CASE REPORT
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Myasthenic crisis in pregnancy: a case report

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ABSTRACT

Introduction: This case report aims to describe the diagnostic strategy and optimal management of pregnancy with Myasthenia Gravis and Myasthenic Crisis.

Case Description: A 27-years-old pregnant female with Myasthenia Gravis complicated by Myasthenic Crisis was hospitalized six times during her pregnancy. Two initial hospitalizations due to acute exacerbation treated with plasmapheresis, and two other hospitalizations complicated with myasthenic crisis treated with massive Therapeutic Plasma Exchange in the Intensive Care Unit. Managing myasthenia gravis in pregnancy, from early pregnancy until delivery, is challenging. Furthermore, the myasthenic crisis in pregnancy is a rare case that requires airway and ventilation support and treatment with plasmapheresis.

Conclusion: Myasthenic crisis in pregnancy is a rare condition. Therefore, a guideline about the prenatal, antenatal, delivery plan, exacerbation, and myasthenic crisis management in pregnancy and pregnancy planning women are urgently needed.

Keywords: case report, myasthenia gravis, myasthenic crisis, pregnancy
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INTRODUCTION

Myasthenia gravis (MG) is an autoimmune-mediated neuromuscular disorder. MG can be life-threatening both to the mother and the baby. Furthermore, the relation to pregnancy is not entirely understood. MG tends to occur in young women, and its incidence peaks in their 20s and 30s. Since this corresponds to the age of pregnancy and childbirth, safe treatment of MG is needed.[1]

Cardinal features of myasthenia are weakness and fatigability of facial, oropharyngeal, extraocular, and limb muscles.[1,2] Although the mortality rate of MG is less than 5%, exacerbations and remissions mark the clinical course. Remissions are seldom permanent, while systemic diseases, concurrent infections, and even emotional upset may trigger an exacerbation. An exacerbation can be life-threatening if not treated immediately.[1] In general, there is a 40% chance of MG exacerbation during pregnancy and an additional 30% risk in the puerperal period.[3] Since the most significant period of risk is within the first year following diagnosis, postponing pregnancy until there is a sustained improvement is reasonable.[1,2]

Myasthenic crisis is an MG exacerbation that is mainly present as severe weakness and potentially fatal respiratory failure due to diaphragm and accessory breathing muscle weakness. MG exacerbations occur roughly in about 15% of patients. The management's primary focus is to achieve remission, a state of no signs or symptoms of myasthenic weakness. Alternatively, a condition where no subjective symptoms and only mild weakness found on objective neurologic examination could be accepted as long as it does not interfere with normal function. Furthermore, this goal should be achieved with the minimal possible side effects from medications.[2] This is particularly important in pregnant women, as drugs may affect fetal development.

This case report aims to describe the diagnostic strategy, optimal management of pregnancy with MG, the influence of pregnancy to MG exacerbation, the influence of MG on pregnancy, the possible influence of MG medication for the growth and development of the fetus, and the timing to terminate the pregnancy along our experience managing such case.

CASE

A 27-year-old 155-cm 52-kilogram Balinese female had been diagnosed with Myasthenia gravis since 2016 and has taken oral Pyridostigmine Bromide routinely. The patient was hospitalized six times during her second pregnancy.

In the first hospitalization, the patient came with dyspnea, difficulty swallowing, and weakness of all her extremities. The patient was diagnosed with MG

with an acute exacerbation equal to the Myasthenia Gravis Foundation of America (MGFA) class IIIB. She was treated with oral Pyridostigmine Bromide 60 milligrams (mg) four times a day (QID) and was planned to undergo plasmapheresis every two days. The patient's clinical condition deteriorated on the second day, so she was planned to have a massive TPE (Therapeutic Plasma Exchange). However, her condition improved and was discharged on the sixth day. The patient had not yet been diagnosed with pregnancy at that time. After a week of discharge, the patient came to Neurology Polyclinic and was diagnosed with a second pregnancy and was consulted to Obstetrics and Gynecology (Ob-Gyn) Polyclinic. The patient was diagnosed with the second pregnancy, intrauterine fetus, gestational age five weeks three days (from gestational sac measurement complemented with Naegele rule determined from the first day of the last menstrual period). She was advised for a reevaluation visit at 12 weeks gestational age.

At second hospitalization, the patient presented with complaints of difficulty swallowing, increased mucus secretions, dyspnea, and dysphonia. She was diagnosed with MG MGFA IIIB acute exacerbation, with gestational age nine weeks six days, and was treated with Pyridostigmine Bromide and Methylprednisolone. She also developed the signs of pneumonia and was consulted to the Ob-Gyn Department for the feasibility of chest X-ray examination and the effects of MG medications on pregnancy. The patient underwent a chest X-ray examination with apron protection and was suggested to administer Methylprednisolone over 12 weeks gestational age. The Pulmonology department consultation and chest x-ray resulted in no lung infection. The patient did not improve for three days, and on day 4, the Neurologist planned to conduct a plasmapheresis every two days for three times (day 5, 7, 9). They consulted the Ob-Gyn Department regarding long-term plasmapheresis effect on the pregnancy. Considering the risks of preterm labor, the Ob-Gyn administered oral Micronized Progesterone 100 mg BID and Folic Acid 400 mcg QD. The patient improved and was discharged on day 12.

At the third hospitalization, the patient presented with dyspnea, cough, difficulty swallowing and chewing, difficulty to lift eyelids, dysphonia, and was diagnosed with MG MGFA IIIB, 15 weeks two days gestational age, suspected bronchial asthma, and Community-Acquired Pneumonia with Pneumonia Severity Index (CAP-PSI) Class III High-Risk Multi-Drug Resistance. She treated with oral Pyridostigmine Bromide 60 mg every 5 hours, intravenous (IV) Methylprednisolone 125 mg TID, nebulization of Ipratropium Bromide combined with Salbutamol Sulfate three times a day (TID), and oral N-acetylcysteine 200 mg TID. The patient was also given an IV Cefoperazone 1000 mg twice a day (BID) and oral Azithromycin 500 mg once a day (QD) by the internists. On the fourth day, the Azithromycin was stopped by the Internist. On the fifth day, a myasthenic crisis occurred, and the patient had an impending respiratory failure that required intubation and was admitted to ICU with a ventilator. The patient was re-diagnosed with MG MGFA V. The Neurologist held a joint conference and concluded that the next step should include the preparation of massive TPE, the continuation of antibiotic therapy, fetal scanning on 20 weeks gestational age, and Intravenous Immunoglobulin (IVIG) if there is no improvement. TPE was done three times, and the patient's symptoms were clinically improved. The patient was discharged on day 20.

At the fourth hospitalization, the patient had difficulty swallowing, cough, and dyspnea. The patient was diagnosed with MG MGFA IIIB acute exacerbation at 19 weeks three days gestational age, but no specific management was done at this hospitalization relative to the previous episode.

At the fifth hospitalization, the patient presented with dyspnea, cough, difficulty swallowing and chewing, and all extremities' weakness. She was diagnosed with MG MGFA IIIB acute exacerbation due to a suspected Community-Acquired Pneumonia at 28 weeks one day gestational age. She also had mild anemia (Hemoglobin 8,75 g/dL) with a normochromic-normocytic morphology suspected due to chronic disease and hypokalemia (potassium serum 3,09 mmol/L). The patient was reconsulted to the Internists and Ob-Gyn Department. The patient treated with intravenous Methylprednisolone 125 mg TID tapering off every two days, oral Pyridostigmine Bromide 60 mg every 5 hours, oral Ambroxol syrup 15 cc TID, nebulization Ipratropium Bromide combined with Salbutamol Sulfate 1 ampule TID, IV Cefoperazone 1000 mg BID, an extra fruit diet and Potassium Chloride (KCl) drip correction. The patient was also given Azithromycin 500 mg QID for a day but was stopped by the Neurologist. On the fifth day, the patient deteriorated and was intubated. The patient, however, stayed in the non-intensive inpatient ward because the ICU was full. The patient was re-diagnosed with MG MGFA V. Initially, the Methylprednisolone would be switched to dexamethasone for fetal pulmonary maturation. Since the patient's condition worsened, dexamethasone treatment was postponed, and Methylprednisolone continued. The Ob-gyn

suggested prioritizing the patient than the fetus. On the seventh day, the patient had an impending respiratory failure due to ineffective manual respiratory bagging. Therefore, the patient was re-intubated and was finally able to be transferred to the ICU. Later, massive TPEs was done three times on day 9, 12, and 14. The patient was extubated on day-15 and discharged on day-19.-

The patient came with watery vaginal discharge at the sixth hospitalization and a Non-Reactive Non-Stress Test (NST) on the Cardiotocography examination. The patient was diagnosed with the second pregnancy, 35 weeks three days gestational age, with MG MGFA II, Premature Rupture of the Membrane, Non-Reactive NST. Cesarean Section with Bilateral Tubectomy with the Pomeroy method was performed. A vigorous male infant was delivered without evidence of neonatal MG (TNMG) or arthrogryposis. She was admitted to the ICU for a day and was transferred to the Obstetrics High Dependency Unit for the next day. Later, the patient was transferred to the postpartum ward for two days. The patient was discharged on day 5 in a stable condition. The patient visited the Ob-Gyn polyclinic a week later and was regularly evaluated in the Neurology polyclinic once a month.

Table 1. Clinical Classification by Myasthenia Gravis Foundation of America (MGFA)

Class	Clinical Symptoms
I	Any ocular weakness
II	Mild Weakness. May also have ocular muscle weakness of any severity.
IIA	Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal, respiratory muscles, or both.
IIB	Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.
III	Moderate weakness affecting other than ocular muscles. May also have ocular muscle weakness of any severity.
IIIA	Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal, respiratory muscles, or both.
IIIB	Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.
IV	Severe weakness affecting other than ocular muscles. May also have ocular muscle weakness of any severity.
IVA	Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal, respiratory muscles, or both.
IVB	Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.
V	Defined by intubation, with or without mechanical ventilation, except when employed during routine postoperative management.

DISCUSSION

Myasthenia Gravis typically present with painless, fluctuating weakness of the skeletal muscles. The diagnosis of MG is established with the aid of the Repetitive Nerve Stimulation (RNS) test with Electromyography (EMG) and the Edrophonium Test. RNS test evaluates a progressive decrement of motor neuron response while the Edrophonium test evaluates any improvement after Edrophonium administration. Serum Acetylcholine Receptor Antibody (AChR-Ab) and serum Muscle-Specific Tyrosine Kinase autoantibody (MuSK-Ab) test, if available, used to detect specific antibody involved. Furthermore, The Chest CT-Scan helps detect the presence of a thymoma. These tests can affect diagnosis and management, therefore, it should be checked.[3]

The patient was first diagnosed with MG in 2016, with clinical symptoms of weakness, ptosis, difficulty lifting the extremity and walk, difficulty chewing, and swallowing. The patient's edrophonium test was positive, RNS was positive, the AChR antibody test was positive, and no mass on mediastinum from thoracal CT-Scan. The patient was then diagnosed with the second pregnancy with AChR-Myasthenia Gravis (AChR-MG) without thymoma. Theoretically, AChR-MG comprised the majority of MG cases (80%). AChR-MG has age characteristics at onset <40 years (so-called Early-Onset MG/EOMG), more common in women with ratio 3:1, serum AChR antibody result is positive. The clinical symptoms begin from difficulty to lift the eyelid (ocular symptom), then develop to generalized weakness.[4] All of the characteristics consistent with the patient's symptoms.

Based on Myasthenia Gravis Foundation of America (MGFA) clinical classification, as seen in Table 1,[5] the patient had five times exacerbation (MGFA IIIB) and two times myasthenic crises (MGFA V) during the second pregnancy. Fifteen to 20% of myasthenic patients are affected by the myasthenic crisis. The predisposing factors are pregnancy, respiratory tract infection, electrolyte abnormality, emotional stress. Certain medications could also trigger a myasthenic exacerbation, although it is also difficult to differentiate from the cholinergic crisis due to anticholinesterase medication overdose. The presence of concomitant CAP in this patient is the suspected predisposing factor that exacerbates the patient's MG's clinical course.

MG is manageable but not curable. The management of MG includes (1) Symptomatic medications, (2) Immunomodulation therapy, (3) Plasmapheresis and IV Immunoglobulin (IVIG), (4) Surgery. Symptomatic medications are

anticholinesterase/acetylcholine-esterase inhibitors, such as Pyridostigmine. This patient has been taking Pyridostigmine since the first time she was diagnosed with MG. Immunomodulation therapy is mainly utilized with corticosteroid administration if exacerbations occur. This patient was given Methylprednisolone during the hospitalization. Management with plasmapheresis and IVIG is administered if a myasthenic crisis presents. This patient was given plasmapheresis therapy twice and massive TPEs throughout her exacerbation episodes. The patient had a history of IVIG administration at her last exacerbation around seven months before her pregnancy. The IVIG and TPE, a slightly different immunologic therapy, started gaining traction in many autoimmune disease management, including MG. The comparison table between IVIG and TPE is shown in Table 2. The patient was not suitable for any surgical management, as there was no indication of thymoma. Nevertheless, Thymectomy is an optional therapy for AChR-MG without thymoma and may improve MG's clinical

Table 2. Comparison of Intravenous Immunoglobulin (IVIG) to Plasma Exchange (PE).[6]

	IVIG	PE
Dose	400 mg/kg x 5 day	one *plasma exchanges* every other day over ten days
Response	Improvement in 4-5 day; effect for 4-8 weeks	Improvement in two days, the effect lasting for 3-4 weeks
Advantages	More readily available	Faster treatment response
Disadvantages	Slower treatment response	Need for special venous access, equipment, and personnel
Contraindications	IgA Deficiency	Hemodynamic instability, unstable coronary disease, current internal bleeding
Serious Complications	Aseptic meningitis, cardiac arrhythmia, thrombocytopenia, thrombotic events	Hemodynamic instability, cardiac arrhythmia, myocardial infarction, hemolysis

Table 3. Drugs that may worsen myasthenia gravis.[10]

Drugs which may worsen myasthenia:

- Neuromuscular blocking drugs
- Aminoglycoside antibiotics such as gentamicin, neomycin, amikacin, and tobramycin
- Fluoroquinolones such as levofloxacin, ofloxacin, ciprofloxacin, and norfloxacin
- Vancomycin
- Beta-blocking drugs such as propranolol, labetalol, and metoprolol
- Anti-arrhythmic drugs such as procainamide and quinidine
- Magnesium
- Chloroquine and hydroxychloroquine
- Quinine
- Penicillamine
- Botulinum toxin
- Monoclonal antibody such as nivolumab and pembrolizumab

Drugs which are usually well tolerated but may worsen myasthenia:

- Inhalation and local anesthetic agents such as isoflurane, halothane, bupivacaine, lidocaine, and procaine
- Antibiotics such as ritonavir, tetracyclines (doxycycline & tetracycline, Macrolide antibiotics (Azithromycin, Erythromycin, and Clarithromycin), Metronidazole, Nitrofurantoin
- Antiepileptic drugs such as carbamazepine, gabapentin, phenytoin, phenobarbital, and ethosuximide
- Glucocorticoids, which started in high doses
- Antipsychotic drugs such as lithium, phenothiazine, butyrophenone
- Calcium-channel blockers such as verapamil
- Statins
- Cisplatin
- Riluzole
- Emetine
- Glatiramer
- Interferon alpha
- Iodinated contrast agents
- Topical ophthalmic solutions such as timolol and tropicamide

outcome, MG exacerbation risk in pregnancy, and TNMG risk. One particular thing to note is that Thymectomy should be done before pregnancy. Medication with antibiotic Azithromycin should not be used because macrolide antibiotics can trigger exacerbation due to its disruption of acetylcholine **release** (see Table 3). Indeed, the myasthenic crisis caused by Azithromycin has been reported in several case reports.[7–9] However, the patient had received Azithromycin before, and this could be the precipitating factor of her myasthenic crisis.

Optimal MG management needs a multidisciplinary team. The patient was managed by obstetricians, neonatologists, and neurologists with the patient and her family's active contribution. The patient never got prenatal counseling, so she did not postpone her pregnancy until at least one year of sustained improvement. In antenatal management, the patient had been informed to have adequate rest, immediate treatment if infection presents, potassium-rich diet, and avoid emotional stress. The patient had done antenatal visits every two weeks in the first and second trimester and every one week in the third trimester.

The pregnancy outcome was satisfying, considering the presence of obstetric indication for emergency cesarean section. The patient presented with a preterm premature rupture of the membrane with non-reactive NST, but the baby was viable (35 weeks three days) with adequate estimated fetal weight. However, if there had been no obstetric indication, the patient should be suggested vaginal delivery because MG does not affect myometrium. The second stage of labor might need to be accelerated with operative vaginal delivery, such as vacuum extraction or forceps delivery, as the patient may have fatigue in the second stage of labor.

All babies born to mothers with MG should be closely monitored for 72 hours in the neonatal intensive care unit with close surveillance, because of the risk of TNMG that manifests as various symptoms related to muscle weakness. TNMG usually resolves spontaneously but can be fatal if supportive respiratory management is commenced quickly. The use of Pyridostigmine, corticosteroid, and IVIG does not restrict breastfeeding, however, take extra precaution for other immunosuppressant drugs such as Azathioprine, Mycophenolate, Cyclosporine, Cyclophosphamide, Methotrexate, and Rituximab.[6,10,11]

In general, MG symptoms will improve in 30% of patients, remain stable in 30%, and worsen 40%. Worsening of myasthenic symptoms is usually seen during the first trimester and in the first month following delivery, while the improvement of myasthenic symptoms was reported during the second and third trimesters. This fact was consistent with the patient because she experienced four exacerbations in the first and early second trimester. Fortunately, newborn prognosis is not related to pregnancy or MG's severity during pregnancy. However, the newborn should be closely observed for the first 72 hours. In general, MG does not affect fetal development and pregnancy per se. There is no increased risk of low birth weight, increased risk for spontaneous abortion, or prematurity.[10] Although proper treatment for the mother and proper selection of medication indirectly may affect fetal development.

CONCLUSION

Myasthenic crisis in pregnancy is a relatively rare condition in pregnant women with myasthenia gravis. It is potentially life-threatening and requires aggressive and specific management. Patent airway and ventilation monitoring are essential. Therefore, ICU treatment for optimal management is a must. Massive TPE might be utilized if condition and supporting facilities available. MG often occurs in a woman during their reproductive age. Thus guidelines regarding exacerbation and myasthenic crisis management during prenatal, antenatal, and delivery, along with neonatal management, breastfeeding, contraception method, and pregnancy planning, are needed.

PATIENT CONSENT

The patient had agreed and signed informed consent regarding publishing the case in an academic journal without exposing her identity.

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CONFLICT OF INTEREST

The author does not have a conflict of interest in this case report.

AUTHOR CONTRIBUTION

All authors contributed equally to the study.

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