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## Chapter 12

# Neuromuscular disorders in pregnancy

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### Abstract

Many neuromuscular disorders preexist or occur during pregnancy. In some cases, pregnancy unmasks a latent hereditary disorder. Most available information is based on case reports or series or retrospective clinical experience or patient surveys. Of special interest are pregnancy-induced changes in disease course or severity and likelihood for baseline recovery of function postpartum. Labor and delivery present special challenges in many conditions that affect skeletal but not smooth (uterine) muscle; so labor complications must be anticipated. Anesthesia for cesarean section surgery requires special precautions in many disorders. The types of conditions reviewed are broad and include examples of autoimmune, hereditary, and compressive/mechanical processes. Disorders include carpal tunnel syndrome and other focal neuropathies, Bell palsy, myasthenia gravis, and other neuromuscular junction disorders, acute and chronic inflammatory neuropathy, hereditary and acquired muscle diseases, spinal muscular atrophy, amyotrophic lateral sclerosis, channelopathies, autonomic neuropathy, and dysautonomia. Many commonly used therapies have fetal animal but no proven human toxicity concerns, complicating treatment and risk decisions. Weaning off effective therapeutic agents or preemptive aggressive treatment or surgery prior to planned pregnancy is an option in some conditions.

### INTRODUCTION

Numerous neuromuscular conditions develop or preexist in women of childbearing age. Some are immune or inflammatory disorders that may be influenced by pregnancy; processes can be incited, improved, or unaffected. Some of the most common and most important conditions are reviewed ([Sax and Rosenbaum, 2006](#); [Guidon and Massey, 2012](#); [Massey and Guidon, 2014](#); [Edmundson and Guidon, 2017](#)). Categories include focal and generalized neuropathy, neuromuscular junction disorders, acquired and hereditary muscle disorders, channelopathies, motor neuronopathies, and autonomic disorders. There are no rigorous studies to rely on with regard to most conditions; treatment advice is also often based on anecdotal case series or on retrospective chart data or patient survey. Many conditions cause difficulty

because of skeletal muscle but not uterine smooth muscle weakness that impacts labor and delivery. Decisions to wean or continue medication treatments are important considerations—most commonly used treatments have animal but no reliable human information on pregnancy safety. The FDA class for some examples is listed in [Table 12.1](#). However, the FDA removed this alphabet system effective mid-2015 in favor of a narrative summary of drug risks during pregnancy and lactation and discussion of the evidence. However, the category system is still referenced and useful to many physicians and patients. The new system was intended to be phased in by 2018, but that review process continues. Therefore, a combination of details is presented in this section. Some conditions, such as orthostatic intolerance or postural orthostatic tachycardia syndrome (POTS), are often paradoxically lessened during pregnancy.

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Table 12.1

**Pregnancy former US FDA category for commonly used neuromuscular disease treatments**

Drug	FDA category
Acetazolamide (Diamox)	C
Amifampridine (Firdapse)	NA
Azathioprine (Imuran)	D
Corticosteroids	D
Cyclosporine A	C
Dichlorphenamide (Keveyis)	C
Duloxetine (Cymbalta)	C
Eculizumab (Soliris)	NA
Edaravone (Radicava)	NA
Fludrocortisone	C
Gabapentin (Neurontin)	C
Intravenous immunoglobulin (IVIg)	C
Mycophenolate mofetil (CellCept)	D
Methotrexate	X
Nusinersen (Spinraza)	NA
Mexiletine	C
Midodrine (ProAmatine)	C
Pregabalin (Lyrica)	C
Pyridostigmine (Mestinon)	C
Riluzole (Rilutek)	C
Rituximab (Rituxan)	NA
Tramadol	C

US FDA category designations were removed June 2015 in favor of description and narrative discussion. However, the replacement system is incomplete, and these designations retain usefulness: (A) Adequate and well-controlled studies found no increased risk; (B) no risk found in animal studies but insufficient human studies; (C) adverse fetal animal studies but no adequate human studies; treatment benefits may warrant use despite potential risk; (D) evidence of human fetal risk based on studies or marketing experience but benefit may outweigh risk; and (X) animal or human studies or other experience find fetal abnormalities so that potential benefit in pregnancy is outweighed by risk. NA, not assigned.

**NEUROPATHIES****Focal neuropathy**

Pregnancy increases the risk of compression, stretch, or entrapment of various nerves. Median neuropathy at the wrist is most common. Delivery and labor and the postpartum period create additional conditional risk. Various conditions and syndromes are reviewed; Table 12.2 includes a listing.

**Carpal tunnel syndrome**

Median neuropathy at the wrist is the most common focal neuropathy—carpal tunnel syndrome (CTS) is the clinical correlate. Pregnancy is a well-known risk factor. Local edema and fluid retention caused by hormonal changes are implicated. Symptoms typically include

Table 12.2

**Neuropathies in pregnancy**

Condition	Type	Timing
Carpal tunnel syndrome	Focal	Third trimester but variable onset
Bell palsy	Focal	Any phase? PP
Obturator neuropathy	Focal	Delivery
Femoral neuropathy	Focal	Delivery
Lumbosacral radiculopathy	Root	Any phase
Fibular (peroneal) neuropathy	Focal	Delivery
Meralgia paresthetica	Focal	Any phase
Brachial neuritis/Parsonage Turner syndrome	Plexus	Any phase
Radial neuropathy	Focal	Delivery
Intercostal neuropathy	Focal	Any

PP, postpartum.

episodic, recurrent numbness and tingling in the fingertips of the first three digits, characteristically more at night. Nocturnal awakening that triggers hand shaking is highly characteristic. Thenar muscle weakness or atrophy occurs only in severe or untreated cases. Incidence varies considerably in published reports based on ascertainment methods. Hand symptoms are relatively common, affecting up to 60% of pregnant women, but some older estimates are much lower. The Italian CTS Study Group surveyed 76 women in their last trimester: 62% had a clinical diagnosis of CTS, but only 43% had a positive electrophysiologic diagnosis (Padua et al., 2001, 2002a). A common belief is that CTS exclusively occurs in the third trimester; however, symptoms and findings can occur at any stage including the postpartum period. Other risk factors include multiple births and age over 30 (Ekman-Ordeberg et al., 1987; Wand, 1990). Gestational diabetes was not a risk factor in one study (Turgut et al., 2001). Also, contrary to common belief, symptoms often improve but do not resolve after delivery but can develop or persist postpartum. Symptoms starting earlier in pregnancy are more likely to persist after delivery. One study noted frequent postpartum symptoms, but only 11% remained symptomatic at 6 months and 4% at 1 year (Turgut et al., 2001). However, a multicenter prospective Italian study found 50% remained symptomatic at the same timepoint (Pazzaglia et al., 2005). In some cases, lactation can trigger CTS symptoms that improve after weaning (Wand, 1990). Conservative nonsurgical treatments including neutral angle or 20 degrees cock-up wrist splinting or local steroid injections are often sufficient. One case of

prospective and multiple sequential nerve conduction studies during pregnancy found early onset and symptom resolution with conservative measures during pregnancy, but responses took between 6 and 20 months postpartum to return to baseline values (Weimer et al., 2002). Neuro-pathic pain medication is generally avoided during pregnancy. Severe or refractory cases can be considered for carpal tunnel release surgery, done under local anesthesia, especially earlier in the pregnancy or after delivery.

### Lumbosacral radiculopathy

Back pain is quite common during pregnancy and can be severe; about 50% of women are affected. Sciatica is much less common, occurring in approximately 1% (Ostgaard et al., 1991; Padua et al., 2002b). In one patient-reported symptom-based study, a male fetus and prior back pain were positive risk factors but prior pregnancy was not. Symptomatic root injury, producing sensory loss or weakness, however, is very uncommon—one older study estimated the incidence to be 1 in 10,000 pregnancies (LaBan et al., 1983). Pregnancy-related pelvic pain and sacroiliac-induced pain can mimic a radicular pattern. Exaggerated lumbar lordosis, direct uterine pressure, and hormonally induced ligamentous laxity are possible factors. Pain often improves after delivery but can persist postpartum. Treatment is generally conservative unless overt root injury develops. MRI scans are feasible in more severe cases. Successful and uncomplicated lumbar laminectomy is reported in refractory, severe cases (Ostgaard et al., 1991; Garmel et al., 1997; Ng and Kitchen, 2008). Neuropathic pain medications are generally avoided.

### Brachial neuritis (Parsonage Turner syndrome)

The risk of idiopathic or a rare hereditary form of brachial neuritis increases mostly in the postpartum period (Lederman and Wilbourn, 1996). Typically, severe shoulder or neck pain occurs without provocation. As the pain subsides, muscle weakness is noted; certain patterns are typical, including scapular winging and anterior interosseous neuropathy. Weakness is expected to slowly improve but recovery is sometimes incomplete. A rare hereditary cause of recurrent brachial neuritis, known as hereditary neuralgic amyotrophy, can be unmasked. A mutation in the SEPTIN9 (formerly SEPT9) gene is causative. One case of 11 in the Cleveland clinic series suggested that pattern (Lederman and Wilbourn, 1996).

### Meralgia paresthetica

Entrapment or injury to the lateral femoral cutaneous nerve produces sensory loss or paresthesia in the lateral

thigh known as meralgia paresthetica—the neuropathy produces purely sensory symptoms and no objective weakness. Weight change, compressive bands, low belts or constrictive garments are recognized risk factors. Hip hugger jeans are an example. The nerve is also vulnerable during hip flexion during delivery and by retractors during cesarean section surgery. Identification and behavior or garment changes can help. Neuropathic pain medications are avoided while pregnant.

### Femoral and obturator neuropathy

Femoral neuropathy rarely occurs during pregnancy. Rates of nerve injury have declined over time with refinements in obstetric care, such as better attention to prolonged lithotomy positioning (al Hakim and Katirji, 1993). One retrospective study found femoral neuropathy affected 0.3% of 6057 live births. Nerve injury causes isolated thigh and medial lower leg numbness (saphenous nerve), quadriceps weakness, and reduced or absent knee deep tendon reflex (Wong et al., 2003; Guidon and Massey, 2012). The iliopsoas muscle that controls hip flexion variably arises from the proximal femoral or distal lumbar plexus and may be affected. If hip adduction is also affected, a more proximal plexus or root injury is supported. Risk factors include primiparous women and prolonged labor. Recovery time depends on the severity of axonal injury but often takes weeks to months to improve (Rowland et al., 2019).

Obturator neuropathy is rare and primarily occurs during delivery. The nerve travels very deeply in the pelvis and innervates most of the hip adductors and a sensory patch on the medial thigh and occasionally in the upper medial calf. Obturator neuropathy can cause medial thigh numbness and pain and hip adductor weakness. Because of the deep position, injury is otherwise quite rare, except in severe trauma or infiltrative processes. During labor and delivery, the fetal head can compress the nerve against the pelvic wall; forceps can also cause injury. Prognosis is related to the degree of injury and nerve axonal loss. Electrodiagnostic studies can distinguish this neuropathy from radiculopathy, plexopathy or femoral neuropathy. However, obturator nerve studies are more challenging because of the deep location.

### Bell palsy

Bell palsy is an acute unilateral peripheral facial neuropathy that is typically idiopathic. Reduced lacrimation, hyperacusis, or loss of taste sensation may accompany facial muscle weakness. Involvement of the forehead muscle (frontalis) can help distinguish from central causes of facial asymmetry. The course may progress to maximum weakness over days, followed by recovery of some, if not all, functions over several months.

More severe cases develop complete paralysis. Most studies support an increased incidence in pregnancy, especially in the third trimester and immediate postpartum periods. The condition must be separated from central conditions that occur in late pregnancy or immediately afterwards; examples include ischemic or hemorrhagic stroke and venous sinus thrombosis. Bell palsy rates range from 3 to 6 times that of nonpregnant women of childbearing age. Hilsinger in 1975 reported rates of 45 and 17.4 per 100,000 in pregnant and nonpregnant women, respectively (Hilsinger et al., 1975). A more recent prospective Italian series found pregnancy to have an increased odds ratio of 5.4, compared to the general population, but only two pregnancy-related cases were included (Monini et al., 2010). Some reports suggest that pregnancy-associated facial neuropathy is more severe and more likely to be complete, leading to a worse prognosis. One retrospective study found about half of pregnant women with severe or complete facial paralysis significantly improved, compared to 80% of others (Gillman et al., 2002). In contrast, a very large and recent retrospective Korean study found no association with Bell palsy and pregnancy or postpartum periods (Choi et al., 2020). That study compared over 63,000 pregnancies to over 126,000 controls employing the national Korean Health Insurance Review and Assessment Service. The extrapolated annual incidence of Bell's palsy per 100,000 women during pregnancy was 43.4%, and in the control group, it was 80.2%; postpartum rates were 60.1% in the patient group and 50.6% in the control group.

Pathogenic mechanisms that may differ in pregnancy-related Bell palsy include altered immune tolerance, hormonal effects on fluid shifts, increased herpes simplex or varicella viral susceptibility, and vasa nervorum thrombosis (Hilsinger et al., 1975; Falco and Eriksson, 1989; Shmorgun et al., 2002). Risk factors include essential or gestational hypertension, preeclampsia, and obesity (Falco and Eriksson, 1989; Shmorgun et al., 2002). Not surprisingly, treatment considerations are more complicated. The American Academy of Neurology treatment guidelines concluded that corticosteroids are highly likely to be effective and should be offered in the acute setting (level A); antiviral agents may provide modest benefit (level C) (Gronseth et al., 2012). However, understandably, pregnant women were excluded from all studies considered for this consensus recommendation. Corticosteroids, including prednisone, are prescribed to pregnant women with Bell palsy and other conditions despite some concerns of fetal toxicity, especially at high dose. Prognosis is dependent on the degree of nerve injury; however, the facial nerve typically recovers better than most other peripheral nerves. One study found further evidence that facial neuropathy

is more severe in pregnancy-associated cases despite corticosteroid treatment (Phillips et al., 2017). Antiviral treatments are more controversial given the unproven benefit. One Danish study found no increase in birth defects in a large cohort of women exposed to acyclovir, valacyclovir, and famciclovir, compared to other pregnant women in the first trimester (Pasternak and Hviid, 2010). Eye patching or lubricating drops and nocturnal ointment should be used in cases of severe eye closure weakness to prevent ocular dehydration injury.

### Miscellaneous other focal neuropathies

Fibular (peroneal) neuropathy causing acute foot drop must be distinguished from acute L5 radiculopathy or lumbosacral plexopathy. Nerve stretch can occur due to several factors, including prolonged squatting during childbirth, external compression by inappropriate stirrup leg positioning, or hyperflexion of the mother's knees (Babayev et al., 1998; Wong et al., 2003). Prognosis for recovery is generally good unless the nerve injury is severe. A rare condition, hereditary neuropathy with tendency for pressure palsy caused by a deletion of the PMP22 gene—the same gene that causes Charcot-Marie-Tooth (CMT) type 1A discussed later—is particularly vulnerable to fibular neuropathy and related foot drop.

Radial neuropathy was reported in two unusual situations. One case was attributed to compression from prolonged use of a birthing bar (Roubal et al., 1996); another case was caused by a compressive synovial cyst that required surgical intervention (Hsiao et al., 2018).

Intercostal neuropathy causing isolated pain and numbness in a thoracic dermatome is described sometimes as thoraconeuralgia gravidarum or intercostal neuralgia (Pleet and Massey, 1980; Skeen and Eggleston, 1999). The condition is said to spontaneously improve or resolve—autoimmune or inflammatory causes similar to brachial neuritis are suspected.

### Generalized neuropathy

Pregnancy does not specifically cause generalized or polyneuropathy. Most forms of polyneuropathy affect the longest nerves exclusively or more severely, leading to the stocking-glove distribution. Most neuropathy cases affect sensory more than motor fibers. There are many exceptions that include disproportionate sensory ataxia, weakness, or asymmetry. The exceptions are often caused by inflammatory or immune mechanisms. Glucose intolerance and gestational diabetes can signal the start of longstanding blood sugar issues and later diabetic neuropathy. Autoimmune or inflammatory conditions in general may change during pregnancy—both

flares or transient improvement are described, depending on the condition. Selected inflammatory, hereditary, and other conditions are considered.

### **GUILLAIN-BARRE SYNDROME (GBS)**

Acute inflammatory demyelinating polyneuropathy or GBS is an acute or subacute onset of ascending weakness, sensory loss, and areflexia—a nadir by definition occurs within 4 weeks after onset. Incidence is about 0.75–2 cases per 100,000 population. Patients may progress to severe weakness or paralysis. Facial, cranial, and autonomic nerve involvement occur in severe cases that can progress to respiratory insufficiency, autonomic instability, and protracted recovery. There is no evidence that the condition is more common during pregnancy, but many pregnant women develop GBS by coincidence, usually in the second and third trimesters. However, incidence seems to be about three times higher in the 30 days postpartum (Chan et al., 2004). Before the advent of immune treatments, such as intravenous immunoglobulin and plasmapheresis, significant morbidity and mortality occurred in pregnant women with GBS (Chan et al., 2004). Typical infectious triggers such as *Campylobacter jejuni* gastroenteritis occur but may be less common in pregnant women (Rees et al., 1995). Cytomegalovirus (CMV), a known GBS trigger, seems to more problematic. Pregnant women have a similar underlying seropositivity to the general population, roughly 10%; however, mothers with CMV and GBS may have more severe respiratory involvement and worse neonatal outcomes (Araki et al., 2010; Lupo et al., 2016). Some advocate testing all pregnant women with GBS for CMV. Zika virus is associated with increased GBS risk (Krauer et al., 2017; Muñoz et al., 2017). A systematic review of Zika-related complications during pregnancy found one report of a pregnant woman with confirmed Zika infection who developed GBS at 28 weeks gestation; she recovered and delivered a healthy infant (Chibueze et al., 2017). An association of GBS to the novel coronavirus COVID-19 is suspected but not yet established.

Standard treatment using either plasmapheresis or intravenous immune globulin (IVIg) is generally safe; significant treatment-related complications are rare. Both are effective. Some prefer to avoid plasmapheresis because of fluid shifts that can trigger hypotension and potentially endanger the fetus. A large Italian series reviewed plasmapheresis complications of 936 procedures during 57 pregnancies; treatment indications were various and included some for myasthenia gravis (MG). They found only 2% had significant adverse events; none required hospitalization or extended ongoing hospitalization (Colpo et al., 2019). Fewer risks and complications are present

for IVIg during pregnancy but concerns include volume overload, hyperviscosity, and hypercoagulability. Termination of pregnancy does not shorten GBS disease duration or improve maternal outcome (Chan et al., 2004). Interestingly, cases that progress to complete paralysis continue to demonstrate normal fetal movements, supporting a lack of placental transmission of the causative factors in most cases. One notable exception reported hypotonia and respiratory distress in a newborn that received successful treatment of both mother and child (Luijckx et al., 1997). GBS does not significantly affect uterine contractility so that vaginal delivery remains the preferred route. Epidural anesthesia is considered to be generally safe in this setting, though one case of acute worsening was reported (Brooks et al., 2000; Wiertelowski et al., 2004). Succinylcholine should be avoided for cesarean section induction (Brooks et al., 2000). Induced preterm delivery is common—35% in one large series—mostly because of maternal neurologic decline (Chan et al., 2004). The need for cesarean section surgery should be based on obstetric indications. Prevention of complications from infection and venous thromboembolism is critical, especially in the postpartum period.

### **CHRONIC INFLAMMATORY, DEMYELINATING IMMUNE NEUROPATHIES**

Chronic inflammatory demyelinating neuropathy (CIDP) of various subtypes causes proximal and distal weakness, sensory loss, and reduced deep tendon reflexes; most forms are relatively symmetric but an asymmetric form is well known. The syndrome is distinct from GBS but many features overlap. The course may be relapsing or progressive; immune treatments are typically highly effective. Onset is most common between 40 and 60 years, but onset also occurs in younger ages, including in childhood and teenage. CIDP in pregnancy is uncommon but described. One study reviewed 61 women of childbearing age with CIDP; 9 became pregnant. Of these 9, 4 developed CIDP during pregnancy, and the disease flared in the other 5 with—the authors concluded that CIDP risk increases during pregnancy (McCombe et al., 1987). A tendency for symptoms to worsen during the third trimester or during the immediate postpartum period was noted. Corticosteroids can be used in CIDP but are often not necessary. Steroid-sparing therapies such as azathioprine (category D) are generally avoided during pregnancy. Plasmapheresis can be used for refractory cases.

Multifocal motor neuropathy (MMN) is a separate and distinct syndrome that causes chronic and multifocal, typically distal weakness in specific nerve territories. A minority of cases are associated with GM1 ganglioside IgM antibodies. Conduction block is demonstrated on electrodiagnostic testing in many. Intravenous immunoglobulin is the preferred and FDA-approved therapy.

Exacerbation of existing weakness or new weakness is known to occur during pregnancy despite treatment; findings generally return to baseline after delivery (Chaudhry et al., 2002). IVIg is generally continued during and after pregnancy. Corticosteroids and plasmapheresis are contraindicated in this disease. One case of suspected transplacental transfer of pathogenic GM1 ganglioside antibodies was reported (Attarian et al., 2004). The mother had MMN and underlying IgG $\lambda$  monoclonal gammopathy. The fetus had decreased movement; the infant had distal weakness and hyporeflexia; and weakness and atrophy persisted at age 4 years.

### HEREDITARY NEUROPATHY AND CHARCOT–MARIE–TOOTH DISEASE

Hereditary motor and sensory neuropathy also known as CMT is a prevalent condition affecting roughly 1 in 2500 individuals. Many subtypes and specific genetic forms are known but CMT1A, caused by a duplication of the PMP22 gene is by far most common. That condition causes progressive distal weakness, areflexia, pes cavus, and associated orthopedic issues. Onset is generally in the teens or soon afterwards so that the condition is often known prior to pregnancy. Penetrance is variable. Autosomal dominant inheritance is most common, though X-linked and recessive forms are known. Data on pregnancy effects are sparse. In general, CMT patients demonstrate no increased risk of miscarriage, fetal malformations, or hypertensive complications. About 50% of patients self-report worsened weakness while pregnant that tends to improve in about a third and not improve or worsen in others afterwards (Rudnik-Schöneborn et al., 1993; Awater et al., 2012). Women with CMT have a higher occurrence of presentation anomalies and postpartum bleeding (Hoff et al., 2005). The rate of operative delivery or forceps requirement was 2–3 times more frequent than for others. The majority of CMT cesarean sections were emergencies. Epidural anesthesia is employed when needed. Succinylcholine should be avoided if intubation is needed because of concerns that it may induce hyperkalemia. Most other forms of hereditary neuropathy are too rare or severe to have sufficient pregnancy data.

## NEUROMUSCULAR JUNCTION DISORDERS

### Myasthenia gravis (MG)

#### OVERVIEW

The autoimmune condition MG causes fluctuating and fatigable muscular weakness—bulbar muscles are particularly vulnerable. Ptosis, diplopia, dysarthria, and dysphagia are common manifestations. Ocular myasthenia

is the term used for isolated ptosis and diplopia but without any other impairment. More severe cases demonstrate muscle weakness, notably proximal. Myasthenic crisis is characterized by severe weakness, severe dysphagia, aspiration, and respiratory insufficiency that requires urgent or emergent intervention. The majority of cases, up to 80%, demonstrate antibodies to the alpha subunit of the nicotinic acetylcholine receptor (binding antibodies). Additional cases are associated with muscle-specific kinase (MuSK), agrin, or lipoprotein receptor-related 4 IgG (LRP4) antibodies. The remainder of cases supported by clinical and electrodiagnostic features are seronegative, roughly 10%. The overall incidence estimates range from about 3 to 40 per 100,000 (MacDonald et al., 2000); an estimated excess of 700,000 people worldwide are affected (Sanders et al., 2016). A bimodal age distribution is well documented but is, overall, more common in women. Women of childbearing age constitute one large spike peaking in the second and third decades; older men make up the other group, who more often have an underlying thymoma. As a result, pregnancy and MG are a relatively common cooccurrence. Congenital myasthenic syndromes are rare genetic defects affecting components of the neuromuscular junction, nerve terminal, or muscle. These conditions are quite rare and distinct from autoimmune MG. Transient neonatal MG is a relevant topic discussed later.

#### PREGNANCY EFFECTS ON DISEASE SEVERITY

Pregnancy-induced disease severity alterations and treatment adjustments are important clinical considerations; a multidisciplinary medical approach that includes an obstetrician and neurologist is best (Norwood et al., 2014). Infections, stress, hormonal fluctuations, fatigue, medications, and surgery can influence MG disease activity—all can occur during pregnancy. Most women with controlled MG have successful delivery and minimal disease alternations. However, pregnancy effects on disease activity are unpredictable. Even previously pregnant MG patients can experience disease differences in later pregnancies. More severe or refractory cases may plan to avoid pregnancy, especially if treatment cessation is considered or potentially teratogenic medications are required for disease control. Milder cases show lower risk of crisis. Mild or ocular disease has the highest risk of generalization in the initial year or two after disease onset. Waiting for conception until the disease course is recognized is a common approach. Several series retrospectively reviewed MG disease alterations during pregnancy (Batocchi et al., 1999; Djelmis et al., 2002; Braga et al., 2016; Ducci et al., 2017). In general, 30%–50% of patients worsened during pregnancy; about

15% of mildly affected patients became relatively severe. About 30% paradoxically improved, and the remainder did not change. Exacerbations tended to be early or late in the course, though one review found the second trimester most critical (Ducci et al., 2017); alterations within 2 months postpartum were also noted. In the same review, transient neonatal MG occurred in 12.9% of live-born infants—no predictors were found.

MG associated with MuSK antibodies demonstrates some clinical and treatment differences. The entity represents about 5%–8% of MG cases overall. African Americans and women overrepresent with MuSK, compared to other MG forms. Onset in women tends to be slightly later than AChR seropositive patients, peaking in the 40s but still overlapping with childbearing age. Patients tend to demonstrate more proximal limb, bulbar, and ocular weakness but typically do not have purely ocular disease; tongue atrophy, muscle cramping, and twitching can occur. Respiratory involvement and disease crises are a risk. One Portuguese series retrospectively examined the pregnancy course in 17 MuSK positive women, of which 13 had more than one pregnancy (27 total pregnancies studied) (Santos et al., 2018). All were on steroids at the time of conception, one on azathioprine and another on IVIg maintenance infusions. Only mild pregnancy-induced changes were noted, but some required medication titration. No changes were considered to be relapses.

MG onset during pregnancy is also well described. Seropositive patients with typical symptoms and signs are straightforward to diagnose, but treatment options are narrowed. Seronegative patients may require additional testing such as repetitive nerve stimulation or single fiber electromyography to confirm the diagnosis, in part to consider treatment and to guide delivery management. To assess for thymoma, an increased risk in MG patients, a chest CT is typically the care standard. During pregnancy, a chest MRI may be indicated depending on the pregnancy stage; if late in pregnancy, the study is often deferred until after delivery.

## MG TREATMENT

The treatment of MG is more complex than other neuromuscular disorders, in part because so many effective therapeutic options are available. Family planning in known MG patients should be proactive so that treatments can be optimized or tapered prior to conception. Counseling in advance is prudent, including the risks for individual ongoing and potential therapies. Thyroid status should be addressed and optimized prior to pregnancy. Some options are strictly contraindicated, but many have limited available medical evidence for pregnancy risks. Pyridostigmine (Mestinon) is an initial and effective treatment for all MG stages. It has been used for

decades. Because of pregnancy-induced changes in intestinal absorption and renal clearance, the pyridostigmine dose may need titration. No fetal risk is known despite longstanding use in pregnancy. Prednisone or prednisolone is typically continued during pregnancy. Corticosteroid risks are discussed earlier, but an optimized dose prior to pregnancy is prudent. Some early studies suggested steroids increased cleft palate risk, but later case-controlled studies did not replicate the findings. Treatment can also suppress normal adrenal output so that stress steroids may be needed during labor and delivery to avoid acute adrenal insufficiency. In general, initiating a new steroid-sparing agent is avoided, if possible, by most practitioners. Azathioprine (Imuran) is the most common steroid-sparing agent. The agent, previously rated Category D by the US FDA, is generally avoided in the United States primarily because of teratogenic effects in laboratory animals and reported hematologic effects in some newborns. Because of this concern, use during pregnancy is rare in the United States. However, azathioprine remains a recommended option in Europe (Norwood et al., 2014), mostly based on experience treating various rheumatologic conditions (Ostensen et al., 2011) and using similar agents such as 6-mercaptopurine to treat inflammatory bowel disease (Francella et al., 2003). No detectable drug was found in neonates of breastfeeding mothers who had been treated (Sau et al., 2007). Because of some ongoing use during pregnancy, this drug and others discussed are part of a National Transplantation Pregnancy Registry to track effects. A recent meta-analysis including a large cohort of contributors concluded that available human studies are lacking to answer the question of azathioprine exposure risk during pregnancy (Belizna et al., 2020). Mycophenolate mofetil (CellCept) was initially classified as category C but was downgraded to category D in 2007 prior to elimination from the FDA rating system in 2015; birth defects and serious teratogenic concerns during pregnancy were recognized. A typical clinical syndrome includes hypoplastic nails, shortened fifth fingers, diaphragmatic hernia, microtia, micrognathia, cleft lip and palate, and congenital heart defects—quoted risk is as high as 25% (Sifontis et al., 2006; Ostensen et al., 2011; Norwood et al., 2014; Perez-Aytes et al., 2017). In general, treatment is tapered off prior to pregnancy. Calcineurin inhibitors such as cyclosporin or tacrolimus are occasionally used to treat MG and show no known teratogenic effects, but there is some concern for spontaneous abortions, prematurity, and low birth weight; the agent may also aggravate gestational diabetes. Methotrexate is strictly contraindicated during pregnancy (former category X).

Thymectomy is demonstrated to benefit MG course, reduce steroid dosage, and increase remission likelihood;



the benefit persists for multiple years (Wolfe et al., 2016, 2019). Thymectomy during pregnancy is rarely indicated unless a benign or malignant thymoma is discovered. Because of the long-term potential benefit, surgery prior to a planned pregnancy is a consideration in generalized seropositive MG patients. MG crisis or inadequate steroid control may require rescue or more aggressive treatment. For MG crisis both plasmapheresis and IVIg are indicated. The risks for each were reviewed earlier with reference to GBS treatment. Clinical use for maintenance therapy with IVIg has steadily increased, but MG is not an indication recognized by the US FDA, so that use is technically off-label. Rituximab (Rituxan) is an option in refractory seropositive MG, especially for MuSK positive cases. Treatment is generally considered to be safe despite some animal toxicity concerns. The newest and most expensive treatment option is the humanized anti-C5 antibody, eculizumab (Soliris). Treatment is reserved for refractory seropositive MG patients that are uncontrolled despite all other options, including IVIg and plasmapheresis. Pregnancy risk information is limited. However, usage is currently generally regarded to be safe (Sarno et al., 2019). Experience from use in various hematologic conditions is available, mostly hemolytic uremic syndrome. Vaccination for meningococcal meningitis is required prior to treatment. Some differences are evident in MuSK MG patients. Pyridostigmine is less often helpful. The course tends to be less responsive to IVIg, but that treatment is still used. Patients often respond to plasmapheresis. MuSK positive patients were specifically excluded from thymectomy trials. In addition, a lack of benefit is generally accepted, so surgery is not indicated for these patients. Agrin and LPR4 seropositive patients seem to respond to treatment similar to AChR positive patients.

### MG labor and delivery

Ongoing prenatal care, including fetal monitoring is expected. Spontaneous delivery at term is the goal, provided there is no deterioration in the mother's myasthenic control (Norwood et al., 2014). Of all potential labor and delivery difficulties, only premature membrane rupture is more common. Infection-induced disease flares are a concern, notably urinary tract infections, especially in women on immune suppression. Infections should be treated; however, aminoglycosides, fluoroquinolones, and macrolides can aggravate the condition. For delivery, conventional epidural or spinal is accepted and preferable to general anesthesia, including women that need cesarean section (C-section). Opiates should be avoided because of potential respiratory depression in mother or fetus. Calcium channel blockers and  $\beta$ -blockers are also generally avoided. Stress steroids

for women on ongoing steroid therapy were previously discussed. MG affects skeletal muscle and not smooth muscle uterine contractions, so that impairment in early labor stages is not expected. Mothers can fatigue in later stages so that assisted delivery may be needed. In one study C-sections were more common in MG patients, but assisted vacuum or forceps deliveries were no more common (Hoff et al., 2003); another Taiwanese study found no difference in C-section rates between MG patients and others (Wen et al., 2009). Magnesium sulfate is generally avoided for eclampsia prevention because of potential interference with calcium influx in the nerve terminal and aggravating acetylcholine release. One case of severe magnesium-induced muscular weakness in a previously minimally affected patient was reported (Bashuk and Krendel, 1990). If eclampsia-induced seizures develop, magnesium sulfate can be given with extreme caution but intubation is expected. Appropriate anticonvulsants can be used instead. If a C-section is required, general anesthesia presents potential concerns. Typical intubation utilizes a muscle relaxer, such as succinylcholine. MG patients are particularly sensitive to these agents; so they should be used at low dose or not at all. If needed, a peripheral nerve stimulator must be used to monitor the effect. Other agents to initiate or maintain anesthesia, such as propofol and volatile anesthetics, are used. Despite these delivery concerns, there is no evidence of increased rates of premature birth, reduced birth weight, congenital malformations, or infant mortality (Hoff et al., 2003; Wen et al., 2009; Guidon and Massey, 2012). Breast feeding is not contraindicated, including for women on active immune therapies.

### TRANSIENT NEONATAL MG

Transmission of antibodies to newborns is well recognized; this can transiently complicate functions. Hypotonia, dysphagia, and respiratory difficulties are most concerning—other findings include ptosis, eye muscle weakness, and other bulbar weaknesses. The incidence of transient neonatal MG ranges from 10% to 30%, depending on the series, though most infants demonstrate transient antibodies in seropositive mothers. Because the mother's MG disease severity seems to bear no predictive value for this entity, neonatologists must screen newborns carefully. In some cases, transplacental passage of antibodies occurs, resulting in reduced fetal movement and postnatal weakness. There are some exceptional cases of antibodies to the fetal AChR  $\gamma$  subunit that can result in severe or sometimes fatal fetal arthrogryposis (Vincent et al., 1995; Oskoui et al., 2008). This form is now known as fetal AChR inactivation syndrome (D'Amico et al., 2012).

AChR seropositive MG is commonly associated with transient neonatal MG; however, other forms, notably MuSK patients, have been reported. A case of a 27-year-old woman with purely ocular symptoms and a negative evaluation including AChR antibodies, repetitive nerve stimulation and single fiber electromyography has been reported (Lee et al., 2017). She delivered a normal infant who quickly developed hypotonia and respiratory failure requiring mechanical ventilation for 3 weeks. The mother later worsened, and MuSK antibodies were uncovered on further evaluation. Anti-MuSK-mediated transient neonatal MG was presumed. This form appears to be less common but more severe (Niks et al., 2008).

### LAMBERT–EATON MYASTHENIC SYNDROME (LEMS)

Autoimmune Lambert–Eaton myasthenic syndrome (LEMS), not from a lung cancer associated paraneoplastic syndrome, can occur in women of childbearing age. Three notable cases have been reported. One patient had an uncomplicated, successful delivery; another had a child with a week of severe neonatal weakness and infant voltage gated calcium channel antibody seropositivity (Schneider-Gold et al., 2006; Reuner et al., 2008). Another previously asymptomatic woman developed third trimester weakness that led to a new LEMS diagnosis (Bayrak et al., 2010). The only FDA-approved therapy amifampridine (Firdapse), previously known as 3,4-diaminopyridine, is highly effective and, often, transformative for affected patients. The drug is associated with fetal animal toxicity but no documented human pregnancy-related concerns.

## MUSCLE DISORDERS

### Inflammatory myositis

Autoimmune forms of myositis are uncommon, representing about 0.5–2 cases per 100,000 population (Munira and Christopher-Stine, 2020). The most common forms, polymyositis and dermatomyositis cause symmetric proximal limb weakness, variably increased creatine kinase, and sometimes dysphagia, head drop, or respiratory compromise. The pathophysiology differs between the two. Polymyositis is almost always a component of a generalized rheumatologic or systemic condition, such as mixed connective tissue disease, systemic lupus erythematosus, or rheumatoid arthritis; some have antisynthetase syndrome. Dermatomyositis is distinct and manifests as variably impacted muscular and characteristic skin manifestations. Muscle pathology shows differing and distinctive features. Both occur during childbearing ages. In general polymyositis tends to have more severe weakness, but most pregnancy-related literature lumps the two conditions. Sporadic inclusion body

myositis is often classified in this group but is not a simple autoimmune condition and almost always occurs after age 50; so that entity will not be discussed further. Necrotizing myositis is a more aggressive and severe form that requires aggressive immune treatment. Fortunately, the combination of necrotizing myositis and pregnancy is rare. Pregnancy does not appear to affect disease activity for the mother. However, disease activity and general health of the mother greatly impacts fetal risk. Patients with controlled disease or remission have low risk of complications and generally good outcomes for both mother and child. In contrast, active disease is associated with increased fetal mortality, low birth weight, and prematurity (Silva et al., 2003; Vánca et al., 2007; Nagy-Vincze et al., 2014; Zhong et al., 2017; Che et al., 2020). A large and recent retrospective series from India reviewed 24 pregnancies resulting in only 6 live births, though some were voluntarily terminated (Gupta et al., 2019). Mothers also have longer hospital stays, more hypertensive complications, and higher C-section rates but no other labor or delivery complications (Kolstad et al., 2018). Neither condition is transmitted to the newborn but interestingly, two asymptomatic newborns were noted to have elevated creatine kinase levels for a few months (Messina et al., 2002). Initial disease onset during pregnancy is rare, but that group may have the highest infant mortality, nearing 100% (Silva et al., 2003; Munira and Christopher-Stine, 2020).

Similar to MG patients, uterine smooth muscle is unaffected but voluntary muscles necessary for labor can fatigue, requiring C-section in some cases. Transient spikes in creatine kinase can indicate muscle breakdown after excessive muscular activity. Treatment considerations during pregnancy are similar to MG. Corticosteroids are the mainstay of treatment. IVIg can be used in refractory patients (Williams et al., 2007; Nozaki et al., 2008; Linardaki et al., 2011). Other usual immune therapies or steroid-sparing agents are highly problematic and discussed earlier, such as azathioprine (category D), methotrexate (category X), mycophenolate (category D), and cyclophosphamide (category D). In refractory cases, severe disease may require aggressive treatment. One was a case of a 30-year-old woman with myositis associated with antineutrophil cytoplasmic antibody. She was in remission on a combination of oral prednisone and rituximab every 6 months that was stopped prior to a planned pregnancy. Treatment was restarted at 16 weeks gestation without complication, despite concerns for rituximab treatment later in pregnancy increasing the risk of neonatal B-cell depletion and cytopenia (Mehta et al., 2019). Similar to other autoimmune diseases, patients on prednisone at the time of delivery should be treated with stress steroids to prevent acute adrenal insufficiency (Briemberg, 2007).

## Inherited muscular disorders

Hereditary and genetic entities represent a higher percentage of muscle disorders than most other areas of neurology. A variety of types of conditions that impact pregnancy are considered in this chapter. There are too many individual conditions to address all, but some groups are detailed.

### Muscular dystrophy

Dystrophinopathies caused by multiple different mutations or deletions in the dystrophin gene are the most common form of muscular dystrophy. Both Duchenne and Becker Muscular dystrophy are X-linked disorders that overwhelmingly affect males. However, female carriers can manifest symptoms and signs (Ishizaki et al., 2018). Information on pregnancy and delivery of these symptomatic patients, however, is very limited.

Myotonic muscular dystrophy is the second most common muscular dystrophy and most common starting in adulthood. Prevalence is 3–5 per 100,000 (Guidon and Massey, 2012).

Myotonic dystrophy type I (DM1) is a multisystem disease caused by an excess of CTG repeats in the dystrophin myotonia protein kinase (DMPK) gene. The number of repeats correlates with disease severity and onset age. Typical symptoms include muscle weakness, cramps and stiffness (myotonia), cardiac conduction delay, endocrine dysfunction, and early cataracts. Of note, mothers with this condition often have children with more severe disease and expanded repeats that can present in infancy (anticipation). In that instance, the term congenital myotonic dystrophy is employed—the risk for affected mothers is approximately one-third (Rudnik-Schöneborn and Zerres, 2004; Johnson et al., 2015). Congenital DM1 is quite severe and includes respiratory insufficiency, hypotonia, generalized weakness, poor feeding, and mental retardation. Only 75% live to 18 months, and 50% reach adulthood. Congenital arthrogryposis can occur because of severe prenatal weakness. One study of 31 women found 39% were unaware of the diagnosis prior to discovery of the affected infant, and fewer were aware of their diagnosis prior to pregnancy (Rudnik-Schöneborn and Zerres, 2004). Obstetric complications of various types were increased. A registry-based review of 375 pregnancies of 152 women with DM1 found a 33% miscarriage rate and various delivery complications, including preterm labor (28%), preeclampsia (10%), and peripartum hemorrhage (14%) (Johnson et al., 2015). Polyhydramnios due to reduced fetal swallowing is a prime cause attributed to the premature labor and delivery. Many women reported disease progression that did not return to the

prior baseline during pregnancy. Despite the overt clinical myotonia, that phenomenon often needs no specific treatment. In contrast to other discussed muscular conditions, smooth muscle including uterine contractions are affected, so that assisted delivery may be needed and hemorrhage risks increased (Sax and Rosenbaum, 2006). The tocolytic ritodrine used to arrest labor is reported to cause rhabdomyolysis, but that agent is no longer available in the United States but is used in Japan (Ogoyama et al., 2017). Depolarizing muscle relaxants are avoided because of the risk of triggering severe and dangerous myotonic spasms. Spinal block and epidural anesthesia have been successfully used; general anesthesia should be avoided if possible (Hopkins et al., 2014). Despite these concerns a series of DM1 patients that underwent general anesthesia for other surgeries found no instances of malignant hyperthermia (MH) or problematic spasms (Mathieu et al., 1997). However, case reports of both complications are known (Edmundson and Guidon, 2017).

Myotonic dystrophy type 2 (DM2), previously known as proximal myotonic myopathy (PROMM), is an autosomal dominant multisystem disorder whose clinical manifestations resemble DM1 but often starts at later ages. Proximal weakness, early cataracts, and myotonia are present but as lesser systemic features. A different repeat sequence (CCTG) of the zinc finger protein 9 (ZNF9) gene is causative. Anticipation is not prominent. A congenital form is not described. Retrospective data from 96 pregnancies in 42 women with DM2 found that previously pregnant women had symptom onset at an earlier age than the general population of men and other women (Rudnik-Schöneborn et al., 2006). Of 96 pregnancies, 13% ended early and 4% as late miscarriages. Roughly 20% had initial symptoms during pregnancy and symptomatically worsened in later pregnancies.

### Other myotonic disorders

Although not muscular dystrophies, there are several hereditary conditions that have prominent myotonia and some similar delivery recommendations. Autosomal dominant (Thomsen disease) and autosomal recessive (Becker disease) are forms of myotonia congenita caused by mutations in a muscle chloride channel (CLCN1). Both have prominent and symptomatic myotonia and abundant myotonic discharges on electromyography. Mild weakness may be present more commonly in the more severe and recessive Becker disease. Paramyotonia congenita is another related condition characterized by either paralysis spells or myotonia, most commonly caused by a sodium channel defect (SCN4A). Labor and delivery concerns are much less than for myotonic dystrophy (Lacomis et al., 1999). Myotonic symptoms

can worsen during pregnancy (Gorthi et al., 2013). Cold is a prominent myotonia trigger; one case of cold inducing a spontaneous abortion was reported in a mother with paramyotonia congenita (Chitayat et al., 1988). Similar precautions as for myotonic dystrophy are important for medications and anesthesia concerns. Mexiletine, a common medication used to treat symptomatic myotonia, may be stopped during pregnancy if possible.

### Facioscapulohumeral muscular dystrophy

The third most common muscular dystrophy is the autosomal dominant condition, facioscapulohumeral muscular dystrophy (FSHD). Prevalence is approximately 4–12 per 100,000; however, many patients are minimally symptomatic or asymptomatic. Unlike many hereditary conditions, weakness is often asymmetric or selective. Facial, shoulder girdle, and proximal arm and foot dorsiflexion weakness are common. Weak abdominal muscles can impact labor. Contraction of D4Z4 repeats in the double homeobox protein 4 (DUX4) on chromosome 4 is causative and represents 95% of cases. A second form accounting for the remainder of cases is linked to a similar process on chromosome 18 (type 2 FSHD). Males are more symptomatic; so some women of childbearing age are unaware of their diagnosis. A survey of 38 women with FSHD reported 105 pregnancies and 78 live births (Ciafaloni et al., 2006). Only about half knew their diagnosis prior to pregnancy. Records found that outcomes were generally favorable, but birth weight was lower, instrument delivery rates higher, and C-section rates higher than the general population. One quarter noted increased weakness during pregnancy that did not resolve postpartum. Miscarriage, preterm labor, and adverse neonatal outcome rates were not increased. Another series included 11 FSHD patients; 3 reported symptom aggravation that resolved after delivery (Rudnik-Schöneborn et al., 1997). Rapid prenatal diagnosis of D4Z4 repeat numbers was reported (Zheng et al., 2020).

### Limb girdle muscular dystrophy and congenital myopathies

A multitude of additional inherited muscular diseases are known resulting from mutations of several dozen different genes. In general, muscular dystrophy is used for progressive conditions. Congenital myopathy is employed for conditions that have distinctive neuropathology and static or very slowly progressive weakness. Most have proximal arm and leg weakness but few other distinctive features. Autosomal recessive forms are most common (LGMD type 2). Type 1 LGMD is autosomal dominant and often associated with allelic disorders. One series included 9 LGMD patients and 12 live births

(Rudnik-Schöneborn et al., 1997). No miscarriages or preterm births were noted. Five had prolonged labor that required assisted vaginal delivery or C-section. All infants were normal except one that had a likely unrelated neural tube defect. Over half noted increased weakness during pregnancy that did not recover but many attributed that change to expected disease progression. The majority needed more family assistance for child care but retained a positive attitude for the pregnancy. The same series included 7 women and 17 pregnancies in patients with congenital myopathy of various forms. The small numbers make conclusions problematic, but findings were similar to the LGMD patients (Rudnik-Schöneborn et al., 1997). Additionally, some forms of congenital myopathies, such as multimincore myopathy and central core disease, have an increased risk of anesthesia-induced MH. During delivery, halogenated inhaled anesthetics and succinylcholine must be avoided, and monitoring must be more detailed. Dantrolene can be used to treat MH associated with C-section. If the diagnosis is known, additional information about individual genetic conditions or even the specific mutation should be sought prior to delivery.

### Metabolic myopathies

Additional conditions related to lipid, carbohydrate, or mitochondrial metabolism can produce specific muscle disorders. Either fixed or exercise-induced weakness depends on the disorder. Fixed or exercise-induced weakness can occur depending on the specific disorder. Myophosphorylase deficiency (McArdle disease) characterized by autosomal recessive inherited bouts of myoglobinuria, is one of the most common conditions. Two case reports noted no specific pregnancy or delivery issues other than one exercise-induced bout of myoglobinuria during the first trimester; both deliveries were successful (Cochrane and Alderman, 1973; Giles and Maher, 2011).

Acid maltase disease (Pompe disease) is caused by  $\alpha$ -glucosidase deficiency; enzyme replacement therapy is well established for this disease. Fixed weakness starting at variable ages, ranging from early childhood to the old age, is characteristic. There are a growing number of reports detailing successful pregnancies during ongoing enzyme replacement (Kłos et al., 2017; Santos et al., 2018; Van Houtte and De Bleecker, 2019). No specific complications were noted. Treatment was interrupted during the first trimester in one case because of organogenesis toxicity concerns, but the mother's weakness progressed and treatment resumed (Zagnoli et al., 2013). A European consensus panel recommended that treatment should be continued during pregnancy (van der Ploeg et al., 2017).

## Mitochondrial encephalomyopathies

Mitochondrial encephalomyopathies are relatively rare, but some published experience during pregnancy in some syndromes is available. Multiple syndromes are known and caused by various underlying genetic defects, including mitochondrial genome mutations or deletions or somatic mutations—overall prevalence is about 1 in 4000. Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) is a discrete but rare multisystem disorder caused by various mitochondrial gene mutations. Onset of myopathy and neuropathy symptoms during pregnancy led to the initial diagnosis in one case (Yanagawa et al., 1998). Severe worsening in one case included severe pulmonary edema, intensive care needs, and fetal demise at 23 weeks (Sánchez and Romero, 2010). A European survey of 46 women with the most common m.3243A>G MELAS mutation reported on 98 pregnancies (de Laat et al., 2015). Results listed 25% preterm delivery (5% prior to 32 weeks), 12% preeclampsia, and 11% gestational diabetes. Deficiency of cytochrome oxidase can cause myopathy and weakness; severely reduced maternal strength to the point of immobility was noted in one patient. Despite this risk others advocate to attempt vaginal delivery (Blake and Shaw, 1999; Soccio et al., 2001). A survey of women with various mitochondrial disorders included 103 women who were pregnant at least once (370 pregnancies and 248 live births) (Karaa et al., 2019). One-third had myopathy. Overall, some increases in common obstetric complications occurred as expected but there was no notable worsening of fetal outcomes, other than various congenital anomalies.

### Periodic paralysis

Several forms of channelopathies causing intermittent bouts of paralysis are known. Hypokalemic periodic paralysis bouts can be severe—triggers include carbohydrate load, glucose and insulin infusion, cold, stress,  $\beta$ -agonists, and potassium-lowering medications. A calcium channel mutation is most common. Specific reports noted attacks during pregnancy triggered by betamethasone, new onset Grave disease, glucose tolerance testing, and excessive caffeine (Damallie et al., 2000; Appel and Myles, 2001; Donovan et al., 2007; Teagarden and Picardo, 2011). Of note, the patient with new onset thyrotoxic form of the disease responded well to thyroid treatment. Asians are highly overrepresented in this subtype including the case described (Donovan et al., 2007).

## MOTOR NEURON DISEASES

### Spinal muscular atrophy (SMA)

SMA is the most common fatal autosomal recessive disorder and results in severe progressive weakness.

Subtypes 1–4 are based on onset age and motor milestones. Weakness onset ranges from prenatal to adulthood. Prevalence is approximately 1–2 per 100,000 persons and incidence is around 1 in 10,000 live births. The condition is caused by a mutation in the survival motor neuron 1 (SMN1) gene; copy numbers of the SMN2 gene affect the phenotype severity. Two current FDA-approved treatments altered the expectations of future prognosis of this condition; additional agents are in the pipeline. Nusinersen (Spinraza) is an intrathecal infusion approved for all ages but is mostly given to infants and children; onasemnogene abeparvovec-xioi (Zolgensma) is a single dose adenovirus vector gene therapy approved for patients under 2 years. The expectation is that the most severe type I patients that previously expired prior to child bearing ages will have a much better prognosis. There is current limited information on pregnancy mainly for later onset types II and III that will hopefully change as children currently treated reach adulthood. A number of successful pregnancy reports have been published (Carter et al., 1994; Pugh et al., 2000; Yim et al., 2003). A recent literature review found that the incidence of maternal and fetal complications was not higher than the general population, but not surprisingly, premature labor and C-section rates were higher (Abati and Corti, 2018). Similar to conditions already discussed, regional anesthesia is preferred, and depolarizing muscle blockers avoided. Weakness exacerbation was reported in a notable percentage of women. Respiratory muscle weakness can hamper delivery and anesthesia management; spinal deformities and surgical hardware can complicate epidural or spinal anesthesia and respiratory management during C-section (Carter et al., 1994).

### Amyotrophic lateral sclerosis (ALS)

ALS is typically a late-onset sporadic progressive fatal disorder—mean age of onset is 60 years. About 5%–10% are inherited conditions that start at younger ages. However, onset during pregnancy occurs (Chiò et al., 2003; Lunetta et al., 2014). Successful pregnancies are also reported (Chiò et al., 2003; Sarafov et al., 2009; Kawamichi et al., 2010; Pathiraja and Ranaraja, 2020). An Italian group reviewed all registered ALS patients of childbearing age and found examples of disease onset during or soon after five pregnancies (Lunetta et al., 2014). Two had genetic forms, namely, superoxide dismutase one mutations. The authors noted a vascular endothelial growth factor promoter genotype that they theorize might impair oxidative stress mechanisms and promote ALS onset. The original FDA-approved treatment is Riluzole; several reports note no recognized negative fetal effects (Kawamichi et al., 2010). The most recently approved infusion, edaravone (Radicava) is

associated with some adverse animal effects. Both vaginal and C-section deliveries are reported, mainly based on the degree of impairment, especially muscular weakness and respiratory capacity. Delivery and anesthesia concerns are similar to other discussed conditions.

## AUTONOMIC DISORDERS

### Autonomic neuropathy, orthostatic intolerance, and postural orthostatic tachycardia syndrome (POTS)

Pregnancy affects autonomic responses in multiple ways. Various studies have documented various differences, which are further altered by preeclampsia (Chaswal et al., 2018; da Corrêa et al., 2019; Garg et al., 2020). Autonomic neuropathy is uncommon but can occur in young women. Significant autonomic neuropathy can create challenges, such as vomiting from gastroparesis—diabetes is the most common cause (Macleod et al., 1990). Much more common is general dysautonomia, often termed orthostatic intolerance or POTS. About 0.5–4 million cases in the United States, predominantly affecting women, are estimated (Garland et al., 2015). Common symptoms include orthostatic lightheadedness and tachycardia, syncope or presyncope, gastrointestinal disturbance, cognitive dysfunction, nausea, exercise or heat intolerance, and fatigue. Symptoms can be disabling. Onset can occur after an acute infection or other monophasic event or progress gradually; a minority of patients have signs of mild but painful small fiber neuropathy, suggesting underlying sensory and autonomic neuropathy following a viral syndrome. The condition must be distinguished from chronic fatigue syndrome, anxiety disorders, simple deconditioning, and cardiac-induced tachycardia. A variety of risk factors are known but most common are various forms of Ehlers Danlos syndrome. That condition can create additional pregnancy and delivery challenges, predominantly from joint hyperextensibility concerns (Karthikeyan and Venkat-Raman, 2018). Contrary to many of the neuromuscular conditions already discussed, these patients often paradoxically improve during pregnancy, most commonly in the second trimester. However, given the heterogeneous nature of this syndrome, no consistent or reliable patterns are present. A review of 11 available reports of pregnancy publications, mostly case reports, highlighted this variability (Morgan et al., 2018). Volume expansion and weight gain during pregnancy can help and reduce the need for supplemental fluids and salt loading. Even significant neurogenic orthostatic hypotension from diabetic autonomic neuropathy can improve in this setting (Scott et al., 1988). Weaning helpful medications, such as fludrocortisone, midodrine, pyridostigmine,  $\beta$ -blockers, and others prior to pregnancy can be problematic in some patients. Most are category C, but no examples of deleterious fetal

medication events in this population are published. Special considerations during delivery can include excess responses to epinephrine and stimulants and inappropriate tachycardia. Some patients improve postpartum, but most return to baseline symptoms after delivery.

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