Myasthenia Gravis and Pregnancy

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KEY POINTS

- Respiratory compromise, bulbar involvement, and autonomic dysfunction are common in myasthenia gravis.
- Careful neurological assessment and regular medication reviews are required throughout pregnancy.
- Neuraxial anaesthesia can be safely performed in patients with myasthenia gravis.
- For myasthenia gravis patients with bulbar involvement or significant respiratory compromise, it is important to consider the risks and benefits for both neuraxial and general anaesthesia on an individual basis.

INTRODUCTION

Myasthenia gravis (MG) is an autoimmune disorder with peak onset amongst women of reproductive age (ie, 20-30 years). Normal physiological changes of pregnancy can lead to deterioration in preexisting associated neurology, for example by exacerbating existing respiratory compromise. Thorough assessment and careful multidisciplinary planning are necessary to provide safe peripartum care.

This tutorial will discuss the pathophysiology of MG and implications for the pregnant patient, including management strategies for labour and delivery.

MYASTHENIA GRAVIS

Incidence and Prevalence

MG is an autoimmune disorder typified by weakness and fatigability of skeletal (striated) muscle and the incidence is approximately 50 to 140 per million, with a prevalence of 1 in 10 000 to 50 000.[1,2]

Pathophysiology and Diagnosis

MG is characterised by autoantibody destruction of nicotinic acetylcholine receptors in the postsynaptic junction leading to reduced transmission of nerve impulses at the motor end plate (Figure 1). MG is characterised by fatigable weakness of voluntary muscles due to reduced acetylcholine release with repeated stimulation.[3] Difficulties with mastication and dysphagia indicate weakness of pharyngeal and laryngeal muscles, described as bulbar involvement.

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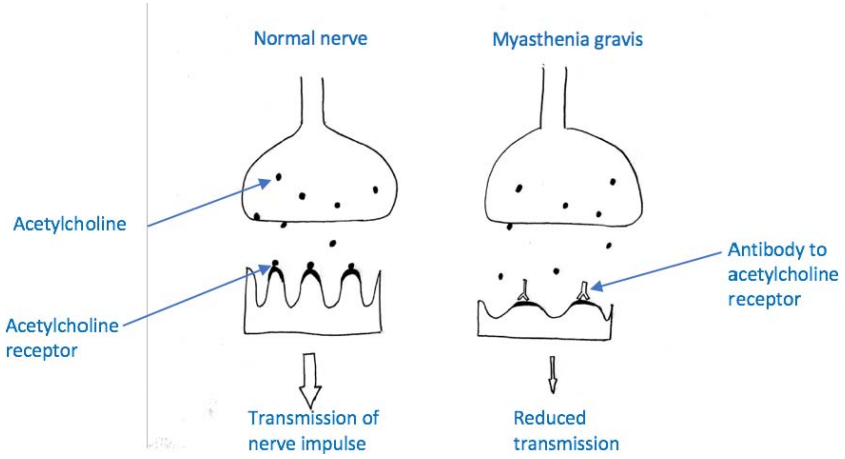

Figure 1. Normal nerve (left) and nerve affected by myasthenia gravis showing antibodies to the acetylcholine receptor resulting in reduced neuronal transmission (right).

MG is diagnosed using an anticholinesterase test, where strength improves with administration of edrophonium (Tensilon® test). Electromyography demonstrates a decreasing response to repeated stimulation of peripheral motor nerves. Anti-acetylcholine receptor antibodies are found in 85% of patients with generalised MG and in 50% to 60% of patients with ocular MG.[4]

MG is often associated with other autoimmune diseases, particularly thyroid disease, rheumatoid arthritis, and systemic lupus erythematosus, so these should be actively screened for.[5]

Treatment

The mainstay of treatment for MG involves anticholinesterases such as pyridostigmine (increases acetylcholine available at the neuromuscular junction) and immunosuppression therapy (reduces antibodies) with corticosteroids, azathioprine, cyclosporine, or mycophenolate.

The dose of anticholinesterase may need to be increased during pregnancy due to a larger plasma volume and greater renal elimination. Hyperemesis of pregnancy may affect drug absorption and the parenteral route may be required to improve reliability of drug delivery.

Systemic steroids are safe to continue during pregnancy, whereas azathioprine and mycophenolate are not recommended due to potential risk of teratogenicity. Involvement of a neurologist (with a special interest in MG) is advised when planning pregnancy in order to evaluate the risks and benefits of continuing each medication.

If symptoms deteriorate, it is important to distinguish between a myasthenic crisis from undertreatment and cholinergic crisis due to overtreatment with acetylcholinesterase inhibitors as the management approach differs (Table 1). Labour, sleep deprivation, infection, surgery, emotional stress, and pain are all precipitants of a myasthenic crisis.[6] Intravenous immunoglobulin or plasmapheresis may be considered in a myasthenic crisis.

There is an association of MG with thymoma (15% of patients) and thymectomy may improve clinical outcomes in MG patients, reducing severity of symptoms and frequency and need for hospitalisation.[8]

In patients with MG, it is important to avoid drugs that may exacerbate weakness at the neuromuscular junction (Table 2). Particular anaesthetic drug considerations are discussed below in ‘Anaesthesia for Caesarean Delivery’.

Disease Course

During pregnancy, the clinical course of MG is difficult to predict; it improves in one third, remains the same in one third, and worsens in one third of patients.[10] Remission or deterioration can occur in any trimester or during the postpartum period.

MG and Physiological Changes in Pregnancy

Anatomical changes in pregnancy decrease the lower oesophageal sphincter tone, which can lead to an increased risk of gastric reflux. Patients with MG and associated bulbar involvement are at particular risk of subsequent pulmonary aspiration as they are less able to clear secretion and protect their airway.

Myasthenic Crisis	Cholinergic Crisis
Nicotinic receptors in skeletal muscle affected • Flaccid weakness • No fasciculations	Features of both nicotinic and muscarinic toxicity from excess acetylcholinesterase inhibitors • Flaccid weakness • Fasciculations
Eyes • Ptosis • Normal pupil	Eyes • No ptosis • Small pupil
Autonomic symptoms may be present but not a prominent feature	Muscarinic toxicity • Cardiovascular: bradycardia, hypotension • Respiratory: rhinorrhoea, bronchorrhoea, bronchospasm, cough, severe respiratory distress • Gastrointestinal: hypersalivation, nausea and vomiting, abdominal pain, diarrhoea, faecal incontinence • Genitourinary: incontinence

Table 1. Comparison of Myasthenic Versus Cholinergic Crisis[6,7]

Intercostal muscle weakness in patients with MG can exacerbate the reduction in functional residual capacity and residual volume that are normal anatomical changes in pregnancy, which could precipitate respiratory failure; however, this is rare.

Pregnancy Outcome

The uterus consists of smooth muscle (ie, nonstriated) and is not affected by MG, therefore the first stage of labour is usually not affected by MG. Striated muscle (skeletal) contributes to pushing in the second stage of labour and therefore assisted delivery may be required to prevent fatigue.

Of neonates delivered to women with MG, 10% to 20% will develop neonatal MG because of placental transfer of maternal antibodies. Affected neonates present with poor feeding, generalised weakness, and breathing problems. Anticholinesterase treatment and a period of invasive ventilation may be required. Neonatal MG tends to be short-lived in most cases and improvement can be expected within 8 weeks.

Breastfeeding should be avoided in neonatal MG as anti-acetylcholine receptor antibodies can be transferred to the neonate via breast milk. Anticholinesterase medication does not cross into breast milk so it is safe in breastfeeding women. It is recommended that mothers taking azathioprine or mycophenolate avoid breastfeeding.[10]

ANAESTHETIC CONSIDERATIONS

There are 3 main areas of consideration for anaesthetic management in patients with MG: respiratory compromise, bulbar involvement, and autonomic dysfunction (Table 3).

RECOMMENDATIONS FOR MANAGEMENT

Patient Assessment

Patients should be referred to a high-risk obstetric anaesthetic clinic with physical assessment to include the following:

- Detailed history and documented examination of preexisting neurological deficits
- Clinical course—stable or frequent/severe exacerbations
- Respiratory compromise and history of ventilatory support
- Bulbar involvement
- Autonomic dysfunction
- Ability to lie supine

Blood Tests

- Full blood count
- Electrolytes

Drug	Mechanism and Features
Calcium channel blockers	• Alleged to affect neuromuscular transmission via blockade of L-type calcium channels • Verapamil prevents potassium outflow at the motor endplate and decreases intracellular ionised calcium levels • Felodipine and nifedipine are known to produce features of MG in patients with known defects of neuromuscular transmission (with long-term use), but can be used with caution for short-term use
Anti-arrhythmics (eg, procainamide, etafenone, peruvoside, propafenone)	• Procainamide is alleged to decrease release of Ach and increase the threshold of the muscle membrane for action potentials • Propafenone and procainamide also act as sodium influx blockers • MG symptoms possible with both short- and long-term use
Quinolone derivatives	• Reduced Ach release due to blockade of sodium channels and depolarisation potentiation
Penicillamine	• Multiple mechanisms including direct immunomodulation to unmasking of autoimmune-mediated defects of neuromuscular transmission; requires close monitoring
H_2 receptor antagonists	• Animal studies have shown inhibition of Ach, but no reports of induction or exacerbation of MG in humans; use with caution
Aminoglycosides	• Wide range of pre- and postsynaptic mechanisms • Gentamicin affects presynaptic release of Ach and can be reversed by neostigmine
Macrolides	• Exacerbations of MG have been reported with use of a large number of antibiotics from this class with unknown exact mechanism
Antiepileptics	• Long-term phenytoin can depress the postsynaptic response to Ach • Carbamazepine is thought to trigger an immune-mediated response and gabapentin is thought to bind to voltage-gated calcium channels and unmask MG • Effects reverse after drug cessation
Magnesium sulphate	• Magnesium sulphate is contraindicated in MG due to neuromuscular blocking effects
Neuromuscular blockers	• Suxamethonium is contraindicated due to risk of severe hyperkalaemia secondary to depolarisation of extrajunctional Ach receptors

Table 2. Drugs with a Tendency to Exacerbate Myasthenia Gravis and Their Mechanisms (Adapted from Ahmed and Simmons[9]) MG = myasthenia gravis; Ach = acetylcholine

- Renal function
- Thyroid function tests and autoimmune screen (if not already completed at diagnosis)

Investigations

- Electrocardiogram
- Pulmonary function tests

After careful assessment, a multidisciplinary team (including anaesthetic, obstetric, neurology, and intensive care input) management plan should be formulated and agreed with the patient.

Labour

- MG alone does not mandate a caesarean delivery.
- Optimise pain control and avoid prolonged labour to reduce weakness from fatigue.
- Avoid exertion and stress, which may trigger a myasthenic crisis.

Respiratory Compromise

- Pulmonary function tests demonstrate restrictive disease with significantly reduced forced vital capacity
- Supine position worsens respiratory compromise
- Frequent monitoring required to assess for perioperative deterioration

Bulbar Involvement

- Intubation and ventilation may be required for surgery
- There should be careful assessment of the risks and benefits of neuraxial and general anaesthesia
- General anaesthesia may increase the risk of aspiration if the airway is not secured, while neuraxial anaesthesia risks decompensation of respiratory reserve with paralysis of accessory muscles
- For patients undergoing general anaesthesia there should be careful assessment of suitability for extubation
- Close postoperative monitoring is vital to allow prompt recognition of respiratory compromise following both neuraxial and general anaesthesia
- Postoperative ventilatory support may be required in the intensive care unit or high-dependency unit

Autonomic Dysfunction

- Delayed gastric emptying
- Increased risk of aspiration
- Reduced variability in heart rate on deep inspiration and on standing
- Cardiovascular instability
- Severe hypertension from laryngoscopy and surgical stimulus
- Profound hypotension from positive pressure ventilation, neuraxial and general anaesthesia, bleeding, and uterotonic medication(s)
- Hypovolaemia poorly tolerated
- Increased sensitivity to direct-acting sympathomimetics
- Impaired respiratory reflexes leading to hypoventilation

Table 3. Common Clinical Challenges Posed by Myasthenia Gravis

- Avoid systemic opioids (intramuscular and intravenous) and patient-controlled analgesia if there is significant preexisting respiratory insufficiency.
- Epidural analgesia is recommended for labour.
- In patients with respiratory compromise, consider cautious titration of epidural analgesia (aiming for a sensory level of T10); maintain using a weak solution of local anaesthetic combined with an opioid (eg, 0.0625% levo/bupivacaine + 2 μg/mL fentanyl, or 0.4 μg/mL sufentanil). Direct (one-to-one) observation with continuous monitoring is advised.
- Consider assisted delivery to reduce fatigue during the second stage.
- Anticholinesterase and steroid therapy must be continued throughout pregnancy, parenteral dosing may be required.

Anaesthesia for Caesarean Delivery

Premedication

- H_2 antagonist (caution: see Table 2) for antacid prophylaxis and metoclopramide to promote gastric emptying.
- Avoid benzodiazepines or systemic opioids due to risk of respiratory depression.

Optimise Fluid Status

- Hypovolaemia is poorly tolerated in patients with autonomic dysfunction, and aortocaval compression on lying supine worsens cardiovascular instability. Ensure left lateral uterine displacement and avoid hypovolaemia.

Invasive Monitoring

- Consider invasive blood pressure monitoring in the presence of autonomic dysfunction.

Both neuraxial and general anaesthesia have safely been administered in patients with MG. Neuraxial anaesthesia allows for earlier return to oral intake of medications. Patients with bulbar involvement and/or respiratory compromise may not tolerate a midthoracic level of neuraxial anaesthesia due to paralysis of accessory muscles, but may also have an increased risk of aspiration associated with general anaesthesia.

Aim to achieve an adequate block for surgery (T4 to cold) while avoiding excessive cardiovascular instability from sympathetic blockade or respiratory impairment from paralysing the intercostal muscles too high. Adding a small dose of opioid to the local anaesthetic reduces the total dose of local anaesthetic required due to a synergistic effect, improves block quality, and reduces systemic opioid requirements postoperatively.

Epidural anaesthesia allows for careful titration of local anaesthetic using incremental bolus doses, which leads to improved cardiovascular stability (compared with a spinal) and avoidance of excessively high blockade. Patients with autonomic dysfunction and/or mild respiratory muscle involvement may also benefit from an epidural technique. The epidural catheter can also be used to administer local anaesthesia for pain control postoperatively.

Spinal anaesthesia is faster and more reliable than epidural anaesthesia. It minimises the total dose of local anaesthetic administered (compared with epidural anaesthesia), which may be beneficial as high serum levels of local anaesthetic may theoretically potentiate neuromuscular blockade.[11] However, spinals are associated with more cardiovascular instability and a potentially higher block as a result of speed of onset and inability to titrate the effect.

Combined spinal-epidural anaesthesia with a low-dose spinal component has the advantages of both a spinal and an epidural; reliable surgical anaesthesia can be rapidly attained whilst maintaining relative cardiovascular and respiratory stability.

General anaesthesia may be required for securing the airway and providing ventilatory support if there is significant respiratory insufficiency. It is also an option in patients that have contraindications to neuraxial anaesthesia. There is overall an increased sensitivity to neuromuscular blockers in patients with MG that greatly reduces the actual required dose, and it is important to closely monitor the depth of neuromuscular blockade (suxamethonium is contraindicated: see Table 2).

Inhalational agents contain muscle-relaxing properties and therefore the dose should be kept to a minimum. Depth of anaesthesia monitoring may be a useful adjunct in view of the increased risk of awareness in obstetric patients. Short-acting intravenous opioids can be administered in patients with MG.[4]

Use of reversal agents is controversial and options include the following:

- Allow for spontaneous recovery from atracurium.
- Administer sugammadex to reverse rocuronium.
- Administer neostigmine to reverse atracurium or rocuronium.

In MG, a high dose of neostigmine risks precipitating a cholinergic crisis where generalised muscle weakness may be difficult to distinguish from a myasthenic crisis (Table 1).

Administration of intravenous oxytocin can worsen preexisting hypotension from autonomic dysfunction related to MG and the vasodilatory effects of anaesthesia; therefore it should be administered very cautiously in divided doses or as an infusion.

Postoperative Care

Ideally, patients should be cared for in the intensive care or high-dependency unit (ie, monitored bed). Assessment of respiratory function using spirometry measurements may allow early detection of clinical deterioration. Respiratory support should be provided with chest physiotherapy, appropriate positioning, assistance with secretion clearance, and noninvasive or invasive ventilation if required.

Cardiovascular monitoring and optimisation of fluid status need to continue in the postoperative period. Oral medications, particularly anticholinesterase, should be recommenced as soon as possible.

SUMMARY

- Normal physiological changes in pregnancy can exacerbate MG.
- Respiratory compromise, bulbar involvement, and autonomic dysfunction are common; when present, careful assessment of severity and detailed documentation are required.
- Neuraxial anaesthesia can be safely administered in patients with MG.
- The risks and benefits of general and neuraxial anaesthesia should be considered for patients with MG, particularly those with respiratory compromise.
- The anaesthetist must weigh up the risks and benefits on an individual basis in a patient with MG, so that the patient can make an informed choice during labour and delivery.

REFERENCES

1. Phillips L. The epidemiology of myasthenia gravis. *Neurol Clin*. 1994;12:263-271.
2. Berlit S, Tuschy B, Spaich S, et al. Myasthenia gravis in pregnancy: a case report. *Case Rep Obstet Gynecol*. 2012;2012:736024.
3. Maselli R. Pathophysiology of myasthenia gravis and Lambert-Eaton syndrome. *Neurol Clin*. 1994;12:285-303.

4. Sanwal M, Baduni N, Jain A. Caesarean section in a patient with myasthenia gravis: a bigger challenge for the anaesthesiologist than the obstetrician. *J Obstet Anaesth Crit Care*. 2012;2:34-37.
5. Nacu A, Andersen JB, Lisnic V, et al. Complicating autoimmune diseases in myasthenia gravis: a review. *Autoimmunity*. 2015;48:362-368.
6. Wendell LC, Levine JM. Myasthenic crisis. *Neurohospitalist*. 2011;1:16-22.
7. Chaudhuri A, Behan PO. Myasthenia crisis. *QJM*. 2009;102:97-107.
8. Wolfe G, Kaminski H, Aban I, et al. Randomized trial of thymectomy in myasthenia gravis. *N Engl J Med*. 2016;375:511-522.
9. Ahmed A, Simmons Z. Drugs which may exacerbate or induce myasthenia gravis: a clinician's guide. *Internet J Neurol*. 2008;10:1-8.
10. Batocchi A, Majolini L, Evoli A, et al. Course and treatment of myasthenia gravis during pregnancy. *Neurology*. 1999;52:447-452.
11. Rolbin W, Levinson G, Schnider S, et al. Anesthetic considerations for myasthenia gravis and pregnancy. *Anesth Analg*. 1978;57:441-447.