasounds may be performed [23]. Some SCIs may be congenital or hereditary in origin, and genetic counseling may be helpful to patients who desire understanding of inheritance in offspring in addition to other risk factors for pregnancy. For example, specific syndromes like

Kippel-Trenaunay or von Hippel-Lindau are associated with augmented risk for epidural or subdural hemangiomas and should receive a pre-conception MRI to determine if neuraxial anesthesia is a safe option [24]. Congenital spinal cord lesions such as meningomyeloceles have a higher risk in offspring and these patients should be on a higher dose of about 4 mg/day of folic acid for prevention [25].

Anesthesia consultation is advised so that a plan for epidural can be made with onset of labor. Early epidural is important in prevention of autonomic dysreflexia [14, 21]. Vaginal delivery is feasible for women with SCI. Moreover, postpartum issues should be anticipated such as difficulty with breastfeeding and need for additional support as well as an increased risk of mental health problems and need for rehospitalization for postpartum depression [26–28].

History of Hydrocephalus with Ventriculoperitoneal (VP) Shunt

Patients with VP shunts placed in the brain secondary to hydrocephalus may consider pregnancy. For these patients, pre-conception planning should include a description of risks with VP shunts during pregnancy and an MRI to establish baseline ventricular size and to verify appropriate shunt function. Considerations for management of pregnant patients with hydrocephalus are discussed at length in Chap. 16.

Risks of VP shunts in pregnancy include shunt malfunction, found in studies to occur in up to 25–50% of pregnancies [29, 30]. In the third trimester of pregnancy, functional occlusion of the shunt can be seen secondary to the increase in intra-abdominal pressure from a large uterus and in turn, obstructed cerebrospinal fluid drainage and elevation in intracranial pressure [31]. Symptoms of shunt malfunction—confusion, nausea/vomiting, tiredness, headache, or nystagmus, for example—should be explained to patients so that they can seek urgent neurosurgical care.

Vascular Disorders of the Brain

Stroke

Women with a history of stroke, ischemic or hemorrhagic, who are planning pregnancy should have full evaluation to prevent recurrence of stroke in pregnancy. It is well known that the pregnancy and postpartum periods are associated with an increased stroke risk [32–36]. Despite this higher risk, overall recurrence rate is low. It is important that women considering conception reduce modifiable risk factors such as smoking or substance use and be aware of risk factors inherent to pregnancy such as gestational hypertension, infection, and cesarean delivery [34, 37–39]. Review of imaging studies such as CT or MRI as well as echocardiography or carotid Doppler studies are useful in discussing prognosis. A review of medications should occur as many patients with a history of stroke may not only have underlying disorders but be on aspirin, clopidogrel, venous thromboembolism prophylaxis, blood pressure medication, or lipid lowering statin therapy. Of these agents, statins must be discontinued due to risk of spontaneous abortion and teratogenicity. There are safe antihypertensive drugs that may be used in pregnancy including labetalol, methyldopa, nifedipine, and hydralazine. However, angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) are contraindicated in pregnancy due to risk of fetal renal damage. Diuretics are not the preferred antihypertensive medication in pregnancy, but may be continued if the patient conceives on hydrochlorothiazide or other medications of this class. Long-acting beta-blockers such as atenolol may cause prolonged beta-blockade of the newborn and may be associated with intrauterine growth restriction (IUGR); a move to an antihypertensive with less risk may be appropriate [40–46]. Additional consideration of prophylactic enoxaparin during pregnancy with plan to switch to heparin around 36 weeks gestation should be discussed for women with a prior history of ischemic/thrombotic stroke [47, 48]. The relative risk of gestational and peripartal

stroke and nuances of treatment are discussed at length in Chaps. 3 (Ischemic) and 4 (Hemorrhagic).

Arteriovenous Malformation (AVM)

It is inconclusive whether there is increased risk for arteriovenous malformation (AVM) rupture in pregnancy. The physiologic hemodynamic changes of pregnancy including larger plasma volume, increased cardiac output, and higher cerebral blood flow may theoretically increase the risk of hemorrhage but the magnitude of this risk is unknown [49]. There is a paucity of data given the low AVM prevalence in the pregnant population. Some evidence suggests increased rupture risk. Very early studies of AVMs in pregnancy showed as high as 21–48% risk for spontaneous hemorrhage [50–53]. Robinson et al. studied 24 women with AVMs who had high rates of adverse fetal outcomes including a 49% fetal complication rate and 26% fetal mortality rate [53]. However, the high risk for adverse outcomes in these early studies may be a result of publication bias.

More recently, Porras et al. provided evidence of a 5.7% hemorrhage risk in pregnant women compared to 1.3% in nonpregnant counterparts [54]. Additional studies have shown approximate AVM hemorrhage rates of 3–9% in pregnancy versus 3–4% when not pregnant [55, 56]. Another study involving 54 women with AVM highlighted an annual hemorrhage rate of 11% during pregnancy compared to 1% outside of gestation [57]. When AVM rupture in pregnancy does occur, it is usually in the third trimester at a mean of 30 weeks gestation, and high maternal mortality rates have been suggested [58].

Yet, other studies must be recognized that suggest no significantly higher risk of AVM hemorrhage in pregnancy [55, 58, 59]. Given the limited and inconclusive evidence [60–62] but continued concern for rupture, some experts recommend treatment of AVMs pre-conception [63]. However, intervention is not without risk, suggesting that curative treatment should be guided by general neurosurgical considerations. This counseling may be impacted by other risk factors for AVM hemorrhage in addition to pregnancy such as prior rupture [64–68], AVM location [67–69], deep venous drainage [70], and associated aneurysms [71]. Moreover, the approach to treatment might also influence rupture risk: a 2014 retrospective review of 253 women with AVMs showed an annual hemorrhage rate of 11.1% for those who became pregnant in the 3-year latency interval between stereotactic radiosurgery and complete AVM obliteration compared to an annual hemorrhage rate of 2.5% for those not pregnant [72]. There are no randomized trials to confirm which treatment is better; one randomized trial comparing medical to interventional treatment of unruptured AVMs was stopped early because of the superiority of medical management [73]. Thus, pre-conception history and imaging are necessary investigations to provide optimal counseling to patients. The evidence relating to risk of AVM hemorrhage and approach to management is discussed in detail in Chap. 19.

Intracranial Aneurysm

Similar to AVMs, intracranial aneurysms may have increased risk of rupture in pregnancy, but the literature is controversial. Studies have shown an increased risk of subarachnoid hemorrhage as a consequence of hemodynamic changes induced by pregnancy [53, 58, 74, 75].

More recently, studies have refuted this increased association [74, 76, 77]. Specifically, a Dutch analysis of 244 women showed no increase in rupture risk [76]. Kim et al. analyzed the Nationwide Inpatient Sample (NIS) from 1988 to 2009 showing aneurysm rupture risk of 1.4% during pregnancy and 0.05% during delivery, which is similar to the annual aneurysm rupture risk in the general population [77]. Since these more current population-based analyses do not suggest worsened risk of bleeding during pregnancy and while an individualized risk assessment must still be performed, the evidence suggests no need to prophylactically intervene pre-conception for asymptomatic and unruptured aneurysms [76, 77].

Nevertheless, an aneurysm has the potential to rupture in pregnancy and if this were to occur, maternal and fetal morbidity and mortality are increased [58]. During pre-conception counseling, the patient should be informed that pre-pregnancy treatment is far preferable to having to treat an unruptured aneurysm during the pregnancy. If the patient conceives before appropriate treatment, or if she refuses advice to undergo treatment prior to conception, it is important to discuss a possible plan for management of a ruptured aneurysm in pregnancy. Immediate neurosurgical intervention with possible clipping or coiling of the aneurysm would be needed during pregnancy to better both maternal and fetal outcomes [78]. From the NIS study, maternal mortality from untreated aneurysmal rupture was significantly higher than in treated ruptured aneurysms [79]. This decision for an emergency operation during pregnancy would be based on neurosurgical need, not obstetrical considerations. In general, the decision to treat an unruptured aneurysm should be based on neurosurgical assessment of risk relating to aneurysm size, enlargement, morphology, and/or associated symptoms. A more detailed discussion of cerebral aneurysm risk assessment and treatment in pregnancy is provided in Chap. 2.

Cavernous Malformations (CM)

Cavernous malformations are not a contraindication to pregnancy. Previous studies, mostly case series and reports, have shown an association between pregnancy and increased risk of growth or hemorrhage of CMs [79–81]. One such study by Porter et al. demonstrated that in 100 patients with brain stem CM, 7 (11%) of 62 women had a hemorrhage in pregnancy [82]. Suggestions for biologic plausibility at that time involved hypotheses around greater expression of vascular endothelial growth factor and basic fibroblast growth factor triggered by the hormones of pregnancy [82].

However, follow-up investigations have not demonstrated this association, and suggest that pregnancy causing enlargement or higher bleeding rates of CMs is likely not true [83–87]. Two more recent large clinical cohorts showed a similar risk of bleeding from CM in pregnant women compared to women not pregnant during childbearing years [88, 89]. Specifically, Kalani et al. [88] showed in a retrospective study of 168 pregnancies that pregnancy or delivery was associated with a 3% risk of CM rupture or 3.4% per patient-year which is not significantly different from the overall annual hemorrhage rate of CM in the general population at 2.4%. Furthermore, a prospective study assessing hemorrhage risk of CM in pregnant women confirmed these findings of no conferred risk and that vaginal delivery is a safe option for appropriate candidates [90]. This literature and the management of CMs in pregnancy is further described in Chap. 19.

Moyamoya

Pregnancy outcomes are generally good in those patients with moyamoya if the disease is known in advance and involves multidisciplinary care. One study involving 70 cases of known moyamoya in pregnancy resulted in only one patient with a poor outcome [91] and another study highlighted reassuring fetal outcomes [92].

The key principles to moyamoya management in pregnancy stem from prevention of ischemic and/or hemorrhagic events. While moyamoya is an uncommon disease, it has potentially fatal consequences due to the progressive nature of the disease with continued stenosis of the internal carotid, anterior, and middle cerebral arteries ultimately resulting in hypoxia and subsequent formation of collaterals and dilation of these perforating arteries, which can possibly rupture causing brain hemorrhage [68, 92–100]. Thus, as long as disease status is known, imaging can be performed pre-pregnancy to determine disease severity. Per Lu et al., the annual hemorrhage rate was 3.9% among 96 female patients regardless of pregnancy [95]. There are limited high-quality studies examining the risk of stroke in patients with moyamoya during pregnancy; case series

have suggested a high risk for ischemic or hemorrhagic stroke, yet there is no data to support a protective benefit of surgical revascularization prior to pregnancy [101, 102]. These concepts are discussed in detail in Chap. 20.

Cerebral Venous Thrombosis (CVT)

In general, a worse prognosis is associated with CVT if associated with hemorrhagic venous infarction, regardless of pregnancy status. It is recommended that patients with history of CVT considering pregnancy be placed on anticoagulation, usually a heparin derivative, for both treatment and secondary prophylaxis. If deemed refractory to medical management, case series and anecdotal reports suggest that invasive endovascular procedures such as mechanical thrombectomy or direct chemical thrombolysis are acceptable [103]. Ideally, any procedure would be performed prior to pregnancy to limit fetal risk. The occurrence of CVT in pregnancy is discussed in Chap. 5, while considerations for gestational anticoagulation are described in Chap. 28.

Headaches (Migraines)

Headaches can be difficult to manage during pregnancy, and it is crucial for pre-conception planning to include review of individualized headache history and discussion of migraine course over pregnancy and options for prevention and treatment as well as awareness of warning signs for ominous headaches. Headaches are a common problem for women during childbearing years, and migraine peak prevalence reaches approximately 40% in those aged between 30 and 50 [104].

There are numerous studies focused on migraine course in pregnancy [105]. The majority of women (about 60–70%) have improvement in migraines during pregnancy [106], especially by the second and third trimesters, and only about 5% have worsened migraines, while the rest have no change [106]. Women who typically have migraines with menstruation or without auras have improvement in the first trimester and often resolution of their headaches [106, 107]. Moreover, the MIGRA study followed 2000 women with headaches over the course of pregnancy and found a significant reduction in migraine frequency, especially in the second and third trimesters [108].

While migraines have not been associated with increased fetal risks such as miscarriage, stillbirth, or teratogenicity [109], studies have linked migraines with a greater prevalence of hypertensive disorders of pregnancy. A 2019 national population-based cohort study compared 22,841 pregnant women with migraines with 228,324 matched controls and found that those with migraines had a 50% increase in adjusted prevalence ratio for hypertensive disorders [110].

Most of pre-conception planning for migraines surrounds treatment strategy. Prior to pregnancy, women employ numerous pharmacologic agents for symptom control and prevention from acetaminophen to nonsteroidal anti-inflammatory drugs (NSAIDs) to triptans, caffeine-barbiturate combinations, and opioids. Medication adjustments should occur prior to pregnancy for the best pregnancy outcomes. In pregnancy, patients should be counseled that acetaminophen is the recommended first-line acute therapy and 1000 mg can be an effective treatment [111] without evidence of fetal risk. Aspirin and NSAIDs are potential next options in early pregnancy, however, are not safe beyond 20 weeks due to risk for premature ductus arteriosus closure in the fetus and neonatal pulmonary hypertension [112]. In general, the use of NSAIDS for more than a few days even in early pregnancy is uncommon. Opioids can potentially be used in pregnancy as well but these are not advised for chronic use due to risk for addiction, medication overuse, and development of chronic daily headaches [113, 114]. Furthermore, chronic opioid use specifically in the third trimester, such as meperidine, codeine, or morphine, can lead to neonatal withdrawal syndrome [107]. If migraines are refractory to these treatments, triptans (5-HT IB/ID receptor agonists) may be con-

sidered [115]. A large study including prospective pregnancy data has been unable to fully delineate risks associated with sumatriptan or naratriptan but has not shown a large increase in risk of major birth defects [116]; thus, lack of data for these medications in pregnancy has prevented creation of clear guidelines.

Steroids such as prednisone can also be used, however there are potential complications with prolonged steroid use [107]. After 14 weeks of pregnancy, the fetus is largely protected from nonfluorinated steroids because these are oxidized by placental 11-β hydroxysteroid dehydrogenase [117, 118].

The use of ergotamine is contraindicated in pregnancy due to potential adverse fetal outcomes from hypertonic uterine contractions or vasospasm/vasoconstriction [119, 120].

Other drugs have proven to be helpful for control of headaches in pregnancy. Caffeine can be utilized alone or in combination with other medications. During pregnancy, intake of up to about 200 mg of caffeine per day is considered low risk [121, 122], keeping in mind that a cup of drip coffee has approximately 100 mg of caffeine [123]. Adjuncts such as metoclopramide, promethazine, and prochlorperazine are safe and have proven to be efficacious with concomitant symptoms such as nausea/vomiting and pain [116].

Education is paramount for prevention and includes nutritional counseling to avoid specific headache triggers as well as recommendations for sleep and exercise. Additionally, randomized clinical trials provide evidence for benefit of nonpharmacologic treatment such as relaxation training, thermal biofeedback, and cognitive behavior therapy [124]. Since there are no prospective randomized clinical trials focused on migraine prophylaxis in pregnancy, prophylaxis for migraines is generally only recommended if migraines persistently get worse over the course of pregnancy. Propranolol or verapamil are drug options for prophylaxis in pregnancy [107, 125]. A detailed discussion to evaluation and management of migraine and other headache syndromes in pregnancy is provided in Chap. 8.

Epilepsy and Seizure Disorders

Pre-conception planning is crucial to confirm the diagnosis of epilepsy or specific seizure disorder after review of patient history, imaging, and electroencephalogram (EEG) results. The latter may be required if a diagnosis of epilepsy is not well established, especially given the presence of mimics for epilepsy or seizures. Furthermore, one study underscored that women with epilepsy have limited knowledge about pregnancy and childbirth [126] and potential complications can be reduced via pre-conception intervention [127]. Providers should discuss pregnancy with all childbearing aged women at each visit [128] to address need for good seizure control if desiring pregnancy or otherwise learning about birth control options and interaction between birth control and certain antiepileptic drugs (AEDs).

Prior to pregnancy, review of a patient's seizure medication by a neurologist is important in order to optimize AED regimen and to potentially switch medications for safety in pregnancy. Patients should be well-informed of the risks and benefits of AED use [129] and specifically the risk of seizure must be weighed against AED risk, such as propensity for congenital malformation, poor neonatal outcome, or adverse neurodevelopment. If a patient has been seizure-free for over 2 years with normal electroencephalogram (EEG), then one may consider tapering off or stopping the AED. Stopping use of an AED is recommended at least 6 months prior to attempting conception to ensure disease-free status, especially because these women are at risk for seizure recurrence after withdrawal during this time period [130]. Women continuing on AEDs should conceive once a minimum dose of medication is being used with the goal of monotherapy when possible. In a recent retrospective cohort study, planned pregnancies were significantly more associated with AED monotherapy and less need for change in AED regimen during pregnancy [131].

There is no one trial delineating the safest AED for pregnancy but an abundance of evidence from epilepsy pregnancy registries shows that

many AEDs should be avoided if possible, especially in the first trimester, including carbamazepine, phenobarbital, primidone, phenytoin, topiramate, and valproate given their association with congenital malformations [132], specifically neural tube defects (NTDs), congenital heart anomalies, cleft lip/palate, and/or urogenital defects. Overall, levetiracetam or lamotrigine are generally the first-line seizure control medications due to data supporting low risk of these complications. There is compiled evidence from the North American Antiepileptic Drug (NAAED) Pregnancy Registry supporting increased rate of major fetal malformations with AED use, including a 9% malformation rate with valproate, for example [133]. Since valproate has been shown to be significantly more teratogenic than other medications, it should be avoided and all other AED options should be considered first. After the first trimester, most medications can be utilized, and specifically, valproate and phenobarbital can be employed especially if seizures cannot be adequately controlled with other agents [134, 135]. If valproate or phenobarbital must be used, the recommendation is for prevention of high plasma levels and administration in a three or four time daily dosing regimen. IQ in children exposed to in utero low dose valproate was about the same as IQ of children exposed to other AEDs in one prospective study [136]. However, in other studies, valproate and phenobarbital have shown potential to cause decreased intelligence in offspring when given after the first trimester and can be stopped if there is an effective alternative for the patient [137, 138].

Moreover, it is key to provide patient education about the need for medication compliance with good seizure control prior to conception. Having no seizures for at least 9 months prior to pregnancy is associated with remaining seizure-free during pregnancy. Patients should also be aware of the possible need to make AED adjustment in pregnancy based on changing AED levels. This may occur because of pregnancy-related physiologic changes like increased hepatic metabolism, alteration in volume distribution, and rise in glomerular filtration rate which in turn may decrease AED levels by increasing renal clearance and decreasing protein binding. Thus, some studies suggest active monitoring of AED levels in pregnancy, especially lamotrigine which has been tied to increased seizure frequency during pregnancy [130]. Optimal target concentration of AED should be established prior to pregnancy so that this can be the goal in pregnancy [128]. After reviewing published evidence in 2009, the American Academy of Neurology (AAN) did not find that epileptic pregnant women on AEDs were at higher risk of cesarean delivery, pre-term labor, or late pregnancy bleeding [129, 139, 140].

With multidisciplinary care and good understanding and treatment of disease, patients should understand that about 90% of women with epilepsy have excellent outcomes with healthy neonates [141]. Yet, patients should be counseled that seizures can be harmful to mother and/or baby in pregnancy [142], and that there is some evidence supporting increased morbidity and mortality in women with epilepsy including complications like pre-eclampsia, pre-term labor, bleeding, placental abruption, fetal growth restriction, or maternal or fetal death [143–147]. None of these risks should be considered a contraindication to pregnancy. AED exposure has been associated with risk of pre-term birth and delivery of a small for gestational age (SGA) infant [128]. The magnitude of increased risk is small for most of these problems, i.e., ranging from 1 to 1.7 times expected rates, except for maternal mortality, which has been shown to be as much as ten-fold higher among women with epilepsy in delivery hospitalization [128]. Studies have not been consistent regarding an increase in fetal death or stillbirth in women with epilepsy. Small increases in risk for miscarriage or stillbirth were shown in a 2015 systematic review and meta-analysis [143] and a population-based retrospective cohort study [144]. Data shows that tonic-clonic seizures can cause hypoxia and lactic acidosis and in turn, harm the fetus [128].

Pre-conception folic acid supplementation is particularly important in this population to reduce risk for congenital malformations like neural tube defects [148], and is shown to be beneficial in cognitive and behavioral studies of children

born to women on AEDs. Guidelines differ regarding suggested dose of folic acid; the ACOG recommends taking 4 mg daily for women at high risk of having a child with a neural tube defect [149] but does not recommend dose above 0.4 mg daily for women on AEDs [150] nor do the 2009 guidelines from the AAN [140]. In the Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study by Meador et al., mean IQ was higher in 6-year-old children of mothers who adhered to periconceptional folic acid when compared to children of mothers who did not take periconceptional folic acid and started folic acid later [136, 147]. Genetic counseling can also provide insight into risk of offspring development of epilepsy. Studies suggest a modestly higher risk of having epilepsy in children who have a parent with epilepsy, but the degree of this risk is dependent upon specific epilepsy syndrome [151–153]. Furthermore, in discussion regarding neonatal risk, there is some suggestion that specific antiepileptics like carbamazepine can be associated with a bleeding problem in the neonate and that Vitamin K can be utilized in both mother and neonate for prevention [129, 154]. Considerations for management of acute seizures, epilepsy, and fetal protection are discussed in detail in Chap. 6.

Myasthenia Gravis

Pre-conception planning is important to first confirm a diagnosis of myasthenia gravis with neurology if it has not been confirmed. Methods for diagnosis range from detection of antibodies against nicotinic acetylcholine receptors or other postsynaptic antigens to detection of neuromuscular junction dysfunction through repetitive nerve stimulation testing or single-fiber electromyography [155]. If a diagnosis has been established, treatment goals and options should be discussed with the patient before becoming pregnant. The disease severity may vary over time and patients must know how to monitor for changes in symptoms and adjust to treatments with plan for optimization of treatment prior to pregnancy. It is important to be aware that MG most commonly affects the periocular, oropharyngeal, and proximal limb muscles with muscles involved in respiration being impacted in severe cases [156]. Furthermore, triggers for worsening of MG can occur in pregnancy and include surgery, infection, select medications, and emotional stress or fatigue [156].

If a patient is considering pregnancy but has yet to have a thymectomy, this should be considered prior to conception to help improve clinical outcomes [157]. Thymectomy has proven effective in disease control with less need for immunosuppressive agents and is generally recommended for all patients under age 65 as standard of care [158, 159]. Clinical benefit over a 3-year time period was found in a randomized single-blinded clinical trial of thymectomy in patients with non-thymomatous, seropositive MG [160]. Moreover, thymectomy appears to confer protection against neonatal MG [161, 162]. The Medical Birth Registry of Norway performed a retrospective analysis showing that neonates born to MG mothers with a prior thymectomy had a lower incidence of neonatal MG when compared to those born to MG mothers without thymectomy [162]. Most experts recommend young women with MG have a thymectomy as soon as possible, as long as they are not pregnant, although thymectomy in the year before conception may not lead to remission of MG symptoms prior to pregnancy given delayed therapeutic benefit [157, 161, 163].

Medications must be discussed and modified if necessary prior to conception to reduce teratogenicity. Two common MG drugs that must be stopped are methotrexate (MTX) and mycophenolate mofetil (MMF); they are contraindicated in pregnancy and recommendation is for stopping MTX at least 3 months and MMF at least 6 weeks prior to conception [164]. Data clearly shows teratogenicity of these medications with MTX being associated with increased miscarriages [165] and MMF with miscarriage and congenital malformations of the lip and palate, distal limbs, esophagus, kidney, and central nervous system of the fetus [166, 167].

Many medications can safely be continued in pregnancy, and necessity for MG treatment should be tailored to disease severity. The recommended treatment for MG in pregnancy is the

acetylcholinesterase inhibitor pyridostigmine and corticosteroids like prednisone at the lowest effective dose, if needed [157, 159]. Rituximab (RTX) can also be employed with no increase in adverse outcomes [165, 168]. Other medications such as azathioprine and cyclosporine may be added to help with MG exacerbations [159]. High-dose intravenous immune globulin (IVIG) and plasmapheresis may be used for acute exacerbations of disease or myasthenic crisis [159, 163, 169–171] and have generally been well tolerated in pregnancy for numerous autoimmune conditions [160, 172].

Understanding the variable impact of pregnancy on MG is important [155, 169]. MG has not been associated with increased risk of spontaneous abortion [162]. Similar to other neurologic disease, optimal control prior to pregnancy usually predicts a stability of disease during pregnancy, although highest risk for exacerbation is during the first trimester and postpartum period [157, 159, 163, 173–175]. Postpartum exacerbation may be triggered by fatigue in caring for a newborn or hormonal plus immunologic changes. Even with well-controlled MG, anxiety remains and discussions between MG patients and care providers must be thoughtful and respectful when discussing pregnancy [176]. All pregnancies may be different for MG patients as well [177] since the disease course is unpredictable. It is suspected that improvement in MG occurs in the second or third trimester due to immunosuppression caused by high AFP [175, 178, 179]. Baseline forced vital capacity should be assessed because respiratory function can become compromised over the course of pregnancy due to the enlarged uterus [175]. Of note, long-term outcomes of MG are not impacted by pregnancy [174].

It should be understood that there is increased risk for complications (about 30% of MG patients) during delivery thus stressing the importance of a multidisciplinary care team involving obstetrics, neurology, and anesthesiology [157, 159]. The disease itself does not affect smooth muscle but given that labor and delivery is impacted by striated muscle, especially in the second phase of delivery, fatigue can occur and it can be prolonged and involve fetal distress [155, 162, 180]. Forceps or vacuum extraction are beneficial, however, MG itself is not an indication for cesarean delivery [161]. Therefore, spontaneous vaginal delivery should be encouraged with cesarean delivery performed for indicated obstetrical reasons [159]. Stress dose steroids should also be considered during labor and delivery if patients have been on long-term oral steroids [157].

Additionally, medications delivered during labor must be monitored closely. Parenteral anticholinesterase medications can potentially strengthen the muscle since oral absorption may be limited. More importantly, it is important to identify and mitigate effects of medications that make MG symptoms worse [155]. Specifically, nondepolarizing muscle relaxants and magnesium should be avoided since they can significantly worsen MG [159]. Magnesium which is commonly employed for management of preeclampsia, eclampsia, or pre-term labor is contraindicated due to precipitation of severe MG crisis [181, 182]. Anesthesiology consultation prior to labor is recommended; MG patients who need general anesthesia may have a higher risk for needing mechanical ventilation [183] and general anesthesia should be avoided if possible. Epidural or combined spinal-epidural anesthesia is recommended by expert opinion to reduce respiratory issues as well as to help with overexertion and fatigue [184]. Spinal anesthesia can also be safely used for MG patients needing cesarean delivery [178].

Neonatologists play an important role in assessing and supporting the needs for an infant born to a patient with MG given the risk for transient neonatal MG or arthrogryposis. Incidence of transient neonatal MG is about 10–30% [174], can be seronegative or involve different antibodies [185–187], and has symptoms ranging from generalized hypotonia to poor suck or respiratory problems. Monitoring for symptoms in the several days after birth is needed because symptom onset can be delayed but this usually all resolves within 1–7 weeks [188]. The issues surrounding pre-conception counseling, gestational and peri-

partal management, and neonatal monitoring are discussed in detail in Chap. 17.

Brain Tumors

While rare, there are a myriad of brain tumors that occur in childbearing aged women such as gliomas, meningiomas, or metastatic brain tumors. It is important to discuss risks and benefits of pregnancy with a brain tumor because symptoms and treatment can be difficult in pregnancy. Management of brain tumors is vast and if surgical resection, radiation and/or chemotherapy are needed, pregnancy should be deferred until these therapies have been delivered. Radiation can have poor outcomes such as spontaneous abortion, malformations, growth, and mental retardation, and possible higher childhood cancer risk [189, 190]. Chemotherapy for malignant brain tumors is also not ideal during pregnancy because most cross the placenta and are teratogenic [191]. Moreover, there may be subtle changes in cardiac and neurocognitive outcomes in these fetuses, which requires more data to be conclusive [192].

There are pregnancy risks for women with brain tumors that should be known since pregnancy can impact tumor symptoms and growth [193, 194]. For example, there is evidence to suggest that some brain tumors such as meningiomas may be negatively impacted by pregnancy hormones [195]. Changes in sex hormones, such as progesterone, during pregnancy can promote growth in meningiomas and vestibular schwannomas due to expression of hormonal receptors [196, 197]. Additionally, 1 study of 11 pregnant women with grade II gliomas showed significant radiologic enlargement of the brain mass during pregnancy when compared to times outside of pregnancy [198]; in this study, there was concomitant increase in seizure frequency suggesting the need for close monitoring for changing neurologic findings and awareness to differentiate adverse events from brain tumors versus eclampsia [198].

Generally, benign or asymptomatic tumors may be observed whereas malignant or symptomatic tumors should be treated regardless of pregnancy with neurosurgical recommendation superseding obstetrical consideration. Management may require use of steroids or mannitol due to potential for pregnancy to promote a higher intracranial pressure or cerebral edema [199–201]. In some cases, this is due to the ability of pregnancy to promote fluid retention and thus contribute to enlargement of vascular tumors [194]. Here, excessive hydration is not recommended given potential for cerebral edema [202]. Clinically, it is important to be able to recognize seizures as a potential complication of tumor enlargement and differentiate these from eclampsia; in a case series by Pallud et al., increased seizure frequency was found in pregnant women with grade II gliomas [198].

Prenatal genetic counseling is important prior to conception because many hereditary tumor syndromes are associated with brain tumors and autosomal dominant diseases such as neurofibromatosis types I and II, tuberous sclerosis, Turcot syndrome, von Hippel-Lindau syndrome, Li-Fraumeni, and Gorlin syndrome [203, 204]. If a genetic syndrome is identified, pre-implantation genetic testing with in vitro fertilization can potentially be an option to mitigate risk. Use of a gestational carrier may also be indicated when patients have neurologic tumors that may be hormonally responsive with an increased potential for accelerated growth in pregnancy. For more details on considerations for counseling, diagnosis, and management of brain tumors in pregnancy, please refer to Chap. 11.

Pituitary Adenomas (Prolactinomas)

Pituitary adenomas comprise about 15% of intracranial neoplasms and are often undiagnosed [205]. Prolactinoma is the most common type of pituitary adenoma and presents particular issues for pregnant patients. One of the biggest concerns for women with lactotroph adenomas, or prolactinomas, is growth of the tumor. Adenoma growth is likely caused by increased serum estradiol in pregnancy, which promotes lactotroph hyperplasia. Studies have shown evidence of

more than doubling in pituitary size using magnetic resonance imaging (MRI) in pregnant versus nonpregnant women [206]. Risk of growth for those with microadenomas (<10 mm in diameter) is low [207, 208]. A review of 14 studies by Molitch et al. showed that only 2.4% of patients with microadenomas showed a symptomatic increase in size during pregnancy whereas 22.9% of women who had macroadenomas without prior treatment with surgery or radiation had significant enlargement [209]. Women should be counseled about neurologic symptoms that could develop, more often in those with macroadenomas (about 13–36%), such as new headaches or visual changes. Additionally, if there is concern during pregnancy about adenoma growth or pituitary apoplexy secondary to ischemia or hemorrhage, MRI can be utilized due to lower fetal risk compared to CT [210]. There may be a small risk for developing pituitary apoplexy during pregnancy in women who have pre-existing pituitary adenomas, which is caused by the pituitary gland enlarging by about 3 mm at the end of pregnancy [211].

Treatment of prolactinomas is usually with dopamine agonists such as bromocriptine or cabergoline, and often these medications are needed to correct prolactin levels and allow for normal ovulation and restoration of fertility. These medications are usually stopped with pregnancy, although there are no known adverse fetal outcomes after exposure to these medications. For example, a study involving over 6000 pregnancies with exposure to bromocriptine during the first month of pregnancy did not harm the fetus and incidence of spontaneous abortion, multiple births, and fetal malformations were comparable to those not on the medication [208]. The same has been found in a large study of cabergoline use at time of conception [209]. Another study followed children up to age 9 who were exposed to bromocriptine in utero and no negative outcomes were found [212]. Interestingly, there is some data that bromocriptine may reduce the risk of miscarriage in women with a history of recurrent pregnancy loss [213, 214].

Women with a macroadenoma should be advised to delay pregnancy until they have a reduction in adenoma size with either a dopamine agonist or surgery, if necessary, due to an adenoma refractory to medication or elevating the optic chiasm, especially given their increased risk for clinically significant enlargement in pregnancy [208]. Surgery lowers the risk for symptomatic enlargement in pregnancy [209].

In regard to planning pregnancy with microadenomas, routine visual field testing is not needed and the Endocrine Society guidelines recommend against measuring prolactin because prolactin can be elevated from pregnancy alone [215]. If a pregnant woman were to develop visual symptoms, then visual testing should be performed. If a pregnant woman has a macroadenoma that extends above the sella, visual testing should be serially checked in pregnancy and subsequent MRI without contrast can be performed if needed. The approach to workup and management of pituitary and sellar tumors is discussed in detail in Chap. 12.

Multiple Sclerosis (MS)

Pre-conception planning for women with MS generally involves understanding disease course in pregnancy and optimizing medications that are safe during pregnancy. MS is a disease that largely impacts childbearing aged women [216], but it significantly improves in pregnancy [217] with fewer relapses. A 2011 meta-analysis of 13 studies that included 1221 pregnancies provided evidence that the period of pregnancy was associated with less MS disease activity whereas the postpartum state was associated with a rise in disease activity [218].

Important data is derived from the Pregnancy in Multiple Sclerosis Study (PRIMS) in which 254 women were followed throughout 269 pregnancies and 12 months postpartum. PRIMS reported mean rates of relapse prior to pregnancy, in the first trimester, in the second trimester, in the third trimester, and in the first 3 months postpartum of 0.7, 0.5, 0.6, 0.2, and 1.2 per woman per year, respectively [217]. Multiple other studies have suggested the same with decreased MS disease in pregnancy and an increase postpartum

[219, 220]. Reasons for postpartum relapses are not fully understood but postpartum triggers may include stress, fatigue, infection, or loss of antenatal immunosuppression impacted by estrogen [221]. Long-term sequelae from MS secondary to pregnancy is less clear [222–224].

While there is some controversy about the impact of MS on obstetrical outcomes, most data suggest that MS usually does not adversely affect pregnancy [225]. For example, spontaneous abortion and congenital malformations have not been higher in women with MS [218, 226, 227]. Also, studies are controversial as to whether birth weight is less [226, 228]; one study analyzing 4730 women with MS showed a small but significant increase in risk for intrauterine growth restriction [227]. Some patients with MS may have increased need for a vacuum-assisted vaginal delivery or cesarean section [227, 228]. Delivery is usually not more difficult in MS however there can be issues with fatigue or spasticity of the pelvic floor. Delivery mode should be determined by obstetrical considerations; the largest prospective study looking at risk of postpartum relapses did not show increased risk of postpartum relapses by delivery mode or epidural anesthesia [229]. Epidural anesthesia is safe for patients with MS and anesthesia should be based on obstetric needs [230].

Women with MS should plan for pregnancy once MS activity has been minimal for at least 1 year and in good control for optimal pregnancy outcome [231]. Women with MS may be on numerous medications such as disease-modifying antirheumatic drugs (DMARDs), antimuscarinics such as oxybutynin for bladder disorders, antispasmodics such as baclofen or diazepam, and anti-depressants. There are conflicting expert opinions regarding medication use and pregnancy, and it ultimately must involve weighing benefits and risk of specific drugs in pregnancy. There is limited evidence on use of DMARDs in pregnancy, and some drugs can be considered in pregnancy whereas others should be stopped [231–234]. Data from review of 761 pregnancies with exposure to interferon-beta showed a lower mean birth weight, shorter mean birth length, and pre-term birth but no increase in spontaneous abortions, congenital malformations, birth weight under 2500 g, or increased cesarean sections [235]. In this same study, data did not show adverse outcomes with either glatiramer acetate or natalizumab. While data on pregnancies exposed to such drugs is limited [235–238], patients should not abort pregnancy for these exposures [235, 239].

Patients with MS should not avoid pregnancy due to fear of passing the disease to their offspring. While there are some MS associated genetic variants [240] that have been studied in large cohorts, MS is not a Mendelian trait and risk of passing on MS is low. Evidence suggests that about 2% of those with MS will have affected children [241, 242]. Chapter 9 provides a detailed response to some of the most commonly encountered questions related to the evaluation and management of MS during pregnancy.

Conclusion

It is clear that pre-conception planning is ideal for all pregnancies and particularly important for women affected by neurologic disorders in which multiple issues may be at play. The key tenants to care include proper diagnosis of neurologic disease and optimal pre-pregnancy management of disease with history and physical, neuroimaging, or medications if necessary. Continued discussion of the risks and benefits to pregnancy as well as multidisciplinary collaboration for those with neurologic disease is paramount to providing education to patients and power for shared decision-making to make the best pre-conception plan.

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