MANAGEMENT OF MYASTHENIA GRAVIS IN PREGNANCY

Rajaa Majid Abdulateef* and Lamyaa Abdulateef Rashid
Ministry of Health, Baghdad, Iraq.

ABSTRACT

As with several autoimmune diseases, myasthenia gravis (MG) occurs frequently in young women in their childbearing years. The treatment of MG in women therefore poses unique and challenging issues to neurologists, obstetricians, and neonatologists as the safety of both mother and fetus needs to be carefully considered when choosing a therapeutic plan. The severity of generalized weakness and the potential for respiratory insufficiency and myasthenic crises in the mother should dictate how aggressive a treatment plan should be. The potential effects of immunosuppressant medications on the fetus should always be weighed against the risk of myasthenic crises and its potential to endanger both mother and fetus. Successful management of MG during pregnancy and in the postpartum period is possible in many cases but requires collaboration between the obstetrician, the neurologist, and a well-informed patient. The neurologist should be able to counsel women and discuss treatment options and pregnancy risks based on the best current knowledge, so that women will be able to make an informed decision and successfully complete pregnancy.

KEYWORDS: Myasthenia Gravis, Pregnancy.

INTRODUCTION

Pregnancy may change the course of myasthenia gravis (MG) and frequently does so in an unpredictable way. The clinical state at the beginning of pregnancy does not predict the occurrence of exacerbations or remissions. Each pregnancy has its effect on MG symptoms and does not predict the course of subsequent pregnancies. [1]
New-onset MG may occur during pregnancy or in the immediate postpartum period. Worsening of MG symptoms occurs in about a third of pregnant patients, and although possible at any time during pregnancy, is more likely in the first trimester.\(^2\)

Sudden and frequently severe exacerbations, including respiratory insufficiency, may occur in the first 3 weeks postpartum; therefore, close monitoring of MG signs and symptoms and timely adjustment of treatment is recommended during that time. The sudden drop in a fetoprotein (AFP) concentration has been implicated as a possible cause of this phenomenon. The risk of mortality during pregnancy tends to inversely correlate with the duration of MG, the highest risk being in the first year and the lowest risk about 7 years from the onset of disease.\(^3\)

Women with MG who experience exacerbations during the puerperium have been shown to have significantly shorter disease duration than those who do not.\(^4\)

Myasthenia gravis (MG) is an acquired autoimmune disorder causing neuromuscular junction dysfunction.\(^5\) It has its highest incidence in the second and third decades of a woman’s life, a period overlapping with the childbearing years.\(^6\)

Therefore, it is not unusual for neurologists to evaluate pregnant patients during the course of the disease. In addition, neurologists should be aware that the initial manifestation of MG can occur during pregnancy or postpartum periods.\(^7\)

Pregnancy does not worsen the long-term outcome of MG.\(^8\) However, pregnancy and postpartum status have been reported as triggers for exacerbating or worsening the disease.\(^9\)

Consistent with this, the course of MG is highly variable and unpredictable during pregnancy. MG can also lead to increases in maternal mortality, morbidity, pregnancy wastage and premature labor.\(^10\)

Improvement is usually observed in 20 to 30% of pregnant women during the second and third trimesters, likely secondary to the immunosuppression that takes place in those phases of gestation. Complete remission may occur in some patients during late pregnancy. Single-fiber electromyography demonstrates electrophysiologic changes concordant to the clinical fluctuations.\(^11\)
In a series of 64 pregnancies in 47 women with known MG, in patients receiving therapy before conception, MG symptoms improved in 39% and remained unchanged in 42%. Worsening was observed in 19% of cases and occurred predominantly during the first trimester (60%).

After delivery, MG symptoms deteriorated in 28% of women. There was no correlation between MG severity before conception and exacerbations during pregnancy. The clinical course of MG during one pregnancy did not predict the course during subsequent pregnancies, supporting the impression that the disease remains highly variable and unpredictable during gestation. Puerperium complications, especially infections, seem to increase the risk for exacerbations of MG symptoms. Respiratory and urinary tract infections should be promptly recognized and treated. The largest available review of the literature showed a higher occurrence of exacerbations during gestation (41%) and in the puerperium (30%), possibly due to the inclusion of several case reports biased toward myasthenic pregnancies with complications or crises. Maternal death was 4% in this review.

To the best of our knowledge, there are few studies showing the relationship between pregnancy and MG and also correlating the characteristics of MG in different groups according to MG severity status. This study is also the first study addressing pregnancy in Iraqi MG patients. The aim of this study was to analyze the outcome and course of pregnancy in Iraqi MG patients as well as the impact of the pregnancy on the course of MG.

BACKGROUND

Treatment considerations in the pregnant patient with MG

Ideally, women with a known diagnosis of MG should seek counseling and advice prior to planning a pregnancy to participate in an informed decision regarding the management of their disease during pregnancy.

The risks and benefits of continuing versus discontinuing or decreasing immunosuppressive medications should be discussed, and recommendations should be based on the severity of MG and the presence of bulbar and respiratory weakness. Clinical improvement should be maximized in all cases prior to pregnancy.
The presence of thymoma should be ruled out and, if thymectomy is deemed indicated, it should be planned prior to pregnancy, as there is no advantage to incurring the added risk of surgery during pregnancy or in the postpartum period. Treatment plans should be modified according to the severity and duration of MG symptoms, the potential for respiratory exacerbations, and the risk posed to the fetus by exposure to immunosuppressive medications. In women with purely ocular symptoms or very mild generalized weakness, especially if of long-standing duration and without previous history of severe exacerbations or myasthenic crises, it is reasonable to avoid immunosuppressive medications while planning a pregnancy. Pyridostigmine bromide (Mestinon) at the recommended dose of less than 600 mg/d may be used safely during pregnancy and can frequently provide sufficient symptomatic improvement in mild cases for a time.

The dosage and dose interval should be adjusted throughout the pregnancy because of the ongoing changes in blood volume and renal clearance and because frequent emesis in the first trimester may interfere with the absorption of any oral medication. Intravenous cholinesterase inhibitors should be avoided, as premature labor may rarely occur.

The American Academy of Pediatrics classifies pyridostigmine as compatible with breastfeeding, but large doses of anticholinesterase drugs may cause vomiting and diarrhea in the breastfed newborn. When severe weakness and potential respiratory compromise pose a risk to both mother and fetus, plasmapheresis and intravenous immunoglobulin (IVIG) can be effective and safe treatments.

Plasmapheresis carries a theoretical risk of inducing premature labor because of the removal of circulating hormones crucial to the integrity of the pregnancy. Hypotension must be carefully monitored and corrected during the exchanges. Although there is a growing body of literature on the treatment of MG with high-dose IVIG, the safety of IVIG therapy for MG in pregnancy has not been established. Hyperviscosity and volume overload may be of greater significance during pregnancy. Complications associated with IVIG therapy include stroke, renal failure, aseptic meningitis, and hepatitis C.

In general, immunosuppressive medications should be discontinued or decreased to a minimum when disease severity allows avoiding potential adverse effects on the fetus. However, the risk posed to both fetus and mother by uncontrolled MG symptoms and life-
threatening exacerbations caused by immunosuppressive medication withdrawal needs to be carefully considered before any decision is made.[22]

Due to increased renal clearance, expanded blood volume, and less predictable gastrointestinal absorption, the dosing of oral medications may need more frequent adjustment during gestation. There is very little data available regarding the safety of immunosuppressive medications in MG patients during pregnancy, and most information is derived from patients with other autoimmune diseases (inflammatory bowel disease, systemic lupus erythematosis, autoimmune hepatitis) and the National Transplantation Pregnancy Registry.[23]

In most available human studies, it is frequently impossible to separate the effects of immunosuppressive medications from the effects of other independent risk factors, such as the underlying maternal illness and the concomitant use of other drugs.[24]

Women with MG taking azathioprine have generally been advised against pregnancy, although there has never been a definite demonstration of teratogenicity in humans at therapeutic doses and many normal pregnancies have been reported during which the mother was taking azathioprine. In the 40 years’ experience with azathioprine as an immunosuppressant in organ transplant recipients, the National Transplantation Pregnancy Registry has identified no predominant or specific fetal malformation patterns that are attributable to this drug, and the epidemiologic data available to date are favorable in the setting of a category D agent.[25]

In a report of four MG patients who were taking azathioprine during pregnancy, all of them gave birth to normal babies. In one patient the sudden withdrawal of azathioprine had no effect on the MG course, although in another, it induced a severe exacerbation of MG symptoms.16 Azathioprine has been reported to be safe during pregnancy in inflammatory bowel disease.[26]

A retrospective review of pregnancy outcome revealed that infants exposed to azathioprine might develop reversible leukopenia, anemia, thrombocytopenia, reduced immunoglobulin levels, infection, and thymic atrophy.[27] Babies born to mothers receiving azathioprine have an increased risk of myelosuppression and immunosuppression.[28]
Breastfeeding is contraindicated in mothers taking azathioprine. Cyclosporine is not a major teratogen in humans but induces a higher risk of low birth weight, prematurity, and spontaneous abortions. Transient neonatal thrombocytopenia, neutropenia, and lymphopenia have occasionally been observed in the newborns of women treated with cyclosporine during pregnancy. Cyclosporine is transferred to the breast milk, and therefore most clinicians recommend against lactation while taking this drug. However, successful breastfeeding has also been reported. Methotrexate is a folic acid antagonist and should not be used in the therapy of MG in women of childbearing age because of its association with cardiac abnormalities and congenital malformations especially involving the central nervous system. Its use is also contraindicated during lactation.

Mycophenolate mofetil (MMF) is a newer immunosuppressive medication and its use during pregnancy is still very limited even in transplant patients. MMF causes fetal resorptions and malformations of the head and eyes in rats and rabbits. Only six reports of live births to female patients taking MMF have been reported to the National Transplantation Pregnancy Registry: no major malformations were reported, but all newborns were delivered prematurely. MMF should not be used during pregnancy until more information becomes available. Myasthenic crisis during pregnancy and the postpartum period should be managed with assisted ventilation and plasmapheresis or IVIG.

**Transient neonatal MG and congenital arthrogryposis**

Neonatal MG is a transient myasthenic syndrome that occurs shortly after birth in 10 to 20% of infants born to mothers with acquired MG. It is caused by transplacental passive transfer of circulating nicotinic acetylcholine receptor antibodies from the myasthenic mother to the fetus.

It is not possible to precisely predict the occurrence and severity of neonatal MG; it is unclear why some infants are clinically affected and others remain asymptomatic, even though they have detectable acetylcholine receptor (AChR) antibodies. In general, a correlation between the occurrence and severity of neonatal MG and overall high AChR antibody titers in the mother as well as in the newborn has been observed; however, exceptions are not infrequent, and some myasthenic women without elevated AChR antibodies have had babies with neonatal MG.
The clinical severity of MG symptoms in the mother does not correlate with severity in the newborn, and neonatal MG has been reported in infants of myasthenic mothers who were in clinical remission. Antibody titer cannot be considered an absolute marker for neonatal MG as other factors in the fetal environment may play an important role in the clinical manifestation of neonatal MG.\[35\]

A clear correlation has been found between the occurrence of neonatal MG and a high ratio of antiembryonic AChR to antiadult muscle AChR antibodies, suggesting a predominant role of the antiembryonic form of AChR antibodies in the pathogenesis of neonatal MG.\[36\]

Clinically, the severity of neonatal MG symptoms varies from child to child, with some showing only mild hypotonia and others having respiratory distress severe enough to require assisted ventilation. Symptoms develop in the first few hours after birth (12 to 48 hours) and include generalized weakness and hypotonia, feeble cry, difficulty feeding, ptosis, facial paresis, and respiratory distress. The delayed onset of neonatal MG symptoms is attributed to the possible transfer of watersoluble anticholinesterase medications from the mother and to the inhibitory effect of AFP on the AChR antibodies. AFP has a powerful inhibitory effect on AChR antibodies binding capacity, and high AFP levels may therefore protect the majority of newborns from developing clinical neonatal MG.\[37\]

The high concentrations of AFP in the amniotic fluid may also explain the clinical improvement or remission frequently observed in myasthenic women during the second and third trimesters of pregnancy. A similar effect attributed to AFP has been reported in other autoimmune diseases.

The syndrome usually resolves within 1 month (18 to 21 days) but can occasionally persist for as long as 4 months. Every newborn of myasthenic mothers should be carefully observed during the first few postpartum days for signs of muscle weakness and impaired respiratory and bulbar function. The symptoms respond to anticholinesterase medications and progressively improve as the antibody titer gradually falls.\[38\]

Anticholinesterase drugs and ventilatory support should be used as necessary until the weakness resolves. Plasmapheresis may be considered in very severe cases. Maternal MG is a rare cause of arthrogryposis multiplex congenita, and placental transfer of antibodies against the fetal AChR has been implicated.\[39\]
Arthrogryposis multiplex congenita consists of nonprogressive multiple congenital joint contractures developing in utero from lack of fetal movement preventing normal joint formation and can lead to intrauterine or neonatal death due to pulmonary hypoplasia and polyhydramnios.\(^\text{[40]}\)

Some infants born with arthrogryposis multiplex congenita from myasthenic mothers have survived although others have died during the neonatal period or early infancy. Recurrent cases in sibships have been reported, even in initially asymptomatic mothers.\(^\text{[41]}\)

A more complex phenotype, including dysmorphic facies, abnormal genitalia, central nervous system atrophy, and lung hypoplasia, has been described in offspring born with arthrogryposis multiplex congenita from MG mothers. Ultrasound evaluation should be used to monitor fetal movements and to detect the development of joint contractures in utero. When counseling MG mothers, arthrogryposis multiplex congenita and its high risk of recurrence need to be discussed among the possible complications. It should also be emphasized that the absence of MG symptoms in the mother does not guarantee the birth of a normal newborn. The potential role of plasmapheresis and immunosuppression during early pregnancy in preventing the occurrence of arthrogryposis multiplex congenita and improving the outcome of newborns is not known.\(^\text{[42]}\)

**METHODS**

Material and methods, we retrospectively analyzed 69 women patients with MG who were followed in our neuromuscular outpatient clinics from 1990 to 2015. We included women who fulfilled the following criteria:

1. MG diagnosis based on clinical features compatible with MG associated with abnormal repetitive nerve stimulation (RNS) and/or the presence of anti-acetylcholine receptor antibody (anti-AChR antibody);
2. Concomitance of MG during the pregnancy period;
3. Neurological and obstetrical assessment follow-up in our hospital during the three-month periods before, during and after pregnancy (women were examined every 3 months); and
4. Information about delivery and newborn outcome. We excluded patients without complete neurological.

Transient neonatal myasthenia gravis (TNMG) was diagnosed based on transient clinical signs of generalized hypotonia, sucking disturbances, weak cry and respiratory difficulties.
The data were analyzed using descriptive statistical methods. Statistical significance was assessed using either Student’s t-test or the Mann–Whitney test for continuous variables and using the \( \chi^2 \) test or Fisher’s exact test for categorical variables. Statistical significance was set at \( p < 0.05 \) with a 95% confidence interval (CI).

RESULTS
Thirty-nine women were excluded because they did not have at least one pregnancy during their MG treatment, and another 13 women were excluded due to the absence of neurological or obstetrical assessment before, during or after the pregnancy.

Our cohort therefore included 28 pregnancies whose ages during pregnancy ranged from 17 to 37 years. Seven pregnancies in six women were concomitantly monitored by obstetricians.

Myasthenia gravis was diagnosed before pregnancy in 20 pregnancies (mean time between MG diagnosis and pregnancy was 6.8 ± 4.9 years) and during pregnancy in one woman.

Serum anti-AChR antibody (binding type) was analyzed in 15 patients and detected in 13. Eighteen pregnancies occurred in serum-positive women, and 15 of these resulted in live births. Table 1 shows the differences between the groups for pregnancies with live births.

RNS was performed in 20 women at the time of MG diagnosis, before the pregnancy in 19 women and during in one (because MG was diagnosed during her pregnancy).

Table 1.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Improvement group</th>
<th>Deterioration group</th>
<th>No-change group</th>
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<tr>
<td>Maternal ages, years (mean ± SD)</td>
<td>26.1 ± 5.5 (p &gt; 0.05)</td>
<td>24.33 ± 4.4 (p &gt; 0.05)</td>
<td>26.2 ± 8 (p &gt; 0.05)</td>
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<tr>
<td>Disease duration since diagnosis of MG, years (mean ± SD)</td>
<td>5.4 ± 4.9 (p = NS)</td>
<td>5.5 ± 4.8 (p = NS)</td>
<td>11 ± 4.8 (p = 0.026)</td>
</tr>
<tr>
<td>MGC before pregnancy (mean ± SD; range)</td>
<td>6.66 ± 7.19 (3–25) (p = 0.012)</td>
<td>1.8 ± 2.5 (0–7) (p = 0.045)</td>
<td>2.66 ± 3.01 (0–7) (p = NS)</td>
</tr>
<tr>
<td>Positive anti-AChR antibody</td>
<td>4/6 (p = NS)</td>
<td>9/10 (p = NS)</td>
<td>2/3 (p = NS)</td>
</tr>
<tr>
<td>Abnormal RNS</td>
<td>7/9 (p = NS)</td>
<td>14/14 (p = 0.028)</td>
<td>2/6 (p = 0.008)</td>
</tr>
<tr>
<td>Previous thymectomy</td>
<td>4 (p = NS)</td>
<td>2 (p = NS)</td>
<td>2 (p = NS)</td>
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Thymectomy was performed before the pregnancy in five patients; 8 pregnancies occurred in thymectomized women, all resulting in live births. Pathologic examination of the thymus revealed hyperplasia in all patients. Table 1 shows the distribution of pregnancies with live births from previously thymectomized women in the various groups.

Other clinical conditions were also diagnosed before pregnancy: systemic arterial hypertension in one patient and autoimmune thyroiditis in another.

In the course of MG among 30 pregnancies with live births, the MG symptoms improved in 9 pregnancies, remained unchanged in 6 and worsened in 15. The patients whose symptoms worsened had abnormal RNS more frequently at the time of MG diagnosis (p = 0.028) and a lower myasthenia gravis composite (MGC) score before pregnancy (p = 0.045).

The improvement group was associated with a higher MGC score before pregnancy (p = 0.012). The no-change group was associated with a longer duration of MG (p = 0.026) and normal RNS (p = 0.008). Table 1 also compares the main characteristics of each group. The MGFA and MGC scores before, during and after pregnancy are presented in Figs 1 and 2, respectively. In the deterioration group, the worsening of MG occurred more frequently in the second trimester (p = 0.028).

Regarding MG therapy before pregnancy, in 35 pregnancies, only 2 patients who were in remission before becoming pregnant had received no therapy, whereas 27 patients were treated using immunosuppressive drugs, such as azathioprine (up to 2 mg/kg/day) and prednisone (up to 1 mg/kg/day). First trimester of the pregnancy (p = 0.064). Regarding the mode of delivery, 18 deliveries were by caesarean section (15 cases for obstetric indication and 5 due to the risk of worsening the symptoms of MG), 2 by vaginal delivery with forceps and 8 by spontaneous vaginal delivery.

During the delivery, spinal anesthesia was performed in twenty-two pregnancies, while local anesthesia was used in two pregnancies. There were no complications with any anesthesia model. In the second pregnancy, the course of MG during the pregnancy differed from the previous pregnancy in 17 cases. Regarding the status of the child after delivery. There was one child born at 32 weeks who presented with cerebral palsy (the mother was asymptomatic on delivery, but she had presented a myasthenic crisis during the first trimester). There were no cases of congenital malformation, although some patients used immunosuppressive
therapy, e.g., prednisone and azathioprine, during pregnancy. In all cases in which the MG diagnosis occurred before pregnancy, the obstetrician, pediatrician and anesthesiologist were informed of the diagnosis, and all these women were considered “high-risk pregnant” in hospital.

DISCUSSION
Women in the no-change group had had the disease for longer and more frequently showed normal RNS. Therefore, we also believe that a change in the self-tolerance mechanism may be involved in these results, not only due to pregnancy but possibly influenced differently by the duration of disease. These are interesting data that can be used in the future to help predict the course of MG during pregnancy. However, we found no other studies that compared these types of data, and not all the factors that can influence clinical severity in MG are known.

Regarding RNS, the mean time between RNS and pregnancy may have influenced our data. Thus, we believe that a further prospective study should be performed in order to confirm the relationship between pregnancy and RNS in pregnant MG patients.

In addition, we would suggest that RNS be performed before, during and after pregnancy in order to better understand its real capacity for predicting the clinical severity in different phases of the pregnancy in MG patients.

Recent publications have shown that spontaneous vaginal delivery should be the aim and actively encourage this in pregnant MG patients. Labor occurred without complications in our patients who underwent vaginal delivery. The data suggest that for MG patients, the mode of delivery must be determined based on obstetric indications. The rate of caesarean sections in MG patients usually ranges from 10% to 47%.

Our study found a high rate of caesarean sections among MG patients (66.7%), even though 75% of the caesarean sections occurred strictly due to obstetric indications. The rate of caesarean sections is markedly higher in Brazil than in other countries, especially developed countries, which may influence our results. However, in a recent European study, the rate of caesarean in Portuguese MG patients was also higher than average (64.3%).

Regional anesthesia has been used during both modes of delivery (vaginal and caesarean). The anesthesia in this specific situation was safe and did not trigger any exacerbation of the disease in the study.
Although MG does not affect the uterine smooth muscle, striated muscle involved in the voluntary expulsive effort of the second phase of labor may be prone to fatiguing; therefore, the obstetrician should be ready to assist in this stage if needed with forceps or vacuum extraction. Cholinesterase inhibitors are better administered parentally during labor due to unpredictable gastric absorption. Neostigmine 1.5 mg intramuscularly or 0.5 mg intravenously equals pyridostigmine 60 mg taken orally. Because of the sensitivity of MG patients to many anesthetic agents, epidural anesthesia is considered safer in both vaginal and operative delivery. Nondepolarizing muscle relaxants may cause a prolonged or exaggerated reaction in MG patients and should therefore be avoided whenever possible. Magnesium sulfate used for the management of eclampsia should be used very carefully in MG women as it can precipitate weakness by interfering with the neuromuscular transmission. Maternal deaths have been reported in MG women who have received magnesium sulfate for preeclampsia.\[49\]

Cesarean section can cause exacerbation and should be performed only when deemed necessary because of obstetric indications. The incidence of spontaneous abortion, premature labor, low birth weight, or perinatal death is not increased in pregnancy with MG but the death rate due to fetal anomalies is significantly higher than in the normal population.\[50\]

REFERENCES


