Recommendations of the AGG (Section Maternal Disease) for Myasthenia Gravis in Pregnancy

Empfehlungen der AGG (Sektion Maternale Erkrankungen) zur Myasthenia gravis in der Schwangerschaft

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Authors

Maritta Kühnert[1], Markus Schmidt[2], Bettina Kuschel[3], Ute Margaretha Schäfer-Graf[4]

Affiliations

1 Obstetrics, UFK Marburg, Marburg, Germany
2 Gynecology & Obstetrics, Sana Kliniken Duisburg GmbH, Duisburg, Germany
3 Frauenklinik und Poliklinik, Klinikum rechts der Isar, Technische Universität München, München, Germany
4 Perinatalzentrum, Klinik für Gynäkologie und Geburtshilfe, Berlin, Germany

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Correspondence

Prof. Dr. med. Maritta Kühnert
Universitätsklinikum Gießen-Marburg, Standort Marburg, Klinik für Frauenheilkunde und Geburtshilfe
Baldingerstraße, 35033 Marburg, Germany
kuehnert@med.uni-marburg.de

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ABSTRACT

Myasthenia gravis is an autoimmune disease with a range of clinical presentations which manifest as combinations of weakness of the ocular, bulbar, and respiratory muscle groups and muscles of the extremities. Young women of reproductive age are most commonly affected. Preconception planning, the impact of pregnancy, prepartum management, drug therapy in pregnancy, myasthenic and cholinergic crises, fetal monitoring, peripartum management including analgesia and anesthesia during labor and cesarean section as well as neonatal management and neonatal myasthenia gravis are described here and the appropriate recommendations are given.

ZUSAMMENFASSUNG

Die Myasthenia gravis ist eine Autoimmunkrankheit mit wechselnder Ausprägung und variabler Kombination von Schwächen der okulären, bulbären, Extremitäten- und respiratorischen Muskelgruppen. Meistens sind junge Frauen in der Reproduktionsphase betroffen. Präkonzeptionelle Planung, Einfluss der Schwangerschaft, präpartales Management, medikamentöse Therapie in der Schwangerschaft, aber auch myasthenische und cholinerge Krise, fetale Überwachung, peripartales Management inklusive Analgesie und Anästhesie unter der Geburt und einer Sectio sowie das neonatale Management und die neonatale Myasthenia gravis werden erläutert und entsprechende Empfehlungen dazu abgegeben.

Definition, Epidemiology

Myasthenia gravis (MG) is an autoimmune disease with different clinical presentations which manifest as varying combinations of weakness of the ocular, bulbar and respiratory muscle groups (accessory respiratory muscles) and muscles of the extremities. Young women are most commonly affected.

Epidemiology

- **Incidence:** 0.2–2.0/100 000 inhabitants per year
- **Prevalence:** 15/100 000 inhabitants
- **Gender:** women > men (3 : 2)

Etiology

In myasthenia gravis, antibodies attack the structure of the postsynaptic membrane at the neuromuscular junction (motor end plate). Acetylcholine receptor antibodies targeting nicotinic acetylcholine receptors are detectable in around 85% of cases. Muscle-specific kinase (MuSK) antibodies or low affinity acetylcholine receptor antibodies or antibodies against the lipoprotein receptor-related protein (LRP4) are detectable in 1–10% of cases. There are also patients with probable myasthenia gravis in whom no antibodies can be detected (seronegative MG).

Interactions between the acetylcholine transmitter and its receptors are prevented or impeded by acetylcholine receptor antibodies: the electrical impulse is no longer transmitted from the nerve to the muscle (the muscle is not stimulated). The number of acetylcholine receptors decreases every 2–3 days, as they are degraded by the immune activities of antibodies binding to acetylcholine receptors. This leads to disintegration of the structure of the postsynaptic membrane.

Possible triggering factors for myasthenia gravis

Infections, extreme stress, anesthesia (with myasthenia-contraindicated substances); drugs (antibiotics, psychotropic drugs, hormone products, contrast media)

Clinical Features

Myasthenia gravis is characterized by weakness and fatigue of the skeletal muscles caused by dysfunction of the neuromuscular synapses. Myasthenia gravis can develop at any age; in women, the initial manifestation usually appears in the 2nd and 3rd decade. Paralysis predominantly affects the smaller muscles but, in principle, all striated muscles can be affected. Muscle tissue without motor end plates such as the cardiac muscle and smooth muscles are not affected by myasthenia gravis.

Two forms exist:

- **ocular** (limited to the eyelids and the extraocular muscles) and
- **generalized** (ocular, bulbar, extremities and accessory respiratory muscles) myasthenia gravis.

More than 50% of patients present with ocular symptoms including ptosis (droopy eyelid) and/or diplopia (double vision), 15% have bulbar symptoms such as chewing difficulty, dysphagia and dysarthria. Fewer than 5% only have weakness in the muscles of the lower legs.

When respiratory muscles are affected, this may lead to respiratory insufficiency and respiratory failure, which presents as a myasthenic crisis. Many patients with acetylcholine receptor (AchR) antibody-positive myasthenia gravis have thymus abnormalities (hyperplasia in 60–70% and thymomas in 10–12%), also known as “paraneoplastic” myasthenia gravis.

Diagnosis

1. **Physical examination:** stress tests
2. **Pharmacological tests:** edrophonium test (previously known as the tensilon test): improvement of myasthenic symptoms following the administration of cholinesterase inhibitors
3. **Laboratory tests:** basic diagnostic workup;
   anti-AChR-Ab: 85% of cases test positive, 50% of cases with ocular myasthenia are positive, 90% of cases with generalized MG are positive; only 15% of cases are positive for MuSK-Ab, LRP5-Ab, Agrin-Ab (seronegative forms may be present despite a suspicion of myasthenia gravis)
4. **Electrophysiological diagnosis:** serial stimulation, individual fiber EMG
5. **Imaging:** CT or thoracic MRI (question: thymoma?)

AGG RECOMMENDATION

Myasthenia gravis should be considered in patients with weakness and fatigue of the skeletal muscles and typical ocular/bulbar symptoms. The basic diagnostic workup consists of detection of anti-AchR antibodies, with 85% of cases testing positive.

Therapy

Symptoms are treated with acetylcholinesterase inhibitors. These drugs improve neuromuscular transmission and inhibit the acetylcholinesterase enzyme and the breakdown of acetylcholine in the synaptic cleft.

In rare cases, methotrexate is used for treatment.

Impact of Pregnancy on Myasthenia Gravis

Pregnancy has multiple effects on the course of myasthenia gravis [1, 2], depending on the status of disease prior to conception. Women whose medication was well adjusted before they became pregnant can assume that their myasthenia gravis will remain stable. Only a small percentage of women showed deterioration of previously existing symptoms postpartum [3].

The 1st trimester and the acute postpartum period are periods with the highest risk of exacerbation of disease [4]. In general, the maternal mortality risk is inversely proportional to the duration of disease: the highest maternal risk is in the first year after the onset of myasthenia gravis.

Preconception Planning in Myasthenia Gravis

Multidisciplinary management consisting of consultations and planning prior to conception is recommended. Multidisciplinary management must involve the treating neurologist, perinatal specialists experienced in treating high-risk pregnancies and early inclusion of an anesthetist prepartum is urgently recommended [3–5]. The safety of the therapy should be discussed, with a particular focus on avoiding or adjusting teratogenic medication (e.g., methotrexate) and the possible impact on the course of pregnancy and disease. If thymectomy is required, it should only be performed after the end of the pregnancy [3].

The following should be evaluated prior to conception or at the very beginning of pregnancy:

- Average motor abilities
- Respiratory status including pulmonary function tests
- Cardiac status should be evaluated with an ECG as rare cases with focal myocardial necroses have been reported in patients with MG.
- Thyroid function should be tested, as there is an association between MG and other autoimmune diseases.

AGG RECOMMENDATION

For patients with myasthenia gravis, multidisciplinary management (involving a neurologist, anesthetist, perinatal specialist, neonatologist) is recommended already prior to conception. Treatment should only include medication which is safe during pregnancy, and if a thymectomy is necessary, it should only be performed when the patient is not pregnant.

Prepartum Management and Medication in Pregnancy

Magnesium sulphate is contraindicated if **preeclampsia/eclampsia** occurs, as it can trigger a serious myasthenic crisis.

Hypertension should be treated with α-methyldopa or hydralazine. β-blockers and calcium channel blockers should be avoided. Levetiracetam or valproic acid may be used as prophylaxis against a hypertensive attack.

If a patient presents with **symptoms of preterm labor** and severe myasthenia gravis or a myasthenic crisis, the decision on how to proceed will depend on the gestational age und maternal status (delivery of the infant or prolongation of pregnancy).

Infections should be treated immediately because of the risk of exacerbation of myasthenia gravis. Dyspnea and cough should be investigated immediately to determine whether they are due to possible aggravation of myasthenia gravis manifesting in the form of increased weakness of the diaphragm and the auxiliary respiratory muscles [6] (▶ **Table 1**).

AGG RECOMMENDATION

When treating pregnant women with myasthenia gravis, it is essential to bear in mind that:

- β-blockers or calcium channel blockers should not be used to treat hypertension.
- Magnesium sulphate must not be used to treat preeclampsia as it can trigger a serious myasthenic crisis. Pulmonary symptoms must be investigated immediately and infections must be treated.

Drug Therapy for Myasthenia Gravis in Pregnancy

The standard first-line therapy consists of acetylcholinesterase inhibitors (e.g., pyridostigmine) [3]. It may be necessary to adjust doses during pregnancy because of increased renal clearance, increasing maternal blood volume, delayed gastric emptying, and frequent vomiting [6]. If the response to pyridostigmine is insufficient, the intervals between drug administrations may be reduced; doses should only be increased if symptoms persist.

IV administration of acetylcholinesterase inhibitors may induce labor and should therefore only be done during delivery [5].

Prednisone is the immunosuppressive agent of choice during pregnancy [3], however, it may lead to a transient deterioration of MG.

Azathioprine and cyclosporin (second-line treatment) should only be used if acetylcholinesterase inhibitors are unable to prevent exacerbation of myasthenia gravis [3]. These agents are relatively safe. However, they should be administered at the lowest possible dose [1].

High doses of azathioprine and cyclosporin can cause spontaneous miscarriage, preterm labor, low birth weight, chromosomal damage (they are contraindicated in the 1st trimester of pregnancy), and hematologic suppression [1]. In these cases, the disadvantages of a high dose must be weighed up against the benefit of controlling myasthenic symptoms.

Patients with acetylcholine receptor antibody-negative myasthenia gravis who are MuSK antibody-positive usually have generalized myasthenia gravis and will usually not respond to acetylcholinesterase inhibitors. In these cases, treatment with prednisone, plasmapheresis or other immunosuppressive drugs will be necessary. This approach should be reserved for patients in whom conventional therapy has failed, and in whom increasing respiratory failure or massive dysphagia and weakness is endangering mother and child.

▶ **Table 1** Drugs which may worsen myasthenia gravis (data from [11]).

Types	Substances
Analgesics	flupirtine, morphine preparations
Antiarrhythmics	quinidine, ajmaline, mexitilene, procainamide
Antibiotics	aminoglycosides (particularly streptomycin, neomycin, less so tobramycin), macrolides (e.g., erythromycin), ketolides (telithromycin/Ketek), lincomycin, polymyxins, gyrase inhibitors (levofloxacin, ciprofloxacin, prulifloxacin), sulfonamides; tetracyclines, penicillin only in very high doses
Antidepressants	amitriptyline-type substances
Anticonvulsants	benzodiazepines, carbamazepine, diphenylhydantoin, ethosuximide, gabapentin
Antimalarial drugs	quinine, chloroquine and analogs
Antirheumatic agents	D-penicillamine, chloroquine, etanercept
β-blockers	oxprenolol, pindolol, practolol, propranolol, timolol – also as a topical application in the form of eye drops
Botulinum toxin	
Calcium antagonists	verapamil, diltiazem, nifedipine and related analogs
Diuretics	azetazolamide, benzothiadiazines, loop diuretics
Glucocorticoids*	transient worsening if high doses are used at the start of treatment
Interferons	interferon α (selected cases)
Lithium	
Local anesthetics	procaine (ester type), the amides used nowadays are unproblematic
Magnesium	high doses as laxatives
Muscle relaxants	curare derivatives, the initial dose should be 10–50 % of the normal dose because of the increased sensitivity succinylcholine should not be used as it cannot be antagonized with pyridostigmine
Psychotropic drugs	chlorpromazine, promazine and related drugs, all benzodiazepines and structural analogs such as zolpidem, zopiclone
Statins	several reports of different cholesterol-lowering drugs

This list is not complete. When any new medication is introduced, the patient must be informed about the possibility of a further deterioration of MG and must be asked about typical symptoms and their intensity. But it is also important to take account of times when a life-threatening disease requires a specific drug.

* Clinically relevant worsening of disease is rare if the dose is increased slowly or medium doses are primarily administered.

AGG RECOMMENDATION

First-line therapy consists of the administration of acetylcholinesterase inhibitors; doses must be adjusted during pregnancy.

Very low doses of azathioprine and cyclosporin may be administered if exacerbation occurs.

If patients are AchR-antibody-negative, treatment with prednisone, plasmapheresis and immunosuppressors may be necessary.

Myasthenic and Cholinergic Crisis

A **myasthenic crisis** is a critical deterioration of myasthenia gravis and can be triggered:

- by drugs which affect neuromuscular transmission
- by mistakes when prescribing and taking “myasthenia” drugs
- by infections and fever
- by anesthesia
- perioperatively (oral intake of drugs is therefore indicated until shortly before surgery)
- by idiopathic causes

Clinical presentation

Severe muscle weakness with respiratory insufficiency and risk of aspiration, frequent aspiration pneumonia. Acute failure of the respiratory muscles is life-threatening. Fasciculations.

Therapy

- The patient should be monitored in an intensive care unit (to secure the respiratory tract and vital functions),
- IV administration of cholinesterase inhibitors (**caution:** may induce labor) or
- plasmapheresis and high IV doses of immunoglobulins.

The latter are used with varying results to neutralize pathogenic antibodies during a myasthenic crisis [1, 4].

A **cholinergic crisis** may be triggered following an overdose of cholinesterase inhibitors such as pyridostigmine.

Clinical presentation

Hypersecretion, bradycardia, diarrhea, miosis

Therapy

Intensive care and intubation for nicotinic (myasthenic) crisis, atropine for muscarinic crisis (cholinergic crisis).

The mortality rate for both is between 4–13 %.

AGG RECOMMENDATION

A patient suffering a myasthenic crisis (severe muscle cramps, respiratory insufficiency and risk of aspiration) must be monitored in an intensive care unit. Treatment should consist of cholinesterase inhibitors administered IV or plasmapheresis and high doses of immunoglobulins administered IV; atropine is used to treat cholinergic crises.

Fetal Monitoring

Prepartum

Abnormal ultrasound findings such as polyhydramnios due to impaired fetal swallowing, reduced fetal movement and breathing have been reported.

The most serious symptom of **neonatal syndrome** is autoimmune-mediated fetal arthrogryposis multiplex congenita, induced by autoantibodies against fetal AChR (gamma subunits). The absence of general fetal movement and of diaphragmatic excursion may lead to joint contractures and lung hypoplasia in rare cases. This is assumed to be due to an association with high maternal AChR antibodies. Maternal plasmapheresis is one therapy option as they would eliminate placental transfer of circulating antibodies (individual decision).

Cardiotocography (CTG) and evaluation of the biophysical profile are the methods of choice. In a myasthenic crisis, continuous CTG monitoring from week 23 + 0 of gestation (a grey area after detailed information and discussion with the prospective parents) is indicated because of the high risk of maternal and fetal hypoxia.

AGG RECOMMENDATION

Regular ultrasound examinations (every 3–4 weeks) with evaluation of the biophysical profile should be carried out to exclude polyhydramnios (impaired fetal swallowing), reduced fetal movement and breathing (fetal syndrome).

Peripartum Management

Cholinesterase inhibitors should be administered using a perfusor rather than orally peripartum or at least in the expulsion phase of labor, as this allows the administered dose to be controlled better; the dose should be increased as required.

Because of her immunodeficiency, the birthing mother has a higher risk of infection. A liberal administration of antibiotics may be considered if the birth is protracted.

Obstetric anesthesia

The pregnant patient should meet with the anesthetist prior to going into labor as patients with myasthenia gravis have a higher risk of requiring mechanical ventilation if they receive a general anesthetic [8]. A regional anesthetic is indicated in patients with mild or moderate disease, and a general anesthetic is indicated for patients with severe disease or impaired respiratory or bulbar status. The extent of bulbar dysfunction and of weakness of the auxiliary respiratory muscles is particularly important.

Analgesia during normal childbirth

The first stage of labor is not affected by myasthenia gravis as the uterus consists of smooth muscles without postsynaptic acetylcholine receptors.

Striated muscles are utilized when pushing during the expulsion phase of labor which may tire easily. Excessive maternal exhaustion may necessitate operative vaginal delivery (vacuum, forceps) or, in rare cases, cesarean section. Stress and overexertion may trigger a myasthenic crisis in rare cases.

A vaginal birth should be attempted initially [3]. Primary cesarean section is not indicated. Cesarean section should be performed if routine obstetric indications are present but may also be considered in cases of severe maternal exhaustion.

Neuraxial blockade is the method of choice for pain therapy during birth for patients with myasthenia gravis, as it reduces the need for a systemic administration of opioids and thereby helps to reduce respiratory compromise.

Cesarean section

Continuous infusion of anesthesia through a catheter (spinal, epidural) is often not tolerated during cesarean section as it can quickly lead to a sensory and motor block. A midthoracic epidural catheter placement is required for caesarean section, which often affects the accessory muscles of respiration. A general anesthesia is therefore often required. A general anesthesia should be the first choice for cases with severe bulbar or respiratory compromise.

AGG RECOMMENDATION

The patient should meet the anesthetist before giving birth to allow the extent of bulbar dysfunction and respiratory status to be evaluated.

AGG RECOMMENDATION

Operative vaginal delivery or cesarean section should be considered in cases of acute maternal exhaustion in the expulsion phase to prevent a myasthenic crisis.
General anesthesia is usually justified in these cases.

AGG RECOMMENDATION

Liberal administration of antibiotics is indicated during protracted delivery because of maternal immunodeficiency.

Neonatal Management – Neonatal Myasthenia Gravis

The birth should take place in a level 1 or 2 perinatal center because of the need for neonatal monitoring postpartum.

All infants born to mothers with myasthenia gravis should be examined by a pediatrician to exclude transient neonatal myasthenia gravis [4]. Respiratory problems, difficulty swallowing, and hypotonia may develop just a few hours after birth and may persist for up to three months.

10–20 % of infants born to mothers with myasthenia gravis develop transient neonatal myasthenia gravis due to placental transfer of IgG acetylcholine receptor antibodies (AChR-Ab). Neonatal myasthenia gravis occurs less often in cases with maternal MuSK antibodies or unknown antibodies.

To date, no correlation has been found between neonatal myasthenia gravis and maternal AChR-Ab titer [9]. The duration of maternal disease and maternal medication are not associated with the occurrence of neonatal myasthenia gravis [10].

There is no risk of myasthenia gravis occurring later in the child.

The probability of recurrence in the next pregnancy following the birth of a child with transient neonatal myasthenia gravis is approximately 75 %.

Autoantibodies can be transferred in colostrum in the early days of breastfeeding but can no longer be measured in breastmilk thereafter. Breastfeeding is permissible during glucocorticoid therapy but not during treatment with azathioprine, cyclosporin or methotrexate [4].

AGG STATEMENT

Pediatric monitoring is required postpartum to exclude transient neonatal myasthenia gravis, which presents clinically as difficulties in swallowing, respiratory problems, and hypotonia.

Conflict of Interest

The authors declare that they have no conflict of interest.

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