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Myasthenia Gravis in Pregnancy-Optimal Outcome with Precision of Care; Case Series from South India and Review of Literature

Dhanya R Shenoy¹, Nina Navakumar^{1*}, Brinda Sabu¹, Vidyalekshmy R¹, Roshini Ambat², Sajith Mohan², Suresh Chandran³, Rafeekha P², Lumiya Malik²

¹Maternal and Fetal Medicine, KIMS Health, Trivandrum, Kerala, India. ²Obstetrics and Gynecology, KIMS Health, Trivandrum, Kerala, India. ³Neurology, KIMS Health, Trivandrum, Kerala, India. *Corresponding author: Nina Navakumar.

Abstract

Introduction: Myasthenia Gravis (MG) is an autoimmune neuromuscular disorder affecting skeletal muscles, particularly in women of reproductive age. Though uncommon with a prevalence of only 0.3 to 2.8 per 100,000, the incidence peaks during 2nd and 3rd decades of life, and can have significant impact in pregnancy. The course of the disease in pregnancy is not entirely understood.

Methodology: Retrospective observational study was designed as the disease prevalence is very less. A retrospective case series analysis of 4 cases were carried out for a period of 5 years from 2018 in a tertiary care center in South India to identify and describe the disease course in pregnancy and effect of disease in the pregnant women and their fetuses. Data was collected and reviewed from their case records. From this study, we aimed to describe the disease course of MG in pregnancy and formulate an optimal management plan, learning from our experience.

Results: All patients included in the study were in a state of remission prior to conception. With vigilant monitoring and collaborative multidisciplinary, two patients successfully carried their pregnancies to term without encountering any complications, maintaining a stable course throughout the antenatal, intrapartum, and postpartum periods. However, one patient experienced an acute exacerbation upon contracting COVID-19 category C. Subsequently, her pregnancy was complicated by late-onset fetal growth restriction, preterm premature rupture of membranes (PPROM), preterm birth and postpartum exacerbation. Despite these challenges, both maternal and fetal outcomes were favorable, attributed to meticulous surveillance and critical care interventions. Another patient experienced an exacerbation at 10 weeks of gestation but otherwise had an uneventful pregnancy, labour, and postpartum recovery.

Conclusion: One third of Myasthenia gravis patients can have exacerbations in pregnancy with a small but significant subset experiencing potentially life threatening Myasthenic crisis. Medications such as Pyridostigmine and Prednisolone are effective for managing the disease. All necessary precautions should be pro-actively taken to prevent factors that could trigger a myasthenic crisis, including cautious drug selection during anesthesia and the avoidance of medications that may exacerbate MG during acute infections. Cesarean section should be for obstetric indications only. Managing myasthenia gravis in pregnancy is quite challenging and requires multidisciplinary input with close monitoring and follow up for the development of complications.

Keywords: autoimmune disease; pregnancy; myasthenia gravis; cesarean section

Introduction

Myasthenia Gravis (MG) is an autoimmune disease which occurs due to autoantibodies to acetylcholine receptors (AChR) in the neuromuscular junction. Clinical features include fluctuating weakness in the skeletal muscles, mainly affecting the ocular, bulbar, limb, and respiratory muscles. MG is relatively uncommon, with a reported prevalence of 0.3 to 2.8 per 100,000 [1]. The incidence of MG peaks during 2nd and 3rd decades of life, where the woman is in the reproductive age; and thus, it can influence

pregnancy and pregnancy outcomes. MG typically has a remitting relapsing course, with occasional exacerbations sometimes progressing to Myaesthenic crisis putting a women's life at risk. Systemic diseases, concurrent infections, electrolyte abnormalities and even emotional upset may trigger an exacerbation. An exacerbation can be life-threatening if appropriate treatment is not initiated early [2]. The course of the disease in pregnancy is not entirely understood. In general, there is a 40% chance of MG exacerbation during pregnancy and an additional 30% risk in the puerperal period [3].

In this study, we present case reports detailing the experiences of four myasthenia gravis (MG) patients from our hospital and their pregnancy outcomes aiming to provide insights into the management of MG during pregnancy and its effects on maternal and fetal well-being.

Aim: To evaluate the management and outcomes of Myasthenia gravis (MG) in pregnancy, focusing on maternal and perinatal outcome.

Objective: Our objectives were to assess the impact of MG on pregnancy, analyses the management strategies employed for MG during pregnancy and to evaluate their maternal and perinatal outcome.

Methodology

This retrospective observational study spanned over a period of 5 years comprising 4 cases from 2018 and was conducted at a tertiary care center in South India, considering the low prevalence of the disease. We performed a retrospective case series analysis to identify and describe the disease course in pregnancy and its effects on pregnant women and their fetuses. Data were collected and reviewed from the case records of the patients. The study aimed to describe the disease course of MG in pregnancy and formulate an optimal management plan based on our experiences. Our objectives were to assess the impact of MG on pregnancy and pregnancy outcomes, analyze the management strategies employed for MG during pregnancy, and evaluate the maternal and fetal outcomes in pregnancies complicated by MG.

Results

All patients included in the study were in a state of remission prior to conception. With vigilant monitoring and collaborative multidisciplinary, two patients successfully carried their pregnancies to term without encountering any complications, maintaining a stable course throughout the antenatal, intrapartum, and postpartum periods. However, one patient experienced an acute exacerbation upon contracting COVID-19 category C. Subsequently, her pregnancy was complicated by late-onset fetal growth restriction, preterm premature rupture of membranes (PPROM), and preterm birth. Additionally, she experienced a postpartum exacerbation. Despite these challenges, both maternal and fetal outcomes were favorable, attributed to meticulous surveillance and critical care interventions. Another patient experienced an exacerbation at 10 weeks of gestation

but otherwise had an uneventful pregnancy, labor, and postpartum recovery.

Case 1

A 28-year-old primigravida at 13 weeks of gestation presented with symptoms suggestive of myasthenia gravis (MG), including increased fatigue, voice changes, tongue weakness, slurred speech, and ptosis; following which MG was confirmed by a nerve stimulation test showing decremental response and positive Anti-choline receptor antibodies. She was Pyridostigmine initiated on and Prednisolone, gradually tapered and had remission for the rest of pregnancy. She was diagnosed to have gestational diabetes mellitus at 24 weeks of gestation, and was managed with medical nutrition therapy and Insulin.

At 26 weeks, she had COVID-19 which progressed to be critically ill and was managed by multidisciplinary team. Team encompassing Maternal & Fetal medicine Specialist, Intensivist, Infectious disease specialist and Respiratory Physician. preparedness of the medical team to address complications as they arose was crucial in ensuring a successful outcome. Careful planning and proactive measures were taken to manage the patient's including the administration condition, appropriate medications such Remdesivir, Tocilizumab, Intravenous Dexamethasone, and LMWH. Although data on their safety in MG patients were limited, the decision to use these medications was based on the perceived maternal benefit outweighing potential fetal risks. Prophylactic Trimethoprim-Sulfamethoxazole for Pneumocystis Carinii was also suggested due to her high-dose steroid therapy.

The patient recovered within a week but subsequently developed late-onset fetal growth restriction. At 36 weeks, she had preterm premature rupture of membranes (PPROM) and progressed to spontaneous labor, resulting in the delivery of a baby weighing 2230g with good Apgar scores and no neonatal complications. Intrapartum stress dose steroids were administered. Postnatally, she experienced a myasthenia gravis exacerbation, characterized by drooping of eyelids and increased fatiguability, necessitating an increase in Pyridostigmine and Prednisolone dosage.

Six weeks postnatally, she experienced another myasthenia gravis exacerbation, prompting the

initiation of Azathioprine therapy. Subsequently, she developed generalized itching and discoloration of the eyes, leading to the diagnosis of autoimmune hepatitis. Further evaluation with autoimmune liver profiles and liver biopsy supported this diagnosis and she was started on hepatoprotective measures. She is currently under the care of medical gastroenterology and neurology for ongoing management and follow-up. Ultimately, collaborative interdisciplinary approach, their preparedness to manage complications, and their timely and appropriate care contributed to the successful outcome of the patient's pregnancy despite her critical illness due to COVID-19.

Case 2

33-year-old, second gravida, previous LSCS with Myasthenia gravis diagnosed 5 years ago when she presented with weakness of both upper and lower limbs, difficulty in chewing and deviation of chin. Prior to pregnancy, she was having a stable course of MG and was on Pyridostigmine. During first trimester, at 10 weeks of gestation, she had exacerbation for which Pyridostigmine dose was increased (Prednisolone) and steroids were added and went into remission after a month. MG was stable during rest of her antenatal period. She was managed by a multidisciplinary team. She underwent elective cesarean section at 39 weeks in view of previous cesarean section maternal request. Intrapartum stress dose steroids were given and anaesthetic drugs were modified not to include Myasthenia precipitating drugs. Postnatal period was uneventful. Baby was term baby of weight 2470g with good Apgar and no neonatal complications.

Case 3

A 28-year-old primigravida with a history of Myasthenia gravis (MG) presented at 14 weeks of gestation. Her initial symptoms included diplopia and ptosis 2 years ago leading to a diagnosis of MG with a CT scan of the thorax showing thymoma. Nerve conduction study showed Post Junction Type of Neuromuscular junction dysfunction. Confirmatory tests, such as the Acetyl Choline Receptor Antibody test, were positive. She was managed with Prednisolone (tapering later) and Pyridostigmine, and was under regular neurology and ophthalmology follow-up. Additionally, she had a concurrent diagnosis of Graves' disease with thyroiditis and was

on Neomercazole, which was later switched to Propyl Thiouracil in the second trimester of pregnancy under the guidance of an endocrinologist. She had a stable course of MG prior to pregnancy and she had a planned pregnancy. She had to undergo an elective Cesarean section at 39 weeks in view of traumatic pubic symphysis diastasis. Intraoperative stress dose steroids were administered. She delivered a healthy male baby weighing 2940g without any complications. Postnatally, she continued Prednisolone 5mg, Neomercazole 5mg, and Pyridostigmine 30mg, under close monitoring by the medical team.

Case 4

24-year-old primigravida who was a diagnosed as a case of Myasthenia gravis from 3 years of age. She had a history of Myasthenic crisis at 9 years of age when she had progressive weakness and breathlessness and was treated with IVIg, methyl prednisolone in high dose. She had a remitting relapsing course since then with her last relapse at 13 years of age. She was in remission phase during conception and had a planned pregnancy with tapered doses of Pyridostigmine and Prednisolone with no exacerbations or complications during pregnancy and postpartum. Postnatally, her steroid doses were further tapered and she is on long term follow up with medical team.

Discussion

Myasthenia gravis (MG) was first described by the Thomas Willis, a physiologist in the 17th century. MG typically present with painless, fluctuating weakness of the skeletal muscles [1,2]. It maybe generalized or confined to ocular muscles. MG affects females more commonly (2:1 ratio), especially during the 2nd and 3rd decades of life, this being a time for increased probability of becoming pregnant [4,5]. There is another peak of incidence between the sixth and seventh decade, but this time mainly affecting males [4,5]. 75% of patients have thymic alterations (85% hyperplasia, 10%-15% thymomas) and 85% with high acetylcholine receptor antibodies [6]. MG occurs due to accelerated degradation of acetylcholine receptors, blocking antibodies or secondary damage to the Nm junction. Myasthenia Gravis (MG) is classified into different types: Congenital MG, which is not autoimmune but arises from genetic defects; Transient neonatal MG, caused by maternal antibodies and typically resolves quickly; Juvenile MG, developing in childhood; Ocular MG, affecting only the orbicularis oculi muscles; and Generalized MG, the most common type, which affects all skeletal muscles.

The Osserman and Genkis classification [7] of MG further divides the condition into subtypes: Class 1, characterized by only ocular myasthenia with ptosis and diplopia; Class 2A, featuring generalized moderate weakness; Class 2B, exhibiting generalized moderate weakness and/or bulbar dysfunction; Class 3, presenting as an acute fulminant condition and/or respiratory dysfunction; and Class 4, representing late

severe generalized compromise. The diagnosis of MG is established by Repetitive Nerve Stimulation (RNS) test which shows a progressive decrement of motor neuron response; and positive Serum Acetylcholine Receptor Antibody (AChR-Ab). MG typically has a remitting relapsing course, with occasional exacerbations sometimes progressing to Myaesthenic crisis putting a women's life at risk. Systemic diseases, concurrent infections, electrolyte abnormalities, certain drugs and even emotional upset may trigger an exacerbation.

Chart 1: Drugs that may worsen myasthenia gravis [8].

Known to worsen myasthenia
Neuromuscular blocking agents
Antibiotics-Aminoglycosides e.g., gentamicin, neomycin, amikacin, tobramycin
Fluoroquinolones e.g., levofloxacin, ofloxacin, ciprofloxacin, norfloxacin
Vancomycin
Antimalarials- Chloroquine, hydroxychloroquine, Quinine
Beta-blockers- propranolol, labetalol, and metoprolol
Anti-arrhythmic- procainamide and quinidine
Magnesium (MgSo4)
Penicillamine
Botulinum toxin
Monoclonal antibodies e.g., nivolumab and pembrolizumab
Usually well tolerated but may worsen myasthenia
Inhalation/local anesthetics e.g., isoflurane, halothane, bupivacaine, lidocaine, procaine
Antibiotics- Metronidazole, Nitrofurantoin, Tetracyclines, Macrolides (Azithromycin, Erythromycin, Clarithromycin)
Antiepileptics- phenytoin, phenobarbital, carbamazepine, gabapentin and ethosuximide
Glucocorticoids in high doses
Antipsychotics -lithium, phenothiazine, butyrophenone
Calcium-channel blockers-verapamil

Myaesthenia Gravis and Pregnancy

Iodinated contrast agents

Statins

Effects of pregnancy in the course of Myaesthenia

Topical ophthalmic solutions-timolol and tropicamide

Djelmis et al., reviewed 69 cases of pregnant females with MG of which 15% deteriorated in antepartum and 16% during peripartum, whilst 17% terminated in caesarean.4 Plauche found that 31% of pregnant females with MG had a stable clinical course, 28% improved and 40% worsened during postpartum period [9]. Among our cases cited here, one patient had exacerbation during pregnancy, while the other patient was diagnosed with MG in pregnancy and had an exacerbation during COVID infection and postpartum period. The risk of clinical deterioration is higher in females who became pregnant during the first year of diagnosis of the disease [4,5]. Recurrent

infection in pregnancy or puerperium can lead to myasthenic crisis with respiratory paralysis [4,10]. MG treatment primarily includes symptomatic management with anticholinesterase agents& steroids and immunosuppressive agents used in more severe refractory cases/myasthenic cases. For crises, intravenous immunoglobulin (IVIG) and/or plasmapheresis are used.

Anticholinesterases like pyridostigmine keep the disease activity under control and hence must be continued in pregnancy; however, the dose may have to be increased due to reduced gastric emptying and poor intestinal absorption in pregnancy [11]. It may increase uterine tone and contractility, but there is no proven risk of spontaneous abortion. Corticosteroids are used in MG exacerbations during pregnancy,

despite the risk of cleft palate. (Category B drug) [11]. Azathioprine is used when there is no response to corticosteroids (Category D drug) Cyclosporine A is also sometimes used [11]. Plasmapheresis is reserved for patients with severe bulbar symptoms/respiratory compromise requiring mechanical ventilation (myasthenic crisis) [4,10,11]. Intravenous immunoglobulin is used plasmapheresis cannot be used [11]. Thymectomy is indicated in patients with a thymoma and/or generalized seropositive disease [5]. However, high quality data regarding the optimal management of MG in pregnancy is lacking.

Effects of Myaesthenia on pregnancy outcome

As regarding pregnancy outcome, maternal effects include increased risk of relapses and worsening of MG in pregnancy and postpartum, pregnancy complications like PPROM, PROM, preterm delivery, increased Cesarean rates; & fetal effects include Fetal growth restriction and Transient neonatal MG. Some studies have reported increased rates of PPROM, preterm birth, small for gestational age babies and increased Caesarean delivery [14-16], while others have reported rates similar to that of the general population [19,20]. Amongst our cases, 1 patient had PPROM, preterm birth and SGA while the other patient had no adverse pregnancy outcomes. The duration of labor is not altered in MG as it affects only skeletal muscles. However, increased incidence of forceps use has been shown due to the lack of expulsive force [12]. In our case reports, 1 of them had an unassisted vaginal delivery & the other had an elective Cesarean for other reasons.

Cesarean section should be done only for obstetric indications. If Cesarean section is required, there should be cautious choice of drugs during anaesthesia (avoid drugs that can worsen MG). During preanaesthetic checkup, their muscular strength for respiration should be evaluated (especially if there is bulbar compromise). Anaesthetists should also keep in mind that patients with MG have increased sensitivity to non-depolarizing relaxants, inhaled anaesthetics, cis-atracurium and mivacurium as seen by faster onset of action and longer blocking-action compared to controls [13-15]. Extreme vigilance is required while using various anaesthetic drugs. Transient neonatal myasthenia gravis (TNMG) is a complication wherein the AChR autoantibodies pass through the placenta and causes a self-limited myasthenic syndrome in the neonate. Risk of TNMG being 10-15%, with some cases reporting rates ranging between 3-4% [16] and 33% [17]. Neither of our patients had any neonatal complications.

Management of Myaesthenia gravis in pregnancy

Based on our clinical experience, the comprehensive management of myasthenia gravis (MG) during pregnancy is a multifaceted endeavor that involves careful planning and coordinated care.

Preconception & antepartum

The journey begins with the deliberate planning of pregnancy, where achieving a state of remission in MG before conception is pivotal. This is followed by thorough prenatal counselling sessions that cover various aspects, including the significance of attaining remission before conception, the potential impact of pregnancy on MG, and the reciprocal effects of MG on pregnancy, encompassing both maternal and fetal risks. Emphasis is placed on the importance of regular monitoring throughout pregnancy to ensure timely intervention if needed. The management of pregnant women with MG is best undertaken in specialized tertiary or quaternary care centers, where a collaborative, multidisciplinary team consisting of high-risk obstetrician, pregnancy neurologist, anaesthetist, and neonatologist can provide comprehensive and tailored care. Active participation of the patient and her family in decisionmaking processes is encouraged to ensure holistic management. Throughout the pregnancy, patients are educated about the potential signs and symptoms of MG exacerbation, such as diplopia, dysphagia, dysarthria, and dyspnea. They are instructed to report any such symptoms promptly, as the risk of MG exacerbation during pregnancy is significant. Regular screening for infections during pregnancy is imperative, involving urine culture and sensitivity tests as well as high vaginal swabs in each trimester. This is crucial as infections can precipitate MG exacerbations.

The management of medications during pregnancy is crucial for MG patients. Some medications used to treat MG, such as pyridostigmine and prednisolone, may need to be continued during pregnancy, while others may need to be adjusted or discontinued. Close monitoring of medication dosages and potential side effects is essential. Avoidance of medications that can worsen MG, such as beta-blockers, aminoglycosides, vancomycin, fluoroquinolones, and neuromuscular blocking drugs, is advised whenever feasible. Monitoring for potential pregnancy complications

such as pre-eclampsia or gestational hypertension is crucial for pregnant women with myasthenia gravis. If an MG patient develops gestational hypertension, caution should be exercised when using labetalol, as it may precipitate myasthenic crisis. Instead, other antihypertensives like methyldopa or nifedipine can be considered. Additionally, in pre-eclampsia patients, the use of magnesium sulfate (MgSO4) should be approached with caution, as it may also precipitate a crisis. Additionally, fetal well-being should be closely monitored with regular ultrasound examinations every four weeks, starting from the 24th week of pregnancy. This careful monitoring helps to detect any signs of complications early, allowing for timely intervention and management to ensure the best possible outcomes for both the mother and the baby.

Intrapartum

The mode of delivery should be carefully considered based on the patient's individual circumstances, including the severity of their MG symptoms and any other pregnancy-related complications. Cesarean section should only be performed when medically indicated. When managing myasthenia gravis (MG) during labor and delivery, it is crucial to carefully select anesthetic agents. Neuromuscular blocking agents should be used with extreme caution or avoided entirely due to their potential to exacerbate muscle weakness in MG patients. Inhalation/local anesthetics e.g., isoflurane, halothane, bupivacaine, lidocaine, procaine may also precipitate MG crisis and should be used with caution. Regional anesthesia options like epidural or spinal anesthesia are often preferred over general anesthesia to minimize the risk of respiratory compromise.

Monitoring of respiratory function is essential throughout labor and delivery. Continuous monitoring of oxygen saturation, respiratory rate, and tidal volume can aid in the early detection of respiratory compromise. Medications that can worsen MG should be avoided, including certain antibiotics, neuromuscular blocking agents, and medications that affect neuromuscular transmission. Any medications given during labor should be carefully selected and administered under close supervision. In cases where the mother is on steroids at a dose exceeding 7.5 mg/day during pregnancy, stress doses of steroids should be administered during labor to prevent adrenal insufficiency.

Postpartum

The postpartum period is a critical time for MG patients, as around 30% of women with MG can experience exacerbations during the puerperium. Close monitoring and follow-up care are essential during this time to ensure that any postpartum complications are promptly identified and managed. Postnatal evaluation of the newborn is essential to rule out any signs suggestive of Neonatal MG. A comprehensive approach, integrating expertise, patient education, and meticulous monitoring is thus necessary to optimize outcomes for both the mother and the baby in pregnancies complicated by MG.

Conclusion

Myasthenia gravis, though a relatively uncommon condition in pregnancy, has important implications. It typically has a remitting relapsing course, with occasional exacerbations and a small but significant subset experiencing Myasthenic crisis- a life-threatening complication. Hence, proper guidelines and treatment strategies are needed for exacerbations and myasthenic crisis management, prenatal, antenatal, intrapartum, and neonatal management. Managing myasthenia gravis in pregnancy is quite challenging and requires multidisciplinary input with close monitoring and follow up for the development of complications.

Conflict of Interest

None.

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