Review Article

Myasthenia Gravis in Pregnancy

Abstract

This literature review provides a comprehensive insight into the management Myasthenia Gravis (MG) during pregnancy. It addresses the complexities of MG as an autoimmune neuromuscular disorder in the context of women during their childbearing period. The review synthesizes perspectives on the interaction between MG and pregnancy, highlighting increased risks and the necessity for tailored management strategies. It also delves into the pathophysiology of MG in pregnancy, including its impact on fertility, pregnancy outcomes, and lactation. The report underscores the importance of multidisciplinary care and individualized treatment plans, reflecting on medication adjustments and the role of thymectomy.

Keywords: Myasthenia gravis, autoantibodies, fertility, pregnancy, immunosuppressive medications, teratogenic, neonatal myasthenia, arthrogryposis and breastfeeding.

INTRODUCTION AND BACKGROUND

Myasthenia Gravis (MG) is a chronic autoimmune neuromuscular disorder characterized by fluctuating muscle weakness affecting voluntary muscle groups.MG is a diverse condition characterized by various subgroups that are defined based on specific factors like serological status, clinical presentation, the patient's age at the onset of the disease, and any associated thymic pathology[1][2][3].

Classification

The type of antibodies present plays a crucial role in the classification, with most MG cases involving antibodies against the nicotinic acetylcholine receptor (AChR) and others targeting muscle-specific tyrosine kinase (MuSK). Recent developments have identified additional antibody targets, including the low-density lipoprotein receptor-related protein 4 (LRP4) and the extracellular matrix protein agrin[4][5]. In cases where antibody tests yield negative results, the condition is classified as seronegative MG. The diagnosis of seronegative MG often relies on clinical assessments and other diagnostic criteria, given the lack of serological markers.Patients with MG are also classified into distinct categories according to age at onset—juvenile (up to 18 years), early (19–50 years), and late (over 50 years)—and the presence of thymoma, which defines the thymoma-associated MG subgroup. The clinical manifestation, whether ocular or generalized, is another key criterion for categorizing MG[1][3].

The heterogeneous nature of the disease in multiple aspects sets a major challenge in predicting the disease's progression. While antibodies linked to MG serve as valuable markers for diagnosis, their levels do not consistently align with the disease's severity or the treatment's effectiveness. Consequently, there is an ongoing need for biomarkers that can more accurately predict the course of MG and the response to therapies. Its management becomes particularly more challenging when intersecting with pregnancy[1][2][6]. Pregnancy can influence the course of MG, and in turn, MG can impact pregnancy outcomes. The evolving dynamics between MG and pregnancy necessitate an in-depth understanding of both conditions for optimal management[1][2].

Epidemiology

The prevalence of Myasthenia Gravis in the United States ranges between 14 and 20 thousand per 100 thousand, showing a distinct epidemiological pattern, being more common in women, particularly during their childbearing years. According to the information available from the Myasthenia Gravis Foundation of America, MG is known to affect women more frequently than men in the younger age groups. This trend is particularly evident in women under 40, a demographic corresponding to the childbearing years.The exact reasons behind this gender and age-specific prevalence are complex and likely involve a combination of hormonal, genetic, and environmental factors[3][7].In terms of hormonal influence, estrogen affects the expression of the autoimmune regulator gene in the thymus of young women. This alteration results in the increased release of autoreactive T cells, a factor that could contribute to the higher occurrence of MG in this demographic[3].

The higher incidence of MG in women of childbearing age has significant clinical implications, especially concerning pregnancy and reproductive health. It necessitates a careful approach to the management of MG in this population, considering both the disease's impact on pregnancy and the effects of pregnancy on the course of MG.

This literature review synthesizes these diverse perspectives, aiming to provide a comprehensive understanding of the management of MG in pregnancy, highlighting the increased risks and the need for tailoredstrategies. This understanding is critical for both neurologists and obstetricians as they navigate the unique challenges of managing this autoimmune disorder in the context of pregnancy.

PATHOPHYSIOLOGYOF MG IN THE CONTEXT OF PREGNANCY

The impacts ofMG on pregnancy, childbirth, and fetal development are closely tied to its nature as an IgG-antibody-mediated disease. In MG, autoantibodies target molecules in the postsynaptic membrane at the neuromuscular junction. These antibodies primarily bind to the acetylcholine receptor (AChR) or related molecules like muscle-specific kinase (MuSK) or lipoprotein-related protein 4 (LRP4). Their binding leads to a decrease in both the activity and number of AChRs, primarily through antibody-induced complement activation and AChR cross-linking, which is considered the key pathological mechanism. Thus, thisprocess leads to the impairment of the neuromuscular junction transmission, weakeningthe voluntary muscle groups[1][2].

The role of the thymus gland in MG varies depending on the type of MG and the presence of a thymoma. In cases with thymoma or early-onset MG characterized by AChR antibodies, the thymus is implicated in disease induction, often showing signs of thymic hyperplasia. Conversely, in MuSK MG, the thymus does not appear to play a pathogenic role. This variability underscores the

complexity of MG and its differing mechanisms, influencing how the disease may affect pregnancy and the developing fetus[1][2][3].

New onset MG in pregnancy

The heightened frequency ofMG in females compared to males during reproductive years suggests that sex hormones, particularly estrogens and progesterone, may influence its pathogenesis[3][8]. Experimental and clinical evidence indicates that estrogen can enhance cytokine and immunoglobulin production in MG patients and animal models[9]. This hormonal effect might also contribute to MG onset during pregnancy, as well as during periods like puerperium and lactation, potentially affecting the disease's course.

A population-based cohort study data from Norway and The Netherlands, which included 246 women with MG onset between ages 15–45, retrospectively investigated the relative risk of MG onset before, during, and after pregnancy. The study found no increased risk of MG onset during pregnancy but a significantly higher risk, approximately fivefold, in the first six months postpartum, with the risk normalizing in the following six months. 15% of MG cases were found to have onset following pregnancy, particularly in the postpartum period. The highest risk was observed after the first childbirth[9].

This finding suggests a genetic predisposition in some women, where the first postpartum period triggers the clinical onset of autoimmune MG. The study also draws parallels with other autoimmune diseases, like autoimmune thyroiditis and rheumatoid arthritis, where a similar increased risk is seen postpartum. The specific causes of this trend are not fully understood. However, several factors have been theorized, such as a drop in alpha-fetoprotein postpartum (which inhibits the binding of AChR antibodies to acetylcholine receptors), immunological rebound after delivery, exposure to fetal antigens, and the stress and physiological changes associated with pregnancy and childbirth, are considered potential contributors to this increased risk[8][9].

The effect of Pregnancy on MG

Studies have shown that while some women with MG experience no change in their symptoms, a notable proportion either report improvement or worsening. Worsening of symptoms is often observed in the first trimester and the first six months post-delivery.Although, the exacerbations tend to be mild to moderate, with myasthenic crises being rare[8].In contrast, improvement is typically seen during the second and third trimesters, possibly due to pregnancy-induced immunosuppression and the rise in alpha-feta protein levels. Besides the hormonal and immunologic contributors discussed earlier, the exacerbation of MG during pregnancy may be attributed to factors like respiratory muscle weakness, infections, certain medications, and the stress of labor and delivery[9][10][11].

Interestingly, the studies showed that no definitive characteristics predict which MG patients will experience exacerbations during pregnancy. Factors like prior thymectomy, AChR antibody levels, or the duration since MG onset do not appear to be decisive[8][9][10]. Generally, more severe MG symptoms before pregnancy tend to persist throughout the pregnancy[9][12].Furthermore, the course of MG in previous pregnancies does not reliably predict future pregnancy outcomes. Additionally, studies exploring the proportion of clinical worsening in pregnant MG patients report a wide range, with varying impacts across different trimesters and postpartum. The variability in pregnancy exacerbation rates for women with MG is quite significant, as highlighted in research studies. Reports indicate that these rates range broadly from 10% to 90% throughout the pregnancy[2][8][9][13]. This wide range underscores the individual variability in how pregnancy can affect MG. Thus, this suggests that pregnancy does not pose a significant risk factor for MG exacerbations, emphasizing the importance of non-pregnancy-related factors in both short-term and long-term disease management. These factors include the individual's health status, the severity and duration of MG, the presence of other health

conditions, and potential genetic and environmental influences[2][8][9][13].

Breastfeeding and Postpartum Risk ofMyasthenia Gravis onset

The connection between breastfeeding and the onset of Myasthenia Gravis symptoms postpartum remains an area of ongoing research. In a study conducted by Boldingh et al., differences in the incidence of postpartum MG onset between the Netherlands and Norway were noted, potentially linked to varying breastfeeding durations. In Norway, where longer maternity leaves are typical, prolonged breastfeeding might be associated with a delayed onset of MG symptoms. This observation raises questions about whether extended breastfeeding could influence the timing of MG symptom emergence[9].

Additionally, there is a hypothesis that elevated prolactin levels during breastfeeding could play a role in disrupting immunity. This concept somewhat resembles the theories proposed in autoimmune conditions like rheumatoid arthritis. Breastfeeding typically leads to reduced estrogen levels, which may amplify the pro-inflammatory effects of prolactin. Such hormonal and immunological changes could be pivotal, especially for first-time mothers who appear to have a higher risk of developing clinical symptoms of MG in the postpartum period. These findings suggest that a complex interplay of hormonal, immunological, and potentially genetic factors may influence the manifestation of MG during this time[8][9][14].

The effect of Myasthenia Gravis on Pregnancy

Myasthenia Gravis does not directly affect fertility, but due to its nature as an autoimmune disease, there is an increased risk for other autoimmune comorbidities, which might influence fertility. Generally, pregnancies in women with MG are uncomplicated, and most complications occur at similar frequencies as in those without MG. However, certain risks are elevated[1][8][15].A study by Nicholls et al., involving 974 deliveries by women with MG, found a higher prevalence of chronic conditions like hypertension, diabetes, and hypothyroidism, as well as an increased risk for acute respiratory failure and longer hospital stays[15].

Neonatal outcomes in MG pregnancies also warrant attention. The same study reported a higher likelihood of premature births, though other common complications like preeclampsia and eclampsia occur at rates similar to the general population. The incidence of preterm premature rupture of membranes, the necessity for cesarean sections, or the need for instrumental vaginal delivery did not show a notable increase in women with MG compared to those without the condition. These results suggest that, in these aspects, MG does not substantially alter the typical risks associated with childbirth[15].Other research has indicated a higher incidence of preterm rupture of amniotic membranes in patients withMG compared to the general population. The reported frequency in MG patients is approximately 6.7%, almost double the rate of around 3% observed in the general population. The exact causes of the heightened risk in MG patients remain unclear, signaling the need for more in-depth investigation and research to explain the underlying mechanisms. [2][10][11].

There is a possibility of a slight increase in the risk of spontaneous abortion in women withMG[1][8][16]. However, a comprehensive registry-based study in Denmark, which examined 463 pregnancies in relation to neurological autoimmune diseases, including MG, found no significant association between pregnancy loss and the later development of MG. Pregnancy loss in this context was defined as miscarriage, blighted ovum, or missed abortion. The frequency of these

outcomes in women with MG was found to be similar to that in women without MG[16]. Furthermore, this finding was supported by another literature review encompassing case series from France, Italy, Turkey, and Brazil. This review included 162 pregnant women with MG and reported a miscarriage rate of 16%, which aligns with the general population's miscarriage rate of 10-20%[8].

The approach to the mode of delivery for women withMG varies. International consensus guidance for the management of MG generally encourages vaginal delivery[17]. However, women with MG often have a higher rate of Cesarean sections, frequently chosen due to muscle weakness or as a precautionary measure[1][8]. Despite this, the rates of emergency Cesarean sections and instrumentally assisted vaginal births, such as those using vacuum or forceps, are not significantly different between women with MG and those without the condition. Cesarean sections in cases of MG are advised to be performed only for obstetric indications, not solely due to the presence of MG[8][15].

Considering the risk of neonatal myasthenia, it is vital for deliveries to take place in hospitals that are well-equipped to provide necessary respiratory support for newborns. For the optimal management of both mother and child, deliveries should ideally occur in tertiary care centers where a collaborative approach involving obstetrics, neurology, anesthesia, and neonatology can be facilitated. This multidisciplinary care is crucial to ensure the best possible outcomes for both the mother and the newborn[8][15][17].

MANAGEMENT

The broad range of exacerbation rates emphasizes the need for careful monitoring and tailored management of pregnant women with MG, considering both the potential for improvement and the risk of exacerbation. Clinicians managing pregnant patients with MG should be prepared for various possible scenarios and adjust treatment plans accordingly.

Pregnancy in MG patients requires careful consideration due to potential exacerbations of the disease and the implications for both maternal and fetal health. Treatment considerations must balance the control of MG symptoms with the safety of medications during pregnancy. Gilhus (2023) offers insights into these considerations, emphasizing the need for a balanced approach to managing MG in pregnant patients[1].Further comprehensive review articles, such as the one by Banner et al. (2022)andRoche and Bouhour (2021), delve into the clinical management of MG during pregnancy, advocating for the importance of individualized care plans[2][18].Additionally, fetal surveillance, as discussed by Cimpoca-Raptis et al. (2021), becomes crucial in pregnancies complicated by MG, ensuring fetal well-being amidst the maternal autoimmune disorder.

Pre-pregnancy planning

Pre-pregnancy planning for women with Myasthenia Gravis involves several critical considerations, including a thorough review of current MG medications. Some immunosuppressants may need to be discontinued or adjusted due to potential risks to the fetus.Decisions should be individualized, considering the severity of MG and the specific risks associated with each medication[1][10].

Principals of Treatment

Pregnancy planning should involve a multidisciplinary team, including neurologists and obstetricians, to optimize maternal and fetal outcomes. This planning should address the timing

of pregnancy, potential risks, and adjustments in MG management. Effective contraception should be used until MG is stable and the patient is on a pregnancy-safe treatment regimen[2][19]

Family planning, patient education and counseling

For women of reproductive age with MG, concerns about fertility, pregnancy, childbirth, and lactation are significant. Providing accurate and supportive information to these patients and their healthcare providers during pregnancy and the perinatal period can positively impact both emotionally and in terms of healthcare outcomes[8].It is common for women with MG to have heightened concerns about these issues, sometimes leading to delayed or avoided pregnancies.

A cross-sectional study conducted in Germany surveyed 801 women with MG to understand the disease's impact on their family planning decisions. Of the 307 respondents who had not completed their family planning at MG onset, 79.8% indicated that MG influenced their decisions. Over half of these women chose or were considering abstaining from having children due to MG. A significant concern among them was the potential impact of MG medications on an unborn child. In their decision-making process, partners and MG treating physicians played crucial roles. Factors like higher age and intensive-care experiences for MG were linked to the decision against having children. In contrast, a lower level of knowledge about MG was associated with discouraging others from having children[20].

These findings emphasize the importance of proper education and counseling on family planning for women with MG. The study highlighted this statement, where over 80% of the respondents emphasized the importance of their treating physician in decision-making, and more than 70% expressed a desire for a guidebook and shared experiences with other women with MG. Despite many choosing not to have children because of MG, over 60% would still encourage others with the condition to consider parenthood[8][20][21].

Contraception and MG

Effective contraceptive strategies are essential for women with MG who are not considering pregnancy, particularly since some MG medications have teratogenic effects. Any decision to modify MG medications in anticipation of pregnancy must be made in consultation with a neurologist to avoid worsening of the MG symptoms.

Various forms of contraception, including oral hormonal methods, vaginal rings, subcutaneous implants, and intrauterine devices, are options for patients with MG. The selection of the most suitable contraceptive method should be made in conjunction with a gynecologist, considering any other existing health conditions. An innovative non-hormonal method involves cycle monitoring using tools like the OvulaRing®, which employs a biosensor to accurately track the fertility cycle and identify the ovulation and fertility window with temperature measurement[22][23].

Regarding the interaction between MG medications and contraceptives, current data suggests that there is no link between MG medications and the reduced efficacy of oral contraceptives. However, it is essential to note that estrogen-based contraceptives can elevate tacrolimus levels, potentially increasing the risk of toxicity. This interaction underscores the importance of carefully considering contraceptive choices in the context of MG treatment plans[24].

Medications used preconception and effect on fertility.

Medication adjustment during pregnancy for women with MG is a principal part of pre-pregnancy planning and management. The goal is to ensure both the safety of the mother and the developing fetus while effectively controlling MG symptoms. Common medications for MG include cholinesterase inhibitors, corticosteroids, and immunosuppressants. Each of these has different implications for use during pregnancy[1][10].

It is essential to provide specific guidance regarding the safety of various therapies while managing MG in women prior to conception. Women should be advised not to discontinue safe immunosuppressive agents or pyridostigmine during pregnancy. Pregnancy should be planned during a stable phase of MG[19].For those planning pregnancy, the use of teratogenic drugs like methotrexate (MTX) and mycophenolate mofetil (MMF) should ideally be avoided. If such drugs are necessary, clear advice on the risks and the need for effective contraception is crucial[25].

While MG itself does not affect fertility, some immunosuppressive medications used in its treatment might. This necessitates careful consideration when selecting an immunosuppressive therapy, especially for women planning a pregnancy.Azathioprine and corticosteroids, which do not interfere with fertility, can be continued. Cyclophosphamide, for instance, which is less commonly used for MG, can reduce female fertility and should be discontinued at least three months before conception[1]. MTX and MMF are not recommended for those trying to conceive. MTX should be discontinued at least three months before attempting conception, while MMF should be stopped six weeks prior. Rituximab-treated women are advised to use contraception for 12 months post-treatment due to unknown effects on fertility and potential risks to neonatal immunity[19][26].

For men with Myasthenia Gravis who are planning on starting a family, it is important to adjust their medication regimen in preparation for conception. Methotrexate should be stopped at least 3 to 4 months beforehand. Similarly, discontinuation of azathioprine should occur three months before trying to conceive. Additionally, the dosage should be carefully managed for those taking cyclosporine, not exceeding a maximum of 2mg/kg/day[27][28].

Folic acid supplementation is recommended for women with MG, as for those without, both before conception and during pregnancy[1]. In terms of vaccinations, while live attenuated vaccines are generally safe for MG, they are contraindicated in patients on immunosuppressive therapy[19].Healthcare providers managing pregnant patients with MG should use clinical judgment and consider the risk-benefit ratio when prescribing necessary medications during pregnancy.

While managing MG, certain medications should be used with caution or avoided, particularly during pregnancy and the postpartum period. These include specific antibiotics like fluoroquinolones and macrolides, as well as medications containing magnesium, beta-blockers, and calcium channel blockers[19]. Magnesium sulfate, in particular, often used for conditions such as eclampsia or hypomagnesemia during pregnancy, should be administered carefully. This is due to the potential risk of triggering myasthenic crises. Barbiturates or phenytoin are regarded as alternative treatment options for eclampsia seizure prophylaxis[17][29]. Hypertension in eclampsia can be managed with hydralazine, and in cases where this proves ineffective, Intravenous labetalol may be utilized, provided that the MG is monitored closely[27].

Table 1 reviews the current medication used, their effect on fertility and their safety during pregnancy.

Table 1 Recommendations for Myasthenia Gravis Medication Management in Preconception, Prenatal, and Postnatal Phases.

Medication	Role in MG Management During Pregnancy	Dosage	Onset of Action	Preconception		Antenatal		Postnatal/ Lactation	Other Comments
				Fertility	Safety	Adverse Effects	Fetal AE		
MG Treatment of Choice									
Cholinesterase Inhibitors (Pyridostigmine)	Symptom Relief (Initial therapy)	60 -120 mg Q3–8 hrs/day	Within 30 min	No Effect	Safe	Nausea, vomiting, Diarrhea.	-	Safe	Avoid IV form during pregnancy due to the risk of uterine contraction
Corticosteroids (Prednisolone)	IS therapy (1st line)	5- 10 mg Daily, increased up to 60 - 100mg for 2-4 weeks	2-4 weeks	No Effect	Relatively Safe	Fluid retention, neuro-psychiatric, GDM, hypertension/pree clampsia, and bone density loss.	prematurity, slightly increased risk of cleft palate (when used in the first trimester)	Safe	Antenatal screening forGDM
Continuation may be considered during pregnancy if the patient is not responding to or tolerating corticosteroids.									
Azathioprine	IS therapy (2nd line)	50 mg, doubled every 2-4 weeks	12 - 18 months	No Effect on women, yet for men - has a mutagenic effect on sperm	Continue with caution	Flu-like symptoms, leukopenia	IUGR, prematurity	Possible use when necessary	Men with MG should stop three months prior to planned conception. Monitor WBC and LFT levels
Cyclosporine (Calcineurin inhibitor)	IS therapy (2nd line)	100 mg twice daily	1 - 3 months	No Effect	Continue with caution	Flu-like symptoms, risk of infection, hypertension, and nephrotoxicity	IUGR, prematurity	Possible use (generally considered safe)	Monitor WBC, LFT and creatinine levels

Tacrolimus (Calcineurin inhibitor)	IS therapy, yet limited data on use in MG patients			No Effect on women, yet for men - if dose above 2mg/kg/day can affect sperm (astheno-terato-sperimia)	Continue with caution	Increased risk of GDM and hypertension, flu-like symptoms	IUGR, prematurity, transient hyperkalemia and renal impairment	Possible use (limited data)	Men with MG - dose should not exceed 2mg/kg/day, monitor WBC, LFT and creatinine levels
Contraindicated (C/I)									
Mycophenolate Mofetil (MMF)	C/I			No Effect	C/I		Teratogenic - Black box warning (EMFO tetrad)	Not recommended (Limited available data)	To suspend at least six weeks prior to planned conception
Cyclophosphamide	C/I	0.5 - 1 g/m2	6 - 12 months	Alters ovarian reserve, even with short courses (dose, duration and age-dependent)	C/I	Hemorrhagic cystitis, infection, bone marrow suppression	Teratogenic and embryo-lethal	C/I	To suspend at least three months prior to planned conception or one ovulation cycle after discontinuation
Methotrexate (MTX)	C/I	10 mg per week		Men - mutagenic effect on spermatogenesis,	C/I	Hepatotoxic, infection	Teratogenic and embryo-lethal, CNS malformation, IUGR, Skull and limb deformities, cardiopathy	C/I	To suspend at least three months prior to planned conception for both genders
Unknown (Limited Data)									

Rituximab	IS therapy, reserved for severe MG			No available data	Not recommended (Limited available data)	B cell lymphopenia, infection risk	Limited data, risk of hematological abnormalities	Not recommended (Limited available data)	
Eculizumab (Complement Inhibitor)	IS therapy, for refractory MG	900 mg per week for 4 weeks	2 - 4 weeks	No human data, animal data showed no effect	Not recommended (Limited available data)		Limited data, risk of fetal loss and developmental abnormalities	Not recommended (Limited available data)	Vaccination against Neisseria meningitidis is required at least two weeks prior to initiating medication
Efgartigimod (FcRn Inhibitors)	ISTherapy	10 mg/kg per week for four weeks per cycle	2 - 4 weeks	No human data, animal data showed no effect	Not recommended (Limited available data)	Infection, headache	No Data available	Not recommended (Limited available data)	
				Myasthenic Crisis Treatment of Choice					
IVIg	Myasthenic crisis	2 gm/Kg for 2-5 days	1 - 2 weeks			Headache, urticaria/ hypersensitivity, thromboembolic event, fluid overload, nephrotoxicity	None reported	Safe	
Plasma Exchange	Myasthenic crisis	3-5 sessions (3-5L each) done on alternate days over	Within days			Hypotension, risk of infection, fluid shift	None reported	Safe	

					7-10 days

Abbreviations: IS: Immunosuppressive, AE: Adverse Effects, C/I: Contraindicated, GDM: Gestational Diabetes Mellitus

Role of thymectomy

The thymus gland plays a crucial role in T-cell differentiation and establishing central immunological tolerance. This process involves the interaction of developing thymocytes with thymic stromal cells, which express self-antigens, leading to the elimination of autoreactive T cells. The thymocytes that develop self-tolerance continue to differentiate and are then sent to peripheral tissues[30].

Normally, thymocytes and stromal cells are the primary cell types in the thymus, with a minimal presence of B cells. However, in most MG patients, especially those with acetylcholine receptor AChR-MG, there are significant structural and functional changes in the thymus. These changes are characterized by the presence of thymoma or the development of germinal centers containing numerous B cells, a condition known as follicular hyperplasia. Early-onset MG (EOMG) commonly shows follicular hyperplasia, while late-onset MG (LOMG) frequently presents with thymomas. These thymic alterations are predominantly associated with AChR-MG[19][30].

Thymectomy, the surgical removal of the thymus, can be an effective treatment for AChR antibody MG, and its timing related to pregnancy needs careful planning[29].Ideally, it should be performed before pregnancy, especially in cases of uncontrolled MG, to potentially minimize the need for immunosuppressive therapy during pregnancy[18][27]. Women who have undergone thymectomy have lower chances of MG exacerbations and neonatal MG than those who have not had the surgery. However, it usually takes around 12 months after the surgery for the therapeutic effects of thymectomy to be fully realized[11][26].It is noteworthy that post-thymectomy patients should be cautious about receiving live-attenuated vaccines. This caution is advised due to the altered immune function that can occur following the removal of the thymus, a critical organ in the immune system's development and regulation[19].

Medications used for MG in pregnancy – Antenatal care

1. Anti-Cholinesterase Inhibitors – pyridostigmine, neostigmine:

These drugs, used for symptomatic relief, are often continued during pregnancy as they are considered relatively safe when used in recommended doses (60 -120 mg every 3–8 hours per day). This medication works by improving neuromuscular transmission, thus alleviating muscle weakness associated with MG[31].However, the dosage may need adjustment as pregnancy progresses due to changes in the body’s metabolism, blood volume and drug clearance[1][17].For lactating mothers, these medications are considered safe postpartum[19].

Only oral forms are recommended, given thatintravenous anticholinesterase inhibitors are generally avoided during pregnancy due to the risk of inducing uterine contractions and preterm labor[10][19].

2. Immunosuppressant - Corticosteroids:

Corticosteroids like prednisone are the most commonly used immunosuppressive agents for MG. They can be used during pregnancy but require careful monitoring due to potential maternal side effects like gestational diabetes and hypertension. Their use during pregnancy is generally considered safe, though there is a slightly increased risk (less than 1%) of cleft palate[10]. Hence, careful consideration is given to starting them, particularly during the first trimester. The palate formation is completed by 12 weeks gestation, and this timeline

is crucial in decision-making regarding steroid initiation[27].

Other potential side effects include premature rupture of membranes and premature delivery. Thus, although relatively safe, the dose should be kept as low as possible while still effectively controlling MG symptoms[18]. A typical regimen might start with 5 to 10 mg of prednisolone daily, increasing by 5 mg every 5–7 days until the target dose (usually 0.75–1 mg/kg body weight). The optimal dose during pregnancy should be guided by clinical response, aiming to use the lowest effective dose[10][31].

In summary, while steroids are a mainstay of immunosuppressive management in MG treatment and are generally safe for use during pregnancy, their administration requires careful consideration of both timing and dosage, alongside monitoring for potential side effects. The goal is to manage MG effectively while minimizing risks to the mother and the developing fetus[17].

3. Immunosuppressants - Steroid-sparing agents:

In the context of MG management during pregnancy, the use of immunosuppressive agents such as azathioprine and cyclosporine requires careful consideration. These medications are deemed relatively safe for expectant mothers who either do not respond adequately to corticosteroids or cannot tolerate them[17]. However, mycophenolate mofetil and methotrexate are known to increase the risk of teratogenic effects and are thus contraindicated during pregnancy. This understanding aligns with the previous Food and Drug Administration (FDA) categorization, which has now been replaced by more detailed summaries of risks during pregnancy and breastfeeding, along with supporting data to guide healthcare providers in prescribing and counseling.

Azathioprine(dose of 50 mg that can be doubledevery 2-4 weeks)

The use of azathioprine, specifically, reflects differing opinions and practices between regions. In Europe, Azathioprine is widely accepted as the non-steroidal immunosuppressant of choice for managing MG during pregnancy. In contrast, in the United States, there is more caution regarding its use, influenced by a limited number of animal studies and case reports suggesting potential risks for infants, including fetal immunosuppression and pancytopenia. This divergence underscores the importance of region-specific guidelines and the need for personalized medical decision-making, taking into account the latest evidence and regional practices[10][17].

The safety profile of azathioprine in pregnancy has been a subject of extensive study. While some research has noted an increased rate of prematurity, intrauterine growth retardation (IUGR), and low birth weight associated with its use, there is no increased risk of fetal malformations in infants born to mothers exposed to azathioprine during pregnancy. This safety aspect is attributed to the lack of a specific enzyme in the fetal liver necessary for converting azathioprine into its active metabolite[1][2][10].

Given these complexities, the decision to use immunosuppressants like azathioprine during pregnancy should be made collaboratively, weighing the benefits of MG symptom control against potential risks to the fetus.

CalcineurinInhibitors –Cyclosporine / Tacrolimus

Calcineurin inhibitors, especially cyclosporine, are commonly used for

immunosuppressive treatment in women with MG. In the context of fertility and pregnancy outcomes, cyclosporine does not appear to reduce female fertility, though higher doses in men might affect sperm quality. Tacrolimus, another immunosuppressant, does not seem to impact fertility either[6][27]. Both drugs have been associated with preterm labor and low birth weight (IUGR) but not with major congenital malformations.Cyclosporine's safety profile during pregnancy can be attributed to the limited placental transfer of these drugs, typically ranging from 5-20%[6].The effects of tacrolimus on newborns, such as transient hyperkalemia and renal impairment, have been observed, necessitating close monitoring of renal function and potassium levels in neonates exposed to this drug during pregnancy[10][27]. It is noteworthy that the risk-benefit assessment of tacrolimus in pregnancy primarily comes from experiences in transplant and other autoimmune conditions rather than MG specifically.

The general recommendation is that cyclosporine can be considered if the benefits to the mother surpass the potential risks to the fetus. The recommended starting dosage is around 1.25 mg/kg body weight twice daily, which can be adjusted based on the patient's response and condition[6][10].

Mycophenolate Mofetil (MMF)

Mycophenolate mofetil (MMF) functions as a reversible inhibitor of inosine phosphate dehydrogenase, but its usage is significantly restricted in patients who are planning to conceive or are already pregnant. This restriction is due to MMF's ability to cross the placenta, significantly increasing the risk of spontaneous abortions, with miscarriage rates reported up to 45%[28]. Because of its teratogenic potential, MMF is labeled with a black box warning against its use during pregnancy. The drug is linked to a specific type of embryopathy called the EMFO tetrad, characterized by a range of abnormalities. These include issues in the Ears (such as microtia and auditory canal atresia), Mouth (including cleft lip and palate), Fingers and toes (manifested as brachydactyly and toenail hypoplasia), and Ocular or major Organs, impacting the central nervous system, eyes, heart, and kidneys[27][28]. This broad spectrum of potential developmental issues underlines the need to stop MMF at least six weeks prior to planned conception[26].

Cyclophosphamide

Cyclophosphamide, while not a standard treatment for MG, is a cytotoxic alkylating agent known for its significant impact on female fertility. This drug can alter the ovarian reserve, with the degree of impact varying based on factors such as dosage, length of treatment, and the patient's age. These effects are particularly evident in the reduced levels of anti-Müllerian hormone (AMH) in plasma and increased gonadotropin levels, which often correlate with the cumulative dosage of cyclophosphamide, even during shorter treatment periods. The use of this medication requires careful consideration due to its potential long-term effects on fertility[28].

In the context of pregnancy, cyclophosphamide is recognized for its teratogenic effects, particularly during the first trimester. It is contraindicated during pregnancy due to the high risk of severe embryopathy, which can include craniofacial malformations, developmental delays, and limb defects[27][28].In specific cases where its use is deemed essential, such as in the diagnosis of breast cancer during pregnancy, administration of the drug is advised only after the first trimester[28].

Ideally, cyclophosphamide should be discontinued at least three months prior to

conception to mitigate risks[1]. Other sources recommend continuing effective contraception until the end of treatment and for at least one ovulation cycle afterward[28].

Methotrexate (MTX)

Methotrexate is strongly contraindicated preconception, antenatally and postnatally during lactation due to its significant risks. In fact, at high doses, this medication is used for terminating pregnancies and is used in the medical management of ectopic pregnancies[28].Even at lower doses, its use is associated with a considerable risk of fetal abortion and a wide range of fetal malformations. Conditions such as Aminopterin syndrome, characterized by CNS malformations, deformities in the skull and limbs, and cardiovascular defects, can result from methotrexate exposure during pregnancy[8][27].

However, for individuals planning to conceive, a treatment-free interval of three months after discontinuing methotrexate is recommended for both men and women. This interval is advised for men, too, because of the mutagenic risk methotrexate poses to spermatogenesis. This precaution helps ensure the drug's effects have sufficiently diminished to reduce the risks of adverse reproductive outcomes[19][28].

Rituximab

The monoclonal IgG antibody that targets the CD20 antigen found on B lymphocytes, Rituximab, is typically usedin patients with severe cases of MG, particularly those who frequently require rescue treatments such as intravenous immunoglobulin (IVIg) or plasma exchange (PE). The use of Rituximab during pregnancy is not well-documented, and due to its prolonged half-life of around three weeks, it is advised to postpone pregnancy for 12 months after treatment[1][27]. This precaution is due to potential risks to the fetus, including hematological abnormalities. In particular, if used in the third trimester, there is an increased risk of causing immunosuppression in the newborn[19][28].

While there are no reported instances of malformations linked to Rituximab, the scarcity of data and unknown long-term effects on fertility and pregnancy lead to recommendations against its use for those planning a pregnancy, applicable to both men and women[12][32].

C5 Complement Inhibitor – Eculizumab

Using eculizumab, a recombinant IgG monoclonal antibody, in pregnant women with generalized myasthenia gravis (gMG) resistant to standard treatments presents a complex scenario. While eculizumab has been effective and well-tolerated in gMG patients, there is a notable lack of data specifically for its use during pregnancy[33].

Interestingly, there have been reports of improved fetal and maternal outcomes, including hematological and renal functions, when eculizumab was used in pregnancy for conditions like hemolytic-uremic syndrome (HUS) and paroxysmal nocturnal hemoglobinuria (PNH). However, since these conditions differ from MG, the risks to both mother and fetus in MG cannot be entirely ruled out[33][34].

Based on the sparse data, significant levels of eculizumab were not detected in breast milk, nor were they found to significantly influence the complement levels in newborns. A case study by Vu et al. in 2021 highlighted the first pregnancy managed with eculizumab in a woman with refractory gMG. This treatment was administered preconception, antenatally, and postpartum, demonstrating a positive benefit-risk balance without any noted adverse effects on either the

mother or the newborn. The patient continued to be neurologically stable while on eculizumab for a duration of five years[34].

This particular case indicates a possible application of eculizumab in treating pregnant women with gMG that does not respond to traditional treatments. Nevertheless, given the scarcity of data and the variability of individual cases, more clinical evidence and research are needed to ascertain the safety and effectiveness of eculizumab fully in such scenarios.

FcRn Inhibitors– Efgartigimod(10 mg/kg per week for four weeks per cycle)

Efgartigimod (ARGX-113) is a modified human IgG1 antibody Fc fragment designed to diminish pathological IgG autoantibody levels in patients with generalized myasthenia gravis (gMG) to improve muscle weakness[35].

During the third phase of the ADAPT trial released in 2021, researchers showcased promising results in terms of the safety and effectiveness of efgartigimod in managing patients with gMG. Out of 167 participants, a higher proportion in the efgartigimod group responded positively (68% of 65 patients) in the first cycle compared to those in the placebo group, with 40% of those with acetylcholine receptor antibodies showing minimal symptoms. A significant improvement was observed within two weeks for most patients who received ARGX-113. During the study, response rates increased with subsequent treatment cycles, reaching 78%. Efgartigimod was generally well-received, with most side effects being mild to moderate and headaches being equally prevalent across both groups[35].

There is no human data on how efgartigimod affects fertility, although animal studies suggest no negative effects on reproductive parameters. Moreover, reproductive studies in animals did not show any detrimental effects on pregnancy or teratogenic effects, even at dosages much higher than the maximum therapeutic dose. However, it is theorized that it might decrease IgG levels in infants, potentially lowering their infection protection shortly after birth. The presence of efgartigimod in human milk and its effects on breastfed children or milk production remain unknown and are yet to be ruled out. Hence, efgartigimod should be avoided when planning for conception unless the benefits justify the potential risks[1][36].

Management of Myasthenic crisis in pregnancy

During pregnancy, the symptoms of myasthenia gravis can worsen, and there is a possibility of a myasthenic crisis requiring emergency treatments[27]. However, specific data on the incidence of MG crisis during pregnancy are lacking. Symptoms commonly escalate in the first trimester and within the first six months after childbirth. These exacerbations are usually mild to moderate, with myasthenic crises occurring infrequently[8].

An impending myasthenic crisis is characterized by a rapid decline in MG condition, which the treating physician believes could lead to a crisis shortly, potentially within days to weeks. A myasthenic crisis represents a severe, life-threatening exacerbation of MG, with the risk of respiratory or bulbar dysfunction leading to airway compromise[17].The diagnostic approach for an MG crisis in pregnant patients mirrors that of non-pregnant patients, including assessing for infections or new medications, particularly magnesium, used for treating preeclampsia or eclampsia[27].

Both impending and actual myasthenic crises are urgent medical situations that demand prompt and thorough management, including hospitalization. Early recognition and intervention are critical due to the potential adverse effects on both the mother and the fetus. An impending crisis necessitates hospital admission for close monitoring of respiratory and bulbar functions, with readiness for transfer to intensive care if the condition escalates. Management focuses on stabilizing the patient's airway and cardiac functions and providing a course of either intravenous immunoglobulin (IVIg) or plasma exchange (PLEX)[12][17][27].

Intravenous Immunoglobulin (IVIG) or Plasma Exchange (PLEX):

Clinically, both intravenous immunoglobulin (IVIg) and plasma exchange (PLEX) are comparably effective in treating both impending and manifest myasthenic crises[17]. Both IVIg and PLEX can be administered safely during pregnancy, with careful monitoring for typical adverse events.

Selecting between IVIg and PLEX is dependent on the patient's health considerations. PLEX is not suitable for use in septic conditions, while IVIg should be avoided in patients with hypercoagulable states, renal failure, or immunoglobulin hypersensitivity. Additionally, the choice may be influenced by treatment availability and the potential for hemodynamic and venous access complications associated with PLEX, which can often be reduced by opting for peripheral instead of central venous access. Professional consensus tends to favor PLEX for its efficacy and rapid action[12][17][27].

Concurrent initiation of corticosteroids or other immunosuppressive agents is common practice to maintain clinical improvement. Due to the possibility of corticosteroids initially exacerbating myasthenic weakness, it may be prudent to delay their introduction until the beneficial effects of PLEX or IVIg are apparent[17].

Labor and Delivery

As previously discussed, the approach to the mode of delivery for women with MG varies. International consensus guidance for the management of stable MG generally encourages spontaneous vaginal delivery at term[17]. The second stage of labor, which involves voluntary contractions of the pelvic floor muscles to help move the baby through the birth canal, is the most likely to be impacted in MG patients. The first stage is driven by uterine smooth muscle contractions, which are unaffected by MG since these muscles have muscarinic AChRs. Consequently, during the second stage, monitoring for prolonged labor and preventing excessive strain is crucial, providing assistance with methods such as vacuum extraction, forceps, or cesarean section when necessary to alleviate weakness from fatigue[27][37].

Women with MG may have a higher propensity for elective Cesarean sections due to muscle weakness or as a preventive strategy[1][8]. Nonetheless, the frequency of emergency Cesarean sections or instrumentally assisted vaginal births does not significantly differ from that of women without MG. Cesarean deliveries should be reserved for obstetric reasons rather than MG alone[8][15]. Women are advised to maintain their regular medications, such as oral anticholinesterases, during labor. As per the recommendations from a UK multispecialty working group, those who have been on long-term oral steroids (exceeding 7.5 mg daily or 15 mg every other day) should receive an increased stress dose of hydrocortisone intravenously (100 mg three times daily) during labor[25].

With the potential risk of neonatal myasthenia and with preterm births, it is essential for deliveries to occur in hospitals capable of providing advanced respiratory support for newborns. Assessing the mother's pulmonary function before delivery and closely monitoring for signs of respiratory distress or signs of impending myasthenic crisis is imperative to quickly address and manage appropriately. Optimal management for the mother and infant is best achieved in tertiary care centers, where a team-based approach with obstetrics, neurology, anesthesia, and neonatology can be executed, ensuring the highest standard of care for both[8][15][17][27].

Anesthesia

In the context of pregnancy andMG, it is imperative for expectant mothers with MG to consult with an obstetric anesthetist before labor to discuss analgesia and anesthetic options, particularly for cesarean section. Regional anesthesia, especially vaginal delivery with epidural anesthesia, is generally preferred for patients with well-controlled or mild-to-moderate MG. These methods not only manage pain effectively but also guard against excessive fatigue due to prolonged exertion, and they can be readily converted to anesthesia for instrumental or cesarean delivery if necessary. While there is a lack of specific studies assessing the effect of pain control on the delivery method, it is reasonable to hypothesize that mitigating muscle fatigue and the stress of delivery could enhance outcomes[10][25][27].

Inhalational nitrous oxide, also known as Entonox, can be administered in patients with MG. In terms of local anesthetics, amide types are preferable due to their safety profile, as concurrent anticholinesterase inhibitor use does not affect their metabolism. Ropivacaine, an amide-type anesthetic, is increasingly favored for its lower tendency to cause motor block. Conversely, ester-type anesthetic agents are rapidly broken down by plasma cholinesterase, increasing the risk of maternal and fetal toxicity. Certain medications should be avoided during labor as they may exacerbate muscle weakness or precipitate respiratory depression. These include neuromuscular blockers and magnesium. As discussed earlier, for managing eclampsia, barbiturates or phenytoin are suggested as alternative treatments. Opioids, such as Pethidine, are also contraindicated due to their potential to aggravate respiratory depression in both the mother and fetus[12][25][27][37].

The primary anesthetic considerations in patients with myasthenia gravis become prominent when regional anesthesia is not viable, necessitating the use of general anesthesia. In cases requiring cesarean section, an epidural block may still be feasible. While MG alone is not a standalone criterion for a cesarean section, the severity of symptoms, particularly bulbar and respiratory muscle weakness, should be evaluated in conjunction with obstetric indications. To further clarify, patients with mild MG who do not have respiratory involvement or those with purely ocular MG are generally well-suited for spinal or epidural anesthesia[25][27]. Combined spinal-epidural anesthesia, utilizing a low-dose spinal component, offers the benefits of both spinal and epidural methods. It provides reliable surgical anesthesia quickly while maintaining relative stability in cardiovascular and respiratory functions[37]. On the other hand, for patients exhibiting bulbar and respiratory muscle weakness, cesarean sections should be conducted under general anesthesia.

Effective management of anesthesia induction and maintenance can be achieved using inhalational agents such as isoflurane or sevoflurane or through intravenous administration of propofol and fentanyl. The utilization of neuromuscular blockers is typically advised against, except in necessary circumstances. When these agents are used in patients with MG, significantly lower doses

should be administered due to their heightened sensitivity to these medications. The employment of reversal agents for neuromuscular blockers, especially when an excessive dose is used, remains a topic of discussion. Available solutions include waiting for spontaneous recovery from atracurium's effects, utilizing sugammadex to reverse the impact of rocuronium, or applying neostigmine to counteract the effects of both atracurium and rocuronium. However, it is crucial to consider that administering a high dose of neostigmine could induce a cholinergic crisis. This condition, marked by widespread muscle weakness, can be difficult to differentiate from a myasthenic crisis[12][25][27][37].

Postpartum Care

It is vital for pregnant women with MG to be made aware of this and other potential complications that could affect their newborns[8][10]. Such knowledge is not only important for their understanding of the health risks to their babies but also ensures they are prepared to seek early medical intervention if necessary. This proactive approach to maternal and neonatal health in the context of MG is essential for optimal care and outcomes.

For example, monitoring for transient hyperbilirubinemia in neonates born to mothers with MG is crucial, especially considering its possible link to the use of medications like prednisone and pyridostigmine during pregnancy[10]. It is also imperative to be aware of additional complications like transient neonatal myasthenia gravis and arthrogryposis arthrogryposis. These conditions will be further detailed below.

1. Transient Neonatal MG

Neonatal myasthenia, affecting 5–20% of infants born to mothers with MG, is a temporary condition[1][8][27]. It is believed to result from the trans-placental transfer of the mother's IgG antibodies (AChR or muscle-specific kinase antibodies) against the postsynaptic muscle membrane antigens during pregnancy. These antibodies bind to their respective antigens in the infant, potentially causing muscle weakness until they are cleared from the child's system. The variability in AChR antibody epitope specificity and the infant's AChR properties are thought to explain the relatively infrequent occurrence of neonatal MG[1][27][38].

Clinical manifestations of neonatal MG include poor sucking reflex due to reduced muscle strength, difficulty swallowing, a faint cry, drooping eyelids, and occasionally generalized muscle weakness. In rare and severe cases, inadequate respiration, aspiration, and pneumonia may occur. These symptoms usually present within the first three days after birth, lasting from a few days to several weeks but not exceeding three months. The diagnosis is inferred from medical history and confirmed through electrodiagnostic tests showing abnormal repetitive nerve stimulation (RNS) and detection of pathogenic antibodies in the infant[1][12][27].

Mothers with MG who have had one child with neonatal myasthenia are at a heightened risk of the condition in subsequent children, reaching up to 75%, irrespective of the mother's MG severity or antibody levels[38].Interestingly, neonatal MG can occur even in infants of mothers with undetectable antibodies. Thymectomy in the mother has been observed to reduce the risk of neonatal MG in future pregnancies[8][27].

The majority of neonatal myasthenia cases are typically mild and transient, often requiring supportive care only, without any specific treatment. Supportive care, which includes assistance with breastfeeding and continuous monitoring to identify any involvement of respiratory or swallowing muscles, is crucial[1][19]. However, low doses of

acetylcholine esterase inhibitors, such as pyridostigmine and neostigmine, have been found effective in improving muscle strength in these cases[12]. Treatments like intravenous immunoglobulin (IVIg) or plasma exchange are advised in exceptionally severe instances. The need for respiratory support and tube feeding is uncommon but critical in some cases[1][8][19].

There are, however, rare instances where neonatal myasthenia leads to lasting disabilities, including multiple joint contractures (AMC) or myopathic symptoms. This condition, known as Fetal AChR Inactivation Syndrome, has been documented in a case series involving eight children from four families[39]. These children exhibited persistent myopathy linked to maternal myasthenia gravis or asymptomatic elevation of maternal AChR antibody levels. Unlike fluctuating conditions caused by the pathologic maternal antibodies, this syndrome represents a permanent alteration in the postsynaptic membrane caused by exposure to these antibodies during fetal development. The children in these reports display permanent muscle weakness, which can be either generalized or localized, such as facial paresis. Enhanced prenatal and perinatal monitoring and treatments may improve outcomes for such cases[8][39].

2. Arthrogryposis

There are two types of autoantibodies against acetylcholine (Ach) receptors that are identified in MG. Firstly, the adult type is linked to maternal and transient neonatal MG. Secondly is the fetal type, present in fetal neuromuscular junctions up to 33–35 weeks of gestation, and is often associated with fetal arthrogryposis congenita[38]. Arthrogryposis multiplex congenita, a condition involving multiple joint contractures at birth, stems from various causes, including neuromuscular diseases, where it has been identified in up to 2% of children born to mothers with MG. This rare syndrome is marked by polyhydramnios, likely attributed to impaired fetal swallowing, skeletal abnormalities, and joint contractures due to limited in-utero movement[8][10][12][38].

MG alone is not a significant risk factor for arthrogryposis in offspring. However, a previous child with arthrogryposis or fetal AChR inactivation syndrome poses a strong risk factor in MG pregnancies. Prenatal diagnosis is possible through ultrasound, indicating symptoms like polyhydramnios, reduced fetal movement, and joint deformities[1][10][38].

There is a consideration for plasma exchange or IVIg treatment for MG women with a history of having a child with these conditions in subsequent pregnancies. This treatment, aimed at reducing AChR antibody levels, should also be initiated immediately upon any signs of arthrogryposis or reduced fetal movements during pregnancy. However, the efficacy of IVIg and plasmapheresis in these cases has not yet been established by data or experience[8][12][38].

3. Lactation

Breastfeeding is generally encouraged for women with MG, including those with and without detectable antibody levels. This is because the IgG levelsin maternal milk constitute about 2% of those in serum, and the IgG that does transfer is then partially broken down in the infant's gastrointestinal tract.In fact, reports show that breastfeeding has been associated with lowering the child's risk of developing autoimmune diseases[1][8]. Table 1 provides an overview of MG medication safety while in the lactation period.

Regarding MG medication safety during breastfeeding, corticosteroids and anticholinesterase inhibitors are considered relatively safe. When using corticosteroids at a dose of 20 mg per day or lower, a minimal amount is excreted in breast milk that does not have adverse effects on the newborn[10][12]. While there have been concerns about the potential effects of breastfeeding while on immunosuppressive medications,

this risk seems to depend on the drug concentration in the milk[27]. Azathioprine metabolites, for instance, appear in very low levels in maternal milk and have not been associated with adverse effects in infants. Similarly, cyclosporine is present in breast milk but is minimally absorbed by infants, making lactation safe while using these medications[12][27].

On the other hand, mycophenolate mofetil (MMF) is not recommended during lactation,as there is nodata regarding its presencein breast milk and its potential risk to infants. The difficulty in researching MMF's safety in this context is compounded by the availability of safer alternative treatments and the drug's known teratogenic risks during pregnancy. Therefore, women who are planning to conceive or are pregnant are typically advised to discontinue the use of MMF. This approach prioritizes both the safety of the unborn child and the health of the nursing infant[8][10][12][27].

Breastfeeding is contraindicated for mothers with MG who are undergoing treatment with certain medications due to their potential adverse effects. Specifically, concurrent use of cyclophosphamide during lactation, as this drug is known to be excreted into breast milk. Similarly, methotrexate, while excreted in minimal amounts in breast milk, is advised against for breastfeeding mothers until more definitive data are available, given the unknown effects on infants[8][12][27].

In terms of biological therapies, the safety of breastfeeding while on Rituximab is currently not well-established, leading to general recommendations against breastfeeding until more comprehensive data becomes available to confirm its safety. As for eculizumab, while it has not been detected in maternal milk in a limited case study, there remains a need for more extensive research to provide definitive guidance on its use during breastfeeding[8][12][27].

For postpartum MG exacerbations, intravenous immunoglobulin or plasma exchange can be safely used, irrespective of breastfeeding status. Women on monoclonal antibody treatments are encouraged to breastfeed and to participate in outcome registries to contribute to a better understanding of the safety and effects of these treatments during lactation[8].

CONCLUSIONS AND LIMITATIONS

This report concludes that managing Myasthenia Gravis during pregnancy requires a patient-oriented, individualized approach. It emphasizes the importance of multidisciplinary teams in planning and managing pregnancy in women with MG. The review highlights the need for careful medication adjustment, considering both maternal and fetal health.Table 1 concisely presents a comprehensive overview of the MG medication, detailing their roles and recommended use throughout the preconception, prenatal, and postnatal phases.When used with caution and closer monitoring some of the newer medications like Eculizumab might be beneficial during pregnancy. Thymectomy might be a safer option when performed prior to the pregnancy for uncontrolled MG and has shown benefit in both maternal and fetal outcomes. The report underscores the critical need for personalized counseling and education for women with MG, considering the implications of MG on fertility, pregnancy, childbirth, and lactation. The findings suggest that with appropriate management and monitoring, women with MG can have successful pregnancies and healthy outcomes for both mother and child.

Limitations of the available literature includes limited data on safety of some of the effective treatments like Rituximab and Efgartimod in pregnancy and lactation. Pregnancy registries in patients with MG can provide larger database to understand the course of MG during pregnancy and vice versa.

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