CASE REPORT

New diagnosis myasthenia gravis and preeclampsia in late pregnancy

John Ozcan,[1] Ian Frank Balson,[1] Alicia T Dennis[1,2]

[1]Department of Anaesthetics, The Royal Women's Hospital, Parkville, Victoria, Australia
[2]The Department of Obstetrics and Gynaecology and The Department of Pharmacology, The University of Melbourne, Parkville, Victoria, Australia

Correspondence to
Associate Professor Alicia Dennis, adennis@unimelb.edu.au

Accepted 30 January 2015

SUMMARY

Myasthenia gravis is a chronic autoimmune disease of neuromuscular transmission resulting in fatigable skeletal muscle weakness. Preeclampsia is a multisystem disease of pregnancy which is characterised by hypertension and involvement of one or more organ systems. Both diseases are responsible for considerable morbidity and mortality for mother and fetus. The occurrence of both preeclampsia and myasthenia gravis in pregnancy is very rare, and conflicts arise when considering the optimal management of each disease.We present a case of a parturient who was newly diagnosed with both myasthenia gravis and preeclampsia in late pregnancy. Myasthenia treatment was started with prednisolone and pyridostigmine, and delivery was by caesarean section at 37 weeks gestation under spinal anaesthesia. Postnatally, the patient developed worsening of myasthenia and preeclampsia symptoms. We consider the anaesthetic implications for both diseases and describe our approach for the management of this case.

BACKGROUND

Myasthenia gravis is a chronic autoimmune disorder affecting the neuromuscular junction. It is characterised by fatigable weakness of skeletal muscles, commonly affecting extraocular, bulbar and proximal limb muscles. Myasthenia gravis is associated with autoantibodies to the nicotinic acetylcholine receptor at the neuromuscular junction, however, up to 20% of patients do not have these autoantibodies.[1] The prevalence of myasthenia gravis has been reported at 4/10 000.[2] The disease affects women more than men, with the peak onset in women occurring in the third decade of life, frequently overlapping with childbearing years. The course of myasthenia during pregnancy is unpredictable; with exacerbation, improvement or no change in symptoms all possible.[3] Postpartum exacerbations occur in approximately 30% of patients, and elevated rates of maternal and fetal mortality are described.[3] Mortality risk in myasthenic mothers is inversely related to duration of disease, with the highest risk in the first year of disease.[4]

Preeclampsia is defined as a multisystem disease of pregnancy, characterised by hypertension arising after 20 weeks' gestation, and involvement of one or more organ systems and/or the fetus.[5] It complicates 5–8% of all pregnancies, and is responsible for considerable morbidity and mortality. An association between myasthenia gravis and preeclampsia has not been described, and there are only six published case reports of myasthenia gravis complicated by preeclampsia.[6–11]

Both myasthenia gravis and preeclampsia have specific management principles and strategies during pregnancy, and both diseases have specific implications for anaesthetic management. Conflicts arise when considering the optimal management of each disease. We present a case of a parturient that was newly diagnosed with myasthenia gravis and preeclampsia in late pregnancy. We consider the anaesthetic implications for this combination of diseases and describe our approach for the management of this case.

CASE PRESENTATION

A 34-year-old primigravida, with a history of coeliac disease, presented at 36 weeks gestation with a 6-week history of progressive dysphagia (worse with solids) and 2 weeks of proximal upper limb weakness. The dysphagia and limb weakness were worse at the end of the day. Examination elicited fatigable weakness of the proximal upper limb muscles. Nerve conduction studies using repetitive stimulation demonstrated reproducible decrement in trapezius, biceps and orbicularis oris muscle groups. Baseline spirometry was performed. Forced vital capacity (4.2 L) and forced expiratory volume in 1 s (3.1 L) were within normal limits. However, maximal inspiratory pressure (59 cm H_2O, 68% predicted) and expiratory pressure (47 cm H_2O) were reduced in keeping with diaphragmatic and respiratory muscle weakness. Acetylcholine receptor autoantibodies were not detected. The diagnosis of seronegative myasthenia gravis was made based on clinical features and supportive nerve conduction studies and spirometry findings.

The patient was admitted to the neurology ward and started on prednisolone 20 mg daily and pyridostigmine 60 mg three times daily. After 1 week of treatment, the patient described an improvement in dysphagia, and examination demonstrated improvement in upper limb power, with fatigable weakness still elicited. Vital capacities remained greater than 3.5 L and the patient was able to ambulate 100 m unaided on the ward.

The patient also had hypertension first detected at 33 weeks gestation (systolic 140–150 mm Hg, diastolic 90–100 mm Hg). She subsequently developed visual disturbance and elevated liver enzyme transaminases, with alanine transaminase 173 IU/L (reference range <34 IU/L) and aspartate transaminase 97 IU/L (reference range <31 IU/L). Proteinuria was not detected, there was no evidence of hyperreflexia or clonus, and platelet count remained normal. A diagnosis of preeclampsia was made given the new onset of hypertension

To cite: Ozcan J, Balson IF, Dennis AT. *BMJ Case Rep* Published online: [*please include* Day Month Year] doi:10.1136/bcr-2014-208323

combined with organ system involvement in the form of raised hepatic transaminases. Initial management was expectant with monitoring of blood pressure and symptoms.

At 37 weeks, myasthenia treatment had been established for 1 week and symptoms and vital capacities were stable. Blood pressure had remained at systolic 140–150 mm Hg without antihypertensive therapy. In addition to obstetric and neurology reviews, the patient had antenatal assessment from anaesthetic and neonatalogy specialist units. A multidisciplinary plan was made to electively deliver the fetus given term gestation had been reached. It was decided that continuing the pregnancy, with risk of deterioration of myasthenia or preeclampsia symptoms, posed a greater level of maternal and fetal risk than delivery. The plan was to proceed with caesarean section under regional anaesthesia, with intensive postpartum monitoring of the mother and infant.

The patient had her usual dose of pyridostigmine and prednisolone on the day of surgery. Her preoperative blood pressure was 150/95 mm Hg and heart rate 82 bpm. Body mass index was 26 kg/m^2, and airway assessment was Mallampati class II with a thyromental distance of 8 cm. A single shot spinal anaesthetic was administered with 2.2 mL of hyperbaric bupivacaine 0.5% plus fentanyl 15 μg. Sensory block height to T4 was established with a dense motor block. After approximately 5 min the patient became bradycardic to 42 bpm. Blood pressure was 105/60 mm Hg, and the patient was asymptomatic. Immediate treatment with atropine 300 μg and ephedrine 3 mg was effective in restoring the heart rate to 80 bpm. The case proceeded uneventfully and a live male infant was delivered. The infant was vigorous at birth, with Apgar scores of 9 at 1 and 5 min, and birth weight of 3108 g. The infant was observed in the neonatal intensive care unit for signs of neonatal myasthenia for 48 h. The infant's intensive care stay was uneventful and he was discharged to his mother's care.

The patient was monitored in the high dependency unit with daily neurology, obstetric and anaesthetic pain service review. Postoperative pain relief was with regular paracetamol, ibuprofen and controlled-release oxycodone (10 mg twice daily), with immediate-release oxycodone available for breakthrough pain. Pain was well controlled postoperatively. Intravenous fluid administration postoperatively was cautious, with frequent reviews of fluid status to avoid pulmonary oedema. On the night following caesarean, the patient became hypertensive to 170/95 mm Hg with associated headache and upper abdominal pain. There was no hyperreflexia or clonus. The patient was started on enalapril 5 mg twice daily with good response, and blood pressure subsequently remained 130–140 mm Hg systolic.

On day 2 post-caesarean section, the patient reported increasing weakness in her upper limbs, with difficulty lifting the infant. Fatigable weakness was present on examination and vital capacity was 2.8 L. Pyridostigmine was increased to 60 mg four times daily and she was treated with a course of intravenous immunoglobulin (2 g/kg Octagam over 5 days). Over subsequent days there was improvement in her weakness. The patient was discharged home on day 8 post-caesarean.

DISCUSSION

The association of myasthenia gravis and preeclampsia in pregnancy is rare, and conflicts in management arise. The optimal management of one disease may interfere with the management of the other. Box 1 lists factors and drugs which may exacerbate myasthenia gravis. However, absolute contraindications are rare and the indication to use these drugs may take precedence over the risk of worsening myasthenic symptoms or crisis. Table 1 lists treatment priorities in the patient with preeclampsia and suggested modifications in the patient with myasthenia gravis.

Control of hypertension is a cornerstone of preeclampsia management. Non-severe hypertension is defined as systolic pressure 140–159 mm Hg and diastolic pressure 90–109 mm Hg. Most guidelines recommend lowering non-severe hypertension to a level of 140–150 mm Hg systolic and 90–100 mm Hg diastolic, with labetalol commonly identified as the drug of choice.[12 13] Other safe agents include methyldopa and nifedipine. In the myasthenic patient, β-adrenoceptor blockers and calcium-channel blockers both have the potential to worsen weakness. Therefore in this patient group methyldopa or oral hydralazine may be the initial drugs of choice in non-severe hypertension.

Severe hypertension (systolic pressure >160 mm Hg or diastolic pressure >110 mm Hg) should be treated, and hypertensive crisis (>180 mm Hg) requires immediate effective treatment. Treatment options include labetalol (oral or intravenous), nifedipine (oral) and hydralazine (intravenous).[14] In the myasthenic patient, hydralazine may be considered the drug of choice for acute blood pressure reduction given the potential of labetalol and nifedipine to exacerbate weakness. However, labetalol use has been described in other case reports of severe hypertension management in preeclampsia and myasthenia gravis.[10] If labetalol is used as a first line or additional agent, the potential for worsening of myasthenic symptoms must be considered, and close monitoring of the patient during therapy is essential.

Magnesium sulfate is recommended as prophylaxis for eclampsia in patients with severe preeclampsia.[15] However, it is well recognised that magnesium can precipitate a myasthenic crisis,[6 16] and is contraindicated for use as eclampsia prophylaxis in myasthenia.[6 9 17] Excess magnesium at the neuromuscular junction inhibits the release of acetylcholine presynaptically and inhibits the excitability of the postsynaptic membrane, resulting in worsening weakness, bulbar dysfunction and respiratory failure. Weakness may develop at serum magnesium concentrations that are well tolerated in the non-myasthenic patient.[16] Onset of weakness may be rapid, and occurred within

Box 1 Factors that may exacerbate myasthenia gravis

1. Pathophysiological
   - Stress response: infection, surgery, trauma, pain, physical or emotional stress
   - Pregnancy and post partum
   - Temperature: hypothermia or hyperthermia
   - Thyroid dysfunction: hypothyroidism or hyperthyroidism
2. Pharmacological
   - Inadequate dosing of anticholinesterase medication
   - Antibiotics: aminoglycosides, tetracyclines, others (erythromycin, clindamycin, lincomycin, ciprofloxacin, ampicillin)
   - Cardiovascular drugs: β-blockers, calcium-channel blockers, quinine, quinidine, procainamide, lidocaine
   - Magnesium
   - Anaesthetic drugs: volatile agents, neuromuscular blocking agents, local anaesthetics
   - Others: phenytoin, gabapentin, lithium, penicillamine, corticosteroids, opioids, iodinated contrast agents, frusemide, thyroxine

Adapted from Ferrero *et al*[21] and Grange[22]

Table 1 Management goals in preeclampsia, usual therapy and modifications in myasthenia gravis

Management goal	Usual treatment	Modifications in myasthenia gravis
1. Maintenance of appropriate blood pressure		
Non-severe hypertension (systolic pressure 140–159 mm Hg and diastolic 90–109 mm Hg)	Most guidelines recommend treatment[12 13] Options: oral labetalol, methyldopa, nifedipine, hydralazine	β-Adrenoceptor blockers and calcium-channel blockers have the potential to exacerbate weakness Consider methyldopa or hydralazine (oral) as first line therapy
Severe hypertension (systolic pressure >160 mm Hg and/or diastolic >110 mm Hg)	Should be treated[14] Options: labetalol (oral/intravenous), nifedipine (oral), hydralazine (intravenous)	Consider hydralazine (intravenous) as first line therapy Use of labetalol (oral/intravenous) described[10]
2. Seizure prevention and treatment		
Seizure prophylaxis	$MgSO_4$ first line[15]	$MgSO_4$ contraindicated.[6 9 17] Consider phenytoin[18] Careful blood pressure control
Eclampsia treatment	$MgSO_4$ first line[14]	Morbidity/mortality benefit of $MgSO_4$ may outweigh risk of myasthenic crisis (especially if prolonged or recurrent seizures) Alternatives (diazepam, phenytoin) are inferior to $MgSO_4$
3. Prevention of pulmonary oedema		
Fluid balance	Cautious management of fluid balance (restrictive fluid therapy if normal renal function present)	Cautious management of fluid balance
4. Safe general anaesthesia		
General anaesthesia	Blood pressure control Obtund cardiovascular response to laryngoscopy (eg, alfentanil, remifentanil)	Consider intubation without muscle relaxant using alfentanil (up to 50 μg/kg) or remifentanil If muscle relaxant required consider reduced-dose rocuronium with sugammadex reversal

10 min of administration in reported cases.[6 16] The short-term use of phenytoin has been recommended for seizure prophylaxis in myasthenic patients with preeclampsia.[18] Long-term use of phenytoin has the potential to exacerbate myasthenia gravis (box 1).

Eclampsia is a life-threatening disease associated with intracranial haemorrhage, cardiac arrest and death with a case fatality rate of 3.1%.[14] Magnesium sulfate is the first-line drug treatment for eclamptic seizures and recurrent seizures.[14] Alternatives which may be considered in the myasthenic patient, such as diazepam or phenytoin, are less effective than magnesium in reducing maternal death[19] and reducing the risk of seizure recurrence.[20] The benefit of using of magnesium sulfate in reducing eclampsia-related morbidity and mortality is likely to outweigh the risk of myasthenic crisis, especially in the setting of prolonged or recurrent seizures. A predetermined plan for eclampsia management in the myasthenic patient should be carefully considered and documented ahead of time with multidisciplinary input of the obstetrician, neurologist and anaesthetist.[17] If magnesium sulfate is to be used, intensive monitoring is mandatory, and facilities for non-invasive ventilation and intubation/ventilation are essential.

Regional anaesthesia is favoured for caesarean section in myasthenic patients unless the patient has significant respiratory compromise or bulbar dysfunction.[21 22] Amide local anaesthetics are recommended, as ester local anaesthetics may have a prolonged half-life due to inhibition of plasma cholinesterase in patients on anticholinesterase therapy.[22] Potentiation of vagal responses, as seen in the present case following neuraxial blockade, should be anticipated in patients on anticholinesterase treatment. Prophylactic administration of atropine or glycopyrrolate may be appropriate, and the use of a gradual onset epidural in a non-urgent case should be considered with the advantage of greater control of block height. Because of increased opioid sensitivity in myasthenic patients, careful consideration must be given to the use of intrathecal opioids, especially long-acting agents such as morphine. If intrathecal opioids are used patients must be closely monitored postoperatively for respiratory depression.

Specific management issues arise for preeclampsia as well as myasthenia gravis where general anaesthesia is required. The hypertensive cardiovascular response to laryngoscopy is exaggerated in patients with severe preeclampsia.[23] Muscle relaxation and reversal have unpredictable effects in myasthenic patients, and when used, neuromuscular monitoring is mandatory. Owing to the reduced number of functioning nicotinic acetylcholine receptors, myasthenic patients are extremely sensitive to non-depolarising muscle relaxants, and display a varied response to depolarising muscle relaxants, with anticholinesterase treatment prolonging the effect of suxamethonium.[22 24] Current guidelines on myasthenia in pregnancy suggest that muscle relaxants should be avoided altogether if possible.[17] One approach would be to blunt the cardiovascular response to laryngoscopy with up to 50 μg/kg of alfentanil and intubate without muscle relaxant.[25] Remifentanil use in myasthenia gravis has also been described.[26] Where muscle relaxation is required, the use of reduced-dose rocuronium and subsequent reversal with sugammadex has been described in myasthenic patients.[27]

Myasthenic patients have increased sensitivity to opioids,[28] and surgical stress and pain are potential triggers for a myasthenic crisis. Therefore a fine balance between adequate analgesia and respiratory depression has to be found. In the present case, we used a reduced dose of controlled release oral opioid (oxycodone 10 mg twice daily) compared with our institution's normal post-caesarean pain protocol. Breakthrough opioid analgesia was available with frequent pain service review for titration. Postoperative pain was well controlled in this patient.

A cautious approach to fluid management is mandatory in preeclampsia as well as myasthenia gravis. Acute pulmonary oedema is a leading cause of death in women with preeclampsia and is a frequent cause for admission to intensive care.[14] In myasthenia gravis, fluid overload puts the patient at risk of respiratory failure. High-dose steroid use may further increase

the risk of pulmonary oedema in the myasthenic patient.[28] Myasthenic crisis arising during pregnancy or post partum may be treatment with intravenous immunoglobulin or plasmapheresis. Both therapies have been used safely in pregnancy.[17] Titration of steroid therapy and acetylcholine esterase inhibitors is also used in myasthenic exacerbation.

The association of myasthenia gravis and preeclampsia during pregnancy is rare. Both of these disorders pose risks for mother and fetus, and conflicts arise when considering the optimal management of both diseases. The management of the parturient with preeclampsia and myasthenia gravis requires a multidisciplinary approach involving obstetric, neurology, anaesthetic and neonatology specialist input. Careful consideration must be given to medication choices, and intensive peripartum monitoring is recommended.

Learning points

- The association of myasthenia gravis and preeclampsia during pregnancy is rare.
- Both diseases pose risks for mother and fetus, and conflicts arise when considering the optimal management of both diseases.
- Management requires a multidisciplinary approach involving obstetric, neurology, anaesthetic and neonatology specialist input, and intensive peripartum monitoring.
- Careful consideration must be given to medication choices for the management of general anaesthesia, hypertension and seizure prophylaxis and treatment.
- Regional analgesia and anaesthesia is indicated in most cases.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Turner C. A review of myasthenia gravis: pathogenesis, clinical features and treatment. *Curr Anaes Crit Care* 2007;18:15–23.
2 MacDonald BK, Cockerell OC, Sander JW, *et al*. The incidence and lifetime prevalence of neurological disorders in a prospective community-based study in the UK. *Brain* 2000;123:665–76.
3 Plauche WC. Myasthenia gravis in mothers and their newborns. *Clin Obstet Gynecol* 1991;34:82–99.
4 Scott JS. Immunological diseases in pregnancy. *Prog Allergy* 1977;23:321–66.
5 Tranquilli AL, Dekker G, Magee L, *et al*. The classification, diagnosis and management of the hypertensive disorders of pregnancy: a revised statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). *Pregnancy Hypertens* 2014;4:97–104.
6 Cohen BA, London RS, Goldstein PJ. Myasthenia gravis and preeclampsia. *Obstet Gynecol* 1976;48:35S–7S.
7 Duff GB. Preeclampsia and the patient with myasthenia gravis. *Obstet Gynecol* 1979;54:355–8.
8 Brogan M, Corcoran DJ. Myasthenia gravis and pre-eclampsia. *Ir Med J* 1983;76:84–5.
9 Benshushan A, Rojansky N, Weinstein D. Myasthenia gravis and preeclampsia. *Isr J Med Sci* 1994;30:229–33.
10 Hamaoui A, Mercado R. Association of preeclampsia and myasthenia: a case report. *J Reprod Med* 2009;54:587–90.
11 Di Spiezio Sardo A, Taylor A, Pellicano M, *et al*. Myasthenia and HELLP syndrome. *Eur J Obstet Gynecol Reprod Biol* 2004;116:108–11.
12 National Collaborating Centre for Women's and Children's Health. 2011 Hypertension in pregnancy. The management of hypertensive disorders during pregnancy. National Institute for Health and Clinical Excellence Guideline 107 Issued August 2010. Modified 2011. http://www.nice.org.uk/nicemedia/live/13098/50418/50418.pdf (accessed 12 Aug 2014).
13 Martin JN Jr, Thigpen BD, Moore RC, *et al*. Stroke and severe preeclampsia and eclampsia: a paradigm shift focusing on systolic blood pressure. *Obstet Gynecol* 2005;105:246–54.
14 Dennis AT. Management of pre-eclampsia: issues for anaesthetists. *Anaesthesia* 2012;67:1009–20.
15 Duley L, Gülmezoglu AM, Henderson-Smart DJ, *et al*. Magnesium sulphate and other anticonvulsants for women with preeclampsia. *Cochrane Database Syst Rev* 2010;11:CD000025.
16 Bashuk RG, Krendel DA. Myasthenia gravis presenting as weakness after magnesium administration. *Muscle Nerve* 1990;13:708–12.
17 Norwood F, Dhanjal M, Hill M, *et al*. Myasthenia in pregnancy: best practice guidelines from a U.K. multispecialty working group. *J Neurol Neurosurg Psychiatry* 2014;85:538–43.
18 Mueksch JN, Stevens WA. Undiagnosed myasthenia gravis masquerading as eclampsia. *Int J Obstet Anesth* 2007;16:379–82.
19 Duley L, Henderson-Smart DJ, Walker GJA, *et al*. Magnesium sulphate versus diazepam for eclampsia. *Cochrane Database Syst Rev* 2010;12:CD000127.
20 Duley L, Gülmezoglu AM, Chou D. Magnesium sulphate versus lytic cocktail for eclampsia. *Cochrane Database Syst Rev* 2010;9:CD002960.
21 Ferrero S, Pretta S, Nicoletti A, *et al*. Myasthenia gravis: management issues during pregnancy. *Eur J Obstet Gynecol Reprod Biol* 2005;121:129–38.
22 Grange C. Miscellaneous skeletal and connective tissue disorders in pregnancy. In: Gambling D, Douglas M, McKay R. eds. *Obstetric anaesthesia and uncommon disorders*. 2nd edn. Cambridge: Cambridge University Press, 2008:145–66.
23 Connell H, Dalgleish JG, Downing JW. General anaesthesia in mothers with severe pre-eclampsia/eclampsia. *Br J Anaesth* 1987;59:1375–80.
24 Thanvi BR, Lo TC. Update on myasthenia gravis. *Postgrad Med J* 2004;80:690–700.
25 Alexander R, Booth J, Olufolabi AJ, *et al*. Comparison of remifentanil with alfentanil or suxamethonium following propofol anaesthesia for tracheal intubation. *Anaesthesia* 1999;54:1032–6.
26 Mostafa SM, Murthy BV, Hughes EO. Remifentanil in myasthenia gravis. *Anaesthesia* 1998;53:721–2.
27 Sungur Ulke Z, Yavru A,Camci E, *et al*. Rocuronium and sugammadex in patients with myasthenia gravis undergoing thymectomy. *Acta Anaesthesiol Scand* 2013;57:745–8.
28 Stafford IP, Dildy GA. Myasthenia gravis and pregnancy. *Clin Obstet Gynecol* 2005;48:48–56.