Management of myasthenia gravis during pregnancy

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Abstract:
The management of myasthenia gravis (MG) during pregnancy requires special skills as both diseases as well as its treatment can have deleterious effects on mother and fetus. MG often affects women in second and third decades of life during the childbearing age. Exacerbations of MG are likely to occur during the first trimester and postpartum period. The treatment of MG during pregnancy needs to be individualized depending on the severity of MG as well as the efficacy of various treatment modalities and their possible harmful effects on pregnancy. In addition, special attention has to be given to avoid drugs and other factors (such as urinary tract infections) which may worsen MG. The key to successful outcome during pregnancy in myasthenic women lies in multidisciplinary care involving obstetricians, neurologists, anesthetist as well as neonatologist. In this review, we discuss various therapeutic options available for the management of MG during pregnancy and provide recommendations based on the current best evidence.

Keywords:
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.[1-4]

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.\[^4,6\] 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.\[^6\]

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.\[^9,10\]

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.\[^6,9\]

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.\[^9]\] 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.

Pregnant myasthenic women should be advised to avoid exertion and take frequent rests. They should be advised potassium-rich diet and avoid undue emotional stress and lack of sleep.

Drug therapy for myasthenia gravis
The mainstay of treatment in MG includes drugs (pyridostigmine and neostigmine) with inhibit acetylcholinesterase 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
Table 1: Drugs which may worsen myasthenia gravis

| Drugs which may worsen myasthenia | Specific drugs and pregnancy-related issues | 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.

### Specific drugs and pregnancy-related issues

#### Anticholinesterase inhibitors (pyridostigmine and neostigmine)

Several studies have shown that pyridostigmine is safe during pregnancy in recommended doses (30–60 mg every 4–8 h).[9,12,13] This drug crosses placenta freely and achieves good concentrations in amniotic fluid. Dose and frequency of administration often need to be changed during pregnancy due to changes in blood volume and renal clearance and should be adjusted according to the clinical status of MG. It may range from small dose such as 30 mg administered on an as and when required basis to frequent administration of large doses. Intravenous anti-cholinesterase inhibitors should be avoided during pregnancy as these can induce uterine contractions.

#### Steroids

Steroids continue to be the most commonly used immunosuppressive agents for the treatment of MG. Their use appears to be safe during pregnancy except for slightly increased (≤1%) risk of cleft palate (OR = 2.74, 95% CI 0.96–7.82). Other side effects reported with the use of steroids include premature rupture of membranes and premature delivery, weight gain, and cushingoid appearance.[14,15] As withdrawal of steroid may lead to exacerbation of MG, pregnant women who are on steroids should continue steroids during pregnancy. However, for women who are not on steroids, one can withhold temptation to start steroids during 1st trimester as palate is completely formed by 12 weeks. A decision on the timing of steroid therapy should be taken only due to myasthenic status of the woman. Steroids should be started at a low dose and increased slowly as 33% of MG patients show worsening of myasthenic symptoms if started with high dose steroids from the beginning. A typical regimen is to start with 5 mg prednisolone once daily and then increase by 5 mg every 5–7 days till target dose is achieved (usually 0.75–1 mg/kg body weight). There are no guidelines for the optimal dose of steroids during pregnancy, and thus, the optimal dose of the steroid during pregnancy should be guided by clinical response with clear-cut aim to use the lowest possible effective dose during pregnancy.

#### Azathioprine

Azathioprine is commonly used as steroid-sparing agent in the management of MG. Although several studies have reported increased rate of prematurity, intrauterine growth retardation and low birth weight, there is no increased risk of fetal malformations in infants born to mothers exposed to azathioprine during pregnancy.[17,18] This is likely related to the absence of enzyme in fetal liver which converts azathioprine to its active metabolite. Currently, azathioprine is considered as non-steroidal drug of choice in the management of pregnant myasthenic women in Europe given in a dose of 2–3 mg/Kg body weight. On the other hand, it is still considered as a risky drug in the USA based on case reports which suggested that infants exposed to azathioprine in utero have increased risk of infections, anemia, leukopenia, and thrombocytopenia.[19,20]

#### Cyclosporine A

Although reported to cross placenta and associated with transient neutropenia, lymphopenia, and thrombocytopenia as well as prematurity, intrauterine growth retardation and abortions, use of this drug is not associated with any serious harm to the fetus.[21]
Most of the data regarding the use of cyclosporine in pregnancy are obtained from transplant recipients and other autoimmune diseases rather than MG per se. However, the current literature suggests that this drug can be used in pregnancy provided the perceived benefits to mother outweigh the perceived risks to fetus.[22] The usual starting dose is 1.25 mg/kg body weight twice daily which can be increased by 0.5 mg/kg at 4–8 weeks interval up to a maximal dose of 4 mg/kg/day. Authors do not have any personal experience of the use of this drug in pregnant women with MG.

**Mycophenolate, methotrexate, and cyclophosphamide**

The current evidence suggests teratogenic effects (short fingers and toenails, cleft palate and lip, and corpus callosum agenesis) as well high rates of spontaneous abortions following the use of mycophenolate during pregnancy. Thus, the use of this drug is contraindicated during pregnancy and recipients of mycophenolate should practice contraception during and for 6 weeks after discontinuation of this drug.[4,19,23] The use of methotrexate during pregnancy is associated with high risk of neural tube defects including anencephaly as well as high rate of abortions. Thus, the use of methotrexate during pregnancy is contraindicated, and women who are on methotrexate should practice contraception.[19,24,25] Similarly, the use of cyclophosphamide during pregnancy is associated with major congenital malformations, and this drug should be avoided in pregnant women.[4]

**Rituximab**

This drug is being used with increasing frequency in the management of MG especially severe MG and MuSK antibody positive MG.[1] Although reported to cross placenta, use of this drug has not been reported to have major fetal adverse effects other than transiently decreased B-cell counts.[8,26] However, experience regarding the use of this drug in pregnancy is still limited, and it should be used only when perceived benefits to mother outweigh perceived risks to fetus. Frequent USG for fetal well-being may be recommended whenever this drug is used in pregnant women with MG.

**Plasma exchange/intravenous immunoglobulins**

Both these treatment modalities provide a prompt though short-lived response in MG and are recommended for the management of myasthenic crisis as well as impending crisis.[1] Although associated with occasional side effects, both these treatment options can be administered during pregnancy with careful monitoring both mother and fetal well-being. While women who receive plasma exchange should be carefully monitored for hypovolemia, women receiving intravenous immunoglobulins should be monitored for hyperviscosity syndromes.[4]

The effects and safety of various medications commonly used in the management of MG during pregnancy is outlined in Table 2.

**Delivery considerations**

Vaginal delivery is safe in pregnant women with MG and should be encouraged. Cesarian 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.[8,9]

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 pre eclamptic 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] Methylprednisolone 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.[27-29] 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.

### Table 2: Treatment options in myasthenia gravis during pregnancy

| Name of the drug | Effects on pregnancy | FDA recommendation | Effects on breastfeeding | Authors recommendation based on current literature |
|------------------|----------------------|--------------------|-------------------------|---------------------------------------------------|
| Azathioprine     | Congenital anomalies, immunosuppression in neonates, intrauterine growth retardation, hematological toxicities (lymphopenia, pancytopenia) in newborn | D (positive evidence of risk) | Excreted in breast milk | Immunosuppressant drug of choice in pregnancy after steroids; used in a dose of 2-3 mg/kg. Administration during breastfeeding should be undertaken only after discussing the possible risk with the mother |
| Mycophenolate    | External ear abnormalities, cleft lip and palate, limb anomalies, cardiac anomalies, renal defects, esophageal anomalies, neural tube defects, spontaneous abortions | D (positive evidence of risk) | Not known if excretion in breast milk present or not | Women should be counseled for contraception during therapy and for 6 weeks after discontinuation of treatment. Not recommended during breastfeeding; Alternatively, breastfeeding has to be stopped |
| Cyclosporine     | Premature births and low birth weight | C (risk cannot be ruled out) | Excreted in breast milk | Can be used during pregnancy in standard doses (2.5 mg/kg/day to 5 mg/kg/day); Not recommended during breastfeeding; Alternatively, breastfeeding has to be stopped |
| Cyclophosphamide | Congenital anomalies | D (positive evidence of risk) | Excreted in breast milk | Women should be counseled for contraception during therapy and for 1 year after discontinuation of treatment. Not recommended during breastfeeding; Alternatively breast feeding has to be stopped |
| Methotrexate     | Fetal death and congenital anomalies (nervous system, cardiac, skeletal), low birth weight | X (contraindicated in pregnancy) | Excreted in breast milk | Women should be counseled for contraception during therapy and for 6 months and one ovulatory cycle after discontinuation of treatment. Not recommended during breastfeeding; Alternatively breast feeding has to be stopped |
| Rituximab        | Prolonged B cell depletion in newborns, low birth weight, infections, premature births | C (risk cannot be ruled out) | Not known if excretion in breast milk present or not | Women should be counseled for contraception during therapy and for 1 year after discontinuation of treatment. Not recommended during breastfeeding; Alternatively breast feeding has to be stopped |
| Intravenous immunoglobulin | Not known | C (risk cannot be ruled out) | Not known if excretion in breast milk present or not | Can be used during pregnancy in cases refractory to steroids; can continue breastfeeding based on current evidence. Use in standard dose of 2 g/kg given in five divided doses over 5 days |
| Steroids         | Cleft lip or palate (rare; only case reports), low birth weight, neonatal hypoadrenalism | C (risk cannot be ruled out) | Excreted in breast milk | Immunosuppressant drug of choice in MG; No contraindication to breast feeding Use lowest possible dose during pregnancy (10-20 mg every other day to 1 mg/kg daily) |
| Pyridostigmine   | No side effects in animal studies | B (no evidence of risk in animal studies) | Excreted in breast milk | Can be used both during pregnancy and breastfeeding; caution while using intravenous neostigmine during pregnancy as it may induce uterine contractions. Standard doses are used depending upon clinical severity and range from 30 mg twice daily to 60-90 mg 4-6 hourly) |

**Breastfeeding**

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.[4] The current status of various drugs during pregnancy and breastfeeding is summarized in Table 2.

**Conclusions**

Most of the myasthenic women can have uneventful pregnancy with good outcomes. Careful planning of pregnancy and a multidisciplinary team approach.
Table 3: Key notes about management of myasthenia in pregnancy

The clinical course of MG in pregnancy is variable with approximately equal chances of clinical remission, worsening or remaining status quo. The maximum chances of worsening are during 1st trimester and postpartum period. Longer the duration of myasthenia before pregnancy, lesser are the chances of worsening during pregnancy.

MG usually does not affect course of pregnancy.

Thymectomy if planned should be done before conception.

Preconception counseling should be offered to all women with MG.

All women should have frequent checkups during the antenatal period. A complete list of all drugs which are known to worsen MG should be given to all women with MG.

The treatment of MG during pregnancy should be individualized.

While anticholinesterase drugs alone may suffice for women with mild isolated ocular weakness, immunosuppression is often needed for more severe MG. Steroids are the immunosuppressant drugs of choice. These should be used in lowest effective dose. In patients who are intolerant or refractory to steroids, azathioprine/cyclosporine may be used as alternate immunosuppressants. If patients are still refractory,

Vaginal delivery should be attempted in all women with MG.

Cesarean section should be performed only for obstetrical indications. The first stage of labor is usually unaffected by MG. The second stage of MG may have to be shortened in case of maternal exhaustion.

Nondepolarizing muscle relaxants, magnesium and sedatives should be avoided during labor. Regional anesthesia may be used if vaginal delivery is contemplated.

All newborn born to women with MG should be observed carefully for at least 72 h due to risk of transient neonatal MG which occurs in 10-20% of neonates born to myasthenic mothers.

MG=Myasthenia gravis

with careful attention to maternal and fetal well-being is the key to the successful outcome. The summary of recommendations for the management of MG during pregnancy is given in Table 3.

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Conflicts of interest

There are no conflicts of interest.

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