

Myasthaenia Gravis

Clinical management issues before, during and after pregnancy

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الوهن العضلي الوبيل قضايا العلاج السريري قبل وأثناء وبعد الحمل

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ABSTRACT: *Myasthaenia gravis* (MG) is an autoimmune neuromuscular disorder which is twice as common among women, often presenting in the second and third decades of life. Typically, the first trimester of pregnancy and first month postpartum are considered high-risk periods for MG exacerbations. During pregnancy, treatment for MG is usually individualised, thus improving its management. Plasma exchange and immunoglobulin therapies can be safely used to treat severe manifestations of the disease or myasthaenic crises. However, thymectomies are not recommended because of the delayed beneficial effects and possible risks associated with the surgery. Assisted vaginal delivery—either vacuum-assisted or with forceps—may be required during labour, although a Caesarean section under epidural anaesthesia should be reserved only for standard obstetric indications. Myasthaenic women should not be discouraged from attempting to conceive, provided that they seek comprehensive counselling and ensure that the disease is under good control before the start of the pregnancy.

Keywords: Myasthenia Gravis; Pregnancy; Postpartum Period; Neonatal Myasthenia Gravis; Disease Management.

المخلص: الوهن العضلي الوبيل هو اضطراب عصبي عضلي مناعي ذاتي. وهو أكثر شيوعاً بين النساء وغالباً ما يصيب النساء في العقدتين الثاني والثالث من العمر. عادة، تعتبر الأشهر الثلاثة الأولى من الحمل و الشهر الأول بعد الولادة فترات عالية المخاطر لتفاقم مرض الوهن العضلي الوبيل. ويكون علاج هذا المرض خلال فترة الحمل مختلفاً من فرد لآخر مما يحسن من فرص الاستجابة للعلاج. ويمكن علاج المظاهر الشديدة للمرض أو الأنتكاسة باستخدام تغيير البلازما والمعالجات المناعية بشكل آمن أثناء الحمل. ومع ذلك، لا ينصح باستئصال الغدة الصعترية بسبب الآثار المتأخرة والمخاطر المحتملة المرتبطة بالجراحة. وأثناء المخاض يمكن إجراء الولادة بالطريقة المهبلية العادية أو استخدام وسائل مساعدة لها مثل الملقاط أو الشفاط. كما يمكن أيضاً إجراء عملية قيصرية تحت التخدير من فوق الجافية عند الحاجة إليها. لا ينبغي تثبيط النساء المصابات بالمرض عن محاولة الحمل مع الأخذ في الاعتبار تهيئة الحصول على المشورة الشاملة وضمان أن يكون هذا المرض تحت السيطرة الجيدة قبل حدوث الحمل.

الكلمات المفتاحية: الوهن العضلي الوبيل؛ حمل؛ فترة ما بعد الولادة؛ الوهن العضلي الوبيل؛ علاج المرض.

MYASTHAENIA GRAVIS (MG) IS AN ACQUIRED organ-specific autoimmune disease in which autoantibodies are directed against the post-synaptic nicotinic acetylcholine receptor (AChR) on the neuromuscular endplate of skeletal muscles, leading to fatigable weakness of the diaphragm and the ocular, oropharyngeal and/or limb muscles.¹⁻³ In Western countries, the prevalence of MG is 50–125 cases per million individuals and can present at any age.¹ However, the incidence is twice as common among women (ratio: 3:2) and typically occurs during the second and third decades of life; in contrast, the disease most commonly presents in males during the sixth and seventh decades of life.² The majority of myasthaenic patients are seropositive for AChR antibodies, while seronegative patients may have antibodies to other targets at the neuromuscular junction (NMJ), such as muscle-specific kinase (MuSK).³

Clinical Presentation of *Myasthaenia Gravis*

Patients with MG may have a wide range of clinical symptoms. The characteristic presentation is fatigability, usually in the form of exercise intolerance, with fluctuating skeletal muscle weakness that worsens throughout the day and improves with rest.⁴ Ocular symptoms of *ptosis* and *diplopia* are presenting symptoms in over 50% of patients, whereas up to 15% of patients present with bulbar muscle weakness manifesting as dysphagia, dysarthria or difficulty in chewing.⁵ Among patients with ocular *myasthenia*, the progression of the disease to generalised muscle weakness usually occurs within two years of onset.⁵

A myasthaenic crisis is a life-threatening exacerbation of the disease which occurs in 15–20% of patients.⁶ It can sometimes result in severe

respiratory and bulbar weakness requiring intubation and mechanical ventilation; as such, affected patients should be treated in an intensive care unit (ICU).⁶ Due to improvements in the management of myasthaenic crises in ICUs over the last four decades, the mortality rate has dropped from 75% to the current rate of <5%.⁷ Known triggers of acute MG exacerbations include infections, surgery, general anaesthesia, hypo- or hyperthyroidism, physical or emotional stress, the menstrual cycle, pregnancy, a postpartum state, extreme temperatures and exposure to certain medications that may increase muscle weakness.⁶

In MG, the thymus performs an important role in the pathological breakdown of immune tolerance towards self-antigens. As such, magnetic resonance imaging or computed tomography is advisable to see if the thymus is enlarged. Approximately 75% of patients with MG have thymic abnormalities.⁶ Of these, 65% have hyperplasia with active germinal centres full of plasma cells expressing the AChR α -subunit on their surface, resulting in the production of autoantibodies to AChRs, while 10% have thymomas, mostly in the form of benign tumors.^{6,8}

Diagnosis of *Myasthaenia Gravis*

A diagnosis of MG is essentially clinical, as fatigability is considered a reliable indicator of the disease.⁶ Subsequently, serological, electrodiagnostic and pharmacological tests are used to confirm the diagnosis. Serum anti-AChR antibodies, which are highly specific for MG, are detected in 80–85% of generalised and 50–60% of isolated ocular MG cases.^{3,6} Serum anti-MuSK antibodies are found in 70% of seronegative generalised MG cases and should therefore be measured when an AChR antibody test is negative.⁹

Repetitive nerve stimulation (RNS) and single-fibre electromyography (SF-EMG) are electrophysiological tests to assess NMJ function. These electrophysiological tests should be considered to confirm the diagnosis, particularly among seronegative patients. At a low frequency (3–5 Hz), RNS shows a gradual decrease in the amplitude of the compound muscle action potential, with a >10% decrement from the fourth response considered pathological.^{3,6} When performed in the weak distal muscles, the test is nearly always positive in generalised MG cases; however, in patients with isolated ocular myasthaenia, a RNS test may be negative in 50% of cases.³ On the other hand, SF-EMG is a more sophisticated and highly sensitive (95–99%) test for detecting neuromuscular

transmission abnormalities. Abnormal jitters (>100 ms) are found in all myasthaenic patients when tested on clinically weak muscles.⁹ Both of these neurophysiological investigations can be performed safely on pregnant women.¹⁰

The Tensilon test consists of administering 10 mg of intravenous edrophonium, a short-acting acetylcholine esterase inhibitor, under a set protocol to improve muscle weakness and sometimes to confirm a diagnosis of MG; it is positive in >90% of myasthaenic patients, but has a relatively low sensitivity (60%).⁶ As such, the results of this test should be interpreted in the context of the patient's clinical features and other investigative findings, as the results may also be positive for brain stem lesions, third nerve palsy, motor neuron disease and mitochondrial myopathies.³ During testing, intravenous atropine (0.2–4 mg) and electrocardiography monitoring facilities should be available to counter serious muscarinic side-effects, like bradycardia or *syncope*. Administration of oral pyridostigmine over several days may result in a subjective improvement in muscle strength and fatigability which might not otherwise be evident after a single dose of edrophonium.¹¹

Treatment of *Myasthaenia Gravis*

Treatment of MG aims to both increase acetylcholine neurotransmission at the NMJ and reduce autoantibody production. Current treatments include a thymectomy, acetylcholinesterase inhibitors (i.e. pyridostigmine and neostigmine), immunosuppressants (i.e. corticosteroids, azathioprine [AZA], mycophenolate mofetil [MMF] and ciclosporin A) and plasma exchange (PE) and intravenous immunoglobulin (IG) therapies.² Acetylcholinesterase inhibitors act on the parasympathetic nervous system and therefore may cause hypersecretion, bronchoconstriction and gastrointestinal tract hypermotility; these side-effects therefore limit their use in patients with asthma, chronic bronchitis and/or diarrhoea.^{3,12} Pyridostigmine is the most commonly prescribed acetylcholinesterase inhibitor and acts by inhibiting the synaptic enzyme, resulting in an increase in the concentration of acetylcholine neurotransmitters at the postsynaptic membrane. This form of treatment is purely symptomatic, is usually effective in the early stages of MG and may be sufficient to treat the mildest form of the disease.⁶

Corticosteroids (e.g. prednisone) are usually used in conjunction with pyridostigmine to treat mild

refractory disease or moderate-to-severe MG. Initially, if administered at a high dose, the patient's symptoms may worsen; therefore, gradual escalation of the steroid dose over one to two months is recommended, with patients initially prescribed low doses of 10 mg/day which are gradually increased up to 60 mg/day.³ Once clinical remission is achieved, the dose is tapered over several months and is kept on an alternating day cycle.⁶

In the long term, nonsteroidal immunosuppressive medications are usually incorporated into the medication regimen, such as AZA and MMF. As AZA requires between 3–6 months to take effect, it should be prescribed concurrently with corticosteroids.⁶ In comparison to other immunosuppressants, the relatively low-level toxicity and rapid-onset therapeutic effects of MMF, which can occur as early as two weeks among patients who respond to the therapy, is a distinct advantage.⁶ In addition, MMF has been shown to play a potential role in the treatment of refractory MG.¹³ While PE and intravenous IG therapies result in rapid improvement for MG patients by removing/interacting with the circulating autoantibodies against AChRs, the effects are unfortunately only temporary (approximately 4–10 weeks' duration).¹⁴ As such, these therapies are indicated in cases of severe disease, myasthenic crises, perioperative management prior to thymic surgery and MG refractory to immunosuppressant therapy.⁶

A thymectomy is mandatory treatment for patients with thymomas, as 30% of thymomas are locally invasive.¹⁵ Although the therapeutic effects of a thymectomy can take years to become apparent, it is often associated with an improvement in disease severity.⁶ Therefore, it is frequently performed for patients with generalised MG occurring before the age of 50 years.⁹ A recent international randomised controlled trial among 126 non-thymomatous patients with early- or late-onset MG has confirmed the clear benefit over a three-year period of an early thymectomy in comparison to medical treatment alone.¹⁶ Moreover, patients who underwent thymectomies demonstrated significant clinical improvement in terms of the reduced need for immunosuppressive therapy and hospitalisation to treat myasthenic exacerbations.¹⁶ In total, 80% of MG patients show symptomatic improvement after undergoing a thymectomy.^{17,18} One year after a thymectomy, the MG remission rate is <20%, although this rises to 50% after 7–10 years.¹⁹ The Association of British Neurologists have previously published detailed clinician guidelines to inform the management and treatment of MG patients.^{20,21}

The Effect of Pregnancy on *Myasthaenia Gravis*

Pregnancy has an unpredictable and variable effect on the clinical course of MG and the experience of previous pregnancies cannot predict the clinical course during subsequent pregnancies.^{22,23} In patients with pre-existing MG, the severity of the disease at the beginning of the pregnancy may not remain the same throughout the rest of the pregnancy; as such, the disease can go into remission, become exacerbated or remain static.²² However, clinical improvement during the second and third trimesters is noted in approximately 20–40% of pregnancies, most likely due to the immunosuppressive effect of late pregnancy.²⁴ According to Batocchi *et al.* and Djelmis *et al.*, 19% and 14.5% of MG cases, respectively, worsened during pregnancy with a further 28% and 15.9% experiencing disease exacerbation during the first six weeks postpartum; in comparison, the course of the disease remained unchanged throughout the pregnancy in 39% and 42% of cases, respectively.^{22,23}

In pregnant women, both hypoventilation due to respiratory muscle weakness and diaphragm elevation due to the growing fetus reduce the capacity of the lungs to inflate fully, hence compromising respiratory function.¹⁰ As such, myasthenic women should be monitored closely throughout their pregnancies for breathing problems to avoid respiratory crises which would require mechanical ventilation. Moreover, changes in blood volume, increased renal clearance, frequent vomiting and delayed gastric emptying during pregnancy may interfere with the intestinal absorption of MG medications and thus necessitate frequent dose adjustments.¹⁰ Puerperal respiratory and urinary tract infections may exacerbate symptoms of MG; therefore, prompt diagnosis and treatment of these infections is required with antibiotics appropriate for use in pregnancy and MG. It is crucial to recognise that selected groups of antibiotics—such as fluoroquinolones (e.g. moxifloxacin and ciprofloxacin), macrolides (e.g. azithromycin and erythromycin) and aminoglycosides (e.g. streptomycin and gentamicin)—may exacerbate myasthenic-related muscle weakness and should hence be avoided.¹⁰ The risk of mortality for a myasthenic pregnant woman is inversely correlated to the duration of the disease, with the highest risk occurring in the first year following onset of the disease and reaching its lowest level after seven years.²⁴ The physiological stress of pregnancy can also precipitate a myasthenic crisis.²⁴

Treatment of *Myasthaenia Gravis* During Pregnancy

Therapeutic regimens for pregnant myasthaenic women should be individualised and based on the severity of the symptoms and distribution of muscle weakness in the mother, while considering the potential side-effects of the medication on the fetus. Myasthaenic patients with the mildest form of weakness may only require close follow-up without treatment. However, involvement of the bulbar and respiratory muscles requires a more aggressive treatment approach because of the potential for life-threatening myasthaenic exacerbations.⁶ Due to its delayed therapeutic effect and possible surgical risks, a thymectomy should not be considered during pregnancy; therefore, both the surgery and thymic imaging should be postponed until after delivery to avoid teratogenic complications.¹⁰ If the pregnancy is planned, a thymectomy can be performed before conception or after delivery, if required.

Acetylcholinesterase inhibitors are the drug of choice for the symptomatic treatment of MG among pregnant women. During pregnancy, pyridostigmine is considered safe at a recommended dosage of <600 mg/day.⁹ However, frequent dose adjustments may be needed because of frequent vomiting or other pregnancy-related changes in intestinal absorption.¹⁰ In cases of severe vomiting, intravenous administration may be required; however, this may cause increased uterine contractions and premature labour.⁹ Immunosuppressant corticosteroids are effective in the majority of pregnant myasthaenic patients and should be considered when the severity of symptoms necessitates their use.⁹ However, corticosteroids may result in carbohydrate intolerance among pregnant women, with an increased risk of cleft palate in newborn infants when used by their mothers during the first trimester.²⁵ As such, corticosteroids should be maintained at the lowest possible dose whenever possible. Premature rupture of the membranes and preterm delivery have also been associated with high doses of corticosteroids.²⁴ In addition, the transient worsening of myasthaenic symptoms has been reported to occur with the initiation of corticosteroid therapy.⁴

While the initiation of immunosuppressive drugs should be avoided before and during pregnancy, the risk of triggering a myasthaenic crisis or exacerbation by dose reduction or discontinuation in pregnant myasthaenic women needs to be balanced against the teratogenic risk to the fetus.²¹ However, recent best practice guidelines support the use of AZA

at therapeutic dosages throughout pregnancy and during the breastfeeding period.^{21,26} Although AZA crosses the placenta, the immature fetal liver has a deficiency of the enzyme responsible for the conversion of AZA to its active metabolites; hence, the fetus is relatively protected from the harmful effects of the drug.²¹ Nevertheless, reversible leucopenia, thrombocytopenia, anaemia, thymic atrophy and decreased IG levels have been reported among infants exposed to AZA.^{24,27} In addition, newborns whose mothers were treated with AZA may also have an increased risk of myelo- and immunosuppression.²⁴ Although considered safe for use during pregnancy and breastfeeding, ciclosporin A may cause prematurity, spontaneous abortions and low birth weight among newborn infants.^{21,24} In contrast, MMF is considered teratogenic, causing a clinical syndrome which includes hypoplastic nails, shortened fifth fingers, oral cleft, *microtia*, diaphragmatic hernia and micrognathia.²¹ Contraception is required before, during and for up to six weeks after MMF therapy.²⁸

Treatment of Acute Myasthaenic Exacerbations During Pregnancy

Both PE and intravenous IG therapies have been proven to be effective, safe and well tolerated during pregnancy.¹⁰ Although these therapies result in a rapid improvement in MG symptoms, the benefits are short-lived and retreatment may be required; as such, they should be reserved for patients experiencing myasthaenic crises or to manage severe myasthaenic symptoms when conventional therapy has failed.^{4,14} However, the hyperviscosity and volume overloading associated with intravenous IG may be dangerous during pregnancy and should be carefully monitored.²⁴ During PE sessions, the occurrence of hypotension must also be carefully monitored and corrected; placing the patient in a left lateral *decubitus* position may be helpful. In addition, PE may cause premature labour by removing the circulating hormones vital for the integrity of pregnancy.²⁴ Although both treatment modalities have been found to have equivalent efficacy in the treatment of myasthaenic exacerbations, PE should be considered a second-line option to intravenous IG therapy due to its effect on blood volume, circulating hormones and coagulation factor changes in pregnancy.² Table 1 summarises the safety and potential side-effects of medications used to treat MG during pregnancy.^{10,21,24}

Table 1: Maternal and fetal side-effects and safety of drugs used to treat myasthaenia gravis during pregnancy^{10,21,24}

Drug	Maternal side-effects	FDA category*	Teratogenic side-effects	Safety during pregnancy
Pyridostigmine	Abdominal cramps, excessive oral and bronchial secretions, diarrhoea and bradycardia	C	Respiratory distress and microcephaly (dose >600 mg/day)	Safe
Prednisone	Weight gain, hyperglycaemia, gastritis, gastric ulcers, mood changes, osteoporosis and myopathy	C	Cleft palate	Safe
Azathioprine	Bone marrow suppression, gastrointestinal disturbances, hepatotoxicity, leukaemia and possible increased risk of lymphomas	D	Reversible leukopaenia, anaemia, thrombocytopaenia, thymic atrophy, sporadic congenital defects such as cerebral palsy, cerebral haemorrhage and cardiovascular defects	Safe [†]
Ciclosporin	Renal toxicity, hypertension, seizures, myopathy, tremors, increased body hair and gingival hyperplasia	C	Prematurity, low birth weight, spontaneous abortions, transient neonatal thrombocytopaenia, neutropaenia and lymphopaenia	Safe [†]
Mycophenolate mofetil	Gastrointestinal disturbances, white blood count reduction and a possible increased risk of lymphomas and other malignancies such as skin cancer	D	Pregnancy loss in the first trimester, cleft lip and palate, micrognathia, ocular hypertelorism, <i>microtia</i> and agenesis of the <i>corpus callosum</i>	Unsafe
Intravenous immunoglobulin therapy	Headache, aseptic meningitis, acute kidney injury, venous thrombosis and stroke	C	Unknown	Safe
Plasma exchange therapy	Hypotension, tachycardia, electrolyte imbalances, sepsis and venous thrombosis	N/A	Unknown	Safe

FDA = Food and Drug Administration; N/A = not applicable.

*FDA pregnancy risk classification using the following scores: A (no fetal risk), B (no evidence of risk in humans, hence the chance of fetal harm is remote but possible), C (chance of fetal harm, but the potential benefits to the mother outweigh the risk) and D (evidence of fetal risk, but the potential benefits to the mother outweigh the risk).

[†]Recent guidelines from the UK consider these immunosuppressive agents safe during pregnancy and breastfeeding.²¹

Labour and Delivery Considerations for Myasthaenia Gravis Cases

Typically, MG does not affect the first stage of labour because of the involvement of smooth muscles. In contrast, during the second stage, maternal fatigability may be pronounced because the voluntary striated muscles are involved.²⁴ At this point, the patient may become exhausted, potentially precipitating a myasthaenic crisis; hence, the obstetrician should be prepared for an assisted vaginal delivery if necessary (e.g. via vacuum extraction or with forceps).^{10,23} Acetylcholinesterase inhibitors can minimise myasthaenic fatigue during labour and should be administered parenterally to avoid erratic gastrointestinal absorption.²⁴ Intravenous doses of pyridostigmine and neostigmine are equivalent to about one-thirtieth of the usual oral dose.²⁹ Neostigmine (1.5 mg intramuscularly or 0.5 mg intravenously every 3–4 hours) is preferable to pyridostigmine, which may cause the formation of sterile abscesses.²⁴ Surgery is very stressful and can cause acute worsening of myasthaenic symptoms; therefore, a Caesarean section

procedure should be reserved only for standard obstetric indications.

As myasthaenic patients are especially sensitive to certain anaesthetic drugs, an anaesthesiologist should be consulted at the beginning of the pregnancy.²⁴ Epidural anaesthesia not exceeding the 10th thoracic vertebra level is preferable in both vaginal and surgical deliveries to provide adequate analgesia.² However, this should be confined to amide-type local anaesthetic agents (e.g. lidocaine, mepivacaine and bupivacaine) because these agents do not affect myasthaenia, whereas ester-type medications (such as benzocaine, tetracaine and procaine) should be avoided because of the risk of exacerbation of the underlying myasthaenia.² Nonsteroidal anti-inflammatory drugs (such as ketorolac tromethamine) and paracetamol (acetaminophen) can be used for postpartum or postoperative pain, while narcotic analgesic agents that may cause respiratory depression should be avoided.⁴

Magnesium sulphate inhibits acetylcholine release by blocking the presynaptic calcium influx at the nerve terminals; however, it is contraindicated for

use in the management of eclampsia in myasthaenic women since it can cause acute worsening of MG symptoms.¹⁰ Levetiracetam and valproic acids are acceptable alternatives for seizure prophylaxis, while phenytoin should be reserved for refractory seizures because it can potentially exacerbate myasthaenic-related weakness.⁴ The treatment of hypertension is a cornerstone of pre-eclampsia management; methyl-dopa and oral hydralazine can be considered the initial drugs of choice to control non-severe hypertension, while intravenous hydralazine should be used to reduce acute blood pressure in severe hypertensives (systolic pressure of >160 mmHg or diastolic pressure of >110 mmHg).³⁰ However, in comparison to hydralazine, intravenous urapidil has shown better tolerability and controllability and is a promising alternative.³¹ Both β -blockers and calcium channel blockers can potentially worsen myasthaenic symptoms and thus should be avoided.³⁰

Neonatal Considerations for *Myasthaenia Gravis* Cases

Among neonates whose mothers have MG, between 10–20% develop transient neonatal MG (TNMG) shortly after birth because of the transplacental passage of maternal AChR antibodies.^{10,32} Commonly, this occurs in cases wherein the mothers are positive for AChR and/or anti-MuSK antibodies, but is rarely seen in neonates with seronegative myasthaenic mothers.^{33,34} Symptoms of TNMG appear within the first few days of life, most commonly 12–48 hours after delivery and characteristically resolve within four weeks (18–21 days); occasionally, symptoms persist for as long as four months.^{9,34,35}

Symptoms of TNMG include a weak cry, *ptosis*, facial weakness, poor sucking, generalised hypotonia and respiratory distress; however, the severity of these symptoms differs from newborn to newborn, with some showing only mild hypotonia and others requiring mechanical ventilation due to significant breathing problems.^{24,32,34} Thus, neonatal ICU facilities should be available at the time of delivery and infants born to myasthaenic mothers should be carefully monitored during their first 48–72 hours for signs of respiratory difficulty and muscle weakness. Ventilatory support and pyridostigmine (0.5–1.0 mg/kg in divided doses) should be administered as necessary until the neuromuscular symptoms have resolved, with PE therapy to be considered in more severe cases.¹⁰

Rarely, the babies of myasthaenic mothers may develop *arthrogryposis multiplex congenita*, a syndrome characterised by nonprogressive contractures of multiple joints throughout the body at the

time of birth.³² A likely mechanism that leads to the development of this condition is reduced fetal movements *in utero*, possibly due to the placental transfer of maternal AChR antibodies that selectively inhibit fetal AChR function.³² Infants born to mothers with a high quantity of AChR antibodies in relation to the fetal γ -subunit of AChR may develop severe fetal *arthrogryposis*.²¹ Ultrasonography should therefore be performed to detect this condition *in utero* by monitoring fetal movement.

Postpartum Considerations for *Myasthaenia Gravis* Cases

During the first postpartum month, close follow-up is recommended to monitor the potential exacerbation of myasthenic symptoms such as weakness and respiratory distress. Breastfeeding is not contraindicated in myasthaenic mothers, but can worsen cases of TNMG as AChR antibodies are secreted in breast milk; it is therefore advisable to avoid breastfeeding symptomatic newborns.²⁴ Symptoms of MG also intensify in the setting of infection; therefore, myasthaenic mothers should be advised to promptly report any symptoms consistent with infections (e.g. urinary, respiratory tract, uterine or wound infections).²

In lactating myasthaenic mothers, choosing a medication regimen is challenging because of the potential teratogenic risks to the infant. Pyridostigmine is considered safe during lactation unless high doses are required, which may cause gastrointestinal symptoms in breastfed infants. Glucocorticoids and AZA can also be used safely by nursing mothers; however, for infants breastfeeding from mothers taking AZA, it is advisable to monitor complete blood count and conduct a liver function test.^{21,24} Breastfeeding is contraindicated in myasthaenic women taking MMF.²

Infant care can be particularly difficult for myasthaenic mothers; the increased fatigue associated with a lack of sleep due to nighttime feedings and the increased exertion related to caring for a newborn may cause a worsening of MG symptoms. In patients for whom immunosuppressive therapy is to be initiated or restarted after delivery, contraceptive counselling is strongly recommended. An effective contraceptive should be prescribed at least four weeks before immunosuppressive therapy begins and should be maintained for six months before a new pregnancy.¹⁰ The cyclic withdrawal of oral contraceptives is well documented to cause exacerbation of myasthaenic symptoms.² Continuous hormonal contraception or an intrauterine device may therefore be better options for myasthaenic women.²

Table 2: Recommendations for the management of women of childbearing age with *myasthenia gravis*²¹

Time period	Recommendations
Pre-pregnancy	<ul style="list-style-type: none"> • Counselling by a neurologist • Effective contraception advice for pregnancy planning • Advice on the safety of different MG treatments during pregnancy (i.e. prednisone, AZA, pyridostigmine and ciclosporin) • MG drugs should not be discontinued without medical consultation • Thyroid function tests • Thymectomy (if necessary)
During pregnancy	<ul style="list-style-type: none"> • Counselling on the possible teratogenic effects of immunosuppressive agents (i.e. methotrexate or MMF) as well as the risk of disease exacerbation with abrupt withdrawal • Interdisciplinary care from neurologists, obstetricians and anaesthesiologists • Consultation with an obstetric anaesthesiologist before the early third trimester • Prompt treatment with suitable antibiotics for infections (i.e. UTIs) • Fetal monitoring • Thymectomy is not advised
During labour and delivery	<ul style="list-style-type: none"> • Delivery at hospitals/birth centres with on-site general ICU and NICU facilities • Multidisciplinary team from an obstetrician, obstetric anaesthesiologist, neonatologist and neurologist • Women with well-controlled MG should aim to have a vaginal delivery with spontaneous onset of labour • Caesarean deliveries should be performed only if necessary • Intravenous hydrocortisone should be given in stress doses (i.e. 100 mg three times a day) to patients on long-term oral steroids • Medications to treat preeclampsia, eclampsia and postpartum pain should be carefully selected • Treatment with magnesium sulphate should be avoided • Epidural analgesia is preferable to general anaesthesia
Postpartum	<ul style="list-style-type: none"> • Breastfeeding should be encouraged for patients receiving pyridostigmine, prednisone or AZA • Early consultation with a neurologist • All infants should be monitored for at least 48 hours for symptoms of TNMG, preferably in the NICU • For infants with TNMG, pyridostigmine should be prescribed until the neuromuscular symptoms resolve • Intravenous IG and PE therapies should be considered in severe TNMG cases

MG = *myasthenia gravis*; AZA = *azathioprine*; MMF = *mycophenolate mofetil*; UTI = *urinary tract infection*; ICU = *intensive care unit*; NICU = *neonatal ICU*; TNMG = *transient neonatal myasthenia gravis*; PE = *plasma exchange*; IG = *immunoglobulin*.

Pre-Pregnancy Counselling for Women with *Myasthenia Gravis*

All myasthenic women who are considering having children should be advised to undergo pre-pregnancy counselling with a neurologist before conception to optimise their myasthenic status, reduce the use of immunosuppressive medications and assess the need for a thymectomy. During counselling, patients should also receive information about the risks of pregnancy and make an informed decision based on the most current data available. A patient who has been newly diagnosed with ocular MG potentially risks developing severe generalised MG within two years.⁵ It is therefore prudent to delay conceiving during this period so as to avoid potential worsening of the disease due to pregnancy.

As pyridostigmine is safe for use during pregnancy and among women with the mildest form of the disease, it can be initiated as a symptomatic treatment even before conception for women planning to get

pregnant.⁹ However, immunosuppressive medications other than corticosteroids and AZA should typically be avoided because of their teratogenic risk.²¹ A pre-conception thymectomy might decrease the need for such medications during the course of the pregnancy; however, the patient should be informed that it may take years before the full therapeutic effects of the surgery become evident.⁶ The patient should also be cautioned that MG severity at the beginning of their pregnancy does not predict the same disease course throughout the rest of the pregnancy and that the course of previous pregnancies does not forecast the outcome of any subsequent pregnancies.^{10,22,23} It should also be noted that the absence of symptoms of MG before or during pregnancy does not guarantee the delivery of a healthy infant.³⁶ As such, the possibility of their newborn developing *arthrogryposis multiplex congenita* or TNMG should always be discussed with MG patients who wish to have children. Table 2 summarises recommendations for management among women with MG of childbearing age.²¹

Conclusion

Treatment of MG during pregnancy is challenging because the disease course is unpredictable and highly variable. Medication regimens must balance the teratogenic risk to the fetus with the potential therapeutic benefits to the myasthenic patient. Immunosuppressive therapy should be discontinued before conception, although corticosteroids, AZA and intravenous IG and PE therapies can be used safely throughout the pregnancy. Forceps or vacuum extraction is often necessary to reduce the length of the second stage of labour, although a Caesarean delivery should be conducted only if necessary according to standard obstetrical indications. Intensive care facilities should be available for newborns due to the risk of TNMG. Throughout their pregnancy, during delivery and in the postpartum period, women with MG require personalised care from a multidisciplinary team comprising neurologists, obstetricians, neonatologists and anaesthesiologists.

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