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Review Article

Myasthenia gravis in pregnancy: a rare disorder with multidisciplinary management

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ABSTRACT

Myasthenia gravis is a rare autoimmune disorder characterized by nicotinic acetylcholine receptor autoantibodies, affecting the neuromuscular transmission leading to progressive weakness. As this disease is seen in the reproductive age group, clinicians need to be aware of this condition and its multidisciplinary management which is the key to successful outcome. Myasthenia gravis especially when associated with pregnancy is a high-risk condition, that may affect both the mother and the fetus and may result in adverse outcome. The pregnancy course is unpredictable with MG.

Keywords: Myasthenia gravis, Pregnancy, Autoimmune disorder

INTRODUCTION

Myasthenia gravis (MG) is an antibody mediated disorder of the neuromuscular junction resulting in variable muscle weakness. Prevalence of MG ranges between 1 in 10,000 to 1 in 50,000 and almost 2/3 patients among them are female.[1] Women are affected in their reproductive years in second and third decades of life.[2] MG can be congenital or acquired and is characterized by an insufficient neuromuscular nerve impulse transmission to striated muscles leading to progressive weakness.[1] There are two clinical forms of MG, ocular and generalized.[1] As MG is seen in the reproductive age group, clinicians need to be aware of this condition and its multidisciplinary management.

MG is a disease with a variable course, with episodic exacerbations requiring more intensive treatment in the form of increased dosages or additional types of medication for symptom control. Myasthenic crisis on the other hand, is a life-threatening complication involving weakness of the respiratory and/or bulbar muscles leading to respiratory compromise requiring ventilatory support.

During pregnancy, MG may affect both the mother and fetus with varying degrees of skeletal muscle weakness and progressive fatiguability and has a variable course in pregnancy. The overall risk of myasthenia gravis exacerbation was reported as 33.8% with a 6.4% risk of myasthenic crisis in pregnancy and 8.2% postpartum.[3-5] The literature is similarly discordant with regard to pregnancy outcome, with some studies reporting increased rates of preterm prelabour rupture of membranes (PPROM), preterm birth (PTB), small for gestational age (SGA) babies and caesarean delivery, and others reporting rates similar to that of the general population.[6-9]

Transient neonatal myasthenia gravis (TNMG) is a complication whereby the autoantibodies pass through the placenta causing a self-limited myasthenic syndrome in the neonate. Risk of TNMG is generally quoted to be 10–15%, with individual series demonstrating rates ranging between 3-4% (10) and 33%.[11]

DIAGNOSIS OF MG

In all the suspected cases of MG, diagnosis needs to be confirmed either by immunological or electrodiagnostic

testing. Seropositive MG are the patients who are positive for acetylcholine receptor antibodies (AChR-Ab) and is a more common type of this disorder seen in 80% of patients. Autoantibodies against AChR-Ab should be tested and if negative, antibodies to muscle-specific tyrosine kinase (MuSK) should be performed. In approximately 40% of MG patients with negative Ach-R-Ab, antibodies against the muscle-specific kinase (MuSK) are found and in some patient's lipoprotein receptor-related protein 4 antibody can also be found.[1,12,13] AChR-Ab is having 80-90% sensitivity in generalized MG patients and 50-70% in ocular MG patients.

Djelmis et al reviewed 69 cases, all are positive for AChR-AB.[5] Pregnancy is rarely reported in anti-MuSK antibody positive patients. Inoue et al in 2020 reported a case of MG in 31-year-old pregnant female who was diagnosed as a case of anti-MuSK antibody positive MG in the postpartum period. In electrodiagnostic testing, repetitive nerve stimulation (RNST) and single fiber electromyography (SFEMG) can be done and electromyography has 92-99% sensitivity.

MG course during pregnancy

It has been shown that in 31% of patients, the disease remained stable during pregnancy, whereas in 29% an improvement and in 40% an exacerbation of myasthenia symptoms was observed.[14] Generally worsening of clinical symptoms occurs in about one-third of MG patients. Although possible at any stage during pregnancy, it is more likely during the first trimester and the first month postpartum.[7,15] Many case reports and review of literature suggest that the symptoms worsen more commonly during the postpartum period and greater complications become evident. Out of 30-40% of females in which clinical worsening is seen, half of them had worsening in the post-partum period.[15,16] An improvement of symptoms has been observed in 20-40% of patients in the second and third trimesters of pregnancy.[15] The clinical course of MG in first pregnancy does not predict the clinical course of subsequent pregnancies.

Banner et al reviewed 824 cases and reported exacerbation in 33.8% of women, while 47.9% had stable disease and 8% had an improvement in their symptoms from baseline.[3] Myasthenic crisis was reported in 6.4% and 8.2% experienced a myasthenic crisis during the postpartum period. Djelmis et al reviewed 69 cases of pregnant females suffering from MG and found clinical deterioration in 15%, a further 16% during the puerperium, Tanacan et al reviewed 27 pregnancies with MG and found exacerbation in 25.9% of cases and Renata et al reviewed 21 cases, an exacerbation was seen in 50% of cases.[4,5,17]

Pregnancy complications

On reviewing the literature, it has been seen that MG doesn't have any great influence on pregnancy. MG is associated with an increased incidence premature rupture of membranes. Banner et al reported preterm birth (PTB) less than 34 and 37-weeks' gestation occurred in 4.3% and 11.9% pregnancies, respectively. The overall risk of PPROM was 6.7%.

In a retrospective study done by Tanacan et al in 2019 they had evaluated 27 pregnancies with MG and showed that 14.8% of patients had PPROM, 11.8% had PTB and 14.8% had miscarriage.[4] This study showed that pregnancies with deterioration of disease were more likely to be associated with high chances of miscarriage, PTB, PPROM, Cesarean section (CS), and neonatal MG. There is no increased incidence of preeclampsia but few case reports are reported. In such cases importantly, magnesium sulphate is contraindicated.

Monitoring of patients

Pregnancy should be monitored regularly by the neurologist and the obstetrician. Frequency and timing of antenatal visits depend on the clinical status of the MG. Women who are in remission phase can be followed less frequently and those who are symptomatic should be followed more frequently, preferably once in two weeks in first two trimesters and once weekly in third trimester. Frequent screening for asymptomatic bacteriuria and early treatment of any infection should be done, as it may exacerbate MG.[1] Recurrent infection during pregnancy or postpartum period could lead to myasthenic crisis with respiratory difficulty. Djelmis et al found that all females suffered from puerperal infections developed myasthenic exacerbations. Out of all infections, respiratory tract and urinary infections were most associated with MG.[5]

Management of MG during pregnancy

It includes multiple therapeutic strategies and approaches. It usually requires multidisciplinary approach comprising of obstetricians, neonatologist/pediatrician, neurologist with important contribution from the patient and her relatives. Thymectomy has been recommended as the standard of treatment for MG patients who have thymoma or thymic hyperplasia. Thymectomy is a primary disease controlling modality. Complete remission of the disease has been seen in approximately 45% of thymectomized patients.[18] Clinical aggravations are more commonly seen in non-thymectomized patients as compared to thymectomized patients. Young women with MG who are not planning pregnancy should undergo thymectomy at earliest and surgery may be delayed during pregnancy till delivery, if possible.[1]

TREATMENT OF MG

The mainstay of MG treatment includes acetylcholinesterase enzyme inhibitors drugs for symptomatic relief as well as steroids and other immunosuppressant drugs. Medical advice depends upon the severity of the disease.[19] Medical treatment should not be changed in pregnancy. Anticholinesterase inhibitors

have been safely used in pregnant patients with MG, and in 50% of patients, single-drug therapy is sufficient.[20] Very few cases of congenital malformations like severe neonatal MG with microcephaly have been reported.[21] Commonly used drugs are pyridostigmine (anticholinesterase inhibitor), steroids, and immunosuppressant drugs like azathioprine.

Myasthenic crisis or severe acute exacerbations may require plasmapheresis or intravenous immunoglobulins along with ventilatory support. Plasmapheresis has been safely accomplished throughout pregnancy especially when a short-term benefit is needed.[22] The risk for prematurity is increased due to the removal of hormones via plasmapheresis. In a case reported by Inoue et al patient was diagnosed as anti-MuSK-MG in the postpartum period, she was started on injection prednisolone, but symptoms didn't improve so she underwent double filtration plasmapheresis after 28 days and the patient was discharged on oral prednisolone. Intravenous immunoglobulins use in pregnancy is still experimental but seems to be an effective and safe therapeutic approach.[23]

Mode of delivery

Vaginal delivery is usually preferred as the uterus doesn't consist of striated muscles and is not affected by autoantibodies.[23] As striated muscles are involved in the second stage of labour; instrumental delivery might be necessary if obstetrical assistance is required as patient may get exhausted. Caesarean section should be performed only for the obstetrical indication as surgery may worsen the disease or even precipitate myasthenic crisis but increased rate of caesarean section are commonly seen, partly due to muscle weakness to avoid exhaustion and partly as a precaution which is usually not needed.[23] Banner et al reviewed 824 cases of MG and found that the overall rate of caesarean delivery done for MG was 3.0%, with an additional 30.2% women having a caesarean delivery for an obstetric indication.[3] The rate of operative vaginal delivery was 10.4%, with 56.3% of women having a spontaneous vaginal birth. Djelmis et al in 2002 reviewed 69 cases of MG during pregnancy and 17% had caesarean section. Tanacan et al Cheng et al and Picone et al showed LSCS in 78%, 76% and 35% of cases respectively.[4,23] In our cases, both the patients had emergency preterm caesarean section for obstetrics indication.

NEONATAL MG

Neonatal MG has been seen in approximately 10-20% of newborns of the mother with MG due to the transfer of AchR antibodies and causing transient muscle weakness.[5,18] Cheng et al Banner et al and Djelmis et al showed neonatal MG in 7.6%, 13%, and 30% of neonates respectively.[3,5,23] Babies born to anti-MuSK antibody positive MG patients have high probability of developing neonatal MG. Newborns usually manifest neuromuscular symptoms clinically within the first 12-48 hours postpartum, so strict monitoring of newborns for any muscle weakness is important.

Neonatal MG is characterized by difficulty in swallowing, crying, sucking, and weakness with recurrent episodes of cyanosis. Symptoms usually reported to reverse with 3 weeks of time but in some cases may last for as long as 4 months. In general, there is no correlation between the severity of maternal disease and the occurrence of a neonatal MG. Djelmis et al showed that neonates born to thymectomized mothers showed lower incidence of neonatal MG as compared to non-thymectomized mothers. Few cases of nonspecific hyperbilirubinemia, polyhydramnios, congenital arthrogryposis multiple congenita (AMC), and pulmonary hypoplasia or aplasia have been reported in newborn of mother with MG.[24]

Djelmis et al showed non-specific hyperbilirubinemia in 20% of infants.[5] Cheng et al reviewed 13 cases of MG in pregnant females over 8 years and showed a congenital anomaly in 15% of neonates.[23]

Breastfeeding is not an absolute contraindication but serum antibodies may transfer via breast milk to new-born and neonatal MG may be exaggerated.[25] A non-significant transfer of pyridostigmine bromide and corticosteroids has been also shown in some studies and it is always better to avoid breastfeeding for 4 hours after taking these medications.[26]

Very few case reports were reported from India, Sanwal et al in 2012 reported a case of 28-year-old female, known case of myasthenia gravis, underwent LSCS for obstetrical indication and developed muscular weakness along with ptosis, dysarthria, and dyspnea on third postoperative day.[27] Patient managed well with the increased dose of pyridostigmine (120 mg three times a day), baby also developed transient neonatal MG but resolved over a period of 10 days. Mother and baby both discharged in a stable condition.

Sikka et al in 2015 reported a case of severe myasthenic exacerbation, 25-year-old female, a known case of MG, presented in an emergency with severe preeclampsia like condition along with limb weakness at 36 weeks of gestation, underwent lower segment caesarean section (LSCS) in view of fetal distress, responded well to injection neostigmine along with oral pyridostigmine and steroids, and discharged in stable condition on 10th post-operative day.[28]

Jaleel et al in 2019 reported a case of young pregnant female, a known case of MG post thymectomy, underwent elective LSCS, and remained stable throughout pregnancy and postpartum period on oral pyridostigmine and steroids.[29] Mother and baby both discharged on 7th post-operative day.

CONCLUSION

MG especially when associated with pregnancy is a high-risk condition, and its pregnancy course is unpredictable. Both the mother and baby should be carefully monitored for neuromuscular symptoms. As this disease is commonly seen in the reproductive age group, Obstetricians need to be aware of this condition and its multidisciplinary management, which is the key to successful outcomes.

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