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Exploring Myasthenia Gravis Subtypes: Impact on Pregnancy and Recent Treatment Advancements

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ABSTRACT

Myasthenia gravis is an autoimmune disorder caused by antibodies that attack the neuromuscular junction. These antibodies target and damage postsynaptic components by binding to the postsynaptic muscle end-plate, leading to disrupted signal transmission and resulting in muscle weakness and fatigue. Advances in understanding the immunological mechanisms behind myasthenia gravis have led to the development of targeted immunotherapies. This review examines the subgroups of myasthenia gravis, therapeutic advances, and the impact of myasthenia gravis on pregnancy and its management. While many patients with myasthenia gravis experience mild to moderate symptoms and manage the condition well, the focus now is on developing therapies that either minimize or enhance tolerance to the specific autoimmune responses that cause the production of autoimmune antibodies and muscle weakness. Certain medications commonly used in obstetrics can worsen the condition. The effects of pregnancy on myasthenia gravis can vary significantly from woman to woman and between pregnancies in the same individual. Common treatments include acetylcholinesterase inhibitors, corticosteroids, immunosuppressants, and proper rest. In some cases, intrauterine exposure to antibodies can lead to temporary effects in newborns.

Keywords: Nicotinic acetylcholine receptor, Myasthenia gravis, Muscle-specific tyrosine kinase, Acetylcholinesterase inhibitors, Immunosuppressants, Neuromuscular junction

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Introduction

Myasthenia gravis (MG) is an autoimmune disorder caused by antibodies that target proteins at the neuromuscular junction, including the nicotinic acetylcholine receptor (AChR), muscle-specific tyrosine kinase (MuSK), and low-density lipoprotein receptor-related protein 4 (LRP4) [1]. The condition has an incidence of 100–200 cases per million in most populations [2]. Gender and age significantly influence the onset of MG: women are typically affected before the age of 50, while men tend to experience a later onset of the condition [3]. The increasing prevalence of MG is attributed to improved diagnostic techniques and greater life expectancy, particularly among the elderly, who were once underdiagnosed [4, 5].

MG is commonly categorized into seven subgroups based on different autoantibodies and clinical manifestations. The disorder occurs when autoantibodies bind to nicotinic receptors at the muscle endplate, disrupting neuromuscular transmission [6, 7]. The rising incidence of MG, especially among older populations, is also linked to the aging demographic. This rare yet treatable disease has been of interest to medical professionals for many years. Additionally, autoimmune disorders are more frequent in MG patients compared to the general population, with 13–22% of MG patients suffering from a secondary autoimmune condition, particularly those with early-onset MG and females [8, 9].

MG subgroups are recognized in clinical guidelines, although definitions may differ, and new subgroups continue to emerge as research advances. These subgroups are based on various factors, including autoantibodies, clinical presentation, and demographic information [10, 11]. Significant progress has been made in identifying the different types of autoantibodies involved, such as IgG1/IgG3, which modulate antigen interactions and contribute to the loss of AChR and the reduction of postsynaptic neurons [12, 13].

MG is regarded as a complex condition with distinct subgroups, including early-onset, late-onset, and thymoma-associated types. Each subgroup presents different clinical features and immune pathways [14]. The disease is more common in women in their second and third decades, which coincides with pregnancy. Managing MG during pregnancy requires medication before, during, and after gestation to ensure both maternal and fetal health. Exacerbations of the disease can occur during pregnancy, even in patients with controlled symptoms before conception. Pregnancy termination has not shown any benefits [15], and long-term outcomes are generally favorable. However, myasthenic crises and increased mortality rates are more likely during the first year or two after diagnosis, including in early pregnancy and postpartum. As a result, delaying pregnancy for one to two years after diagnosis is often recommended. Women with MG should consult with a neurologist before conception to discuss the importance of thymectomy, optimize clinical management, and reduce reliance on immunomodulatory therapies [16]. The treatment goal is to minimize disease severity in the mother while reducing potential risks to the fetus. For optimal care, a multidisciplinary team of neurologists, gynecologists, and anesthesiologists should be involved in the management of these patients during pregnancy and the postpartum period.

This review examines the subgroups of myasthenia gravis, treatment advancements, and the impact of myasthenia gravis on pregnancy and its management.

Results and Discussion

Epidemiology

Myasthenia gravis (MG) is an autoimmune disorder with an overall prevalence ranging from 40 to 180 cases per million people and an annual incidence of 4 to 12 cases per million individuals [17]. Recent data on prevalence and incidence tend to be more accurate than older reports, particularly for late-onset MG, due to enhanced diagnostic techniques and more widespread use of autoantibody testing. The aging population and improved survival rates have impacted both the incidence and prevalence of MG.

AChR-associated myasthenia gravis typically exhibits a bimodal age distribution, with one peak occurring in young adults around the age of 30 and a second, more gradual increase in incidence in those older than 50 years [18]. The peak in young adults is primarily attributed to a higher frequency of the disease in women, which is characteristic of many autoimmune disorders. However, late-onset MG is slightly more common in men [19]. There is no evidence suggesting an increase in MG cases due to external factors like infections or diet changes. Overall, the incidence and prevalence of MG show minimal geographical variation, though some subgroup variants of the disease may exhibit different distributions [20].

Juvenile myasthenia gravis, which is an early-onset form of the disease, is more prevalent in East Asia, where up to 50% of cases begin before the age of 15, often accompanied by visual symptoms. In Canada, MG is found in 1 to 2 per million children annually, with Asian populations, particularly those with visual manifestations, being more affected [21]. Among patients without AChR antibodies, 19% test positive for LRP4 antibodies, while 33% test positive for MuSK antibodies. According to epidemiological data, LRP4-related MG tends to be less severe than MuSK-related MG, with the latter occurring at an estimated incidence of 0.3 patients per million per year [22]. Geographical variations in the prevalence of MG and its subtypes are likely influenced by both genetic predisposition and external factors such as infections or nutrition **(Figure 1)**.

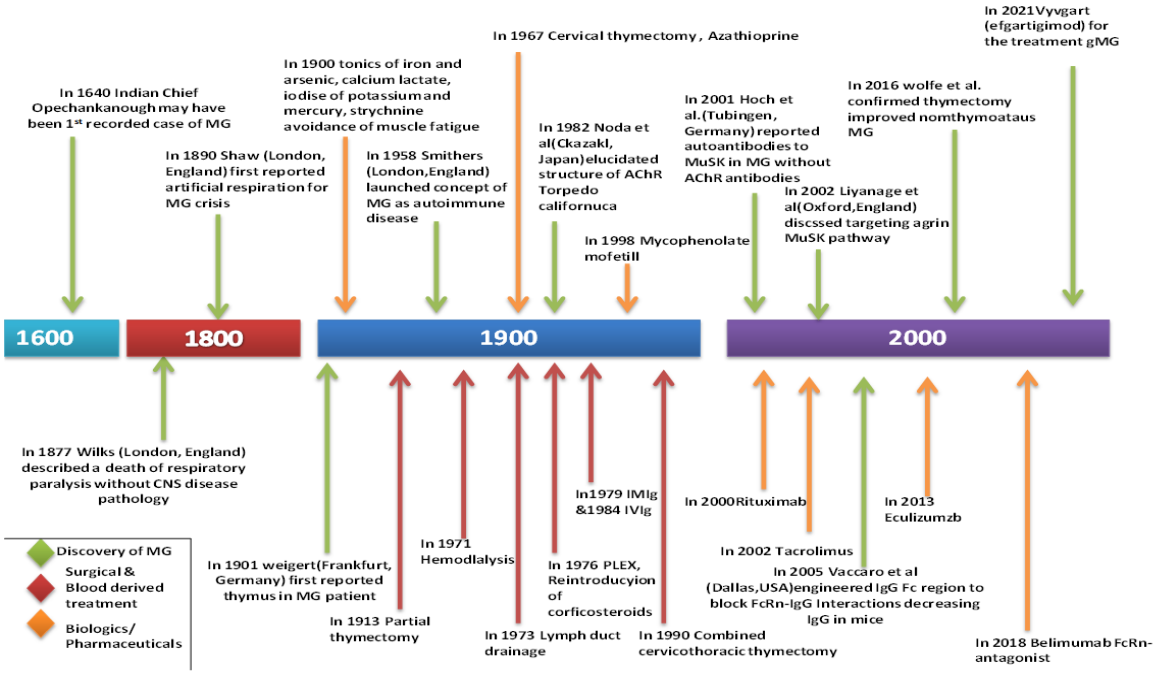

Figure 1. History of myasthenia gravis

Early-onset AChR antibody-positive myasthenia gravis

Early-onset myasthenia gravis (MG) is characterized by the emergence of symptoms before the age of 50, in line with established diagnostic criteria. The presence of acetylcholine receptor (AChR) antibodies in the plasma is typically detected through standard diagnostic testing [23]. This subgroup of MG excludes patients who have been diagnosed with thymoma through imaging or medical intervention. While thymic follicular hyperplasia is common in these patients, it is not required for diagnosis, and this subgroup often responds positively to thymectomy [24]. Female patients are affected at a rate three times higher than males.

Early-onset MG is also linked to certain genetic markers, including HLA-DR3, HLA-B8, and other autoimmune risk factors. Furthermore, autoimmune disorders are more frequently reported in the families of those with this subgroup of MG, suggesting a potential genetic predisposition. Studies indicate subgroup variations in the etiology of MG, with weak HLA associations observed in HLADR2, HLA-B7, and HLA-DRB1* in some cases [25, 26].

Myasthenia gravis subgroups

Sporadic myasthenia gravis

Myasthenia gravis associated with sporadic cases is primarily characterized by the absence of a clear underlying cause, though some cases can be related to thymomas or other autoimmune disorders. Thymoma-related MG, in particular, is a well-known autoimmune disease that is linked to infections. Thymomas, which are tumors of the thymus gland, are found in approximately 10-15% of patients with MG, though AChR antibodies are detectable in all cases. Additionally, thymomas are associated with other conditions such as red aplasia and neuromyotonia, but these associations are not observed in other autoimmune diseases. Approximately two-thirds of patients with thymomas also develop MG, while a higher percentage of those without thymomas test positive for AChR antibodies **(Figure 2)** [27].

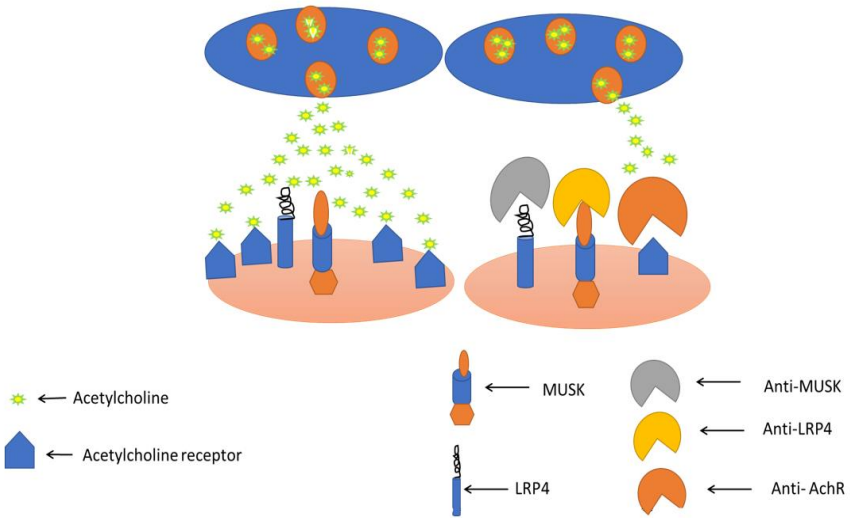

Figure 2. Thymoma-associated myasthenia surgery

Myasthenia gravis associated with MuSK

Muscle-specific tyrosine kinase (MuSK) is a key protein expressed in the postsynaptic muscle membrane, essential for maintaining the function and clustering of acetylcholine receptors (AChRs). Approximately 1–4% of individuals with myasthenia gravis (MG) have detectable antibodies against MuSK, though with the use of more sensitive assays, this proportion may increase [28]. MuSK-associated MG is more frequently identified in adults than in children or the elderly [29]. Unlike AChR-positive MG, there are no consistent pathological changes in the thymus in MuSK-MG, and patients generally derive limited benefit from thymectomy.

MuSK antibodies belong predominantly to the IgG4 subclass, which are functionally monovalent and non-complement-fixing [30]. Rather than directly affecting AChR function, these antibodies reduce the density of AChRs at the neuromuscular junction and impair their proper localization between the motor nerve terminal and the postsynaptic membrane. They bind to the extracellular N-terminal Ig-like domains of the AChR, interfering with synaptic maintenance.

Myasthenia gravis associated with AChR antibodies

Antibodies targeting the AChR are present in approximately 70% of MG cases when assessed using standard diagnostic methods [31]. These antibodies predominantly bind to the extracellular domains of the receptor, disrupting acetylcholine-mediated signal transmission. Most AChR antibodies are of the IgG1 and IgG3 subclasses, which activate the classical complement pathway, leading to complement-mediated damage at the postsynaptic membrane.

Due to their bivalency, these antibodies can also cross-link receptors, inducing antigenic modulation. A minority of AChR antibodies target the acetylcholine binding site, potentially interfering directly with receptor activation; however, such antibodies are relatively rare and affect a limited subset of patients. The clinical severity of MG is influenced by the specific epitope targeted, with antibodies against the main immunogenic region (MIR) of the α-subunit being more pathogenic than others [32].

Although an increase in AChR antibody levels may reflect disease exacerbation and declining levels suggest clinical improvement, symptom severity correlates more strongly with the degree of functional receptor loss than with total antibody levels. This receptor depletion results from a combination of antibody subtype, specificity, and non-antibody factors [33, 34].

Myasthenia gravis associated with LRP4 antibodies

Low-density lipoprotein receptor-related protein 4 (LRP4) functions as a receptor for agrin and a critical activator of MuSK, thereby playing a pivotal role in AChR clustering and neuromuscular transmission. It is expressed in the postsynaptic muscle membrane. LRP4 antibodies have been detected in a subset of MG patients who are seronegative for both AChR and MuSK antibodies [35].

Patients with LRP4-related MG typically present with either ocular or mild generalized symptoms. Approximately 20% exhibit isolated ocular involvement. Respiratory muscle weakness is uncommon, particularly in those with

coexisting MuSK antibodies. In about two-thirds of patients, thymic histology is age-appropriate, although cases of hyperplasia have also been reported [36].

Myasthenia gravis and pregnancy

The course of myasthenia gravis during pregnancy varies widely among women and can differ between pregnancies in the same individual [37]. Physiological changes during pregnancy—such as nausea, increased blood volume, altered renal clearance, and changes in gastrointestinal absorption—can influence the pharmacokinetics of medications used to manage MG, thereby affecting disease control in the short term [38]. Additionally, infections associated with pregnancy (e.g., urinary tract infections or chorioamnionitis) can trigger symptom exacerbation.

However, pregnancy does not appear to significantly affect the long-term prognosis of MG [39]. Disease exacerbations are more common during the first trimester, while symptom improvement is frequently observed in the second and third trimesters, potentially due to pregnancy-induced immunosuppression [40]. Importantly, terminating pregnancy does not reduce the risk or severity of MG exacerbations. Likewise, there is no evidence of increased miscarriage rates in women with MG.

During pregnancy, mechanical changes such as upward displacement of the diaphragm and greater reliance on intercostal muscles can affect respiratory function. Therefore, careful monitoring of respiratory status is essential [41].

The risk of maternal mortality is highest within the first year following MG diagnosis and lowest after seven years [42]. Consequently, delaying pregnancy for at least two years after diagnosis is generally advised [43]. Despite potential challenges, pregnancy has not been shown to worsen the long-term course of MG [44].

Impact of myasthenia gravis on pregnancy and the fetus

In general, myasthenia gravis (MG) does not pose significant risks to the course of pregnancy [45]. There is no clear evidence that women with MG have an increased risk of spontaneous miscarriage or preterm delivery [46]. However, neonates may be affected by transient neonatal myasthenia, a condition occurring in approximately 10–20% of cases due to the transplacental transfer of maternal immunoglobulin G (IgG) antibodies during the second and third trimesters [47].

Affected neonates typically present with hypotonia, weak cry, poor feeding or latching, ptosis, and respiratory difficulties, often manifesting between the second and fourth day of life. Close observation and supportive care are necessary, but symptoms generally resolve within three weeks as maternal antibodies are metabolized [48].

A more severe and potentially fatal form—congenital myasthenic syndrome—may occur in rare cases. This condition arises in infants born to mothers who produce antibodies targeting the fetal isoform of the AChR, rather than the more common adult isoform. These antibodies can impair fetal movement during early gestation, leading to arthrogryposis multiplex congenita, polyhydramnios, and joint contractures. Additionally, premature rupture of membranes and preterm labor are possible complications [49].

Treatment advances in myasthenia gravis

Several pharmacologic agents have been associated with MG exacerbation, either through direct immunologic mechanisms or secondary effects. Consequently, medications known or suspected to aggravate MG should be prescribed with caution and only when indicated. Clinicians should inform patients of potential risks before initiating new medications, especially those with significant bulbar or respiratory involvement, as they are more susceptible to adverse outcomes. However, most patients with stable or mild disease, particularly when in remission, can tolerate short-term use of many medications with minimal risk.

Immunosuppressive therapy

Immunosuppressive therapy is recommended for patients who do not achieve adequate disease control with symptomatic treatment alone. In patients with generalized MG, thymoma-associated MG, and MuSK-positive MG, immunosuppression is often essential to reduce autoantibody production and mitigate antibody-mediated damage at the neuromuscular junction.

While early-onset MG may initially respond to symptomatic therapies, many patients eventually require immunosuppressive treatment, although frequently temporarily. Conversely, individuals with LRP4-positive MG, which typically presents with mild symptoms, rarely necessitate immunosuppressive intervention.

In ocular MG, immunosuppression aims to both alleviate symptoms such as ptosis and diplopia, and to prevent progression to generalized disease [50]. The efficacy and side effects of immunosuppressive agents are dose-dependent, emphasizing the importance of individualizing both drug selection and dosing strategy. Combining multiple immunosuppressive agents is often preferred, as this approach can enhance therapeutic outcomes while minimizing toxicity **(Table 1)** [51].

Table 1. Classification and features of immunosuppressive medications in myasthenia gravis

Therapeutic category	Drug	Advantages	Limitations	References
First-line therapy	Prednisone	Enhances muscle strength	Contraindicated in patients with diabetes	[52]
	Prednisolone combined with Azathioprine	Improves muscle strength; reduces progression to generalized MG	Not recommended for diabetic patients; potential for leukopenia	[53]
Second-line therapy	Mycophenolate mofetil	Inhibits the proliferation of B and T lymphocytes	Teratogenic risk; may cause gastrointestinal symptoms like nausea, diarrhea, and mild headaches	[54, 55]
	Rituximab	More effective in MuSK-positive MG compared to AChR-positive MG	Risk of progressive multifocal leukoencephalopathy (PML) due to JC virus reactivation	[56]
Alternative second- or third-line therapy	Methotrexate	—	May lead to hypertension	[57]
	Cyclosporine	—	Often associated with more severe disease characterized by anti-RyR, anti-titin, or anti-KV1.4 antibodies	[58]
	Tacrolimus	Enhances muscle strength	—	[59]

Thymectomy in myasthenia gravis (MG)

Multiple studies have confirmed that thymectomy significantly influences the clinical course of MG. It is generally recommended for patients with early-onset MG, especially shortly after symptom onset. Complete removal of thymic tissue is necessary for optimal outcomes. Minimally invasive approaches—such as video-assisted thoracoscopic surgery (VATS) and robotic-assisted methods—are often preferred by patients due to quicker recovery and lower complication rates [60].

Thymectomy is considered safe even in pediatric cases, including children as young as five years old [61]. Since both thymic follicular hyperplasia and thymoma contribute significantly to MG pathophysiology, especially in acetylcholine receptor antibody-positive MG (AChR-MG), thymectomy is commonly performed in such patients. Thymic follicular hyperplasia, in particular, is implicated in initiating immune sensitization against AChRs and acts as a reservoir for antibody production, justifying thymectomy even in non-thymomatous MG cases [62].

The therapeutic effects of thymectomy are not immediate. According to follow-up studies, symptom improvement may evolve gradually over several months and continue up to two years post-surgery [63]. However, thymectomy has not been shown to alleviate coexisting autoimmune conditions.

In cases of confirmed or strongly suspected thymoma, thymectomy is mandatory from an oncological standpoint to prevent local invasion or spread into the pleural space. That said, symptom relief in MG patients with thymoma is generally less predictable compared to those with early-onset MG [64].

Patients with MuSK-MG, LRP4-MG, or purely ocular MG are not advised to undergo thymectomy, as no clinical benefit has been demonstrated in these subtypes. Thymic hyperplasia is often not visible on imaging in generalized MG with low-affinity AChR antibodies, making surgical decision-making more complex. Even antibody-negative MG patients may benefit from thymectomy, though their responses are not markedly different from other MG subgroups.

Surgery should be scheduled when the patient is clinically stable and not during a myasthenic crisis. Preoperative use of intravenous immunoglobulin (IVIG) or plasma exchange is beneficial to reduce symptom severity, minimize surgical risk, and enhance postoperative recovery [65].

Emerging therapies for myasthenia gravis

Complement inhibitors

- *Eculizumab*
  Eculizumab is the first complement inhibitor approved by the FDA for MG treatment. It is a humanized monoclonal antibody that targets the C5 component of the complement system, preventing its cleavage into C5a and C5b [66]. In the Phase III REGAIN trial, it showed significant improvement in Quantitative MG (QMG) scores in patients with refractory, AChR antibody-positive generalized MG [67]. A major concern with this drug is the increased susceptibility to *Neisseria meningitidis*. Vaccination is required at least two weeks before starting therapy, with follow-up booster doses after two years [68].
- *Zilucoplan*
  Zilucoplan is a synthetic macrocyclic peptide that binds to the C5 region and prevents the formation of the terminal complement complex. Unlike eculizumab, it is administered subcutaneously and overcomes certain drawbacks such as the need for intravenous administration and genetic resistance seen in disorders like PNH [69, 70].
- *Ravulizumab*
  Ravulizumab is a modified version of eculizumab with an altered Fc region that allows for a longer half-life due to enhanced recycling via the neonatal Fc receptor. As a result, it only requires administration every eight weeks compared to eculizumab's biweekly schedule [71, 72]. A Phase III trial is ongoing to evaluate its effectiveness and safety in generalized MG.

FcRn receptor antagonists

- *Nipocalimab (M281)*
  Nipocalimab is a deglycosylated IgG1 monoclonal antibody with high affinity for the neonatal Fc receptor (FcRn), effectively blocking IgG recycling and reducing serum IgG levels. Phase I trials using both single and multiple doses (up to 60 mg/kg) showed up to 80% reduction in IgG without significant adverse effects [73, 74]. A Phase II study showed promising results for patients with AChR or MuSK antibody-positive MG. Its potential safety in pregnancy is an added benefit, and trials are underway to explore its use in preventing hemolytic disease of the fetus and newborn [75].
- *Efgartigimod*
  Efgartigimod is derived from human IgG1 Fc fragments and engineered to bind FcRn across a range of pH levels. It promotes IgG degradation by directing it to the lysosomes. In phase I studies, a single 50 mg/kg dose reduced IgG by 50%, and repeated doses lowered levels by 75%, with IgG gradually returning to baseline within eight weeks [76, 77]. These reductions are comparable to those achieved with plasma exchange.
- *Rozanolixizumab*
  Rozanolixizumab is a humanized monoclonal IgG4 antibody that also targets FcRn with high affinity. Animal models and phase I trials demonstrated a significant IgG reduction, especially when administered at 50–150 mg/kg doses every three days. Side effects like nausea, headache, and chills were more commonly observed with intravenous administration compared to subcutaneous routes [78-90].

Corticosteroids in myasthenia gravis

Prednisone and its active metabolite, prednisolone, are widely prescribed for managing myasthenia gravis (MG) [91, 92]. However, women with MG who plan to conceive should be informed about the slightly increased risk of orofacial clefts in newborns associated with corticosteroid use [93]. To mitigate this risk, initiating corticosteroid therapy after the 12th week of pregnancy is a possible strategy.

Immunosuppressive treatment becomes necessary for patients who fail to achieve remission or have inadequate control of symptoms with pyridostigmine alone [94]. When corticosteroids are needed in the first trimester, prednisone is the preferred option due to its low teratogenic risk, despite a marginal increase in the chance of cleft palate formation [95]. However, high doses have been associated with complications such as early rupture of membranes and gestational diabetes.

Use of immunoglobulins during pregnancy

Intravenous immunoglobulin (IVIG) is typically reserved for treating myasthenic crisis during pregnancy or for cases where symptoms are unresponsive to corticosteroids or pyridostigmine. Although specific research on IVIG use in pregnant MG patients is lacking, its effectiveness has been well-documented in other autoimmune conditions. Nonetheless, side effects such as hyperviscosity and fluid overload may be more frequent during pregnancy and should be monitored closely [96].

Plasmapheresis in pregnant MG patients

Plasmapheresis can pose risks during pregnancy, including the potential to induce premature labor due to hormonal shifts. Additionally, changes in oncotic pressure during the procedure can cause fluctuations in blood pressure, possibly impairing placental blood flow. The removal of immunoglobulins and clotting factors may also increase the likelihood of bleeding and infections. Despite these concerns, plasmapheresis has been successfully and safely used in pregnant women with MG and for other clinical indications [97].

Certain medications commonly used to treat MG are contraindicated during pregnancy due to possible adverse effects. These drugs are summarized in **Table 2**.

Table 2. Medications for myasthenia gravis that should be avoided during pregnancy

S. no.	Medication	Adverse effects during pregnancy	References
1	Mycophenolate mofetil	• Increased risk of miscarriage, especially in the first trimester • Elevated rates of birth defects affecting the ears, mouth, esophagus, kidneys, and nervous system	[98]
2	Methotrexate	• Known to be teratogenic • Significantly raises the risk of pregnancy loss	[99]
3	Rituximab	• Associated with reduced B-cell levels in newborns	[100]

Conclusion

Myasthenia gravis (MG) results from different types of autoantibodies that attack proteins on the postsynaptic membrane at the neuromuscular junction, leading to muscle weakness and paralysis. The clinical presentation, disease progression, and response to treatments vary between MG subgroups depending on the specific autoantibody involved.

To date, the most recognized autoantigens responsible for generating symptoms include AChR, MuSK, and LRP4. Interestingly, the overall amount of antibodies is less critical than the exact site they bind (epitope specificity) and the nature of the antibodies themselves when it comes to determining how severe the disease will be.

Treatment should be individualized based on patient-specific factors. Subgroup classification—which considers antibody type, age at onset, thymic abnormalities, and degree of muscle weakness—is essential for choosing the most effective treatment strategy.

Current management includes symptomatic therapy, immunosuppressive drugs, supportive care, and in some cases, thymectomy. Ongoing monitoring helps personalize treatment, reduce relapses, and adjust medication as needed.

Newer targeted immunomodulatory therapies are gaining traction. These include complement inhibitors, FcRn blockers, B-cell-targeting therapies, and even CAR-T cell approaches. Many of these have shown strong safety and efficacy profiles in clinical trials, and eculizumab, a complement inhibitor, has already received global regulatory approval for use in refractory AChR-antibody-positive MG.

While these new options are promising, current clinical trials often exclude certain MG subtypes, such as ocular MG and seronegative MG, leaving gaps in understanding their effectiveness across all patients. Additionally, guidance on when to initiate, stop, or switch treatments, along with information on drug interactions, remains limited.

Regarding pregnancy, MG itself doesn't directly cause complications, and many symptom-controlling medications are considered relatively safe during pregnancy. While MG doesn't impair fertility, some immunosuppressants can. Discussions about family planning must begin early between female patients and their healthcare providers.

Drugs like methotrexate and mycophenolate mofetil are not safe for women trying to conceive and should be discontinued well in advance—three months for methotrexate and six weeks for mycophenolate. In contrast, medications like azathioprine and corticosteroids are generally considered safe for fertility.

For women planning pregnancy who haven't yet undergone a thymectomy, it may be a good option to consider beforehand to improve disease control. Overall, the increasing understanding of MG and its treatment should not discourage family planning. Instead, it should encourage closer collaboration between neurologists, gynecologists, and pediatricians to ensure safe and effective management throughout pregnancy and beyond.

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