Myasthenia gravis and pregnancy review

Shinde vaishnavi[1], Pratiksha eakurke[2], Bhosale mulje Tanuja[3], Renuka R. Deshpande[4]
[1,2,3]*B.Pharmacy second Year Student, Latur College of Pharmacy Hasegaon, Tq. Ausa, Dist. Latur-413512, Maharashtra, India*
[4]*Assistant Professor, Department of Pharmaceutics, Latur College of Pharmacy Hasegaon, Tq. Ausa, Dist. Latur-413512, Maharashtra, India*

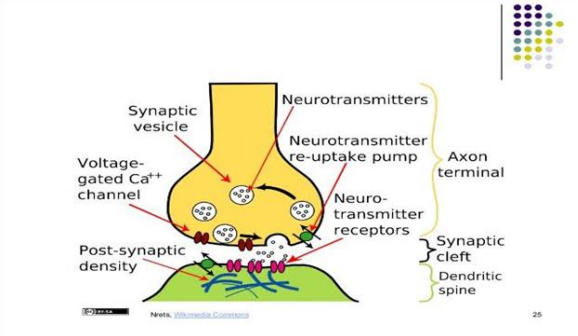
Abstract- **The myasthenia gravis is twice as common in women as in men and frequently affects young women in the second and third decades of life, overlapping with the childbearing years. Generally, during pregnancy in one third of patients the disease exacerbates, whereas in two thirds it remains clinically unchanged. Complete remission can occur in some patients. To describe the clinical course, delivery and neonatal outcome of 18 pregnant women with the diagnosis of myasthenia gravis. Retrospective chart review of pregnant patients with myasthenia gravis, followed at the National Institute of Perinatology in Mexico City over an 8-year period. Data was abstracted from the medical records on the clinical course during pregnancy, delivery and neonatal outcome. From January 1, 1996 to December 31, 2003 18 patients with myasthenia gravis were identified and included in the study. The mean ± SD maternal age was 27.4 ± 4.0 years. During pregnancy 2 women (11%) had an improvement in the clinical symptoms of myasthenia gravis, 7 women (39%) had clinical worsening of the condition of 9 other patients (50%) remained clinically unchanged. Nine patients delivered vaginally, 8 delivered by cesarean section and 1 pregnancy ended in fetal loss. Seventeen infants were born at mean ± SD gestational age of 37.5 ± 3.0 weeks and a mean birth weight of 2710 ± 73 g. Only one infant presented with transient neonatal myasthenia gravis. No congenital anomalies were identified in any of the newborns. The clinical course of myasthenia gravis during pregnancy is variable, with a significant proportion of patients experiencing worsening of the clinical symptoms. However, neonatal transient myasthenia was uncommon in our patient population.**

Index terms- **Azathioprine, myasthenia, pregnancy, pyridostigmine, steroids**

INTRODUCTION

Myasthenia gravis (MG) is an autoimmune disorder of neuromuscular junction (NMJ) with a prevalence of 150–250 per million. It is characterized by weakness of skeletal muscles due to damage inflicted to NMJ by autoantibodies directed either against acetylcholine receptors (AchRs) or other functionally related molecules on the postsynaptic membrane.[1,2] Although a commonly reported neurological disorder during pregnancy, there are controversies surrounding optimal management of MG in pregnancy. In this review, we discuss management of MG during pregnancy. Myasthenia gravis: General characteristics pertaining to women MG affects women twice as often as men. It commonly affects women in second and third decade of life, i.e., during the childbearing age. The clinical severity of MG ranges from pure ocular muscle involvement (ocular MG) to generalized muscular weakness (Generalized MG). Generalized MG is further graded into mild, moderate, and severe depending on the degree of weakness. Approximately 80%–90% of generalized MG patients and 50%–70% of ocular MG patients have AchR antibodies in their serum. Other antibodies which are commonly seen in myasthenic patients include (1) anti-MuSK (muscle-specific kinase) antibodies (seen in about 40% of AchR antibody negative MG patients) and (2) antibodies against lipoprotein receptor-related protein 4. Approximately 10% of patients with MG have thymoma.[1,2,3,4] Effects of myasthenia gravis on pregnancy and vice versa As MG commonly affects women of childbearing age, it is not uncommon to encounter a pregnancy complicated by MG. The effects of pregnancy on the severity of MG are variable. In one study, while 30% of patients did not show any change in the status of MG, 29% reported improvement and 41% reported worsening of myasthenic symptoms during pregnancy.[5] Worsening of myasthenic symptoms was usually seen during 1st trimester and in 1st month following delivery while the improvement of myasthenic

symptoms was reported during 2nd and 3rd trimesters likely related to pregnancy-induced immunosuppression which occurs during these trimesters.[4,5,6] The main causes of exacerbations of MG during pregnancy include: (a) hypoventilation due to weakness of respiratory muscles and elevation of diaphragm during pregnancy, (b) puerperal infections, (c) drugs, as well as (d) stress of labor and delivery. A factor which may be predictive of maternal mortality due to MG itself is the duration of MG before index pregnancy. In one study, the risk of maternal mortality was highest during the 1st year after diagnosis of MG and minimal 7 years after diagnosis of MG. However, in general, long-term outcome of MG is not reported to be altered by pregnancy.[6,7] Furthermore, clinical severity of MG at onset of pregnancy does not predict its course during pregnancy and behavior of MG during index pregnancy does not predict its course during future pregnancies. In general, MG does not affect pregnancy to a large extent. There is no increased risk of low birth weight, spontaneous abortion or prematurity, although an increased risk of premature rupture of membranes does exist in myasthenic women, reason of which is not very clear.



MANAGEMENT ISSUES

The optimal management of MG during pregnancy requires a multidisciplinary team approach comprising obstetrician, neonatologist/pediatrician, and neurologist with active contribution by the patient and her relatives.

PRENATAL COUNSELING

All women with MG who are planning pregnancy should be counseled about the possible effects of MG on pregnancy and vice versa. As far as possible, women should be involved actively in treatment decisions. The possible nature of treatment required as well as chances of adverse effects on fetus should be explained in detail. The nature of treatment regimen chosen should be guided by the severity of MG with special attention to bulbar or respiratory symptoms.

A very important issue which is pertinent to the treatment of MG in women is the timing of thymectomy. Approximately 10% of MG patients have thymoma while 60%–80% have thymic hyperplasia.[1,3] Thymectomy is a standard treatment option for myasthenic patients who have thymic hyperplasia or thymoma. It improves clinical outcomes in MG over a 3-year period. The chances of exacerbations of MG during pregnancy as well chances of neonatal MG are lower in women who have undergone thymectomy as compared to women who did not undergo this procedure. However, there is a lag before therapeutic effects of thymectomy become appreciable.[11] In addition, thymectomy is a major surgical procedure with obvious adverse implications if performed during pregnancy. Thus, young women with MG who are planned for thymectomy should undergo it at the earliest if they are not contemplating pregnancy. If they are pregnant, they should be advised to postpone thymectomy till delivery, if possible.

ANTENATAL CARE

Timing and frequency of antenatal visits in pregnant women with MG should be guided by clinical status of MG and nature of rituximab. While women in clinical remission can be followed less frequently, those who continue to be symptomatic should be followed frequently preferably once every 2 weeks during the first two trimesters and once every week during 3rd trimester. Women should be advised to count fetal movements and report to the treating physician/obstetricians if they feel that fetal movements are decreased. The timing and frequency of ultrasonography (USG) for fetal well-being is again dictated by clinical status of mother and chances of teratogenicity which is dictated by nature of drugs being administered for MG. In general, USG is carried out frequently in pregnant women with MG to look for fetal well-being and hydramnios. USG is performed even more frequently during MG

exacerbations to look for any signs of fetal hypoxia.[4] Women should also be screened frequently for asymptomatic bacteriuria and any infection should be treated promptly as it might worsen MG.[4] In addition, all the women should undergo periodic detailed assessment of motor power, respiratory and cardiovascular status as well as thyroid function tests. Several drugs which are used for infections or otherwise during pregnancy may be associated with myasthenic exacerbations. A complete list of all drugs [Table 1] which can worsen MG should be handed over to patients or their relatives.

Table 1

Drugs which may worsen myasthenia gravis

Drugs which are likely to 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 antibodies 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 and tetracycline), macrolide antibiotics (azithromycin, erythromycin, and clarithromycin), metronidazole, nitrofurantoin

Antiepileptic drugs such as carbamazepine, gabapentin, phenytoin, phenobarbitone, and ethosuximide

Glucocorticoids which started in high doses

Antipsychotic drugs such as lithium, phenothiazines, butyrophenones

Calcium channel blockers such as verapamil

Statins

Cisplatin

Riluzole

Emetine

Glatiramer

Interferon alpha

Iodinated contrast agents

Topical ophthalmic solutions such as timolol and tropicamide

DRUG THERAPY FOR MYASTHENIA GRAVIS

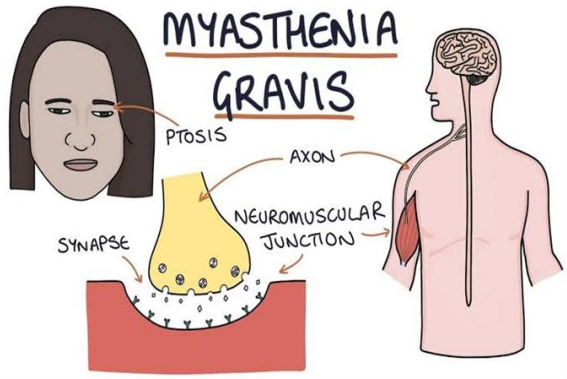
The mainstay of treatment in MG includes drugs (pyridostigmine and neostigmine) with inhibit acetyl cholinesterase enzyme for symptomatic relief as well as corticosteroids and alternate immunosuppressant drugs (methotrexate, azathioprine, mycophenolate, cyclosporine, cyclophosphamide as well as pulse intravenous immunoglobulins). Severe exacerbations or myasthenic crisis require either plasma exchange or intravenous immunoglobulin with supportive care including ventilator support if required. The choice of treatment is dictated by clinical severity of MG and risks of therapy. For instance, a patient with ocular MG and few symptoms can be successfully managed with pyridostigmine alone, while a patient with generalized MG needs immunosuppressive therapy.

DELIVERY CONSIDERATIONS

Vaginal delivery is safe in pregnant women with MG and should be encouraged. Cesarean delivery should be carried out only for obstetrical indications as surgery is often associated with worsening of MG and can even precipitate myasthenic crisis. Uterus, being composed of smooth muscle, is not affected by disease process in MG and its contractility is not compromised. Thus MG does not affect 1st stage of labor. However, as second stage of labor requires the use of striated muscle, the patient may get exhausted during this stage and may require forceps or vacuum extraction.

During labor, epidural analgesia should be used to relieve pain. The use of narcotic and neuromuscular blocking agents should be avoided. Local anesthetic agents should be avoided if possible as these can block neuromuscular transmission. Nondepolarizing neuromuscular blocking drugs should be avoided. Sedatives and opioids should be avoided as these

may precipitate respiratory depression. If these drugs are needed, women should be monitored aggressively for respiratory functions. Women who are on chronic low dose steroids may be given stress dose of hydrocortisone during intrapartum period. If required cholinesterase inhibitors can be used parenterally (preferably neostigmine). In preeclamptic and eclamptic women use of magnesium sulfate should be avoided as it can interfere with neuromuscular transmission by blocking release of acetylcholine.[4,8,12,19] Methyldopa and hydralazine are drugs of choice for treating severe hypertension in pregnancy.



NEONATAL CONSIDERATIONS

Maternal AchR antibodies can cross placenta and induce transient muscle weakness in 10%–20% of neonates born to myasthenic mothers. Thus all infants born to women with MG should be observed carefully for any signs of muscle weakness including bulbar and respiratory muscles. Although reported to reverse within 3 weeks, this syndrome has been reported to last for as long as 4 months.[27,28,29] There is no correlation between the occurrence of neonatal MG and maternal antibody titers as well as the severity of MG in mother, and thus, it is impossible to predict likelihood of neonatal MG in an index woman. Treatment usually includes administration of cholinesterase inhibitor drugs. Rarely ventilator support or even small volume plasma exchange may be required.[30]

Other complications which are rarely reported in infants born to myasthenic mothers include pulmonary aplasia and arthrogryposis multiple congenita (AMC). The former results from lack of diaphragmatic movements (required for normal lung maturation) due to passive transfer of AchR antibodies to neonates while the later results due to decreased limb movements again due to passive transfer of maternal AchR antibodies to neonates.[31,32] A positive correlation has been reported between maternal AchR antibody titers and occurrence of AMC in neonates. Polyhydramnios may result in mother due to impaired fetal swallowing. All the pregnant women with MG (even those without clinically significant MG) should be counseled against the possibility of these two complications. Transient hyperbilirubinemia is another complication may occur in neonates born to myasthenic mothers likely related to use of prednisone and pyridostigmine during pregnancy. feeding Corticoids and anticholinesterase inhibitors are relatively safe in breastfeeding. On the other hand, other drugs such as azathioprine, mycophenolate, cyclosporine, and cyclophosphamide are excreted in breast milk and breastfeeding should be avoided in patients taking these drugs.

CONCLUSIONS

Most of the myasthenic women can have uneventful pregnancy with good outcomes. Careful planning of pregnancy and a multidisciplinary team approach with careful attention to maternal and fetal well-being is the key to the successful outcome.

REFERENCES

[1] Gilhus NE. Myasthenia gravis. N Engl J Med. 2016;375:2570–81. [PubMed] [Google Scholar]

[2] Carr AS, Cardwell CR, McCarron PO, McConville J. A systematic review of population based epidemiological studies in myasthenia gravis. BMC Neurol. 2010;10:46. [PMC free article] [PubMed] [Google Scholar]

[3] Ferrero S, Esposito F, Biamonti M, Bentivoglio G, Ragni N. Myasthenia gravis during pregnancy. Expert Rev Neurother. 2008;8:979–88. [PubMed] [Google Scholar]

[4] Ferrero S, Pretta S, Nicoletti A, Petrera P, Ragni N. Myasthenia gravis: Management issues during pregnancy. Eur J Obstet Gynecol Reprod Biol. 2005;121:129–38. [PubMed] [Google Scholar]

[5] Da Silva FC, do Cima LC, de Sa RA. Myasthenia gravis and pregnancy. In: Minagar

A, editor. Neurological Disorders and Pregnancy. Burlington, MA: Elsevier; 2011. pp. 55–68. [Google Scholar]
[6] Chaudhry SA, Vignarajah B, Koren G. Myasthenia gravis during pregnancy. Can Fam Physician. 2012;58:1346–9. [PMC free article] [PubMed] [Google Scholar]
[7] Berlit S, Tuschy B, Spaich S, Sütterlin M, Schaffelder R. Myasthenia gravis in pregnancy: A case report. Case Rep Obstet Gynecol. 2012;2012:736024. [PMC free article] [PubMed] [Google Scholar]
[8] Batocchi AP, Majolini L, Evoli A, Lino MM, Minisci C, Tonali P, et al. Course and treatment of myasthenia gravis during pregnancy. Neurology. 1999;52:447–52. [PubMed] [Google Scholar]
[9] Hoff JM, Daltveit AK, Gilhus NE. Myasthenia gravis in pregnancy and birth: Identifying risk factors, optimising care. Eur J Neurol. 2007;14:38–43. [PubMed] [Google Scholar]
[10] Hoff JM, Daltveit AK, Gilhus NE. Myasthenia gravis: Consequences for pregnancy, delivery, and the newborn. Neurology. 2003;61:1362–6. [PubMed] [Google Scholar]
[11] Wolfe GI, Kaminski HJ, Aban IB, Minisman G, Kuo HC, Marx A, et al. Randomized trial of thymectomy in myasthenia gravis. N Engl J Med. 2016;375:511–22. [PMC free article] [PubMed] [Google Scholar]
[12] Djelmis J, Sostarko M, Mayer D, Ivanisevic M. Myasthenia gravis in pregnancy: Report on 69 cases. Eur J Obstet Gynecol Reprod Biol. 2002;104:21–5. [PubMed] [Google Scholar]
[13] Dominovic- Kovacevic A, Ilic T, Vukojevic Z. Myasthenia gravis and pregnancy – Case report. Curr Top Neurol Psychiatr Relat Discip. 2010;18:40–3. [Google Scholar]
[14] Gur C, Diav-Citrin O, Shechtman S, Arnon J, Ornoy A. Pregnancy outcome after first trimester exposure to corticosteroids: A prospective controlled study. Reprod Toxicol. 2004;18:93–101. [PubMed] [Google Scholar]
[15] Park-Wyllie L, Mazzotta P, Pastuszak A, Moretti ME, Beique L, Hunnisett L, et al. Birth defects after maternal exposure to corticosteroids: Prospective cohort study and meta-analysis of epidemiological studies. Teratology. 2000;62:385–92. [PubMed] [Google Scholar]
[16] Gaudier FL, Santiago-Delpin E, Rivera J, Gonzales Z. Pregnancy after renal transplantation. Surg Gynecol Obstet. 1988;167:533–43. [PubMed] [Google Scholar]
[17] Armenti VT, Radomski JS, Moritz MJ, Gaughan WJ, Philips LZ, McGrory CH, et al. Report from the national transplantation pregnancy registry (NTPR): Outcomes of pregnancy after transplantation. Clin Transpl. 2002:121–30. [PubMed] [Google Scholar]
[18] Goldstein LH, Dolinsky G, Greenberg R, Schaefer C, Cohen-Kerem R, Diav-Citrin O, et al. Pregnancy outcome of women exposed to azathioprine during pregnancy. Birth Defects Res A Clin Mol Teratol. 2007;79:696–701. [PubMed] [Google Scholar]
[19] Sander DB, Wolfe GI, Benatar M, Evli A, Gilhus NE, Illa I, et al. International consensus guidelines for management of myasthenia gravis. Neurology. 2016;87:419–25. [PMC free article] [PubMed] [Google Scholar]
[20] Radomski JS, Ahlswede BA, Jarrell BE, Mannion J, Cater J, Moritz MJ, et al. Outcomes of 500 pregnancies in 335 female kidney, liver, and heart transplant recipients. Transplant Proc. 1995;27:1089–90. [PubMed] [Google Scholar]

AUTHOR DETAIL


vaishnavi sanjeevan Shinde
Student of B.pharmacy 2nd year, Latur College of Pharmacy, Hasegaon.


Pratiksha Ramdas eakurke
Student of B.pharmacy 2nd year, Latur College of Pharmacy, Hasegaon.


Bhosale mulje Tanuja Balaji
Student of B.pharmacy 2nd year, Latur College of Pharmacy, Hasegaon.


Renuka R. Deshpande,
Assistant Professor, Department of Pharmaceutics, Latur College of Pharmacy, Hasegaon